CORTEX 75 (2016) 260–261

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Commentary

A commentary on Karlebach and Francks, (2015)

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Since the beginning of the 20th century, the observation that handedness runs in families led to the development of genetic theories about lateralization (Ramaley, 1912). While some of these theories had immense influence on how we understand the development of handedness and other forms of functional lateralization (e.g., McManus, 2002), one big problem with all of them is the fact that they are based on the distribution of the phenotype rather than actual molecular genetic data. This phenotype-driven approach is particularly problematic for single-gene theories, since no genetic study has ever successfully identified a gene explaining a sufficient amount of phenotypic variance to qualify as the single determinant of any form of lateralization (Ocklenburg, Beste, Arning, Peterburs, & Güntürkün, 2014). For example, Armour, Davison, and McManus (2014) conducted a genome-wide association study (GWAS) with 3940 twins. Not able to detect an SNP reaching genome-wide significance, they reasoned that these results disprove single-gene theories, and that handedness must be determined by a multifactorial model which includes at least 40 genes. However, it is doubtful that a GWAS represents the best way to investigate genetic determination of lateralization, at least with a sample size in the lower thousands. With samples including less than a 6-digit number of participants this method might not provide enough power to detect small effects of multiple interacting genotypes (Eriksson et al., 2010). Moreover, results might be imprecise due to inflated type two error rates after correction for multiple comparisons (Williams & Haines, 2011). Furthermore, it has to be taken into account that complex phenotypes like handedness or language lateralization are not only influenced by genes and environmental factors directly involved in their development. Rather, genes and environmental factors determining general brain development and development of the relevant cognitive system (e.g., the language system for language lateralization) also influence the phenotype, multiplying the number of involved ontogenetic factors.

Which, then, is the ideal way to determine candidate genes for handedness and other forms of lateralization? One idea that has been brought forward by Geschwind and Miller (2001) is that the molecular roots of lateralization can be traced back to left-right asymmetries in gene expression level. As these asymmetries are thought to constitute the ontogeny of lateralization, Sun and Walsh (2006) studied gene expression levels in the right and left hemisphere of the human embryo. They were able to identify 27 asymmetrically expressed genes which are mostly responsible for gene expression regulation, signal transduction, and cortical development. While these findings in embryos were very promising, analysis of gene expression in the adult human brain yielded less clear results. For example, Hawrylycz et al. (2012) compared mRNA expression profiles among different regions of two adult human brains, with no significant results obtained between analogous regions across cerebral hemispheres. Similar results were reported in a further study including 57 brains in different life stages (Pletikos et al., 2014).

In the study by Karlebach and Francks (2015), the authors performed a re-analysis of the two datasets of Hawrylycz et al. (2012) and Pletikos et al. (2014). Importantly, they focused on specific regions involved in speech production and perception, and could show lateralization of individual genes as well as gene ontology (GO) groups in two language-related areas, the superior temporal sulcus (STS) and Heschl's Gyrus (HG). The lateralized gene sets included sets responsible for neuronal electrophysiology, synaptic transmission (especially the G-protein coupled receptor signalling pathway), nervous system development, and glutamate receptor activity. The contrasting results compared to Hawrylycz et al. (2012) and Pletikos et al. (2014) may be explained by the different analysis

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http://dx.doi.org/10.1016/j.cortex.2015.04.005

methods performed by Karlebach and Francks (2015). Some of these methods provide significant improvement when compared to former studies and are worth being highlighted: As STS and HG are asymmetrical in function, anatomy and neurophysiology, it is methodically reasonable to focus on these anatomically defined regions. Genes are differentially expressed across the human brain, which makes an analysis of gene expression over relatively large cortex areas like in the study by Sun and Walsh (2006) difficult to interpret. The more brain areas and life stages are lumped together, the more possibly hidden expression asymmetries are balanced out, and no statistical significant results are found. Moreover, whereas Hawrylycz et al. (2012) and Pletikos et al. (2014) aimed to detect expression rates on the level of individual genes, Karlebach and Francks (2015) proposed that lateralization could better be detected at the level of functional GO groups, which was indeed the case as small effects were increased. This approach might be particularly useful when investigating the role of genes determining general brain development and development of the relevant cognitive system for a specific form of lateralization, since it is difficult to understand the functional relevance of such genes in isolation.

Thus, in our opinion, the paper of Karlebach and Francks (2015) constitutes a major stepping stone towards understanding the genetic determinants of functional lateralization. The asymmetrically expressed genes and gene groups identified by Karlebach and Francks (2015) provide an objective starting point for a multitude of possible candidate gene studies (Ocklenburg, Beste, & Güntürkün, 2013) which could link genetic variation in these genes to behavioural or anatomical asymmetries. In a field in which many theories are based on phenotypic distribution or pure speculation, this is a resource that is direly needed. Candidate genes could for example be investigated in more detail by quantitative polymerase chain reaction (qPCR) which allows a more precise quantification for these selective genes or gene groups (see Pletikos et al., 2014). Moreover, the work of Karlebach and Francks (2015) also enables the construction of knockout-models for further examination of the contribution of individual genes or gene groups to lateralization, similar to the model of Li et al. (2013) which shows that unilateral variation of *Lmo4* expression in the embryo alters paw preferences in mice.

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Received 27 March 2015
Accepted 8 April 2015