Neuroscience and Biobehavioral Reviews 43 (2014) 191–198

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

The ontogenesis of language lateralization and its relation to handedness

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ARTICLE INFO

Article history:
Received 18 January 2014
Received in revised form 5 April 2014
Accepted 15 April 2014

Keywords:
Laterality
Lateralization
Functional Hemispheric asymmetries
Speech
Ontogenesis

ABSTRACT

Dominance of the left hemisphere for many aspects of speech production and perception is one of the best known examples of functional hemispheric asymmetries in the human brain. Classic theories about its ontogenesis assume that it is determined by the same ontogenetic factors as handedness because the two traits are correlated to some extent. However, the strength of this correlation depends on the measures used to assess the two traits, and the neurophysiological basis of language lateralization is different from that of handedness. Therefore, we argue that although the two traits show partial pleiotropy, there is also a substantial amount of independent ontogenetic influences for each of them. This view is supported by several recent genetic and neuroscientific studies that are reviewed in the present article.

Contents

1. Introduction

Relative dominance of the left hemisphere for most language-related tasks in the majority of the population is a defining characteristic of the human language system (Corballis, 2009, 2012; Friederici, 2011; Friederici and Alter, 2004; Hugdahl, 2000, 2011; Ocklenburg et al., 2011b). However, the ontogenesis of this phenomenon is still not well understood. While it is now widely accepted that the ability to produce and understand language is a multifactorial trait that is determined by several different genetic and non-genetic factors (Fisher et al., 2003; Grigorenko, 2009; Hayiou-Thomas, 2008; Newbury and Monaco, 2010; Takahashi et al., 2009), it is still largely unclear which genes and environmental factors determine individual language lateralization. Interestingly, many theories about the ontogenesis of language lateralization assume that handedness and language lateralization are determined by the same gene (e.g., Crow, 2010; Annett, 1998), an idea that has been called the "Broca-Annett axiom" (Crow, 2004). For example, Annett (1998) assumed that a single, unspecified gene (called the RS or right-shift gene) determines both handedness and language lateralization. According to this

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http://dx.doi.org/10.1016/j.neubiorev.2014.04.008
0149-7634/

theory, one allele (RS+) increases the probability of an individual to be right-handed and left language dominant, while the other allele (RS−) leaves the direction of handedness and language lateralization up to chance. Accordingly, carriers of two RS+ alleles have the highest chance of being right-handed and left-lateralized for language, while this probability is reduced in RS+− carriers. Carriers of two RS− alleles have an equal chance of being right-handed/left-lateralized or left-handed/right-lateralized. However, the idea that complex brain phenotypes such as handedness and language lateralization are determined by a single gene has recently been criticized by many authors, mainly because no such gene has been identified in genome-wide association studies (e.g. Armour et al., 2013; Francks et al., 2007; McManus et al., 2009; Ocklenburg et al., 2013c; Rentería, 2012). Accordingly, McManus et al. (2013) suggested that multi-locus models are more suitable to explain the genetic background of handedness than single-locus models.

In the present article we argue that this shift from monogenic to multifactorial models of handedness and language lateralization is only one aspect of ontogenetic models for these traits that needs to be revisited. We review recent genetic and neuroscientific findings about the ontogenesis of language lateralization and its relation to handedness, and show that both the neurophysiological basis of language lateralization and its genetic correlates are substantially different from those of handedness. Although the two traits show partial pleiotropy, independent ontogenetic influences and neurophysiological correlates have to be taken into account in order to gain better theoretical understanding of the factors regulating the development of language lateralization.

