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The best of times, the worst of times for psychiatric disease

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Abstract

As long-awaited advances in psychiatric genetics begin to materialize in force, promising to steer us safely to the best of times in psychiatric disease research, many pharmaceutical companies pull away from the challenge of drug development, threatening to bring us to the worst of times for the field. There is a real danger of missed opportunities and a sense of urgency for defining a clear path forward.

At a US National Institutes of Health–funded meeting in late May 2011, titled “Genetic and Neural Complexity in Psychiatry,” a group of geneticists and neuroscientists considered how best to proceed in building translational bridges between human genetics, animal models and neural circuits. While acknowledging the many complex issues, the group agreed on a number of recommendations: research effort and funding should be directed toward identification of rare, highly penetrant mutations and the generation of a few (possibly a dozen) animal and cellular models anchored in unequivocal highly penetrant mutations, with the goal of using existing and newly emerging powerful neuroscience techniques to identify convergent synaptic processes or circuits. Here we briefly summarize our rationale for these proposals and outline our recommendations for research in this area.

Although it was accepted that much of the phenomenology of psychiatric disease is attributable either to disordered circuitry or to disordered activity in brain circuitry, incomplete understanding of disease pathophysiology means that we need to reappraise or even abandon many of the current theories of psychiatric disease etiology involving dysregulated neurotransmitter systems and derivatives and instead develop more sophisticated hypotheses by engaging in unbiased circuit-centered approaches. The best way

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to determine convergent pathophysiological mechanisms lies in starting with genetic discoveries in humans because they discard hypotheses about mechanism and test gene function without prejudice. Debate about the most appropriate genetic strategy has been polarized between advocates of genome-wide association studies (GWASs) of common variants and advocates of rare variant discovery approaches. However, for the downstream experiments that will form the basis of subsequent functional and translational analyses, causative mutations are needed rather than just associated variants. Thus, regardless of the starting point, genetic strategies converge, as a GWAS hit can only be turned into a confirmed gene by finding an excess of rare deleterious mutations in it, which means eventually searching for rare variants. With next-generation sequencing now possible on a population scale, DNA technology is sufficiently mature to find structural variants and coding mutations. Given the unanticipated extent of background genetic variation, however, attention should also be paid to the samples that are being used. Family-based samples in which the *de novo* nature of a mutation or its co-segregation with disease can be unequivocally determined offer a safe haven, compared with case/control samples, from hidden ethnic stratification effects and immense neutral background variation.

The path taken to arrive at that point will likely vary depending on the disease being studied: in schizophrenia and autism there is clear evidence that a direct search for rare variants would be fruitful, either for structural variants or rare deleterious coding mutations. The genetic architecture of other psychiatric disorders, such as major depression and anxiety disorders, may be different, but, in the absence of an adequately powered GWAS or the genetic characterization of appropriate family samples, this question remains unanswered. The discovery of a core of excellent gene targets hit by recurrent mutations whose disruption unequivocally cause psychiatric disorder would transform research, providing a substrate for animal- and cell-based experiments. Rare variant discovery should be a first priority. In particular, given the unanticipated extent of innocuous variation, observation of recurrent gene targets of rare mutations (genes hit at least twice by different mutations) should be a primary goal. Focusing on exomes (that represent 1–2% of the genome) should be sufficient to uncover a great number of relevant targets in a costefficient and interpretable manner.

New genetic findings may lead to the redefinition of diagnostic categories, which might have specific therapeutic implications. A clear priority is to understand how genetic heterogeneity relates to variation in clinical features. On the one hand, there is evidence that variants in the same gene predispose to different disorders; on the other hand, evidence suggests that variants in many different genes predispose to similar disorders. It is essential to know the extent to which categorizing patients by the underlying genetic cause of their disease explains variability in clinical presentation. In this respect, the genetic investigation of endo-phenotypes (phenotypes that are believed to reflect disease processes, such as alteration in brain structure and function) should be secondary to the core goal of characterizing illness in genetically defined patients. A commonly used contrary argument is that endo-phenotypes more directly index biology than behavioral phenotypes and that being closer to the biological root means individual genetic effects will be larger, requiring smaller sample sizes for their detection. However, given that our aim is to understand disease etiology, we need to start with the disease itself, rather than phenotypes situated an unknown

distance from the cognate disorder that may be equally as complex at a genetic level as the disorders to which they are related.

The generation of a core of a dozen animal models for each disease entity anchored on genuine recurrent mutations associated with well-defined narrow clinical presentations will greatly facilitate circuit-based analysis of psychiatric disease and must be a high priority. A major goal of this research will be to reconcile the unexpected genetic heterogeneity of psychiatric disorders with their more homogeneous clinical presentation by illuminating affected synaptic assemblies and processes and the diverse ways in which they can be compromised. Elucidating the causal pathway from mutation to behavioral disorder will be challenging, and multi-level analysis will be necessary for testing causal connections among findings at various hierarchical levels of affected networks. Along these lines, we are optimistic that sophisticated circuit perturbation approaches (such as optogenetics and cell type–specific expression of non-native ligand-gated ion channels) designed to recapitulate specific circuit disruptions observed in mutant models will begin to elucidate the pathophysiological mechanisms underlying prominent psychiatric symptoms in a manner that can be translated into human brain imaging studies with genetically homogeneous patient populations.

Along the same lines, progress in reprogramming skin cells from patients into functional neurons affords us the opportunity to develop cellular disease models. Given the degree of genetic complexity, this approach will be far more productive and reliable if it focuses on patients carrying recurrent, highly penetrant mutations rather than being agnostic to the underlying genotype. Only this class of patient cells will allow genetic rescue of the mutant phenotype, a critical control. Reprogramming focused on recurrent mutations will also allow comparison with results from corresponding animal models. Although such cellular models have the potential to faithfully capture cell-autonomous disease-related developmental and synaptic deficits, caution is warranted until several technical challenges are overcome. One pressing challenge is the need to control for intrinsic variations among induced pluripotent stem cell (iPSC) lines; results based on a single line may not be meaningful. It was suggested that at least three iPSC lines should be analyzed and that genetic rescue should always be a goal. Another challenge stems from the limited repertoire of differentiated neurons, which may not include disease-relevant cellular populations.

Our overarching goal is to develop new and effective treatments and to reverse the retreat from psychiatric disease research that has occurred in pharmaceutical companies. In the long run, the biological reconstruction of psychiatric diagnoses will advance treatment and substantially reduce investment risk by concentrating drug development efforts either on smaller, biologically stratified subsets of patients guided by genetic findings, or on specific circuits and synaptic processes. In the short run, repurposing or repositioning existing drugs with well-known safety profiles by taking advantage of the increasing number of valid genetic animal and cellular models may be another prospect for clinical studies and pharmaceutical partnerships, while leveraging the many investments that the US National Institutes of Health has already made or is making toward this goal. However, investment in high-quality basic science is essential to make much-needed progress and build translational

bridges from mechanism to disease on the clinically important problems of psychiatric disease.

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