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GUEST EDITORIAL

Intermediate phenotypes in schizophrenia genetics redux: is it a no brainer?

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Genes do not encode for psychopathology; nor for hallucinations, delusions, thought disorganization; panic attacks or sadness. To the extent that genes are associated with such characteristics, for example the symptom constellation that we call schizophrenia, they do so by affecting the development and function of brain cells and neural systems that mediate the expression of such behavioral and perceptual phenomena. A basic tenet of behavioral neuroscience is that abnormal behavior reflects abnormal brain function. However, the obverse that abnormal brain function necessitates abnormal behavior is not obligatory, because compensation can be made with other brain systems and functions. Brain cysts, cortical dysplasias and vascular lesions are routinely found in human brain at autopsy without obvious clinical correlations. A logical extension of this to the field of behavioral genetics is that changes in brain function related to genetic variation may or may not have behavioral readouts. These points are incontrovertible, and they are the foundations of the interest in intermediate brain phenotypes in psychiatric/behavioral genetics just as they are in other fields of medicine.

Patients with schizophrenia have changes in cognition, in brain function and in brain structure that are found more frequently in their unaffected siblings, including unaffected monozygotic co-twins, than in control subjects, suggesting that these various deviations represent biological expressions of increased genetic risk. That these biological changes are found in at-risk individuals who do not manifest a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis suggests that they are susceptibility-related phenotypes, intermediate between the cellular effects of susceptibility genes and the manifest psychopathology.[1–6] As obvious as this may seem, dissenting voices have been raised arguing that the evidence for stronger gene effects at the intermediate phenotype level is spurious or worse, even illogical.[7,8] A number of challenges have been made to the value of intermediate phenotype studies in psychiatric genetics. Some of the key points include: (1) that the phenotypes have not been shown to be heritable, (2) that they are complex and not necessarily any simpler genetically than schizophrenia itself, (3) that gene effects are not more penetrable or observable at the level of these putative intermediate phenotypes than at the level of a DSM-IV clinical diagnosis and (4) that putative intermediate phenotypes related to schizophrenia have not been shown to exist before the typical clinical illness appears in affected individuals, which would be expected in a true intermediate phenotype involved in disease genetic mechanisms. We believe that these voices have not given due consideration to a rapidly growing body of data that argues against each of these points. We will address these data in the following discussion.

Are so-called intermediate phenotypes heritable?

Many differences between people are not because of genes. For any difference to reflect genetic variation, the phenotype should represent a heritable trait. Clearly, classic tests of heritability (that is, comparisons of deficits in related individuals at varying levels of genetic risk, optimally between monozygotic and dizygotic twin pairs) have not been done for some of the so-called schizophrenia-associated intermediate phenotypes, but for others, the evidence is good. Cognitive functions related to aspects of memory, speed of processing, attention and IQ are highly heritable in the human species (with evidence from twin studies),[3,6,9] though measures on every cognitive test do not show strong heritability results, in some instances more likely because of the psychometrics of the test than the cognition involved.[10] Several cognitive abnormalities associated with schizophrenia are found with increased prevalence in healthy siblings of patients with schizophrenia, including healthy monozygotic co-twins, and the evidence from twin studies suggests that the cognitive deficits related to IQ, working memory and attention are heritable traits.[3,6] Functional neuroimaging of prefrontal cortical changes during working memory and cognitive control also have been observed to be familial and probably heritable.[2,11,12] Healthy siblings of patients with schizophrenia show similar P300 evoked potential abnormalities more often than found in appropriate control subjects, suggesting that the P300 abnormality associated with schizophrenia also is a heritable trait. Studies in twin samples confirm that P300 amplitude is a highly heritable human characteristic.[13] In terms of brain structure, brain volume is highly heritable,[14] and neocortical gray matter volumes are heritable and correlate with multiple cognitive domains;[15] hippocampal, neocortical and cortical volume deficits have also been observed to be related to genetic risk for

schizophrenia in family-based studies.[5,16–18] Thus, for many biological changes related to brain function and structure that are associated with schizophrenia and with increased genetic risk for schizophrenia, the evidence for their heritability is strong.

Do genetic associations show greater penetrance at the level of intermediate phenotypes?

