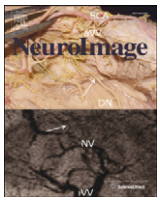
NeuroImage 62 (2012) 1286–1292

Contents lists available at SciVerse ScienceDirect

NeuroImage

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



Review

The future of fMRI and genetics research

Andreas Meyer-Lindenberg *

Central Institute of Mental Health, J5, 68159 Mannheim, Germany

ARTICLE INFO

Available online 28 October 2011

Keywords:
Imaging genetics
Psychiatric disorders
Polymorphisms
Copy number variants
Gene–environment-interactions

ABSTRACT

I provide a brief and subjective view of where the field of imaging genetics is heading. After recapitulating early debates between imagers and geneticists revolving around the topic of candidate gene studies, I point out the importance of genome-wide significant, rare and common variants. I propose that the next stages will be dominated by large-scale multi-site studies that will enable the examination of rare-high penetrance variants and methodological developments that will be required to properly assess the effects of pleiotropy, epistasis, and gene-by environment interactions. The incorporation of new sources of biological information such as whole genome sequencing, proteomic, lipidomic and expression profiles and cellular models derived from induced pluripotent stem cells opens new vistas for imaging genetics in a translational enterprise that is ultimately hoped to improve and create therapeutic options for psychiatric disorders.

Contents

Introduction

"Imaging genetics" is a research approach in which genetic information and fMRI data in the same subjects are combined to define neuromechanisms linked to genetic variation (Hariri and Weinberger, 2003). Pioneered a little over 10 years ago, this approach has already gathered its share of ups and downs, controversies and debate. All in all, the field of imaging genetics has seen massive growth. In preparing a special issue of *Neuroimage* on the topic in 2010 (Pezawas and Meyer-Lindenberg, 2010), Lukas Pezawas and I were overwhelmed at the number of submissions and the literature that already had to be covered by meta-analyses and -according to Pubmed and citation statistics- that growth continues unabated.

Of imagers and geneticists

On the face of it, neuroimagers and geneticists have much in common. Both have a tendency of generating high-volume data sets characterizing important aspects of human biology. Consequently, both have statistical and conceptual problems with handling that complexity without generating too many false positives or false negatives (more on that later). On the practical side, both groups of scientists have a tendency to show up at the Dean's office year by year explaining why they urgently need exactly that brand-new and more expensive equipment to continue their work that they cannot do with the machines bought last year. Both disciplines have also enjoyed tremendous growth and scientific success, which is one reason why the Dean's office may be inclined to grant their requests. Specifically as seen from the point of neuropsychiatry, although the same is certainly true for many other disciplines of neuroscience, both genetics and imaging have been imbued with very high hopes to provide the breakthroughs needed to finally solve the mystery of mental illness, which leads to a biologically based understanding and taxonomy of these illnesses, and to find new treatments. Corresponding to those very high expectations, both genetics and neuroimaging have also been viewed with a degree of disappointment that these breakthroughs have not (yet) happened in the time frame originally envisioned (Insel, 2010; Insel and Scolnick, 2006).

Given these communalities, it could be assumed that combination of these two approaches to better understand human neurobiology and disease might be natural, especially since the tools to validate

* Fax: +49 621 1703 2005.
E-mail address: a.meyer-lindenberg@zi-mannheim.de.

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.10.063

and mechanistically underpin their findings in ever more sophisticated animal and cellular models is rapidly advancing. However, it is probably fair to say that the process has not been smooth. Since I was fortunate enough to be at NIMH when the first results showing an association of common genetic variants in human brain function were obtained (Egan et al., 2001; Hariri et al., 2002; Heinz et al., 2000; Small et al., 2000), I could see that almost from the very beginning, geneticists were skeptical whether single variants could have effects that big, and have continued to suspect that many imaging genetic findings are false positives. That debate at time became controversial enough that it received the attention of the general scientific community including features journals such as *nature* (Abbott, 2008).

Part of that debate is conceptual and concerns different viewpoints on the common goal of understanding neurobiological causes and modifiers of normal cognitive function and, especially, mental illness. Consider Fig. 1, which was introduced by Daniel Weinberger (this recent example is taken from Rasetti and Weinberger, 2011) and has by now become almost ubiquitous in imaging genetics talks. It depicts a cascade in which genetic variation impacts on neuronal function, which leads to systems-level dysfunction, which then alters information processing in brain linked to mental illness. The linear arrangement belies the fact that the interactions between the various levels are in fact very complicated, a fact that was originally intended to be shown by the divergent errors between each level, and depicted more directly in other conceptual papers from the Weinberger lab, where the complexities of genotype-phenotype interactions in schizophrenia were discussed in detail (Weinberger et al., 2001). In later visualizations (Meyer-Lindenberg and Weinberger, 2006), we have therefore tried to depict the relationships between genes, the brain and behavior as a network (Fig. 2). A given genetic variant is likely to impact on several neural phenotypes (pleiotropy), genetic variants interact which each other (epistasis) and with the environment (G×E), and there is no one to one mapping between neural systems and the behavioral level, or, indeed, between behavioral components such as cognitive sub-processes and mental illness.

