Neuroscience and Biobehavioral Reviews 37 (2013) 2788–2793

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Handedness: A neurogenetic shift of perspective

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ARTICLE INFO

Article history:
Received 27 June 2013
Received in revised form
16 September 2013
Accepted 24 September 2013

Keywords:
Left-handedness
Right-handedness
Hemispheric asymmetry
Laterality
Ontogenesis
Genetics
Neuroscience

ABSTRACT

Handedness is the single most studied aspect of human brain asymmetries. For long it has been thought to be a monogenic trait that can produce an asymmetrical shift of cerebral mechanisms, thereby producing right handedness. Nevertheless, a single gene explaining a sufficient amount of phenotypic variance has not been identified. The results of several recent studies using advanced molecular genetic techniques suggest that a multifactorial model taking into account both multiple genetic and environmental factors, as well as their interactions, might be better suited to explain the complex processes underlying the ontogenesis of handedness. In this article, we review the new insights into handedness genetics provided by these studies and discuss, how integrating results from genetic and neuroscientific studies might help us to generate more accurate models of the ontogenesis of handedness. Based on these thoughts, we suggest several candidate gene groups (e.g. genes involved in the formation of the corpus callosum, asymmetrically expressed genes or genes involved in the development of structural left–right asymmetries) whose investigation would help to further understand the complex relation of genes, the brain and handedness.

Contents

1. Introduction

Handedness is a human trait that has fascinated the general public like only few others. Using the search terms "Barack Obama" and "left-handed" on www.google.com yields more than 43 million search results, reflecting the immense interest in this politically rather irrelevant characteristic of the 44th president of the United States. Handedness has also stimulated a large number of psychological, biological and medical studies which investigated its relations to an enormous number of other traits. Traits for which significant differences between left- and right-handers have been reported include, but are not limited to, general cognitive ability (Nicholls et al., 2010), personality (Grimshaw and Wilson, 2013), motivation (Brookshire and Casasanto, 2012), perception (Ocklenburg et al., 2010a), and language (Knecht et al., 2000). Moreover, depression (Denny, 2009) and schizophrenia (Sommer et al., 2001) have been linked to handedness, with a significantly higher frequency of non-right-handers in patients than in healthy control groups. In addition, medically relevant variables like alcohol consumption (Denny, 2011) or breast cancer risk (Olsson and Ingvar, 1991) have been shown to be related to handedness. Despite this broad interest in the topic and its high relevance for clinical research, surprisingly little is known about the molecular and neural basis of human handedness.

2. Handedness is a genetic trait

Although left-handedness runs, at least to some extent, in families (Reiss and Reiss, 1999), direct associations between specific genes and handedness or other forms of functional hemispheric asymmetries have been notoriously difficult to establish. Despite these difficulties, however, there is compelling evidence for the notion that the ontogenesis of handedness is to some extent determined by genetic factors (Corballis, 2009; Francks et al., 2007;

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http://dx.doi.org/10.1016/j.neubiorev.2013.09.014

Jordan, 1911; Raymond et al., 1996; Scerri et al., 2011). This evidence includes for example the massive over-representation of right-handers compared to left-handers (on average around 90% to 10%, however, the frequency of left-handedness varies between different cultures from about 0.5% to 24%; Corballis, 2009; Geuze et al., 2012). Moreover, there is a positive correlation between the handedness of a child and the handedness of its biological parents (Reiss and Reiss, 1999) that was not found for adoptive parents (Carter-Saltzman, 1980). Laland (2008) estimated the probability of a child being left-handed to be 8% when both parents are right-handed, 22% when one parent is left-handed while the other is right-handed and 36% when both parents are right-handed. Interestingly, there is a higher prevalence of left-handedness in children with a right-handed father and a left-handed mother, than in children with a left-handed father and a right-handed mother, possibly indicating a sex-linked genetic effect on handedness (Llaurens et al., 2009). Another finding that supports the assumption that handedness is to some extent genetically determined is the fact that identical twins are more likely to be concordant for hand preference than non-identical twins (Sicotte et al., 1999).

