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Twin Research and Human Genetics / Volume 15 / Special Issue 03 / June 2012, pp 267 - 272
DOI: 10.1017/thg.2012.20, Published online: 15 June 2012

Twin Research and Human Genetics
Volume 15 ▌ Number 3 ▌ pp. 267–272 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.20

Guest Editorial

Neuroimaging and Genetics: Exploring, Searching, and Finding

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This issue on the genetics of brain imaging phenotypes is a celebration of the happy marriage between two of science's highly interesting fields: neuroscience and genetics. The articles collected here are ample evidence that a good deal of synergy exists in this marriage. A wide selection of papers is presented that provide many different perspectives on how genes cause variation in brain structure and function, which in turn influence behavioral phenotypes (including psychopathology). They are examples of the many different methodologies in contemporary genetics and neuroscience research. Genetic methodology includes genome-wide association (GWA), candidate-gene association, and twin studies. Sources of data on brain phenotypes include cortical gray matter (GM) structural/volumetric measures from magnetic resonance imaging (MRI); white matter (WM) measures from diffusion tensor imaging (DTI), such as fractional anisotropy; functional- (activity-) based measures from electroencephalography (EEG), and functional MRI (fMRI). Together, they reflect a combination of scientific fields that have seen great technological advances, whether it is the single-nucleotide polymorphism (SNP) array in genetics, the increasingly high-resolution MRI imaging, or high angular resolution diffusion imaging technique for measuring WM connective properties.

The articles presented in this issue may also reflect promises kept. The outlook for the field of imaging genetics presented previously (e.g., Pezawas and Meyer-Lindenberg, 2010) sketched a picture of interesting novel findings in the then upcoming years from GWA studies on brain phenotypes that were reliably linked to behavioral phenotypes, including psychopathology. Consistent with this prediction, Ousdal et al. (2012) in this issue point to the PHOX2B gene in a GWA study on individual variability in amygdala activation after emotional stimuli using fMRI. Alternatively, de Geus (2010) argued that the strength of the field studying the genetics of brain phenotypes may lie in candidate-gene studies in a neurobiological follow-up — *after* GWA studies have identified genetic variants associated with behavioral variation of psychopathology. These studies would estimate how genetic variants exert their influence on these phenotypes via brain structure and function. In response, Hibar et al. (2012) in this issue show that an Alzheimer's disease-risk gene (GAB2) has effect on brain volumes in otherwise healthy controls at an age well before disease onset, while Rose et al. (2012) also show an effect of the schizophrenia risk gene NRGN on ventromedial prefrontal cortex fMRI activity, but not structure. Clearly, both the genome-wide and candidate-gene association studies have delivered on the promises.

The second target for this issue is to provide the field of imaging genetics with novel findings in the quantitative genetics of brain phenotypes. Twin and family studies form the basis of this field by showing that these phenotypes are heritable traits. Several studies provide new evidence for the genetic contribution to structural and functional brain phenotypes, including MRI volumes, DTI anisotropy, and EEG-derived biomarkers. Finally, this issue presents a highly innovative tool for visualizing GWA results in aid of the imaging genetics community, and presents several sample descriptions and overviews of genetic studies. In the following sections, we highlight these findings and descriptions.

RECEIVED 4 April 2012; ACCEPTED 4 April 2012.

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Molecular Genetic Studies

Over the past five years research on the genetic background of individual trait variation and neurological diseases or psychiatric disorders has greatly advanced due to the emerging use of genome-wide association analyses (Visscher et al., 2012).