The litmus test of whether gene effects show greater penetrance at the level of an intermediate phenotype than at the level of a more complex clinical disorder is that genetic association should be seen with the intermediate phenotype in individuals who do not have the clinical diagnosis. As noted in the prior section, there is strong evidence that this is the case with many schizophrenia-associated intermediate phenotypes. In a family study of the association of a promising schizophrenia susceptibility gene, *DISC1*, with P300 waveforms, almost every subject with a structural abnormality in the *DISC1* gene had an abnormal P300 response, even if they had no psychiatric diagnosis.[19] Individuals in the same family lacking the *DISC1* abnormality also lacked a P300 abnormality. This is compelling confirmation of the basic principles noted above that a gene linked with the behavioral abnormalities that we call schizophrenia is more strongly associated with a measure of brain function related to schizophrenia and genetic risk for schizophrenia even in the absence of the clinical readout. The principle of greater penetrance at the level of an intermediate phenotype predicts that schizophrenia susceptibility genes should map onto brain measures of abnormal structure and function also associated with schizophrenia even in normal subjects who carry risk alleles in those genes, and this has been confirmed in a number of studies with a number of genes.[20–22] Clearly, as the individuals in these studies showing genetic effects are non-cases, there is no penetrance at the level of illness, only at the level of the intermediate phenotype. Analogous results are routinely found in other areas of medicine where genetic effects that are relatively weakly associated with common complex medical conditions are more strongly associated with a biological measure closer to the likely biology of the gene even in clinically well samples (for example, APOE4 and brain phenotypes[23] and the type II diabetes gene FTO with body mass index[24]).

However, it should be noted that because the detailed characterization of intermediate phenotypes related to schizophrenia is in its early stages, issues of specificity and reliability need to be considered carefully. In interpreting measurements of prefrontal function, for example, task paradigms may differ across laboratories and may sample different component cognitive and neural processes. Different versions of the N-back task exist, some taxing greater updating and executive processes than others, the former having much greater power to capture related dopaminergic gene effects.[25] Thus, if one were to lump different versions of the N-back task into a meta-analysis to examine the effect size of a dopamine-related gene association as if all versions of this task were psychometrically and neurobiologically identical, this would be misdirected and potentially misleading. The same can be said for attentional tasks and for various imaging and electrophysiological phenotypes. Some authors looking for gene effects on cognition have combined measures from healthy individuals and schizophrenia patients, disregarding the possibility that gene effects on cognition or physiology in the latter group would be confounded by medications, by smoking and/or other chronic disease-associated effects.[8] Thus, there is potential for generating apparent inconsistencies and confusion about the reproducibility of intermediate phenotype findings by lumping independent data sets without careful consideration of the cognitive components sampled by a particular task and the underlying biology. Nevertheless, the evidence for greater penetrance of putative schizophrenia susceptibility genes at the level of intermediate phenotypes based on brain structure and information processing is strong for a number of genes tested so far.

Are intermediate phenotypes less genetically complex?

While intermediate phenotypes should by definition be simpler genetically than the multi-faceted phenomenon that we call schizophrenia, most intermediate phenotypes related to cognition and brain physiology will still be expectedly polygenic and heterogeneous. Examples of intermediate phenotypes from other fields of medicine, such as body mass index and type II diabetes,[24] or periodic limb movements and restless legs syndrome,[26] or macular degeneration and visual loss[27] support the contention that simpler phenotypes do exist, even while they are still multifactorial traits that are also more strongly associated with genes that ultimately impact the more complex disorder. Does this mean as some suggest that legitimate intermediate phenotypes have not been found, and are not likely ever to be found?[8]

The various studies summarized above argue that this conclusion overlooks an abundance of existing data. Part of this more extreme argument is based on the observation that quantitative protein expression of numerous individual genes in animal models, presumably under direct genetic control, are nevertheless each associated with no fewer number of quantitative trait loci and are apparently no less genetically complex.[8] The finding that a majority of individual genes are expressed under complex control by layers of interacting networks is, however, not surprising. An emergent property of biological networks is their 'small worldness' and organization into subsystems around a smaller number of highly connected 'hubs' extensively influencing a larger number of peripheral node proteins/genes.[28] Measurements of phenotypes encompassing some composite measure of these system characteristics, as might be expected in

legitimate intermediate phenotypes, should therefore be more closely associated with the 'hub' gene effects. The individual expression of most peripheral proteins would not be likely to describe these emergent system characteristics to a large extent. On the other hand, a substantial percentage of human proteins have expression levels that are highly heritable, strongly map onto genetic variation also implicated in complex diseases, and therefore have characteristics of intermediate phenotypes with the potential to link susceptibility alleles and the genetic regulation of key disease-related proteins within physiological networks.[29,30] Ultimately, the answer to the question of the relative genetic complexity of promising intermediate phenotypes awaits further study. The current evidence showing clear effects of genes associated with schizophrenia at the level of heritable phenotypes based on brain structure and function in the absence of a clinical diagnosis is consistent with the prediction that these phenotypes should be less complex.