2. The relation of language lateralization and handedness

How did the idea of handedness and language lateralization being determined by the same gene(s) develop? Evidence supporting this assumption is mostly provided by behavioral studies comparing the frequency of left and right language dominant individuals among left- and right-handers. Interestingly, language dominance has been found to be associated with handedness. About 95% of right-handers, but only between 70% and 85% of left-handers show typical left-hemispheric language dominance (Knecht et al., 2000; Perlaki et al., 2013). Moreover, in the context of the abovementioned right-shift theory, it has been shown that the distribution of right- and left-handed dysphasia patients with unilateral right- or left-hemispheric lesions is congruent with the idea that the two traits are determined by the hypothetical RS gene, if it is assumed that the chance effect of RS− allele is independent for handedness and language lateralization (Annett, 1975, 1976a). A relation between handedness and language lateralization has also been reported for handedness as assessed by motor performance (as opposed to a preference questionnaire). Flowers and Hudson (2013) reported that in epilepsy patients undergoing the Wada test, individuals who performed similarly fast with both hands on a handedness motor performance task also showed more ambiguous speech representation. In contrast, patients with a large between-hands difference in speed showed clear unilateral speech representation.

A major challenge for the assumption that handedness and language lateralization have the same ontogenetic base comes from fTCD (functional transcranial Doppler sonography) and fMRI (functional magnetic resonance imaging) studies investigating language lateralization in left-handers. For example, Knecht et al. (2000) used fTCD during word generation in 326 healthy left- and right-handed participants to measure language dominance. They found that atypical right-hemispheric language dominance increased linearly with the degree of left-handedness from 4% in strong right-handers to 15% in ambidextrous individuals and to 27% in strong left-handers. While these results clearly show a relation between handedness and language dominance, they also illustrate that 73% of strong left-handers show typical left-hemispheric language dominance, just as most right-handers do. Even if it is presumed that language lateralization is up to chance in all strong left-handers since their RS genotype is RS−, this number is far higher than the 50% that would be expected under this assumption. Thus, it is likely that some of the ontogenetic factors influencing language lateralization are not influencing handedness and vice versa. Moreover, studies that actually report statistical measures of correlations between handedness and language lateralization typically show that correlations are far from perfect. For example, Badzakova-Trajkov et al. (2010) used fMRI to measure brain activation during word generation in a sample of 155 adult subjects and correlated it with the handedness LQ (laterality quotient) obtained from a 12-item questionnaire. The correlation coefficient for the correlation between the laterality index for frontal activation asymmetries during word generation and the handedness LQ was $r = 0.357$. The coefficient was significant at the $p < 0.001$ level, indicating that individuals with stronger right-handedness were also more likely to show a strong leftward bias for speech-related brain activity in the frontal lobe. However, the coefficient of determination r^2 for this correlation coefficient is 0.127, indicating that roughly 13% of the variance in the handedness data could be explained by the language lateralization data. Similar evidence is provided by a recent study by Groen et al. (2013) who investigated the association of hemispheric asymmetries during speech production (as measured with functional transcranial Doppler ultrasonography) and three different handedness assessments in 57 children between 6 and 16 years of age. Handedness measures included a short and a long version of the Edinburgh Handedness Inventory (Oldfield, 1971), the peg-moving task (Annett, 1976b) as a measure of relative hand skill, and performance on a reaching task. They found significant correlations between the extent of language lateralization and handedness as assessed with the short version of the Edinburgh Handedness Inventory ($r = 0.29$) as well as handedness performance on the reaching task ($r = 0.40$). However, for the long version of the Edinburgh Handedness Inventory ($r = 0.16$) and the peg-moving task ($r = 0.13$), correlations were small and failed to reach significance. Interestingly, even the significant correlations were in the small to medium range, leading Groen et al. (2013) to conclude that their work supported the idea that different lateralized functions in the human brain are unlikely to be determined by a single common cause, but are considerably independent from each other. Taken together, these findings indicate that handedness and language lateralization are likely to share some of their ontogenetic influence factors. However, they also emphasize that the two traits are largely independent of each other.

