



Review

Laterality and mental disorders in the postgenomic age – A closer look at schizophrenia and language lateralization



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ABSTRACT

Most people are right-handed and show left-hemispheric language lateralization, but a minority exhibits left-handedness and right-hemispheric language lateralization. This atypical laterality pattern is observed significantly more often in schizophrenia patients than in the general population, which led several authors to conclude that there is a genetic link between laterality and schizophrenia. It has even been suggested that a failure in the lateralization process, orchestrated by genes, could be the primary cause of schizophrenia. However, the molecular genetic evidence for a link between laterality and schizophrenia is weak. Recent genetic evidence indicates that schizophrenia is not a single disorder but a group of heritable disorders caused by different genotypic networks leading to distinct clinical symptoms. To uncover the link between schizophrenia and laterality we therefore suggest a paradigm shift where genetics are not mapped on schizophrenia as a whole but on discrete schizophrenia symptoms. In addition, we provide a critical evaluation of current theories on the genetic link between schizophrenia and brain asymmetry.

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1. Introduction

At this moment around 21 million people worldwide are suffering from schizophrenia (World Health Organization, 2010). Although a wide range of treatments and medication has been developed that has drastically improved the prognosis for these patients, a cure does not exist and the cause(s) of schizophrenia are still largely unknown. Over the last decades, however, significant progress regarding the etiology of schizophrenia has been made, especially in genetics and neuroimaging. Among the vast array of functional, structural, neurochemical and molecular brain alterations (Goghari et al., 2010; Harrison, 1999; Shenton et al., 2001; Taylor and Tso, in press; van den Heuvel and Fornito, 2014) is the striking and reliable finding that schizophrenia patients frequently display atypical laterality patterns (Crow, 2013; Gur and Chin, 1999; Li et al., 2009; Oertel-Knöchel and Linden, 2011). It has been proposed that laterality and schizophrenia have a common genetic basis and that schizophrenia might even be the consequence of a failure in brain lateralization (Crow, 1993, 1997a,b; Crow et al., 1989). Although an elegant idea, the molecular genetic evidence for a link between schizophrenia and laterality is weak so far.

The main aim of this review is to advocate for a paradigm shift in the pursuit of the ‘missing link’ between schizophrenia and laterality. Recent genome wide association studies imply that schizophrenia is a group of heritable disorders caused by different genotypic networks that cause distinct clinical symptoms (Arnedo et al., 2015). Thus instead of treating schizophrenia as a whole syndrome it appears more fruitful to link laterality to specific schizophrenia symptoms, particularly auditory hallucinations. The secondary aim of this review is to evaluate current theories on genetic links between schizophrenia and laterality – for instance, by drawing on research in language impairments which has also been hypothesized to arise from atypical lateralization. Together we hope this will benefit our understanding of the underlying neural relationship between laterality and schizophrenia.

2. Atypical lateralization in schizophrenia

At first glance, the two hemispheres look fairly similar. They also exhibit a great degree of functional symmetry in sensorimotor control, perception and higher mental functions. Nevertheless, both hemispheres also display a high degree of functional specialization: For example, the left hemisphere is more strongly involved in language perception and production, tool use, complex motor actions, arithmetic, while the right hemisphere specializes in attention, visuo-spatial abilities, geometrical patterns and faces as well as language prosody (cf. Davidson and Hugdahl, 1995; Hellige, 1993; Hugdahl and Westerhausen, 2009; Ocklenburg and Güntürkün, 2012). Besides functional specialization, differences between the two hemispheres can also be found on structural and neurophysiological levels (Samara and Tsangaris, 2011), notwithstanding the most prominent behavioral example of laterality: right-handedness (Ocklenburg et al., 2013c). Taken together, laterality is a fundamental principle of brain organization.

There is a wealth of empirical evidence that schizophrenia patients often deviate from the typical laterality pattern found in healthy individuals. The most extensively researched indicator for laterality is handedness – a valid but coarse indicator (Ocklenburg et al., 2014). Two meta-analyses consistently reported that schizophrenia patients are more often non-right-handed than controls (Dragovic and Hammond, 2005; Sommer et al., 2001a) implying that they display more often atypical (i.e., reduced or inverted) lateralization (Carey and Johnstone, 2014; Knecht et al., 2000; Rasmussen and Milner, 1977). Suggestions that the excess

of non-right-handedness could be a sex artifact (Buijsrogge et al., 2002; Deep-Soboslay et al., 2010) or the result of unreliable self-report questionnaires have been disproven by a more recent meta-analysis (Hirnstein and Hugdahl, 2014). The excess of non-right-handedness is a valid finding but it is also relatively small with consistent odds ratios (ORs) between 1.5 and 1.8 (Dragovic and Hammond, 2005; Hirnstein and Hugdahl, 2014; Sommer et al., 2001a). That is, if 10% of the normal population is non-right-handed, then about 15% of schizophrenia patients are non-right-handed.