These factors have lead several authors to propose genetic models for the ontogenesis of handedness and other forms of lateralization (e.g. Annett, 1964, 1998, 2002; Crow, 2008; Jones and Martin, 2010; Klar, 1996; McManus, 2002; McKeever, 2004). While it was initially thought that handedness might be a monogenic trait determined by a single hypothetical gene with two alleles (e.g. Annett, 1998, 2002; McManus, 2002), this view has now been abandoned by most authors (Francks et al., 2002; McManus et al., 2013; Piper et al., 2013; Scerri et al., 2011). This is largely due to the fact that, despite continuous efforts to do so, no single gene explaining sufficient amounts of phenotypic variance in handedness has yet been identified. Interestingly, there are several recent studies suggesting that handedness may not be a monogenic but instead a multifactorial trait that is determined by multiple genetic and environmental factors, as has recently also been suggested for structural brain asymmetries (Rentería, 2012). The strongest evidence against the assumption of a purely monogenic determination of handedness comes from genome-wide association studies (GWAS; e.g. Eriksson et al., 2010; McManus et al., 2013). For example, Eriksson et al. (2010) conducted a web-based GWAS that incorporated 535,076 different SNPs. In a sample of 4268 participants, no single SNP reached genome-wide significance. In fact, the top hit for handedness did not even represent a trend towards significance. While one might argue that with a sample size of less than 5000, this study may have been underpowered to detect small effects of genetic variation on handedness, one would typically expect a rather large effect if the trait were indeed determined by a single gene. The findings of the Eriksson et al. (2010) study were recently replicated by another GWAS in 3750 individuals (McManus et al., 2013), in which also none of the investigated SNP's reached genome-wide significance.

Moreover, candidate gene studies that specifically investigate the relation between variation in one or more candidate genes and left- and right-handedness typically either fail to find any relation between genetic variation and handedness, or report rather small effects that are in accordance with a multifactorial inheritance of the trait. For example, Van Agtmael et al. (2002) investigated the role of several different genes involved in anatomical left-right axis differentiation and organization (*DNAHC1*, *DNAHC2*, *DNAHC6*, *DNAHC8*, *DNAHC13*, *LRD*, *NODAL*) in a sample of 27 nuclear families consisting of two right-handed parents and at least two left-handed children (173 individuals in total). In a first step, the authors conducted an allele sharing analysis, expecting that a gene qualified to be the single genetic determinant of handedness should have about 75% allele sharing in the tested families. The largest amount of allele sharing observed within their sample was 41% for the D3S3647 microsatellite within *DNAHC1*. Thus, the authors concluded that it was unlikely that any of the investigated genetic markers were linked to a single locus for handedness. Subsequently, the authors conducted a linkage analysis which showed that all candidate regions included in the study could be excluded from harboring a gene that would be in accordance with the monogenic models of Klar (1996) and McManus (2002). These results were confirmed by the linkage analysis in a follow-up study within the same sample, in which a genome-wide scan was used in the initial step (Van Agtmael et al., 2003). More negative results were provided by Ocklenburg et al. (2013) who investigated the association between 16 different SNP's that had previously been linked to schizophrenia and handedness in 444 healthy individuals and did not observe any significant effect. Moreover, Ocklenburg et al. (2011) investigated the association between variation in the schizophrenia-related *N*-methyl-*d*-aspartate receptor 2B subunit gene (*GRIN2B*; Demontis et al., 2011) and handedness in 424 healthy individuals, but the only SNP yielding a significant effect (rs4764011) was not in Hardy–Weinberg-Equilibrium so that these results could not be interpreted.