3. The phylogenesis of language lateralization and handedness

One way to identify ontogenetic mechanisms relevant for the development of handedness and language lateralization in humans is to look at the phylogenesis of these two traits (Fitch and Braccini, 2013; Forrester et al., 2013; Meguerditchian et al., 2013; Ocklenburg and Güntürkün, 2012; Vallortigara and Rogers, 2005). While the strong and consistent right-sided population bias observed in human handedness seems to be unique within the vertebrate subphylum, the preferential use of one limb over the other for manipulative actions is not. Ströckens et al. (2013) systematically analyzed studies investigating limb preferences in all non-extinct vertebrate orders by employing cladographic comparisons. They identified 119 different species in which evidence for left- or right-sided limb preferences had been reported. Overall, about 68% of these showed evidence for either population

or individual-level asymmetries, while 32% showed no evidence for specific preferences. These findings support the position that limb preferences represent a common feature in non-human vertebrates and might constitute an evolutionary predecessor to human handedness, even though animal limb preferences are typically less marked than in humans.

Regarding the evolution of language lateralization, there are two major lines of research. On the one hand, lateralization of conspecific vocalization in non-human vertebrates might be an evolutionary predecessor to human language lateralization. Using a similar method as Ströckens et al. (2013), Ocklenburg et al. (2013e) identified all vertebrate orders in which lateralization of production and perception of conspecific vocalization had been investigated. While the number of species in which this feature had been investigated was much smaller than for limb preferences, evidence for lateralization of conspecific vocalization had been found for several primate species, a few non-primate mammals (e.g. horses) and some avian species within the Passeriformes orders. This finding led Ocklenburg et al. (2013e) to conclude that language lateralization in humans may have resulted from an inherited dominance of the left hemisphere for those aspects of human language that are similar to the sensory or motor properties of conspecific vocalization in animals. Interestingly, this idea implicates that genes or non-genetic factors relevant for formation or functioning of brain structures involved in these low-level aspects of speech production and perception might be involved in the ontogenesis of human language lateralization, but not handedness.

The other major line of research regarding the evolution of language lateralization is centered on the idea that hand preferences for gestural communication in primates might constitute a precursor to language lateralization (Fitch and Braccini, 2013; Liebal and Call, 2012; Meguerditchian et al., 2013). This idea is mainly based on the fact that all studies that investigated hand preferences for gestural communication in primates found stronger right-sided population-biases for communicative gestures as compared to non-communicative actions, thus indicating stronger involvement of the left hemisphere during communicative gesturing (Meguerditchian et al., 2013). Meguerditchian et al. (2013) further pointed out that two independent evolutionary pathways might have influenced primate handedness, one based on the left-hemispheric preference for gestural communication, and the other based on preferences for bimanually coordinated gestures without communicative meaning. This idea is also supported by a recent series of studies by Forrester et al. (2011, 2012, 2013) which showed that in both gorillas and chimpanzees, handedness is modulated by the target to which the animals direct a manual action. Targets were classified as animate (e.g. a conspecific) or inanimate (non-living functional objects), and both gorillas and chimpanzees demonstrated a right-handed bias for actions directed at inanimate targets, but not at animate targets. Thus, these studies also support the assumption that handedness and language lateralization likely share some ontogenetic influence factors (e.g. genes or non-genetic factors relevant for brain structures involved in the production of temporal sequences of actions), but nevertheless are largely independent of each other.