A similarly well-established finding is reduced structural asymmetry in language areas. For instance, in healthy individuals the planum temporale is typically larger in the left than right hemisphere (Geschwind and Levitsky, 1968). Several (e.g., Hugdahl et al., 2008; Kasai et al., 2003; Kwon et al., 1999; Oertel et al., 2010; Takahashi et al., 2010) but not all studies (e.g., Deep-Soboslay et al., 2010; Kulynych et al., 1995; Shapleske et al., 2001) using post-mortem, computer tomography, or structural magnetic resonance imaging (MRI) reported an absence or reversal of this leftward asymmetry in schizophrenia. A reduced leftward planum temporale asymmetry was also found by two meta-analyses (Shapleske et al., 1999; Sommer et al., 2001a). Sommer et al. (2001a) additionally reported reduced asymmetry of the Sylvian fissure in schizophrenia patients, which in healthy individuals is longer in the left than in the right hemisphere (Falkai et al., 1992).

Not only structural but also functional language lateralization is reduced in schizophrenia. The most frequently used behavioral indicator of functional language lateralization is dichotic listening. When two auditory stimuli are presented simultaneously, healthy individuals tend to report the stimulus from the ear opposite to the specialized hemisphere, a result of the stronger connection between the specialized hemisphere and the contralateral ear (Kimura, 1967). Speech stimuli thus typically yield a right ear/left hemisphere advantage. Several studies reported a decreased right ear advantage for speech – indicative of reduced leftward language lateralization in schizophrenia patients (Hahn et al., 2011; Løberg et al., 1999; Rossell and Boundy, 2005) – but there are also null findings (Løberg et al., 2002; Ragland et al., 1992). However, a recent meta-analysis confirmed that schizophrenia patients in general have a reduced right ear advantage (Ocklenburg et al., 2013d).

When functional language lateralization is assessed with neuroimaging, several studies using fMRI (Alary et al., 2013; Bleich-Cohen et al., 2012; Dollfus et al., 2005; Oertel et al., 2010; Razafimandimby et al., 2007; Weiss et al., 2004, 2006), electroencephalography (Angrilli et al., 2009; Jalili et al., 2010) or positron emission tomography (Artiges et al., 2000) found reduced activation in the left hemisphere or increased activation in the right hemisphere (Sommer et al., 2001b, 2003) for both language perception and production. Here too, however, null findings exist with no activation differences between patients and controls (e.g., Razafimandimby et al., 2011). A recent study found a correlation between structural and functional language asymmetries in healthy individuals but not schizophrenia patients, with the latter exhibiting the typical leftward asymmetry reduction both structurally and functionally (Alary et al., 2013). This implies that functional and structural asymmetry reductions in schizophrenia can occur independently. Both, however, were reported to correlate (modestly) with the severity of auditory hallucinations (Oertel et al., 2010).

There are indications that the reduction in language lateralization is not limited to the left hemisphere. Prosody, the intonation, stress, and rhythm of language, is typically lateralized to the right hemisphere in healthy individuals (Mitchell and Ross, 2008) but schizophrenia patients display reduced (Alba-Ferrara et al., 2013) or inverted, left-hemispheric lateralization (Mitchell et al., 2004). This highlights that atypical language lateralization extends to the right hemisphere (Mitchell and Crow, 2005).

Finally, there is a growing body of evidence that hemispheric asymmetries in brain connectivity are altered in schizophrenia (Ribolsi et al., 2014). For instance, diffusion tensor imaging studies found reduced leftward asymmetry in various white matter tracts including the superior occipitofrontal fasciculus (Kunimatsu et al., 2008), the uncinate fasciculus (Kubicki et al., 2002), and the arcuate fasciculus, an important tract for language connecting Broca's and Wernicke's area (Abdul-Rahman et al., 2012). However, bilaterally reduced connectivity in the arcuate fasciculus (Čurčić-Blake et al., 2015), altered integrity in the right arcuate fasciculus (Wu et al., 2014), and similar laterality patterns in overall connectivity in schizophrenia patients and controls (Miyata et al., 2012) have also been reported. A recent meta-analysis comprising five studies found reduced fractional anisotropy in the left but not right arcuate fasciculus (Geoffroy et al., 2014) and a recent review article (Ribolsi et al., 2014) concludes that: "On the whole, the DTI findings seem to confirm the hypothesis of a reduced leftward asymmetry (p. 5)". They further speculate that the anomalous lateralization patterns in connectivity are mainly driven by dysfunctional inter-hemispheric communication. This sounds reasonable given the large number of studies showing abnormalities in corpus callosum structure (e.g., Hulshoff Pol et al., 2004; Narr et al., 2004) and function (e.g., Bleich-Cohen et al., 2012; Whitford et al., 2011) in schizophrenia.

Taken together, there is overwhelming evidence that atypical laterality is, in fact, very typical in schizophrenia (for a recent comprehensive review see Crow, 2013). Some researchers go as far as suggesting that anomalous laterality constitutes a biomarker for schizophrenia (Oertel-Knochel et al., 2012). Here, however, we call for caution. While the link between laterality and schizophrenia is evident, several other neurodevelopmental disorders including depression, Tourette's syndrome, attention deficit hyperactivity disorder, and autism have also been associated with abnormal lateralization (for review Klimkeit and Bradshaw, 2006). More importantly, about 5–10% of the population have bilateral or reversed language lateralization – without any neurodevelopmental detriments (e.g., Badzakova-Trajkov et al., 2010; Corballis, 2008). Thus, atypical laterality lacks specificity as a biomarker for schizophrenia.