Even if this complexity is properly understood, the motivations of imagers and geneticists to engage in unraveling this network still differ (Meyer-Lindenberg, 2010b). For geneticists, the impetus is often to find new genetic causes and modifiers of a phenotype that they regard as given. In other words, a geneticist will tend to read Fig. 1 from left to right, from gene to brain to behavior. From this angle, neuroimaging phenotypes may be attractive, because they are closer to the biology of genetic function than illness or cognitive phenotypes are. If that is true, the penetrance of genetic variation on that level should be higher and it should be easier to find genes that impact on this phenotype. That, in a nutshell, was the original impetus for the "endophenotype" concept of Gottesman and Shields (1967). It has especially taken hold in psychiatric neuroscience, because the need to find a biological basis is greatest in this discipline. Psychiatric illnesses are currently defined as behavioral and psychopathological syndromes observed by the clinician or the patient, combined with course criteria, and have little biological validity by themselves.

For neuroimagers, the direction of reading of Fig. 1 tends to be the reverse, from right to left. They are interested in discovering how cognitive functions and mental illnesses work on the level of brain and therefore regard genes as a means to that goal. Taking a gene that has been associated with a given mental illness or cognitive function or biological process relevant for brain functions such as neural development, they will use imaging to try and understand what neural mechanisms are associated with that genetic variant. In other words, from the point of view of geneticists, a given neuroimaging phenotype (regarded as fixed) is a tool for finding new genetic variants, from the point of view of the neuroimager, the genetic variant (viewed as given) is the engine of discovery for discovering the neural function. Of course, these two points of view are not only not contradictory, they should be mutually reinforcing. Nevertheless, a considerable amount of cultural debate and misunderstanding has been sparked by these diverging vistas on a common landscape.

Returning to the initial question of whether imaging genetics is even possible, initial reviewers very reasonably demanded replication studies, for example in the landmark paper on 5-HTTLPR and amygdala function in *Science* (Hariri et al., 2002). At the same time, in the laboratory where I was working in Danny Weinberger's program at the time, headed by Karen Berman, we took a different tack to provide a genetic "proof of principle": We studied an illness in which the genetic "lesion" was unambiguous and there was a clear associated neuropsychiatric phenotype, and we tried to see whether we could link the two using neuroimaging. That condition was Williams Syndrome, a rare hemizygous deletion of about 28 genes on chromosome 7, that has a distinctive uneven profile of peaks and valleys in neuropsychological function and behavior, the most conspicuous of these two being a marked deficit in visual constructive function (the ability to create a whole from its parts, like a puzzle from its pieces) and marked hypersocial behavior (Meyer-Lindenberg et al., 2006b). In series of studies, we and others showed how mechanisms for these behavioral features of Williams Syndrome could be uncovered using functional and structural neuroimaging (Meyer-Lindenberg et al., 2004; Reiss et al., 2004).

Candidate gene studies

From those early beginnings, candidate gene studies have seen explosive growth in imaging genetics. A candidate gene is a genetic variant

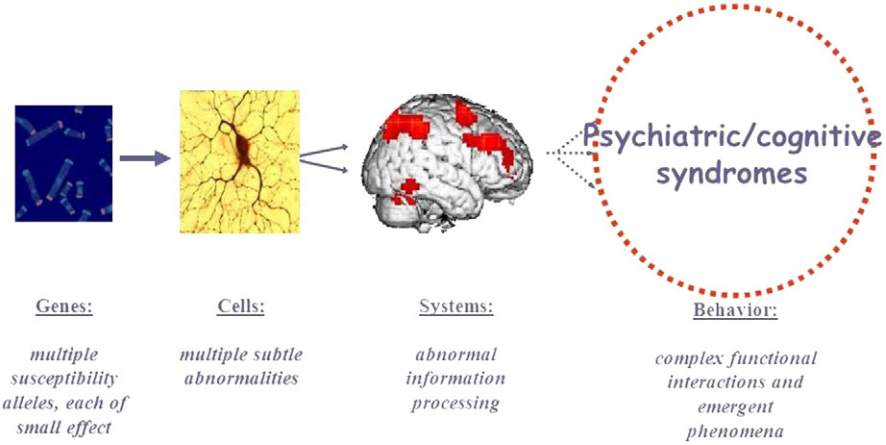


Fig. 1. A figure depicting a cascade from gene to cell to the systems to the behavior level, as introduced by Daniel Weinberger. See Rasetti and Weinberger (2011) for a recent depiction.