Are intermediate phenotypes intermediate in terms of disease mechanisms?

The term 'intermediate phenotype' is used here to refer explicitly to core pathophysiologic phenomena that bridge the gap between genetic variation and the biologic systems underlying the behavioral disturbance. We would submit that the more popular term, endophenotype, is a misnomer for cognitive deficits and other neural system phenotypes related to schizophrenia, as none of these are hidden or occult, any more than is macular degeneration with respect to visual loss or body mass index with respect to diabetes, and the term endophenotype does not explicitly imply an intermediate stage in a pathogenic mechanism. The effects of genes on neural systems are much closer to the biology of those genes than, behavior; indeed, it could be argued that certain intermediate phenotypes are more likely the phenotypes of primary interest related to schizophrenia susceptibility genes than are the diagnostic symptoms.

The validity of the intermediate phenotype concept has been further challenged by the claim that for these phenotypes to be truly intermediate, they should exist before the emergence of the diagnostic phenotype.[31] This challenge appears to have been met by abundant research evidence that is remarkably consistent in confirming that cognitive deficits exist before the emergence of the clinical syndrome.[32,33] Neural correlates of these abnormalities as measured by functional magnetic resonance imaging (MRI) of executive cognition are seen in high-risk and first-episode schizophrenia patients,[12,34,35] with accompanying changes in the neocortex on structural MRI before the onset of psychosis.[36,37]

Since specific cognitive abnormalities and regional neurophysiology and morphology are critically associated with the core features of psychosis and its genetics, and are manifest before the emergence of the diagnostic symptoms, these links should facilitate the elucidation of neural mechanisms. This is a principal value of studying intermediate brain phenotypes and their genetic associations, that is, the characterization in brain of neural system mechanisms of the clinical genetic associations.[22] An illustrative example is prefrontal cortically mediated working memory, a core feature of schizophrenia and increased genetic risk for schizophrenia. Working memory has been studied very extensively in animal and computational models, and is dependent on cortical dopamine modulation of glutamatergic and GABAergic systems that maintain signal-to-noise in reverberatory cortical circuits.[38,39] These neurotransmitter systems and related candidate genes have also been implicated in schizophrenia,[40] but the mechanism by which genetic susceptibility impacts human brain function has been obscure. Neuroimaging genetics is a promising research strategy for elucidating such mechanisms,[22] and the effect of genetic variation on these component brain systems, including epistatic interactions of genes regulating various neurotransmitter systems,[41,42] has begun to translate genetic risk into systems neuroscience.

The intermediate phenotype strategy is a dynamic landscape, with target phenotypes evolving as novel insights into basic neural functions emerge. For example, building on the basic and computational modeling literature about dopaminergic function in prefrontal–striatal networks,[43] a recent cognitive imaging study of working memory suggests that a larger share of the dopamine-related gene effects involves the working memory subprocess engaging executive processing across time, rather than simple retrieval of already stabilized information. Thus, certain working memory tests taxing these executive operations will be more adept at capturing genetic variation related to the dopaminergic effects in dissociable prefrontal–parietal-striatal circuits.[25] In an analogous cognitive model, three dopamine system genes, DARPP-32, DRD2 and COMT, have been shown to impact differentially on specific processes in prefrontal-striatally mediated reinforcement learning from positive and negative outcomes.[44] Further work is needed to increase our understanding of these various measures and to elucidate a finer-grained understanding of the genetic modulation of brain processing, which will have the potential to converge important trends in genetic, molecular, cognitive and disease models of the human brain. In the meantime, based on the abundant evidence that brain-based intermediate phenotypes are expressed in advance of the emergence of the diagnostic symptoms and elucidate neural mechanisms of genes in brain associated with schizophrenia, it is a strong argument that these phenotypes are intermediate between DNA sequence and behavior.