3. Theories about laterality and schizophrenia

Unsurprisingly, the strong association between laterality and schizophrenia has inspired scientists to develop etiological models in which laterality plays a crucial role. One of the first theories, put forward by John Gruzelier (1984, 1994, 1999), is largely based on psychophysiology data (i.e., electrodermal and EEG findings). It posits that hemispheric balance is shifted in schizophrenia (hence the "hemispheric imbalance model"): Stronger left-hemispheric activation as compared to controls is said to give rise to positive symptoms (e.g., behavioral hyperactivity, manic and paranoid ideas, affective delusions), the so-called "active syndrome". Stronger right-hemispheric activation, on the other hand, is said to precipitate negative symptoms such as social and affective withdrawal, poverty of speech, and catatonia ("withdrawn syndrome"). A third category ("unreality syndrome") is thought to be unrelated to hemispheric imbalance and comprises Schneiderian first rank symptoms such as auditory hallucinations. According to Gruzelier (1999) an interaction of genes, hormones, early experience, and stress leads to aberrant transcallosal and thalamo-cortical communication which gives rise to the imbalances in hemispheric activation. The exact genes or genetic mechanisms are not further elaborated but especially genes on the sex chromosomes are deemed relevant (Gruzelier, 1994).

The probably most influential theory regarding laterality and schizophrenia has been put forward by Timothy Crow (Crow, 1993,

1997a,b). He proposes that about 100,000–250,000 years ago a genetic mutation arose that "lateralized" the human brain and gave rise to language (Crow, 1997a). With this new capacity, however, also came the risk of developing psychosis in case normal language lateralization failed. According to this view, the development of laterality was the "speciation event" of *Homo sapiens* and schizophrenia is the price we pay for language (Crow, 1997a). Based on findings of a sex difference in the onset and course of illness (e.g., males develop schizophrenia earlier and have more severe symptoms, Markham, 2012) as well as a sex difference in laterality (e.g., males are assumed to be more lateralized than females, McGlone, 1980), Crow concluded that both laterality and schizophrenia are under the control of genes located on the sex chromosomes – specifically, "the Protocadherin11XY gene pair in Xq21.3/Yp11.2 in coordination with a gene or genes within PAR2 (the second pseudo-autosomal region)" (Crow, 2013, p. 800).

In the meantime, myriad of studies confirmed the existence of laterality in all vertebrates classes and several invertebrate species (Bisazza et al., 1998; Frasnelli et al., 2012; Frasnelli, 2013; Hopkins, 2006; Manns and Güntürkün, 2009; Rogers, 2014; Rogers et al., 2013) and there is large consensus that laterality existed way before humans arrived on the scene (Corballis, 2008; Hugdahl and Hirnstein, 2013; MacNeilage, 2014; Ocklenburg and Güntürkün, 2012; Ströckens et al., 2012; Vallortigara et al., 1999). Thus, it did not develop de novo in humans 100,000–250,000 years ago questioning the evolutionary context of Crow's theory. However, it is well possible that our capacity for language could only arise because of the asymmetric brain organization we inherited from our ancestors (Corballis, 2009). Crucially in this context, a failure in the lateralization process may still be the driving force for schizophrenia.

4. Both schizophrenia and laterality are heritable

After the sequencing of the human genome was finished in the early 2000s (Lander et al., 2001; Venter et al., 2001), considerable effort has been put into identifying the genetic bases of schizophrenia and, to a lesser extent, laterality. The idea that the two traits might be heritable mainly arose because both seem to run in families. The lifetime prevalence of schizophrenia in the general population is around 0.3–0.7%, with some variation depending on gender and ethnicity (American Psychiatric Association, 2013). However, relatives of schizophrenia patients have a significantly higher probability than the general population of being diagnosed with schizophrenia themselves. For example, the life-time risk for being affected by schizophrenia rises to 6.5% in first degree relatives of affected individuals and to over 40% in monozygotic twins of patients (Picchioni and Murray, 2007).

There is, however, some disagreement about the exact extent of the heritability in liability to schizophrenia. For example, a meta-analysis on 12 twin studies estimated the heritability of schizophrenia to be 81% (Sullivan et al., 2003). In contrast, a recent large scale family study by the Consortium on the Genetics of Schizophrenia (Light et al., 2014) estimated the heritability of schizophrenia to be 31% and 44% for nuclear and extended families, respectively.