In contrast to such negative results reported by previous studies, there are also studies which actually report associations between genetic variation and handedness, thereby being in favor of a multifactorial rather than a monogenic approach to handedness heritability. For example, Medland et al. (2005) investigated the association between the number of polymorphic polyglutamine CAG repeats in the androgen receptor gene *AR*, located at Xq12, and handedness for writing in overall 783 individuals. They found that females with a greater number of CAG repeats in *AR* were more likely to be left-handed, while the opposite effect was found for males. Here, a greater number of CAG repeats in *AR* was correlated with a lower incidence of left-handedness. Since the CAG repeat length is positively correlated with testosterone levels in males, while a negative correlation is found in females, these results support the idea that lower testosterone levels are related to left-handedness. A relation between *AR* CAG repeat length and handedness was also confirmed in a recent study by Hampson and Sankar (2012), although the direction of the effect was different from that observed by Medland et al. (2005). In a sample of 180 male participants, Hampson and Sankar (2012) observed mixed-handers (defined as individuals with a score between 31 and 40 in the Crovitz–Zener Handedness Inventory; Crovitz and Zener, 1962) to carry a significantly longer CAG repeat in the *AR* gene than either strong left- or strong right-handers who did not differ significantly from each other in terms of CAG repeat length. The apparent difference between the two studies might be at least partly explained by the fact that in the Medland et al. (2005) study, participants were categorized as either left- or right-handers. Thus, mixed-handers were possibly included in both groups.

Another gene that has been investigated in relation to handedness is the Alzheimer's disease related apolipoprotein E gene *APOE*, located at 19q13.2. In a sample of 147 children aged between 11 and 16, Bloss et al. (2010) compared handedness for writing between children with at least one *APOE* ε2 allele to ε3 homozygote children and children with at least one ε4 allele. Interestingly, ε2 allele carriers showed a significantly higher prevalence of left-handedness (29.2% left-handed and 70.8% right-handed individuals) compared to the other two groups (8.9%/6.1% left-handed and 91.1%/93.9% right-handed individuals). However, this effect was not replicated by two recent studies in adults (Piper et al., 2013; Hubacek et al., 2013), suggesting that it might be either specific to children, or that the earlier results by Bloss et al. (2010) were a statistical artifact.

Interestingly, the most promising findings regarding the genetics of handedness to date have not been obtained in healthy cohorts but in clinical groups. For example, Savitz et al. (2007) investigated the role of variation in the catechol-*O*-methyltransferase

gene *COMT* for hand preference – measured with the Waterloo Handedness Questionnaire (Elias et al., 1998) – and relative hand skill – measured by asking participants to make dots in each of a series of circles arranged on a sheet of paper as quickly as possible (Tapley and Bryden, 1985) – in a sample of 240 adults which compromised 55 bipolar disorder patients and their relatives. Savitz et al. (2007) found a significant association between the *COMT* Val158Met polymorphism and relative hand skill but not hand preference, with the Met allele of this polymorphism being associated with greater right-handed skill. They also investigated the role of several other bipolar disorder and cognition candidate genes on handedness, including the serotonin transporter gene *SERT*, the dopamine 2 receptor gene *DRD2*, the dopamine 4 receptor gene *DRD4*, the dopamine transporter gene *DAT*, the Apolipoprotein E gene *APOE* and the prion protein gene *PRNP*, but did not find any associations. While Savitz et al. (2007) do not make any assumption about the exact functional relation between *COMT* and handedness, they note that their findings are in accordance with the idea that handedness may be a complex polygenetic trait. Further evidence for this idea is provided by a series of studies investigating the effect of variation in *LRRTM1* (leucine rich repeat transmembrane neuronal 1), located at 2p12, on handedness (Francks et al., 2002, 2003a, 2003b, 2007; for discussion of these studies see: Crow et al., 2009; Francks, 2009; McManus et al., 2009). *LRRTM1* codes for a transmembrane protein that induces presynaptic differentiation in contacting axons (Linhoff et al., 2009). While earlier studies identified a quantitative-trait locus on chromosome 2p12–q11 that was linked to handedness (Francks et al., 2002, 2003a, 2003b), a more recent study identified *LRRTM1* as the relevant gene (Francks et al., 2007). Here, the authors genotyped 87 SNPs with four candidate genes on 2p12–p11 (*LRRTM1*, *LRRTM4*, *CTNNA2* and *DNAH6*) in 222 dyslexic siblings and their parents, and investigated their association with a quantitative measure of handedness determined with the peg board test. They identified a haplotype comprised of three SNPs located within a region spanning the first exon and 137 kb upstream of *LRRTM1* (rs1446109, rs1007371, rs723524) that was related to increased left-handedness. The risk variant of this haplotype (the minor allele on all three SNPs) had a frequency of 9% and was related to a shift of 1.1 standard deviations toward left-handedness when inherited paternally. This relation was not replicated in a sample of 215 Australian twin-based sibships, possibly indicating that *LRRTM1* interacts with dyslexia susceptibility genes or environmental factors related to this disorder.