4. The ontogenesis of language lateralization and handedness

If handedness and language lateralization are indeed largely independent of each other, which genes are involved in the formation of one trait, but are irrelevant for the other one? Research on the genetics of handedness has made tremendous progress over the course of the last few years (for review see McManus et al., 2013; Ocklenburg et al., 2013c). While handedness had been thought of as a monogenic trait for several decades (Annett, 1998), due to tremendous advances in genetics that have since been made it is now generally accepted that it is determined by multiple genetic and non-genetic influence factors (Francks et al., 2007; McManus et al., 2013; Medland et al., 2006; Piper et al., 2012; Rentería, 2012; Scerri et al., 2011). Genes associated with handedness include *LRRTM1* (Francks et al., 2002, 2003a,b, 2007), *PCSK6* (Arning et al., 2013; Brandler et al., 2013; Scerri et al., 2011), *AR* (Hampson and Sankar, 2012; Medland et al., 2005), *COMT* (Savitz et al., 2007) and *APOE* (Bloss et al., 2010; but see: Hubacek et al., 2012; Piper et al., 2012). In addition to these studies in humans, Li et al. (2013) recently reported that knocking out the asymmetrically expressed transcriptional regulator *LMO4* in mice modulates the animals' paw preferences. Unfortunately, no studies investigating these genes in relation to language lateralization have been published yet.

In contrast to handedness, the emergence of language lateralization critically depends on the proper functioning of neural networks involved in speech generation and perception. Thus, an obvious step toward identifying candidate genes for language lateralization is to take a closer look at genes that have previously been related to language impairment such as the forkhead box P2 gene *FOXP2* (Graham and Fisher, 2013). This approach was chosen by Pinel et al. (2012) who investigated the role of different single-nucleotide polymorphisms (SNPs) within *FOXP2* and a *KIAA0319*/*TTRAP*/*THEM2* gene cluster associated with reading disability for brain activation patterns during an fMRI-based reading task. Two *FOXP2* SNPs, rs6980093 and rs7799109s, were associated with differential activation in the left frontal cortex, while one SNP in the *KIAA0319/TTRAP/THEM2* locus (rs17243157) was associated with activation asymmetries in the superior temporal sulcus. More evidence for a link between *FOXP2* and language lateralization has recently been brought forward by Ocklenburg et al. (2013a) who reported an association between the *FOXP2* SNPs rs2396753 and rs12533005 and performance on the dichotic listening task, a behavioral measure of language lateralization. The rare alleles of the two intronic SNPs in high linkage disequilibrium (LD) with each other were found to be associated with more pronounced left-hemispheric language dominance. Interestingly, no association with handedness LQ was found for either SNP.

In addition to *FOXP2*, several other genes have been linked to speech, speech perception and language-related disorders, thus also constituting interesting candidate genes for language lateralization while probably being unrelated to handedness. These include for example *ATP2C2*, *CMIP*, *CNTNAP2*, *DCDC2*, *DYX1*, *KIAA0319* and *MRPL19/C2ORF3* (Bishop, 2013, Darki et al., 2012; Newbury and Monaco, 2010; Scott-Van Zeeland et al., 2010; Tan et al., 2010; Whalley et al., 2011).

In addition to genes directly related to language, genes relevant for the dopamine and glutamate transmitter systems have also been linked to language lateralization but not handedness. Ocklenburg et al. (2013b) found that individuals carrying the rare C allele of the Cholecystokinin A receptor gene *CCKAR* rs1800857 SNP showed a marked reduction of the typical left-hemispheric dominance for language processing on the dichotic listening task, while no association with handedness was observed. A similar pattern of association was also reported for a polymorphism in the NMDA receptor 2B subunit gene *GRIN2B.* Individuals heterozygous for the *GRIN2B* rs1806201 SNP showed more pronounced left-hemispheric language dominance as compared to the homozygous genotype groups. However, no association of this SNP with handedness could be observed (Ocklenburg et al., 2011a).