For handedness, genetic influences are suggested by the fact that despite some geographical variation in the exact frequencies of left- and right-handedness, there is no culture with a higher percentage of left- than right-handers (Raymond and Pontier, 2004). Moreover, family and adoption studies suggest strong genetic influences on handedness. In a large-scale adoption study, Carter-Saltzman (1980) found that the distributions of right- and non-right-handedness in biological children were a function of parental handedness, while the handedness distribution of

children that were adopted were unrelated to parental handedness. Within biological families, [Reiss and Reiss \(1999\)](#) found a clear positive correlation between handedness of children and parents. They reported that two right-handed parents had a chance of 93% to also have a right-handed child. This percentage was reduced to 79% in couples with one right- and one left-handed parent. No percentages were given for children with two left-handed parents since the sample size was too small. Additional evidence for an at least partly genetic determination of handedness is also provided by twin studies, since identical twins have been found to show a higher concordance for handedness than non-identical twins ([Sicotte et al., 1999](#)).

Similar to schizophrenia, the exact heritability values for handedness also vary to some extent. For example, [Lien et al. \(2015\)](#) measured handedness in college students and their first-degree relatives using a hand preference questionnaire and determined the heritability of different handedness measures. They found that degree of handedness (i.e., how strongly an individual prefers one hand over the other regardless of direction) had a higher heritability (67%) than an integrated hand preference index (52%) or direction of handedness (39%). For hand motor skill assessed with the peg board test, [Francks et al. \(2003b\)](#) determined heritability to be 41%. Importantly, however, there is compelling evidence for the assumption that handedness is only partly determined by genetic factors and that environmental and/or epigenetic factors also play a role for its development. For example, [Medland et al. \(2009\)](#) conducted a large-scale twin study on genetic influences on handedness and estimated that additive genetic effects accounted for about 24% of the variance in their handedness data, while non-shared environmental influences accounted for about 76% of the variance. The results of [Medland et al. \(2009\)](#) are in line with a recent genetic linkage study by [Somers et al. \(2015\)](#). These authors estimated heritability of left-handedness measured with the Edinburgh Handedness Inventory to be 0.24 and heritability of language lateralization measured with functional transcranial Doppler sonography to be 0.31.

5. Schizophrenia and laterality have partly overlapping genetic determinants

Interestingly, a recent family study by [Oertel et al. \(2010\)](#) suggests that the genetic determinants of schizophrenia also seem to modulate functional and structural asymmetries in the auditory system. [Oertel et al. \(2010\)](#) obtained anatomical MRI scans as well as functional MRI scans during stimulation with spoken words from schizophrenia patients, their first-degree relatives, and healthy controls. As expected, patients showed a marked reduction of both leftward planum temporale asymmetry and leftward functional activation asymmetry during word perception. Remarkably, the relatives of the patients also show reduced structural and functional lateralization compared to controls, but not as much as the patients.

Similar to these results for language lateralization, healthy siblings of patients with schizophrenia have also been shown to exhibit abnormal functional motor lateralization. [Altamura et al. \(2012\)](#) used fMRI to compare brain activation during a visually guided motor task in clinically unaffected siblings of schizophrenia patients and healthy controls. They found that healthy controls mainly showed contralateral activations, with only a small ipsilateral component. In contrast, unaffected siblings of schizophrenia patients had strong bilateral brain activations, resulting in significantly reduced lateralization in motor regions. [Altamura et al. \(2012\)](#) concluded that the genetic risk of schizophrenia is related to abnormal functional lateralization of motor circuitry.

The picture is less clear, when it comes to behavioral markers of lateralization. In a large scale study with several hundred schizophrenia patients and unaffected controls, [Deep-Soboslay et al. \(2010\)](#) found that non-right-handedness was not more frequent in family members of patients with schizophrenia than in controls. Similar findings have also been reported by [Byrne et al. \(2004\)](#) and [Clementz et al. \(1994\)](#). Moreover, [Erlenmeyer-Kimling et al. \(2005\)](#) reported that there was no evidence for the hypothesis that children of parents with schizophrenia showed atypical handedness.

6. Schizophrenia and laterality are complex traits

In addition to heritability studies investigating the degree to which schizophrenia and laterality runs in families, a multitude of studies investigated to which extent variation in specific genes is associated with these traits. Based on these studies, today most authors agree that for both schizophrenia and laterality multiple genetic factors and environmental exposures interact in complex ways to determine individual phenotypes ([Armour et al., 2014](#); [Braff et al., 2007](#); [McManus et al., 2013](#); [Ocklenburg et al., 2013c, 2014](#); [Sullivan et al., 2003](#); [Uher, 2014](#)). Since handedness and language lateralization are the two forms of lateralization that have most reliably been shown to be altered in schizophrenia ([Dragovic and Hammond, 2005](#); [Ocklenburg et al., 2013d](#); [Sommer et al., 2001a](#)), we will now review the evidence for genetic influences on these traits, specifically focusing on overlaps with genetic contributions to schizophrenia. Please note, however, that there also studies suggesting specific genetic contributions to other lateralized functions, e.g., for lateralization of pain and emotion ([Watanabe et al., 2015](#)).

For handedness, [McManus et al. \(2013\)](#) estimated that at least forty and possibly more than a hundred loci are involved in determining the phenotype. At the moment, three genes have been linked to handedness by multiple independent studies and there is single-study evidence for an association for several other genes. However, it is clear that at the present point we are far from having a complete picture of the ontogenesis of handedness, especially since we only begin to understand the role of environmental factors, gene-environment interactions and gene-gene interactions for handedness ([Ocklenburg et al., 2013c](#)).

