Intermediate or brainless phenotypes for psychiatric research?

A. Meyer-Lindenberg*

Central Institute of Mental Health, Mannheim, Germany

For highly heritable brain disorders, such as schizophrenia and autism, investigating genetic effects on the level of neural systems seems an obvious approach. Nevertheless, the usefulness of the intermediate phenotypes (’endo’ phenotypes) continues to be debated energetically. We argue that, while not all intermediate phenotypes are created equal, the hypothesis-driven investigation of the translational cascades linking genetic variation to disturbed behavior is a viable and important strategy that should not be supplanted by an exclusive focus on brainless, clinical/ categorical phenotypes investigated in very large numbers of participants.

Received 15 August 2009; Revised 13 October 2009; Accepted 13 October 2009; First published online 26 November 2009

Key words: Endophenotypes, fMRI, genome-wide association, intermediate phenotypes, schizophrenia.

Introduction

It has been established for decades that for many severe psychiatric illnesses, such as schizophrenia, bipolar disorders and autism, the majority of disease risk is attributable to genetic factors (81% for schizophrenia; Sullivan et al. 2003). For most others, such as depression, attention deficit hyperactivity disorder, personality disorders and anxiety disorders, the genetic risk component is still substantial (37% for major depression; Sullivan et al. 2000). Put another way, one key to unlocking the as-yet largely unknown pathophysiology of these common and disabling conditions is in the genes. As these are brain disorders, few would doubt that, directly or indirectly, many such genetic variations will be found to act on the human brain. It is also clear that genetic risk variants cannot act directly on the level of psychiatric disease categories, since these are clinical-behavioral entities far removed from the level of molecular biology. Instead, genetic variation will be phenotypically manifest on a variety of levels of description from gene to cell to neural systems to the clinical and social, making understanding phenotypic variation on each of these levels a valid question for research (Gottesman & Gould, 2003). Beyond being a valid line of inquiry, it would be imprudent if research would not try to mine this established circumstance for the discovery of mechanisms mediating genetic risk, because this is one of the very few avenues available to arrive at mechanismovarly novel treatments, an area where psychiatry has fallen conspicuously behind other medical disciplines and where the field’s track record in reducing mortality and morbidity is disappointing (Insel & Scolnick, 2006).

These considerations notwithstanding, intermediate phenotypes in psychiatry have been subjected to energetic debate (Meyer-Lindenberg & Weinberger, 2006; Munafo et al. 2008), including in this journal (Flint & Munafo, 2007). Several of these disagreements revolve around matters of content. However, part of the debate concerns conceptual differences of how intermediate phenotypes are viewed and pursued in psychiatry. It is some of these latter points that I would like to discuss here. While I take my examples mainly from schizophrenia, I believe that the points they illustrate pertain to the application of intermediate phenotypes in all areas of psychiatry.

Distinction between forward and reverse genetics

Most of the psychiatric genetics literature assumes phenotypes to be fixed entities for which genes are then mapped (genes ‘for’ schizophrenia, personality, brain volume, etc.). This is comforting since it allows the pursuit of these genes in complete ignorance of how these phenotypes arise, as long as they can be reliably measured. In this context, the original conceptualization of an ’endophenotype’ by Gottesman & Shields (1967) proposed that they would be useful for the identification of genes in the hypothesized polygenic systems conferring vulnerabilities to disorders’. Instead, intermediate phenotypes are usually applied...
identifies neural systems that not only correspond to the topography of serotoninergic innervation in the brain but are also known to be involved by previous evidence in neuropsychological mechanisms, such as extinction. This provides a systems-level mechanism for previously observed genotype–environment interaction of this gene in behaviour in males (Caspi et al. 2002). In schizophrenia, genetically distinct, but biologically linked variants in genes PPP1R1B, encoding DARPP-32 (Meyer-Lindenberg et al. 2007) and AKT1 (Tan et al. 2008), tagging crucial regulatory proteins in the canonical and non-canonical signal transduction pathways for dopamine, respectively, have been shown to converge on a circuit linking striatum to dorsolateral prefrontal cortex. This clarifies the neural system through which dopaminergic genetic variation plays out to increase risk for psychosis, a system that has been implicated before in schizophrenia in basic neuropsychological functions such as gating (Swerdlow et al. 2001). Also in this example as in several others, neural changes found in healthy carriers of risk alleles recapitulate features found, usually in more pronounced form, in patients with schizophrenia and their relatives (Rasetti et al. 2009). Characterizing genetic effects across these levels of description, if successful, thus provides not only novel information about the biology of mental illness, but also convergent evidence that these variants are functional – again, a point sometimes missed by traditional geneticists who regard these biological data as fixed phenotypes, ignore the biology linking them and then in the extreme case may demand multiple comparison corrections for them, the exact opposite of what these data mean.