A comment on controlling for statistical error

One of the important caveats in studies of genetic association with intermediate phenotypes is that

many phenotypes can be tested against many genetic variations. Setting the statistical criteria at low thresholds and taking any single positive finding to infer whole-sale acceptance of the hypothesized genetic disease mechanism is potentially disastrous and could lead to highly misleading false positives, including false-positive replications.[45] This is not unique to behavioral genetics but is germane to any multi-dimensional data analysis. Having clear quantitative ideas regarding the potential for such error is critical. It has recently been shown that standard methods used to measure putative intermediate phenotypes based on functional MRI and structural MRI are strongly resistant to false positives, with an overall study false-positive rate significantly less than 5% per genetic variant tested despite the apparent large number of brain voxels examined.[46]

Statistical correction for multiple testing is a strategy for limiting Type I error, but it is not a singular, universal routine. A hierarchical strategy that deductively parses associations at the level of brain, starting with cognitive phenotypes that sample specific cognitive operations related to schizophrenia risk and then exploring the specific neural processing behind those cognitive processes with neuroimaging, is a deductive, hypothesis-driven approach based on the scientific method. With such an approach, it is reasonable to interpret imaging genetics tests in the context of earlier findings of the same genetic variation and in terms of their convergence or non-convergence upon a hypothesized brain mechanism. It is illustrative to consider an example of this approach. We can re-examine using simulations, the false-positive rate of the strategy used previously in a multi-staged study of GRM3.[47] For this purpose, we can simulate 16 tag SNPs in GRM3 in 1 000 000 presumed healthy individuals based on the CEU Hapmap population.[48] We can then examine the rate at which each of the 16 tag SNPs could falsely meet all of the following 3 criteria in 1000 samples each with 1000 subjects: (1) a positive study in the simulated case–control genetic association data where disease labels are randomly assigned to half the subjects; (2) at least 1 associated cognitive factor out of 7 randomly generated independent 'cognitive' intermediate phenotypes[49] in the 500 nested normal controls and (3) a positive study using a randomly generated imaging phenotype in 70–80 controls. By definition, any positive finding would be false. Setting a threshold of $P<0.05$ for each test stage, the simulated false-positive rate of the entire strategy whereby the 3 converging criteria were met in the nested data set is <0.001 per genetic variant, or ~ 0.012 for falsely implicating one or more of the 16 SNPs in this gene. This is a low rate of false discovery and argues that GRM3, whatever its *P*-value in a simple test of clinical association, is a part of the risk biology of at least the intermediate phenotypes linked to schizophrenia and likely of some cases of schizophrenia. In the actual study,[47] the SNP showing the strongest clinical association was also associated with several cognitive measures and several imaging phenotypes related to the known biology of the gene, including epistasis with dopaminergic modulation.[42]

Further research will be needed to refine the statistical parameters by which combinations of disease-association and intermediate phenotype tests could be extended to more genes. But it would appear that multi-staged nested strategies can be designed such that combinations of hypothesis-driven tests of sufficient power, when integrated, will give reasonably low overall false-positive call rates, while offering insights into human disease mechanisms. In formulating these strategies, it is also worth considering what 'costs' the field might find acceptable in terms of being occasionally 'wrong'. This has been conceptualized in the decision-making literature as being a function of the projected benefit/cost ratio.[50] Given the present bottleneck in translating basic findings to potential disease mechanisms in humans, we argue that approaches in this endeavor might be viewed as having relatively high benefit/cost metrics. Hence, at least, while the field of human brain intermediate phenotypes and the pathophysiology of schizophrenia are at their initial exploratory stages, predictive probabilities and expectations need to be moderated accordingly.

Challenges moving forward: genetics, biology and combinatorics

An apparent 'catch-22' arises if we accept schizophrenia as a valid phenotypic target, as an association with diagnosis would still be required before a gene and its putative mechanism via the intermediate phenotype route can be inferred to be on a pathway to disease (rather than an epiphenomenon). Consequently, one perspective has been that genetic association with genome-wide significance should first be obtained in large-scale data-driven studies before embarking on the search for mechanistic understanding, the latter perhaps with the aid of intermediate phenotypes.[31] This is a debatable recommendation. Just because the *P*-values are small does not mean that the clinical or biological significance is large. As already demonstrated in genome-wide association studies of common medical diseases with much more definable biology and clinical phenotypes (for example, diabetes, stroke, myocardial infarction, rheumatoid arthritis, multiple sclerosis), associations that survive statistical correction from these biologically agnostic studies, if replicated (which has proved surprisingly inconsistent[51]), turn out to explain only a tiny degree of risk in the population. In studies of type II diabetes, the total risk now explained by the replicated genes that have emerged from multiple genome-wide association studies is less than 5%.[52] In studies of multiple sclerosis, it is less than 1%. This is because the statistical thresholds are so high that only common factors showing little risk variation across large samples of ill individuals can be found. These are