One of the major genes associated with handedness is *PCSK6* ([Arning et al., 2013](#); [Brandler et al., 2013](#); [Scerri et al., 2011](#)). *PCSK6* encodes an enzyme that cleaves NODAL, a protein involved in establishing bodily left/right axis asymmetry, into its active form ([Brandler et al., 2013](#)). In a recent genome-wide association study meta-analysis, [Brandler et al. \(2013\)](#) reported that in 728 patients with dyslexia, the *PCSK6* rs7182874 SNP (single nucleotide polymorphism) showed the strongest association with hand skill ($p = 8.68 \times 10^{-9}$). Also in patients with dyslexia, [Scerri et al. \(2011\)](#) showed an association of the *PCSK6* rs11855415 SNP with hand skill ($p = 4.7 \times 10^{-7}$). Interestingly, [Arning et al. \(2013\)](#) showed a significant association of the *PCSK6* rs10523972 SNP with degree of handedness in healthy adults. Regarding schizophrenia, we are not aware of any published study linking variation in *PCSK6* to disease susceptibility. Thus, while *PCSK6* might represent a molecular link between atypical handedness and dyslexia, it is unlikely to represent a shared genetic influence to handedness and schizophrenia.

Another gene that has been associated with handedness by several studies is the androgen receptor gene *AR* ([Arning et al., 2015](#); [Hampson and Sankar, 2012](#); [Medland et al., 2005](#)). For example, [Arning et al. \(2015\)](#) showed that in male participants, mixed-handedness was significantly associated with longer CAG repeat blocks. Moreover, women homozygous for longer CAG repeats showed a tendency for stronger left-handedness. [Arning et al.](#)

(2015) concluded that longer *AR* CAG repeats are related to a higher incidence of non-right-handedness. Interestingly, Tsai et al. (2006) investigated the relationship between *AR* CAG repeat length and schizophrenia in a sample of 225 patients and 247 controls. They found no association between *AR* CAG repeat length and schizophrenia symptom onset or general schizophrenia susceptibility in either sex and concluded that *AR* does not play a major role in schizophrenia pathogenesis. In addition to these studies in humans, Li et al. (2013a) reported that in mice, unilateral right-hemispheric knockdown of the transcription factor *Lim* domain only 4 (*LMO4*) increased rightward paw preferences. However, no study has linked variation in *LMO4* to either handedness or schizophrenia susceptibility in humans, yet.

However, there are also studies that indicate partial overlap of the genetic determinants of handedness and schizophrenia. The strongest molecular evidence for this idea comes from studies investigating *LRRTM1* (Brandler and Paracchini, 2014; Francks et al., 2002, 2003a, 2007). For example, Francks et al. (2007) observed a significant association of a haplotype upstream of *LRRTM1* with performance in the peg board test, a measure of hand skill, in a cohort of dyslexic siblings. Importantly, they found the same haplotype to be overtransmitted paternally to patients with schizophrenia. These findings are supported by a recent non-clinical study by Leach et al. (2014). These authors found that the risk alleles of the three schizophrenia-linked *LRRTM1* SNPs were significantly related to higher schizotypy. While there was no direct relationship between genetic variation in these SNPs and handedness, there was at least an indirect link: Mixed handedness was associated with methylation levels in a block of CpG sites in the assumed promoter region of *LRRTM1*. In addition to these findings, other studies linked *LRRTM1* to schizophrenia (e.g., Brucato et al., 2014; Ludwig et al., 2009), strongly suggesting that this gene represents a genetic link between handedness and schizophrenia.

A second genetic link between handedness and schizophrenia might be represented by *COMT*, a candidate gene for schizophrenia (Riley and Kendler, 2006). In a sample of patients with bipolar disorder, Savitz et al. (2007) found the *COMT* Val88Met polymorphism to be significantly associated with performance on a test of relative hand skill (participants were asked make dots in a series of patterned circles). Patients with the Met allele showed higher relative hand skill scores. While this is only one paper in a small clinical sample, several studies linking *COMT* to schizophrenia susceptibility (e.g., Gatt et al., 2015; Ira et al., 2013; Williams et al., 2007) indicate that *COMT* might be an interesting candidate gene for future studies investigating the link between handedness and schizophrenia.

Also worth mentioning is the finding that Bloss et al. (2010) found an association between genetic variation in the apolipoprotein E gene *APOE* and handedness during writing in 147 schoolchildren. While *APOE* is more commonly known as being associated with the incidence of Alzheimer's disease, some authors also suggested an involvement in schizophrenia (e.g., Gibbons et al., 2011). However, since both Hubacek et al. (2013) and Piper et al. (2012) could not replicate the association of *APOE* and handedness reported by Bloss et al. (2010), it is unlikely that *APOE* constitutes a major genetic overlap between handedness and schizophrenia.