Not all intermediate phenotypes are created equal

Another misunderstanding that stems from the same source is the assumption that any quantitative trait located closer to the level of the biological antecedent is by virtue of that fact a useful intermediate phenotype, or the converse assumption that if one has provided evidence that one such intermediate phenotype is not clearly useful, one has provided arguments against that whole approach. The evidence is, in fact, in favour of the conclusion that some, for example, cognitive, intermediate phenotypes for some diseases and genetic variants may not exhibit higher genetic penetrance or a simpler architecture (Flint & Munafò, 2007). While that argues against a simplistic assumption that cognitive disturbances ‘underlie’ mental illnesses such as schizophrenia, in the sense that they are obligatory causal antecedents of these disorders, it does not provide an argument against an intermediate phenotypes approach as such.
Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?

Intermediate or brainless phenotypes for psychiatric research?
significant common variants in ZNF804A, Neurogranin, TCF4 and genes located in the major histocompatibility complex (International Schizophrenia Consortium, 2009; Shi et al. 2009; Stefansson et al. 2009). Recent work on ZNF804A (Esslinger et al. 2009), in fact, confirms long-standing assumptions about the pathophysiology of the illness; in this case, the importance of disturbed connectivity in neural circuits linked to the dorsolateral prefrontal cortex in the disorder (Stephan et al. 2006).

Moving forward

An intermediate phenotype approach will easily be able to accommodate additional sources of reliable data about genetic variation. In particular, in addition to confirming that a large proportion of heritable risk for schizophrenia is likely to be polygenic (International Schizophrenia Consortium, 2009), not attributable to rare variants, GWAS studies have also discovered rare structural variations in the genome associated with a high risk for schizophrenia that may be subject to negative selection (International Schizophrenia Consortium, 2008; Walsh et al. 2008). Since intermediate phenotypes have been quite successful in dissecting neural mechanisms contributing to neurocognitive and behavioural phenotypes in the 22q11 microdeletion (Gothelf et al. 2005) and in Williams Syndrome (Meyer-Lindenberg et al. 2006b), imaging genetics should be used to study brain mechanisms underlying these more common copy number variants. Further, if evidence for multiple rare variants should surface, for example, through a deep sequencing approach, an intermediate phenotypes approach could still be applicable if these rare variants can be appropriately grouped, for example, by gene or region.

But biological heterogeneity is not the only important issue for understanding and treating mental illness that is accessible to an intermediate phenotypes strategy. Interactions with the environment are potentially major factors in the risk architecture for illnesses such as schizophrenia (van Os & Sham, 2003). The delineation of neural mechanisms underlying gene–environment interactions in risk for psychiatric disorders using intermediate phenotypes is in fact a topic of consortia, such as the IMAGEN (Wong & Schumann, 2008) and EU-GEI (van Os et al. 2008) initiatives in Europe.

Finally, as mentioned at the beginning, intermediate phenotypes, through an account of the biological cascades through which genetic risk becomes manifest, hold considerable promise for drug discovery. In the available literature, intermediate phenotypes strategies towards personalized treatment strategies based on genetics (Apud et al. 2007), promising novel drug targets (Huffaker et al. 2009) and imaging genetics data (Tan et al. 2007), underpinning mechanistically new drugs in later phase development (Patil et al. 2007) can already be found. Again, consortia are forming that hope to mine intermediate phenotypes for much-needed advances in the treatment of severe psychiatric illness such as NEWMEDS (Hughes, 2009).

For all of these approaches, even a complete list of definitive risk variants for psychiatric disorders would just mark the beginning of the final chapter. Only through translational strategies that incorporate intermediate phenotypes across levels of biological description can this genetic information be turned into an engine of discovery for pathophysiology, diagnosis and, perhaps most importantly, treatment.

Acknowledgments

This work was supported by grants from DFG, BMBF and NARSAD to A.M.L.

Declaration of Interest

None.

References