Another argument against a completely mutual ontogenetic base of handedness and language lateralization comes from studies investigating the role of non-genetic factors for their development. For example, the individual extent of hemispheric language

dominance in women not using hormonal contraceptives has been shown to be modulated by hormone level fluctuations due to the menstrual cycle. Hausmann and Güntürkün (2000) showed that these so-called activating effects of sex hormones lead to decreased language lateralization (as measured with a behavioral lexical decision task) during the midluteal cycle phase when progesterone levels are lowest. In contrast, handedness seems to be more stable, and to date no study reporting cycle-dependent fluctuations in left- and right-handedness has been published. In addition to activating effects, sex hormones also can have organizing effects on brain structures (Chura et al., 2010), as can be evident for example in behavioral or neuroanatomical sex differences. Interestingly, findings on sex differences in handedness and language lateralization are somewhat contradicting. For handedness, Papadatou-Pastou et al. (2008) reported that in a meta-analysis of 144 studies with a total sample size of over 1.5 million participants, males showed a greater tendency toward left-handedness than females. Thus, one would expect males to show more atypical right-hemispheric language lateralization. However, Hirnstein et al. (2013) could show that the effect of sex on language lateralization seems to be age-dependent. While male adolescents indeed showed reduced left-hemispheric language dominance compared to female adolescents, younger male adults showed greater asymmetry than younger female adults. In contrast, no sex differences were found for children or older adults. Thus, organizing effects of sex hormones seem to differentially affect handedness and language lateralization. Furthermore, it was also shown that prenatal sex hormone exposure seems to differentially affect handedness and language lateralization. Lust et al. (2011) assessed the prenatal testosterone level for unborn children of healthy pregnant women using radioimmunoassay, and correlated them with handedness and language lateralization at ages 6 to 8. Higher prenatal testosterone exposure was related to a decrease in strength of handedness and increased left hemisphere dominance for language. In addition, handedness has been shown to be influenced by a number of other non-genetic factors which have not yet been related to language lateralization, such as cultural pressures (e.g. stigmatization of left-handedness; Schaafsma et al., 2009; Zverev, 2006), season of birth (Abel and Kruger, 2004; Jones and Martin, 2008), early visual experience of the hands (Michel, 1981; Ocklenburg et al., 2010; Ocklenburg and Güntürkün, 2009) and parental influence (Laland, 2008). Also, twin studies strongly support the idea that non-genetic factors influence handedness. While identical twins are more likely to be concordant for hand preference than non-identical twins (Sicotte et al., 1999), this concordance is less than 100%, and discordant handedness is observed in about 20–25% of identical twins (Gurd et al., 2006). Interestingly, monozygotic twin pairs discordant for handedness are not necessarily discordant for language lateralization. Sommer et al. (2002) investigated handedness and language lateralization as measured by fMRI in a sample of 12 monozygotic twin pairs concordant for handedness and 13 monozygotic twin pairs discordant for handedness. While handedness and language lateralization were highly correlated in the handedness concordant group, the correlation failed to reach significance in the handedness discordant group. Here, five twin pairs were also discordant for language dominance while the other eight twin pairs were concordant for language dominance, further arguing against a completely mutual ontogenetic base of handedness and language lateralization.

5. Candidate genes shared between language lateralization and handedness

To date, no study has identified any genetic variation that is associated with phenotype differences in both handedness and language lateralization. However, due to the correlation between the two traits it is likely that they share at least some genetic influences. Which candidate gene groups might account for these putatively shared genetic influences? While we can only guess at the present moment, one candidate gene group that might actually be relevant for both traits are genes involved in the formation of the corpus callosum, the largest commissure in the human brain, or the myelin system in general. Structural properties of the corpus callosum have repeatedly been linked to functional language lateralization (e.g. Musiek and Weihing, 2011; Westerhausen and Hugdahl, 2008), and interestingly, interhemispheric inhibition mediated through the corpus callosum has been shown to be relevant for handedness development (Hayashi et al., 2008; Wahl et al., 2007). Thus, genes involved in the formation of myelin in the central nervous system such as the proteolipid protein 1 gene *PLP1* (Hoffman-Zacharska et al., 2013) or the glycoprotein M6B gene *GPM6B* (Werner et al., 2013), as well as genes involved in the formation of the corpus callosum such as the spastic paraplegia 11 gene *SPG11* (Ma et al., 2013) constitute interesting candidate genes for both handedness and language lateralization. In addition to the asymmetrically expressed transcriptional regulator *LMO4* which has been related to paw preferences in mice (Li et al., 2013), a number of other asymmetrically expressed genes have been reported, such as the transcriptional repressor *HEY1*, the laminin receptor 1 gene *LAMR1*, the stathmin-like 4 gene *STMN4*, and the insulin-like growth factor binding protein 5 gene *IGFBP5* (Sun and Walsh, 2006). These constitute interesting candidate genes for both handedness and language lateralization. However, to date, this notion remains entirely speculative, and more research is clearly needed to determine whether there are genes that influence multiple forms of hemispheric asymmetries.