While fewer studies investigated the molecular determinants of language lateralization than those of handedness, several genes have been associated with this trait over the last couple of years. For example, in a recent fMRI study, Pinel et al. (2012) found an association of the *KIAA0319/ITRAP/THEM2* rs17243157 SNP with asymmetries in brain activation in the superior temporal sulcus. These authors also reported an association of the *FOXP2* SNPs rs6980093 and rs7799109 with brain activation variation in the frontal cortex of the left hemisphere. An association of *FOXP2* and language lateralization was later confirmed by Ocklenburg

et al. (2013b) who found that the *FOXP2* SNP's rs2396753 and rs12533005 were related to performance in the dichotic listening task. Interestingly, genetic variation in *FOXP2* has also been linked to schizophrenia disease susceptibility in general (Li et al., 2013b) and susceptibility for language impairments (Tolosa et al., 2010) and auditory verbal hallucinations (McCarthy-Jones et al., 2014).

Another gene that has been associated with both schizophrenia (Cherlyn et al., 2010; Li and He, 2007) and language lateralization is the N-methyl-D-aspartate receptor 2B subunit gene *GRIN2B*. Ocklenburg et al. (2011) reported that participants with the CT genotype in the *GRIN2B* rs1806201 SNP had a stronger left-hemispheric language dominance (measured with the dichotic listening task) compared to both homozygous CC and TT individuals. Moreover, the cholecystokinin A receptor gene *CCKAR* has been linked to both schizophrenia and language lateralization. Ocklenburg et al. (2013a) found a significant association of genetic variation in the *CCKAR* SNP rs1800857 and dichotic listening performance, with participants carrying the C allele of this polymorphism showing a reduction of left-hemispheric language dominance. Interestingly, this allele had been identified as a schizophrenia risk allele for male individuals in a previous study by Koefoed et al. (2009).

Taken together, *FOXP2*, *GRIN2B* and *CCKAR* all represent interesting candidate genes for shared genetic influences between language lateralization in schizophrenia. In addition to these candidate gene studies, Karlebach and Francks (2015) recently published a very interesting re-analysis of two transcriptomic datasets derived from post mortem human language cortex. The authors found left-right differences of gene expression in a number individual genes and gene ontology groups, mostly involved in synaptic transmission, nervous system development and glutamate receptor activity. While it is beyond the scope of the present article, to review all of these genes in detail, the article by Karlebach and Francks (2015) might help to identify candidate genes for future studies investigating the relationship between language lateralization and schizophrenia.

Another way to identify candidate genes for shared genetic influences of atypical laterality and schizophrenia is to identify genes that have been associated with schizophrenia and are expressed in tissue that is relevant for laterality (i.e., the brain). For example, the latest genome-wide association study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) identified 128 independent genetic associations with schizophrenia at 108 different loci that reached genome-wide significance. Interestingly, genes expressed in both various parts of the immune system and the brain were overrepresented among the significant associations found. While a detailed discussion of all 108 loci with respect to their relevance for laterality is beyond the scope of the present review, several of the brain-associated genes identified in this study could be interesting candidate genes for the ontogenesis of laterality; for instance, those involved in dopaminergic (e.g., *DRD2*) or glutamatergic neurotransmission (e.g., *GRM3*, *GRIN2A*, *SRR*, *GRI1A1*).

7. Schizophrenia might not be a single trait

A question that is tremendously important for our understanding of the ontogenetic base of the link between schizophrenia and atypical laterality is whether schizophrenia is a single trait. Schizophrenia is a highly heterogeneous disorder (Picardi et al., 2012) and two patients with the same diagnosis can exhibit very different symptoms. The diagnostic criteria for schizophrenia (295.90) according to DSM-5 (American Psychiatric Association, 2013), require the patient to show two or more of the following "A" criteria for a significant amount of time during a one month

period: Delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior or negative symptoms (i.e., diminished emotional expression or avolition). At least one of the diagnostic criteria that have to be met by the patients are delusions, hallucinations, or disorganized speech. From a neurophysiological systems perspective it seems unlikely that all of these rather heterogeneous symptoms are driven by the same genetic processes, since they are likely to originate in different neuronal systems. For example, disorganized speech likely involves the brain correlates of language, while catatonic behavior is more strongly related to the motor system.

This enormous heterogeneity between patients with the same diagnosis has led some authors to question the validity of using general disease susceptibility as phenotype in genetic studies investigating schizophrenia (e.g., DeRosse et al., 2008). Instead, it has been suggested to use so called symptom-based phenotypes, that is, the severity of specific schizophrenia symptoms (DeRosse et al., 2008). This idea is supported by a recent genome wide association study (Arnedo et al., 2015) that included schizophrenia patients and healthy controls. In a first step, Arnedo et al. (2015) identified so called SNP sets, that is, sets of interacting SNPs that cluster within particular participants independent of clinical status. Then, the risk of schizophrenia was tested for each SNP set. Moreover, the authors also clustered phenotypic sets (e.g., specific symptom clusters) independent of the individual genetic background and tested, whether specific SNP sets were related to specific phenotypic sets. The results of the study were striking, as the authors identified 42 SNP sets that were associated to a 70% or greater risk of schizophrenia, but 17 of these networks of SNP sets did not share any SNP or subject. Most importantly, these unrelated genetic sets were related to differential phenotypes, with large variations in symptom occurrence and symptom severity. These findings led Arnedo et al. (2015) to the conclusion that schizophrenia might not be a single disorder but a group of heritable disorders caused by different genotypic networks that cause distinct clinical symptoms.