Another association between handedness and genetic variation in dyslexic samples has been reported by Scerri et al. (2011) who conducted a genome-wide association study in a sample of 192 dyslexic individuals. They tested over 2 million SNPs for association with handedness measured with the pegboard task. While no SNP gave a p-values below 5×10^{-8} (the value commonly used as threshold for genome-wide significance of an association; Panagiotou and Ioannidis, 2012), the most highly associated SNP identified was rs11855415 within an intron of the proprotein convertase subtilisin/kexin type 6 gene *PCSK6*, a gene involved in the regulation of left–right axis specification. The association between this SNP and handedness had a p-value below 4.7×10^{-7}, with the minor allele being related to a shift of 0.6 standard deviations toward right-handedness. While this effect was replicated in two other dyslexic samples, no such relation was observed in a sample of 2666 healthy children. Parallel to the findings of Francks et al. (2007) for *LRRTM1*, this result might indicate an interaction between *PCSK6* and dyslexia susceptibility genes or environmental factors related to this disorder. However, a recent candidate gene study (Arning et al., 2013) found a significant association between genetic variation in the *PCSK6* rs10523972 SNP and degree of handedness (consistent vs. inconsistent handedness), but not direction (left-handedness vs. right-handedness) in a sample of 1113 healthy adults, showing that a relation of handedness and *PCSK6* is not limited to dyslexic cohorts.

Taken together, several different genetic associations with handedness, all of them with rather modest effect sizes, have been reported. Moreover, the fact that some associations found in clinical groups apparently do not exist in healthy cohorts (Francks et al., 2007) and the existence of a strong sex difference for at least one reported genetic association (Medland et al., 2005) further support multifactorial models of handedness ontogenesis. Since none of the putative genetic associations with handedness have yet been confirmed by follow-up studies, replication of these results in larger and independent samples is a crucial next step in order to further advance our understanding of the molecular basis of handedness. Moreover, the modest sizes of the observed effects suggest that it is likely that several other, as yet uninvestigated, genes may play a role in handedness inheritance.

3. Integrating neuroscience

The idea that most of the genes involved in handedness are yet unidentified is also supported by a recent analysis by McManus et al. (2013) that estimated the number of handedness-relevant genes to be at least 30 to 40 and potentially up to 100. How can these genes be identified? Besides the failure to identify a single gene responsible for handedness, another major weakness of single gene models is that they are solely based on statistics about the distribution of the phenotype and completely disregard specific brain functions underlying it. Handedness is not a simple dichotomous trait, but rather a continuous variable (Brenneman et al., 2008). The concepts “left-hander” and “right-hander” are simplified terms that indicate the individual likelihood of using the left or right hand to perform complex motor tasks in a variety of situations. As such, handedness (like all complex behavioral phenotypes) is not directly controlled for by genes or proteins, but genes have an indirect effect on it by determining development of relevant brain parts and other structures (Atkinson and Braddick, 2011). Thus, one would expect that at least some of the genes relevant for handedness would have an impact on development and/or function of brain areas and white matter pathways that have been related to handedness. This, in turn, implies that integrating mechanisms from the perspective of neuroscientific research could tremendously aid the search for the genetic determinants of handedness.