In GWA studies, an unbiased search across the entire genome is performed for variants of genes, that is, SNPs, that lead to differences in individual traits (de Geus et al., 2008; Hirschhorn, 2009; McCarthy et al., 2008; Pattyn et al., 1999; Stein et al., 2012; Thompson et al., 2010). This hypothesis-free approach has by now already yielded the discovery of many candidate genes possibly involved with human trait variation or disease/disorder phenotypes. Recently, initiatives have also started to perform GWA studies on biomarkers derived from neuroimaging (Stein et al., 2012; Thompson et al., 2010). Compared with complex behavioral endpoints, the use of neuroimaging endophenotypes potentially increases the power to detect relevant associations, given that variance in brain structure or function is likely related more closely to genetic variation than complex behavior (de Geus et al., 2008). In this issue, a first attempt is made in healthy adult participants to find genetic variants across the entire genome that underlie individual variability in amygdala activation (Ousdal et al., 2012). The association of genome-wide data with those from functional MRI led to the discovery of an SNP near the paired-like homeobox 2b (PHOX2B) gene. Knowledge that this gene is importantly involved in autonomic nervous system development (Pattyn et al., 1999), and monoamine biosynthesis (Brunet & Pattyn, 2002; Jacob et al., 2007), together with the fact that it surfaced from an a priori hypothesis-free association test across more than 500,000 SNPs, provides strong support for the hypothesis that amygdala reactivity is influenced by monoaminergic signaling pathways as proposed by many previous candidate-gene studies (Brunet & Pattyn, 2002; de Geus et al., 2008; Hariri, 2009; Jacob et al., 2007; McCarthy et al., 2008; Pattyn et al., 1999; Stein et al., 2012; Thompson et al., 2010).

Many gene polymorphisms have been put forward as associated with human trait variability and the risk for neurological diseases or psychiatric disorders (de Geus et al., 2008). In follow-up studies, however, very often no differences are found at the overt cognitive level between people carrying the risk variant as compared to non-risk allele carriers, as indicated by normal behavioral performance on cognitive tests. It may well be, however, that the tests are not challenging or well-suited enough to reveal genetic effects on overt behavioral performance, and/or that gene effects are masked by compensation strategies, such as increased activation of specific brain regions, or recruitment of other or additional brain regions, to perform the task. Despite apparently unaffected overt behavior, it may then be that differences are evident at the level of alterations in functional activation of the brain. In this special issue, Rose et al. investigated the effect on brain structure as well as brain function, during a spatial working memory task, of the rs12807809 SNP located upstream of the neurogranin (NRGN) gene, identified as a risk variant for schizophrenia. In agreement with earlier studies (e.g., Donohoe et al., 2009; Krug et al., 2011), subjects homozygous for the risk 'T' allele showed unaffected behavioral performance during the cognitive task as compared to non-risk 'C' allele carriers ('CT' and 'CC'). Structural MRI also indicated no anatomical differences; however, functional MRI did reveal a failure to disengage the ventromedial prefrontal cortex during execution of the task, suggestive of a processing deficiency in risk allele carriers. Since executive function changes in schizophrenia have been related to structural and functional changes of the medial frontal cortex (Kawada et al., 2009; Pomarol-Clotet et al., 2008), this finding indicates a mechanism by which NRGN may influence the risk for schizophrenia.

In case of an identified gene variant that confers increased risk for a brain disease or psychiatric disorder, it is also important to investigate if there are already abnormalities in the brains of healthy young adults that carry the risk polymorphism. In addition to lending further support for the notion that the gene is indeed relevant, assessment of brain changes in young at-risk individuals provides insight into the neurobiology of the disease, factors that may promote or delay disease development, and differences or commonalities of neurobiological abnormalities that underlie different psychiatric disorders. In this issue, Hibar et al. (2012) looked for the presence of structural brain changes in 755 young adult twins that carry the major allele rs7101429 of the growth receptor bound protein 2-associated protein (GAB2) gene, which has been associated with increased odds for late-onset Alzheimer's disease. The study demonstrated detectable associations between this Alzheimer's disease risk gene and morphological brain differences long before the typical age of onset of the disease. Their finding is highly relevant as it supports the contention that GAB2 has functional importance for neural development and is useful for identifying individuals at risk for late-onset Alzheimer's disease.

Heritability of Imaging-Based Traits

Family and twin-based studies are essential for answering the initial question in all genetic studies: what proportion of the trait variance is due to genetic influences? By measuring the similarity of a trait between related subjects, the degree of genetic influence on a trait can be determined. Blokland et al. (2012) meta-analyze the results of a number of published studies, showing that structural neuroimaging-derived traits are indeed generally highly heritable, a finding that may increase confidence in their use. Two large twin studies described in this issue aim to extend and enhance the literature on heritability of brain structure and function.

From Australia, the TWIN-E study will assess 1500 twins with a battery of cognitive tasks, a subset of which will undergo EEG and MRI (Gatt et al., 2012). From The Netherlands, the Brain SCALE study follows adolescents from 112 families with psychometric, neuropsychological, and neuroimaging measures (van Soelen et al., 2012). Both studies have a longitudinal component, which will allow measurements of heritability through time, giving insight into genetic influences on brain structure and function throughout the development of the nervous system.