8. Symptoms vs. syndromes as phenotypes

The finding of Arnedo et al. (2015) is particularly important for our understanding of the relationship between atypical lateralization and schizophrenia. If there are indeed multiple, genetically distinct “schizophrenias” like Arnedo et al. (2015) suggest, it is unlikely that all of them are related to atypical laterality in the same way. Some lateralized functions, like language, for instance, can be directly linked to certain symptoms (e.g., auditory verbal hallucinations, disorganized speech) because both pertain to the same cognitive system (i.e., language). Other symptoms, such as catatonic behavior, for instance, may not show such a clear-cut association with atypical laterality. There is indeed empirical evidence that the presence of atypical laterality in schizophrenia patients is symptom-dependent, especially with respect to auditory verbal hallucinations and atypical language lateralization. For example, using a dichotic listening task Hugdahl et al. (2008, 2012) found a gradual reduction in left-hemispheric language lateralization with increasing frequency of hallucinations. Importantly, there were no significant correlations with negative symptoms. This was corroborated by a recent meta-analysis (Ocklenburg et al., 2013d). The authors statistically integrated studies that used the dichotic listening task to investigate language lateralization in patients with schizophrenia and healthy controls. In a first meta-analysis, Ocklenburg et al. (2013d) compared schizophrenia patients in general with healthy controls. As expected, patients showed less language lateralization than controls but the effect size was small.

Then, in a second meta-analysis, the authors compared dichotic listening performance between patients with auditory hallucinations and non-hallucinating controls. Here, the effect size was substantially larger, indicating a stronger relationship between language lateralization and auditory verbal hallucinations than between language lateralization schizophrenia disease susceptibility in general.

These findings can be explained using a neuroscientific model (Hugdahl et al., 2008), according to which auditory verbal hallucinations are internally generated speech misrepresentations. As such, they involve speech perception areas in the temporal lobe of the left hemisphere. Thus, patients experiencing hallucinations should have problems to identify external speech sounds presented to the right ear which are mainly processed by the left hemisphere, leading to decreased lateralization. In turn, patients without auditory verbal hallucinations should show less reduction of language lateralization than those who experience hallucinations, further supporting the notion of a symptom-based approach to investigate the relationship between laterality and pathology. Interestingly, a recent study found that patients who experienced auditory verbal hallucinations displayed a reduced left-ear advantage for emotional prosody, compared to healthy controls and non-hallucinating patients (Alba-Ferrara et al., 2013). This suggests that not only language but also emotional prosody lateralization is affected by auditory hallucinations.

9. Toward a symptom-based approach for the relationship between schizophrenia and laterality

In a recent article, Bishop (2013) investigated the idea that atypical laterality might be the cause of developmental language disorders. The author suggested four different models for the relationship between atypical laterality and pathology. The endophenotype model assumes that genetic variation causes atypical laterality which in turn increases the risk for developing a pathological condition. Thus, the same genes should affect both traits. This is also assumed by the pleiotropy model but in this model, there is no causal relationship, since the two traits are thought to have common genetic origins without causally influencing each other. In the additive/interactive risks model, pathology is mainly determined by genetic factors that do not influence laterality, but atypical laterality is considered an additional factor that further increased the probability of developing a pathological condition. The last model, called the neuroplasticity model, assumes that pathology causes lasting changes in brain architecture that in turn influence laterality.

With respect to schizophrenia, the neuroplasticity model, however, is not very likely. A study by Crow et al. (1996) found that children with atypical laterality patterns are at a higher risk to develop schizophrenia later in life, implying that atypical laterality develops earlier than schizophrenia. This is in line with Crow's theory that genes give rise to atypical laterality which in turn increases the vulnerability to develop schizophrenia. The currently available evidence reviewed here, however, argues against such an endophenotype model – and also the pleiotropy model: Although there is robust evidence for a genetic link between laterality and schizophrenia, correlations between both traits tend to be relatively small. This leaves the additive/interactive risks model, presumably intermixed with some partially pleiotropic influences, since some genes like *CCKAR* influence both traits. As we hope to have clarified, however, the significant but small correlations might become stronger, if a symptom-based approach is used. We therefore propose a novel multi-layered model (see Fig. 1) according to which specific symptoms related to schizophrenia as a syndrome are genetically associated with specific lateralized functions, presumably those they share a cognitive system with.