not likely to be very predictive of individual risk status and are almost by definition general risk factors that show little heterogeneity across samples (genetic and environmental). It may be analogous to discovering an association of owning a driver's license with risk for car accidents. The population attributable risk of genes discovered with this approach is large because the risk factor is common, but the individual relative risk is typically marginal. The heterogeneity of schizophrenia, both phenotypically and biologically, makes it unknown whether even very large genetic studies on disease association will yield any highly significant replicable gene findings. We think that genetic heterogeneity leads to complex, overlapping phenotypic syndromes and not to a monolithic disease. Indeed, it could be argued that the goal and chances of finding any universal mechanism or universal intermediate phenotype runs counter to most of the evidence so far. It should also serve the field to be reminded that seemingly incontrovertible statistical genetic association *per se*, that is, a statistical *P*-value of some arbitrary level, does not guarantee biologic importance or even identify what the biologic factor (or gene) is.[53] Statistical association only indicates a relationship between a genetic variation and a phenotype. It does not identify a mechanism for this association or even demonstrate conclusively that the gene containing, or even closest to the polymorphism is responsible.

In our view, it is equally plausible that concurrent progress can be made with a series of converging results from candidate gene studies informing large data-driven studies, as well as vice versa. Genes that are positive in many prior smaller samples data sets (for example, DTNBP1, NRG1, ErbB4, COMT, AKT1, DISC1 and so on) have prior probability of showing association and should be treated differently from polymorphisms with no prior probability in large-scale genotyping analyses. An example of this is a susceptibility gene for type II diabetes, PPAR-γ, originally identified in small candidate gene studies,[54] and then explicitly searched for and replicated in a large genome-wide association study.[55] It is probable that an increasingly large number of subtle genetic associations will be found moving forward, many of which will be shy of strict genome-wide significance, joining the ranks of many of the present findings from linkage and candidate gene studies. We would suggest that genetic findings of small effect will only be understood as risk factors for schizophrenia by putting them in the context of brain mechanisms. Ultimately, it is critical to demonstrate that variation in a gene impacts on the biology of the human brain such that it converges on the biology of the illness.[56] If individual genes related to mental illness turn out to explain across heterogeneous populations only tiny percentages of overall liability no matter how large the sample, it will be essential to develop alternative strategies to prioritize further investigation of candidates genes. We predict that an iterative strategy based on hierarchical association with biological phenotypes will provide the necessary information.

Conclusion

In this editorial, we suggest that as originally conceived, intermediate phenotypes potentially enhance the power with which genetic variation can be linked to complex disease mechanisms.[57] An increasing number of cognitive, neurophysiological and neuroimaging phenotypes have emerged to evidence heritability and association with increased genetic risk for schizophrenia, showing increased genetic penetrance even in individuals who do not have the clinical diagnosis, and are compelling candidate neurodevelopmental disease processes predating the overt onset of the clinical disorder. Moving forward, we envisage that the strategy to characterize the genetic associations of these phenotypes will provide an important platform on which hypothesized biologic disease processes developed in basic scientific models can be examined in human subjects. This is a challenging enterprise, more so in an ill-defined behavioral disorder like schizophrenia. However, the endeavor potentially satisfies critical unmet needs by integrating basic neurobiology with specific human phenotypes that are potentially tractable genetically. Of note, even while we anticipate the fruits of modern psychiatric genetics in terms of future medicines to be far off, it is encouraging that there has been some convergence between candidate gene, cognitive and intermediate phenotype findings in GRM3,[47] and independent early findings of efficacy in a new treatment for schizophrenia targeting this same receptor.[58] This bodes well for the possibility that integrated genetic, cognitive and brain imaging strategies of intermediate phenotypes could be further developed to potentially enhance human models of pharmacological efficacy prediction so needed in the treatment of psychosis.

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