Continuing with the developmental theme, the study by Geng et al. (2012) provides direct insight into the heritability of WM development in a large sample of neonatal twins. In addition to demonstrating that estimates of heritability are larger for WM in neonates than those reported previously in adults, the authors provide novel evidence that regional genetic variation may be modulated by maturation status. Interestingly, estimates of high heritability for WM structures appear to be consistent across species, as Phillips et al. find the corpus callosum to be highly heritable in a sample of pedigree baboons. Moreover, like Geng et al. (2012), they show that genetic contributions to regional corpus callosum size in baboons may be modulated by rate of development. Findings of cross-species homologies in terms of brain structure heritability are rare, so these results are a welcome contribution to the special issue.

Complementing the findings for cerebral WM, Eyler et al. (2012), using data from the Vietnam Era Twin Study of Aging, provide evidence that GM measures are likewise heritable. They adopt a novel approach: measuring areal expansion in addition to cortical thickness, finding higher estimates of heritability for the former measure. Whether heritability of GM imaging endophenotypes is relevant for psychiatric disorders is addressed by Turner et al. (2012). They use independent data from two large patient and control samples to investigate the stability and heritability of regional GM concentration abnormalities in schizophrenia. Using a novel application of source-based morphometry as a data reduction technique, they find evidence for replicable familial and potentially heritable components of GM deficits in that disorder.

Twin Studies of Functional Brain Activity

Functional brain activity is one step further than anatomical brain measures in the causal pathway from genes to behavior as indicators of information processing during tasks or in rest. In this issue, two types of brain activity measures have been investigated. The first is EEG recording. One clear advantage of EEG recordings is the unparalleled time resolution, which may reach sub-millisecond scale. Precisely this feature was exploited by Molenaar et al. in their article about intra-individual heritability estimation. The model presented, called iFACE, requires many longitudinal observations for which dense time-series are particularly suited. The complex model requires time-series data from only two, non-identical siblings such as dizygotic (DZ) twins — the authors chose to analyze event-related potentials (ERP) data from two DZ pairs performing a standard oddball task. Based solely on ERP data, and without genotyping subjects, the model can estimate the actual genetic overlap between DZ twins, and provide individual estimates for additive genetic (A), common environmental (C), and unique environmental (E) parameters. Although the article was written as a proof-of-principle, the first application of the model to real ERP signals provides evidence that estimates of A, C, and E differ across individuals. The commonly held assumption in quantitative genetics is that A, C, and E are constant within a population, and the somewhat disconcerting conclusion is that it may not always hold. Even so, this is an excellent example of a situation where brain phenotypes may have the edge over behavioral phenotypes: by measuring time-series of brain activity, additional information on sibling covariation is obtained. Here, the additional information pertains to individual differences in the evolving brain activity in response to an external stimulus on a millisecond scale.

Even though EEG is still widely used, fMRI has surpassed EEG as the technique of choice for registering brain activity. However, more recent developments have shown that the two are not unrelated, and may provide different windows into the same events in the brain. This is generally investigated with direct comparison between so-called functional measures — EEG and fMRI BOLD signals — in the resting state. Often, the EEG–fMRI comparison is the advancement of concurrent EEG–fMRI registration, identifying patterns of coactivation and suggesting that BOLD resting-state networks and oscillatory brain activity recorded at the scalp are correlated (e.g., Britz et al., 2010; Musso et al., 2010; Mantini et al., 2007). But the link between imaging techniques and EEG is not exclusively the domain of functional measures (Whitford et al., 2007). Variation in resting-state EEG parameters is also very likely the result of anatomical makeup. In a simple twin design, Smit et al. (2012) linked MRI-based brain volumes to EEG variation, showing that the moderate correlations between EEG oscillation power and both GM and WM volumes are largely genetically mediated. The combination of imaging techniques and the twin design has shown to be highly informative in relating EEG power to the genetics of the underlying anatomical structure.