6. Different neural networks are relevant for language lateralization and handedness

Language lateralization and handedness are complex behavioral phenotypes and it is therefore likely that the individual phenotype is influenced by structural and functional properties of relevant brain regions (Abrahams and Geschwind, 2010). With regard to language lateralization, obviously, the neuronal networks involved in producing and perceiving spoken language and reading words are relevant (for a comprehensive review see Price, 2012). While the networks for these three forms of language-related processing overlap, they are not identical. This poses an essential problem when discussing the genetics of language lateralization, since it is not clear whether it represents a single phenotypic trait or whether there are several different forms of language lateralization that are partly independent of each other. For example, asymmetrical brain activation induced by speech production can be assessed using a word generation task in the fMRI scanner. In this task, participants are instructed to think of as many words starting with a previously presented probe letter as possible within a timeframe of 30 s. Participants are specifically asked to think of, rather than overtly speak, words in order to prevent movement-related artifacts in the fMRI data. Using this method, Badzakova-Trajkov et al. (2010) found stronger left-hemispheric activations in the inferior frontal gyrus, the supplementary motor area, the precentral gyrus and the superior and inferior parietal lobules as well as in the inferior occipital gyrus. In turn, asymmetrical brain activation induced by speech perception can be assessed by presenting spoken words in the fMRI scanner. Using this method, Bethmann et al. (2007) found greater left- than right-hemispheric activation in the inferior frontal sulcus, the inferior part of the inferior frontal gyrus, the posterior part of the superior temporal sulcus and the ascending branch of the superior temporal sulcus. Thus, while there were

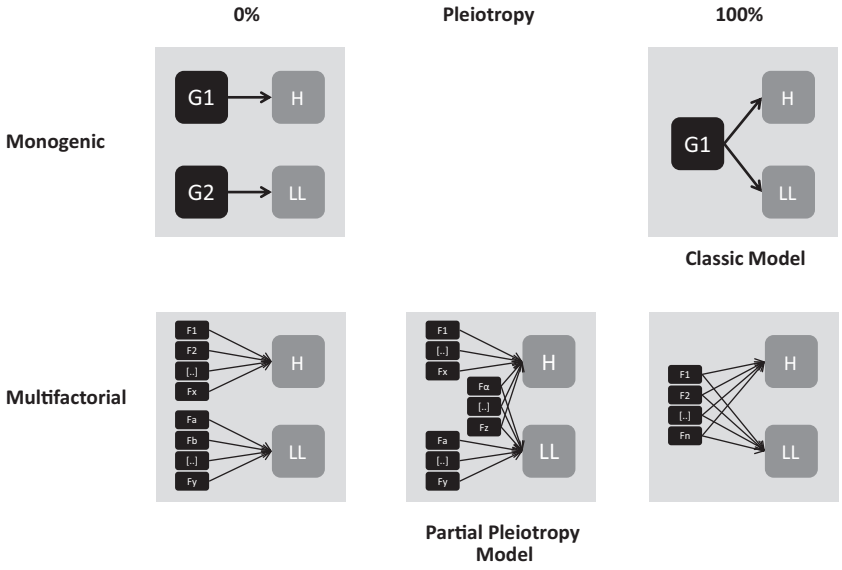

Fig. 1. Theoretical models for the ontogenesis of handedness and language lateralization. Models vary with regard to the amount of pleiotropy assumed to exist between the two traits (between 0% and 100%), and the number of genetic and non-genetic factors which are thought to be relevant (between one and possibly several hundred). (H: handedness; LL: language lateralization; G: genetic influence factor; F: an ontogenetic influence factor that could be genetic, epigenetic or environmental).