To investigate the neuronal correlates of handedness, a standard paradigm is to measure brain activity in the motor cortex of left- and right-handers during unilateral or bilateral finger movements (Gut et al., 2007; Klöppel et al., 2007; Grabowska et al., 2012). For example, Klöppel et al. (2007) used fMRI to investigate the impact of handedness on neuronal activation of the primary sensorimotor cortex, supplementary motor area and dorsal premotor cortex during simple unilateral and bilateral finger movements in right- and left-handers. No group difference was observed for unilateral right index finger movements, while for left index finger movements, left-handers showed greater activation of the supplementary motor area and right frontal opercular cortex than right handers. Also when simultaneous bilateral movements were compared to unilateral movements, right-handers showed a relative increase of activity in the right and left dorsal premotor cortex and the right primary sensorimotor cortex that was not observed in left-handers. In addition to bi- or unilaterality of the performed movements, its complexity is an important factor in regard to handedness. Grabowska et al. (2012) investigated the neuronal control of simple and complex finger movements in right- and left-handers using fMRI and found the both groups showed

a general activation predominance of the hemisphere contralateral to the dominant hand. While movements of the dominant hand activated mainly the contralateral hemisphere of both groups, movements of the non-dominant hand lead to a greater involvement of the ipsilateral hemisphere. Interestingly, more complex movements lead to an increase in the volume of consistently activated areas and a stronger involvement of the ipsilateral in addition to contralateral hemisphere. It has been shown, that this ipsilateral activation in the primary motor cortex does not only reflect ipsilateral inhibition, but also transcallosal inhibitory control from the primary motor cortex in the contralateral hemisphere and that this asymmetric interaction between the two primary motor cortices contributes to handedness (Hayashi et al., 2008). Thus, the efficacy of interhemispheric inhibition, largely mediated through the corpus callosum, the largest interhemispheric commissure in the human brain, seems to play a role in handedness development. This assumption is also supported by a recent study that investigated the role of the callosal motor fibers that connect the primary motor cortices (Wahl et al., 2007). Using a combined functional magnetic resonance imaging and diffusion tensor imaging fiber-tracking approach Wahl et al. (2007) could show a significant positive correlation between the microstructure of callosal motor fibers that connect hand areas of the primary motor cortices with interhemispheric inhibition between these areas. Moreover, a relation of corpus callosum structure and handedness is also supported by a diffusion tensor imaging study that reported substantial differences in callosal macro- and microstructure of right- and left-handers (Westerhausen et al., 2004). On the macrostructural level, the corpus callosum had a larger overall area in right-handed compared to left-handed subjects, while on the microstructural level right-handed subjects showed an enhanced fractional anisotropy and reduced mean diffusion compared to left-handers. Thus, the corpus callosum could be an essential brain structure that mediates between handedness genotype and phenotype. Therefore, a first candidate gene group that should be investigated to specifically reflect the unique neurobiological properties of the human handedness system are genes involved in the formation of the corpus callosum. This could for example include genes that are relevant for white matter integrity such as *ErbB4* (Zuliani et al., 2011) or myelinisation such as *MBP*. This is also especially interesting since two of the major genetic associations reported for handedness (Francks et al., 2007; Scerri et al., 2011), have been observed in dyslexic samples and a recent study linked variation in dyslexia-related genes (*MRPL19 and C2ORF3*) to white matter structure in the posterior part of the corpus callosum (Scerri et al., 2012).