As mentioned, functional brain activity can be monitored as fMRI BOLD signals. The advantage of the high spatial resolution from this technique was fully exploited by den Braber et al. (2012), who investigated twins who scored high or low on obsessive compulsive symptoms (OCS). The authors selected monozygotic twin pairs that scored concordant high on OCS, concordant low on OCS, or discordant high-low on OCS, arguing that concordant high-scoring twins may have a more genetically mediated variant, while

twins high on OCS from discordant twin pairs have a more environmentally-mediated variant of obsessive-compulsive symptomatology. All subjects performed a Stroop task during scanning, as the inhibitory control in this specific task is hypothesized to be altered in obsessive patients. Although there were no differences in overt behavioral performance, fMRI brain activation differences between concordant OCS high and concordant OCS low twin pairs were distinct, compared with fMRI brain activation differences between discordant OCS high-scoring versus low-scoring twins at several brain regions, including the anterior cingulate cortex and hypothalamus. One of the most important findings was, however, that dorsolateral prefrontal cortex in concordant OCS high-scoring twins, as well as in the high-scoring OCS twins of the discordant twin sample, was activated more by the inhibitory control task than in OCS low-scoring subjects. This finding marks this structure as a possible key region for disturbances in obsessive compulsive disorder, rather independent of whether the symptoms are genetically or environmentally mediated.

Hemispheric Asymmetries

One of the most prominent features of the brain is the central fissure separating the two cerebral hemispheres. These hemispheres are not identical — that is to say, mirrored — copies, but differ in both structure and function. These hemispheric asymmetries are not without cause and consequence. Rentería (2012) in this issue provides a clear overview of the antecedent conditions of asymmetries of many cortical structures, including genetic, environmental, and gender effects. Behavioral implications such as handedness, and linguistic information-processing variability, including dyslexia (e.g., Galaburda et al., 1985), are discussed. This review lists many of the MRI and fMRI asymmetries reported in the literature, thus providing a rich overview of the neurobiology of brain asymmetry.

A Genetic Study Tool

The great breadth of data generated in highly multidimensional imaging genomics research requires new tools for visualization of the results. In GWA studies, millions of SNPs are routinely examined for association with several phenotypes. In this issue, a novel tool to plot and compare the results from GWA studies of multiple neuroimaging phenotypes is presented (Novak et al., 2012). This tool also allows users to plot and compare interactively their own association data next to the results. Easier visualization of these highly dimensional results can lead to new insights in the field of neuroimaging genetics.

Sample Descriptions

Though imaging endophenotypes are likely to be more penetrant than complex and heterogeneous neuropsychiatric disease phenotypes, effect size of specific genetic variants on imaging traits are still expected to be modest. In order to identify the genetic underpinnings of imaging traits, large and well-characterized samples are needed to achieve sufficient power. These samples consist of both genotype and neuroimaging data, and generally other neurocognitive traits as well. Individually, and in collaboration, these large samples are bases for current and future genetic discoveries. Three such samples are described in detail in this issue. From Norway, the Norwegian Cognitive Neurogenetics Study (NCNG) is a large sample of approximately 700 healthy individuals initiated in 2003 (Espeseth et al., 2012). The NCNG sample consists of genetically homogeneous individuals aged across the lifespan. Genome-wide genotypes were acquired on a large proportion of the sample; phenotypic measures include structural, diffusion, and resting-state neuroimaging data, as well as data from a battery of psychometric and experimental cognitive psychology tasks. The twin studies described above may also be used in the future for GWA studies (Gatt et al., 2012; van Soelen et al., 2012).

Outlook

We expect that work in the field of imaging genetics is far from complete. Increasingly dense molecular genetic SNP sampling, imputation, and genome-wide sequencing are being incorporated into the field. Likewise, higher resolution imaging is increasingly becoming available in genetically informative family, twin, and genotyped but unrelated samples. Yet progress will not be limited to quantitative leaps in performance. Innovations are likely to come from relatively novel techniques, such as the assessment of copy number variants, estimation of the effects of rare variants on brain phenotypes, and combining the effects of SNPs within functional gene groups (Ruano et al., 2010). On the phenotypic side, multivariate approaches of genetic network modeling may require advanced modeling techniques that are only just being explored (Borsboom et al., 2011). The holy grail of imaging genetics research — a causal functional variant found by searching the genome for association to a brain-based trait which creates risk for a neuropsychiatric disease and identifies new druggable pathways — may be right around the corner. For now, the genetics of brain imaging phenotypes is a prime area of research for the further exploration of how genes are linked to behavior.

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