overlaps between activated brain areas for auditory speech production and perception, they were not identical. Furthermore, both language production and perception can be assessed not only in the auditory modality but also in the visual modality, e.g. by using a reading task to assess visual word perception (Price, 2012), or a writing task to assess language production (Segal and Petrides, 2012) in the fMRI scanner. Since written words are perceived by the visual system, associated sensory processing leads to activation of brain areas different from those that underlie the processing of speech, i.e. mainly the ventral occipitotemporal cortex (Price, 2012). Comparably, writing activates different neural networks than speaking, with activation foci in several regions of the posterior parietal cortex which are connected to language processing areas, motor and visual sensory areas (Segal and Petrides, 2012). Thus, taking into account these differences in brain activation patterns for different forms of language lateralization, it is plausible that they are determined by partly non-identical ontogenetic factors.

Moreover, a much wider range of methodological approaches has been used to investigate language lateralization than handedness, ranging from lesion studies (Stowe et al., 2005) and the Wada test (Baxendale, 2009) to behavioral techniques such as the dichotic listening task (Hugdahl, 2011) or visual half-field paradigms (Hirnstein et al., 2010) and neuroimaging techniques like fMRI (Van der Haegen et al., 2011). While findings from these different tests (e.g. determination of the language-dominant hemisphere) typically correlate, the predictive validity of one test result for the outcome on another test often is not very high. For example, Fontoura et al. (2008) compared results obtained on the dichotic listening test with brain activation during verb generation in the fMRI, finding a significant correlation of $r = 0.62$ between the two measures. In addition to these methodological differences, language lateralization can refer to both hemispheric asymmetries during speech production and speech perception. Thus, the technique used to measure the phenotype (e.g. behavior vs. brain activation), the sensory system used to process the stimuli (auditory vs. visual), and the specific aspect of the language system (production vs. perception) have to be taken into account when developing a model about its ontogenesis. Moreover, it has recently been shown that structural asymmetries in intrahemispheric white matter pathways connecting language relevant gray matter areas influence functional language lateralization (Ocklenburg et al., 2013d). Therefore, the strength of these connections should be considered, too. This is especially interesting from a developmental perspective, since Dubois et al. (2009) recently showed that in infants from 1 to 4 months of age, both the language-relevant arcuate fasciculus and the handedness-relevant cortico-spinal tract show leftward asymmetries in microstructure, but only the arcuate fasciculus shows macroscopic left-right differences.

Handedness refers to a preference to perform certain motor tasks (e.g. writing) with one hand rather than the other. Thus, its neuronal correlates are often assessed using motor tasks such as different types of finger movements (Gut et al., 2007; Klöppel et al., 2007; Grabowska et al., 2012; for a review, see Ocklenburg et al., 2013c). Using such tasks, differential brain activations in left- and right-handers have been shown for example in the supplementary motor area, the right frontal opercular cortex, bilaterally in the dorsal premotor cortex, and in the right primary sensorimotor cortex (Klöppel et al., 2007), but not in any of the fronto-temporal networks relevant for language lateralization. Moreover, it has been shown that the use of the dominant hand largely leads to contralateral activations, while the use of the non-dominant hand leads to greater ipsilateral activations in addition to contralateral activations (Gut et al., 2007; Grabowska et al., 2012).