Another way to integrate neuroscientific findings into research on handedness genetics is to look at the expression rates of specific genes in the brain. For example, further potential candidate gene groups are genes which are asymmetrically expressed in the two hemispheres of the brain (Geschwind and Miller, 2001). Using serial analysis of gene expression, Sun and Walsh (2006) determined gene expression levels in the left and right hemispheres of 12-week-old human fetal brains, and identified 27 genes which were differentially expressed in the two hemispheres, most of them having a function in either gene expression regulation or signal transduction. For example, the transcriptional regulator *LMO4*, the stathmin-like 4 protein gene *STMN4* and the insulin-like growth factor binding protein 5 gene *IGFBP5* had a higher gene expression level in the right hemisphere, while the transcriptional repressor *HEY1, RABL2B* and *DAPPER1* had a higher gene expression level in the left hemisphere.

Moreover, following up on the approach chosen by Van Agtmael et al. (2002), investigating further genes involved in the development of anatomical left-right asymmetry could be a worthwhile approach, as has been shown by a number of recent studies in zebrafish (Concha et al., 2012). Zebrafish and cichlids show a strong anatomical asymmetry in the epithalamus, with the left habenular nucleus being larger than the right in most individuals and the development of this anatomical asymmetry has been linked to *NODAL* signaling (Dadda et al., 2010; Gutiérrez-Ibáñez et al., 2011; Reddon et al., 2009; Roussigné et al., 2009). Interestingly, this anatomical asymmetry has been related to behavioral asymmetries and it has been discussed to be particularly relevant for behavioral lateralization in relation to prey capture (Rogers et al., 2013). Moreover, Barth et al. (2005) could show that in the frequent-situs-inversus (fsi) line of zebrafish, which shows a reversal of the typical epithalamic asymmetry, also some lateralized behaviors are reversed compared to wildtype fish.

Furthermore, genes that are involved in psychiatric disorders (e.g. schizophrenia; Sommer et al., 2001) or learning disabilities (e.g. dyslexia; Annett and Kilshaw, 1984) that have been related to atypical handedness could represent worthwhile candidate genes for handedness development. While it is notoriously difficult to establish genetic associations with complex psychiatric disorders, the considerable effort that has been put toward investigating these relationships has led to some interesting discoveries, such as the association of schizophrenia and *DISC1* (Girard et al., 2012).

In addition to investigating further candidate genes, another worthwhile endeavor in order to get a better understanding of handedness ontogenesis would be to further look into the role of non-genetic factors and especially their interaction with genetic factors (e.g. Jones and Martin, 2008; Schaafsma et al., 2009; Tzourio-Mazoyer et al., 2010), since they also play a substantial role for handedness development. For example, Medland et al. (2009) investigated handedness in 54,270 individuals from 25,732 twin families and estimated handedness heritability estimates using variance component modeling. They found that about 76% of the handedness variance in their data originated from non-shared environmental influences, while only about 24% originated from additive genetic effects, a finding that was consistent with the results of an earlier meta-analysis (Medland et al., 2006). Environmental factors that have been proposed to modulate handedness include for example parental influences representing a combination of imitation, instruction and inadvertent shaping (Laland, 2008), social pressures (Schaafsma et al., 2009; Zverev, 2006) and early visual experience (Ocklenburg et al., 2010b; Ocklenburg and Güntürkün, 2009).

4. Conclusion

Over the last two decades, the idea that handedness is a complex multifactorial phenotype instead of being determined by a single gene has been brought forward by several different authors (e.g. Francks et al., 2002; McManus et al., 2013; Piper et al., 2013; Scerri et al., 2011). While several molecular genetic studies have recently supported this view, monogenic models are still widely cited in the literature. One reason for that might be the fact that the majority of the estimated 30 to 40 genes involved in handedness are yet to be identified. Thus, while independent replication of reported associations and further GWAS in larger cohorts are important steps in order to understand the heritability of handedness, theory-driven identification of new candidate genes is an equally important endeavor, especially since current handedness GWAS might be underpowered to detect small effects (Eriksson et al., 2010) and possibly suffer from inflated type two error rates due to overly conservative correction for multiple comparisons (Williams and Haines, 2011). In order to determine relevant candidate genes, it is critical to integrate recent neuroscientific finding about the neuronal base of handedness into the search for its genetic determinants..

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