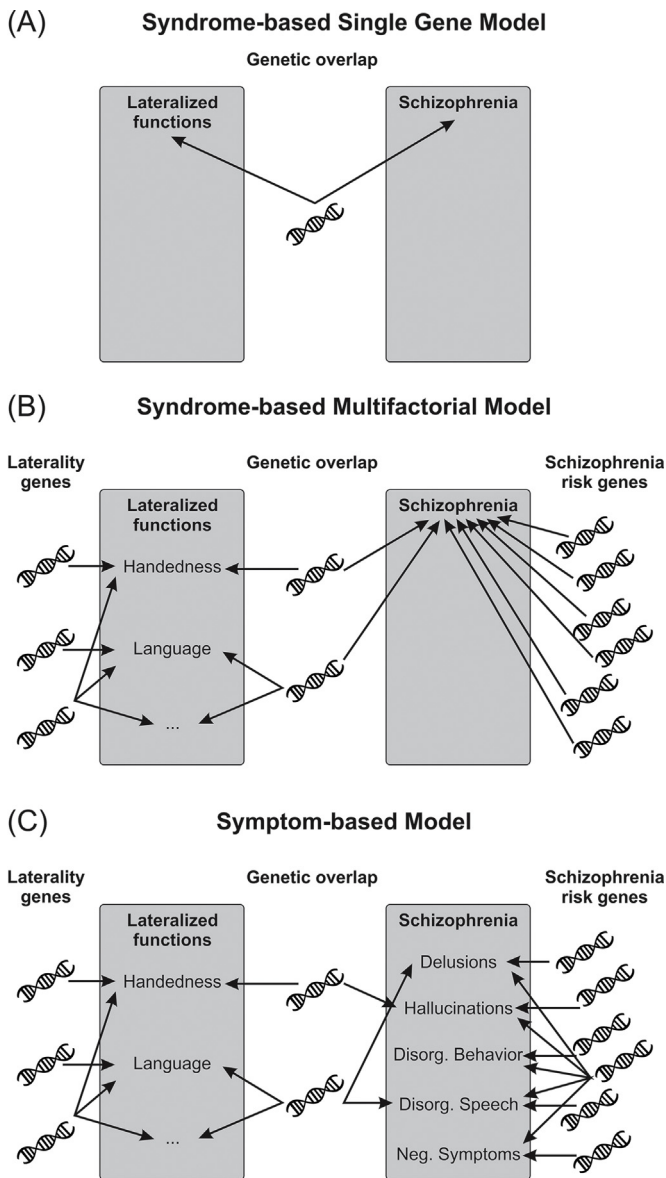


Fig. 1. Possible models for the genetic association between atypical lateralization and schizophrenia. The simple syndrome-based single gene model (A) assumes that both atypical lateralization and schizophrenia are determined by the same gene. Since a considerable amount of literature suggesting that both schizophrenia and different forms of lateralization are multifactorial traits, a syndrome-based multifactorial model (B) assuming a multitude of partly overlapping genetic influences for both schizophrenia risk and lateralization is probably a more realistic depiction of the association between the two traits. However, based on the work of Arnedo et al. (2015) we would suggest a symptom-based model, with differential genetic influences on different schizophrenia-related symptoms. Please note that for the sake of simplicity we only show genetic influences in the figure. We are of course aware that the depicted traits might also be influenced by environmental and epigenetic factors.

10. Conclusion and outlook

Taken together, there is little doubt that atypical laterality and schizophrenia are associated and there is convincing empirical evidence that this association arises from partly overlapping genes. Unveiling the nature of the association as well as the underlying genes would provide valuable insights about the etiology of schizophrenia. However, most attempts yielded relatively little success so far. Based on the findings reviewed here, we believe that a symptom-driven approach, in which specific symptoms are associated with specific lateralized functions, would be more

promising. To test the model we proposed, the same phenotypes need to be examined in patients with schizophrenia and healthy controls. Since simply having schizophrenia appears to be an insufficient phenotype, each major schizophrenia symptom should be additionally assessed with more detailed and specialized questionnaires such as the Psychotic Symptom Rating Scales (PSYRATS, Haddock et al., 1999) or the Auditory Hallucinations Rating Scale (AHRs, Hoffman et al., 2003) for hallucinations and delusions and the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1982), the Negative Symptoms Assessment (NSA, Alphas et al., 1989), or the Clinical Assessment Interview for Negative Symptoms (CAINS, Kring et al., 2013) for negative symptoms, for example. Doing so would allow for an easy comparison of syndrome- and symptom-based phenotype approaches. Moreover, since different lateralized functions seem to have partly independent genetic determinants, we would suggest to always assessing hand preference, hand skill and a behavioral measure of language lateralization (e.g., the dichotic listening task) as basic asymmetry phenotypes. In addition, behavioral markers of other lateralized functions (e.g., emotional or spatial processing) and markers of structural brain asymmetries (e.g., measured with voxel-based morphometry of diffusion tensor imaging) might be of interest.

We hope our ideas can help to stimulate new research that might help to finally disentangle the riddle of how laterality is related to schizophrenia. Furthermore, the proposed model may be serve as a blueprint for studying other psychiatric disorders that have been associated with aberrations in laterality such as depression, Tourette's syndrome, autism, and attention deficit hyperactivity disorder (for review Klimkeit and Bradshaw, 2006).

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