7. Conclusion: Partial pleiotrophy

While classic models (e.g. Annett, 1998) assume that handedness and language lateralization are determined by the same single gene, several other theoretical models are conceivable (see Fig. 1). These models vary with regard to the amount of pleiotropy they assume to exist between the two traits, i.e. between 0% (no shared influences) and 100% (the same ontogenetic influence factors determine both traits). Also, conceivable models vary regarding the number of genetic and non-genetic factors which are thought to be relevant (from one gene to multiple genetic and non-genetic influence factors).

Thus, besides the classic model that assumes a single gene and 100% pleiotropy between handedness and language lateralization, another monogenic model is possible, namely the idea

that one gene determines handedness and another one language lateralization. However, this model is not suited to explain why handedness and language lateralization have consistently been found to correlate to some extent (Badzakova-Trajkov et al., 2010). Moreover, both monogenic models fail to reflect the results of several recent studies that indicate multiple, non-identical genetic influence factors for both traits (e.g. Francks et al., 2007; McManus et al., 2013; Ocklenburg et al., 2013a,b,c; Pinel et al., 2012; Scerri et al., 2011). How many factors are likely to influence these traits? Based on a meta-analysis of handedness genome-wide association studies, McManus et al. (2013) estimated the number of genetic loci involved in determining handedness to be at least 40, but possibly up to 100. When also taking into account the growing evidence for non-genetic factors influencing the ontogenesis of hemispheric asymmetries (Schaafsma et al., 2009), it becomes clear that multifactorial models (Fig. 1, lower panel) are better suited than monogenic models to explain how handedness and language lateralization develop.

Since several different genetic and non-genetic influence factors have been identified for both traits, we suggest separate multifactorial models (Crow, 2010; Rentería, 2012) specifically reflecting the unique neurobiological properties of the language and the motor system. The ability to produce and understand language is a quantitative trait which is determined by several different genetic and non-genetic factors. Since this ability is a necessary prerequisite for the existence of language lateralization in an individual brain, its ontogenetic base should be integrated into a model of language lateralization. Similarly, the neurobiological properties of the motor system should be taken into account when developing a model of the ontogenesis of handedness (see Ocklenburg et al., 2013c). Since there is a medium correlation between the two traits and there are some non-shared genetic influences, but also candidate genes that are likely to be shared, we assume that neither a model that assumes 0% pleiotropy nor one that assumes 100% pleiotropy is capable to correctly describe the complex ontogenetic relation between handedness and language lateralization. Thus, a partial pleiotropy model that assumes several shared and several unique influence factors provides the best fit with current empirical evidence. This partial pleiotropy (Fig. 1, lower panel) may be caused by possible shared ontogenetic factors, e.g. by genes involved in the formation of the corpus callosum or myelin per se, and/or by asymmetrically expressed genes. Identifying these factors as well as further non-shared genetic and non-genetic influences on handedness and language lateralization should be a major aim of future studies on the ontogenesis of the two traits. Only a few of the assumed 40 or more loci related to handedness (McManus et al., 2013) have as yet been identified, and this number is even smaller for language lateralization. Moreover, while few genome-wide association studies have investigated handedness (McManus et al., 2013), none have been conducted for language lateralization. Moreover, single genes as identified by candidate gene studies rarely influence complex behavioral phenotypes in isolation. Epigenetic regulation of gene expression (Kumsta et al., 2013) as well as epistatic (gene-gene) interactions (Li et al., 2012) are important ontogenetic phenomena that need to be investigated in the context of the ontogenesis of handedness and language lateralization. Since lateralization represents a general organizational principle in the vertebrate nervous system (Vallortigara and Rogers, 2005), greater knowledge about the ontogenesis of functional asymmetries, and possibly a functional neurobiological model explaining their development, would tremendously aid our general understanding of vertebrate brain architecture. Moreover, since atypical lateralization has repeatedly been related to a number of psychiatric and neurological disorders (e.g. schizophrenia; Brandler and Paracchini, 2014), such a model might also be of clinical relevance.

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