

# Psychotic Disorders and the Neurodevelopmental Continuum

Michael J. Owen

## Abstract

This chapter considers a related group of conditions: adult psychiatric disorders such as schizophrenia and bipolar disorder, which are believed to have their origins in disturbances of neurodevelopment, and childhood neurodevelopmental disorders, particularly autism spectrum disorder and intellectual disability. The primary focus is on the challenges faced in trying to understand etiology and pathogenesis as a prelude to developing more effective treatments.

Recent findings, particularly genetic studies that indicate extensive pleiotropy, reinforce the view that current categorical diagnostic systems do not map onto the underlying biology of psychiatric disorders. Unless these findings are integrated into research, understanding etiology and pathogenesis will most likely be impeded. A simple model is presented that integrates current knowledge. It hypothesizes that severe mental illnesses can be conceived as occupying a gradient with the syndromes ordered by decreasing relative contribution of neurodevelopmental impairment.

Emerging evidence from genetic studies indicates a convergence onto specific areas of synaptic biology, but the genetic architecture of psychiatric disorders is undeniably highly complex. This complexity poses both cultural and technical challenges to efforts to translate these findings into new mechanistic insights. In particular, networks rather than individual genes and proteins need to be studied, and experimental systems in which multiple variables can be manipulated and multiple endpoints studied need to be developed. The complexity and mutability of psychiatric phenotypes, and the shortcomings of current diagnostic criteria, pose additional challenges for clinical neuroscience, and require new ways of stratifying patients in neurobiologically meaningful ways, such as those specified by the Research Domain Criteria (RDoC) project. In both basic and clinical neurosciences, an increased focus must be allocated to large-scale experimentation, collaboration, statistical robustness, and reproducibility.

## **Introduction**

In this chapter, focus is on the so-called “functional psychoses” (schizophrenia and bipolar disorder) and their relationship with “neurodevelopmental” disorders that occur in childhood, particularly autism spectrum disorder (ASD) and intellectual disability (ID). I will discuss the impact that recent research, particular genetics, has had on our conceptions of psychiatric diagnosis and classification, and the emerging implications that genetic and other findings have for future research on etiology and pathogenesis. A Gordian knot impedes progress in understanding psychiatric disorders: the complexity and inaccessibility of the brain has made it difficult to understand basic disease mechanisms, and this has meant that diagnoses cannot be validated in terms of etiology and pathogenesis. The lack of valid diagnostic criteria has, in turn, impeded progress in research on mechanisms. How we unpick this knot is the central challenge currently facing psychiatric research.

## **Current Approaches to Psychiatric Diagnosis**

In the absence of a solid understanding of pathophysiology, psychiatric diagnoses are descriptive and largely syndromic in nature. Most Western clinicians use either the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) or the International Classification of Diseases (ICD). These operationalized, largely descriptive classifications were developed in the final third of the twentieth century to provide a reliable way of assigning a patient to a diagnostic category that represents one of the clinical syndromes recognized by clinicians. They were never intended, however, to define disease entities, and their uncertain validity was explicitly acknowledged. While the reliability of these systems has had many benefits on research and practice, the diagnostic categories have unfortunately become reified in the minds of many practitioners and researchers (Hyman 2010); they have been treated as if they are pathologically meaningful and relatively circumscribed disease entities rather than provisional and temporary clinical syndromes as originally intended.

This categorical and syndromic approach to diagnosis has been creaking under the weight of discrepant findings for some years (Craddock and Owen 2005, 2010). Substantial heterogeneity within diagnostic categories makes it possible for two patients with the same diagnosis to have few, if any, symptoms in common. It has been difficult to demonstrate clear boundaries (points of rarity) between diagnostic categories as well as between illness and wellness. In addition, patients often present with the features of more than one diagnostic category.

This has been addressed in two ways. First, in some instances interforms are recognized, the most prominent, and notorious, being schizoaffective disorder (Malaspina et al. 2013; Cardno and Owen 2014). This diagnosis, which

is frequently used in clinical practice, reflects the fact that features of schizophrenia and severe mood disorder often occur in the same individual both concurrently or separately at different time points over the life span. Illnesses of this sort have posed challenges to classification systems over many years (Malaspina et al. 2013), and their relationship to the prototypical disorders continues to be debated (Cardno and Owen 2014). The second approach is to recognize so-called diagnostic “comorbidity”; that is, a patient can be diagnosed with more than one disorder. This may be clinically useful but it is often obscured in research through the use of diagnostic hierarchies or exclusions (Owen 2011).

Diagnostic categories in current use by psychiatry are extremely fuzzy, both in respect to other disorders as well as to wellness. Moreover, they are not underpinned by biological validity, and this no doubt explains why concerted efforts to develop diagnostic biomarkers have failed (Lawrie et al. 2011; Owen 2011). This clearly suggests that exclusive reliance on current diagnostic categories is likely to impede research into causes and mechanisms. These concerns have become impossible to ignore in the light of recent genetic findings.

### **Impact of Genetics on Classification**

Genetics, in the form of family history and other genetic epidemiological data, has traditionally been regarded as a cornerstone of psychiatric nosology. It constitutes one of the three criteria proposed by Robins and Guze (1970)—the other two being clinical features and outcome—to justify nosological categories in the absence of a solid understanding of pathogenesis. Thus, the robust identification of genetic risk at the level of DNA variation has been eagerly sought for the insights it was expected to provide into the basic biological architecture of, and relationships between, psychiatric phenotypes, as well as for its contributions to understanding disease mechanisms.

Genetic epidemiology and population genetics suggest that a spectrum of allelic risk is likely to underlie complex traits, such as schizophrenia and other common diseases (Wang et al. 2005; Craddock et al. 2007). We should expect contributions from alleles that are common in the population but whose effect sizes will tend to be small due to the effects of natural selection, as well as from rare alleles, some of which might have a large effect on disease risk pending their removal from the population by selection. Although much of the genetic risk for psychiatric disorders remains unexplained, empirical data now support this general framework in psychiatric disorders (Sullivan et al. 2012). Of crucial importance to the present discussion, the findings to date point to extensive pleiotropy with respect to diagnostic outcome, though some examples, described below, suggest a degree of specificity.

Evidence for quite an extensive overlap in genetic risk between psychiatric disorders has come from the study of both common and rare risk alleles. In

respect of common alleles, genome-wide association studies (GWAS) have found evidence for overlap at the level of individual genome-wide significant risk alleles (Green et al. 2010; O'Donovan et al. 2008; Williams et al. 2011), genes (Moskvina et al. 2009), and the *en masse* effects of multiple risk alleles (International Schizophrenia Consortium et al. 2009; Lee et al. 2012). A recent study (Cross-Disorder Group of the Psychiatric Genomics et al. 2013) found evidence for substantial sharing of the relatively common genetic risk variants that are tagged by the single nucleotide polymorphisms genotyped in GWAS between schizophrenia and bipolar disorder, bipolar disorder and major depressive disorder, schizophrenia and major depressive disorder, attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder, and, to a lesser extent, between schizophrenia and ASD.

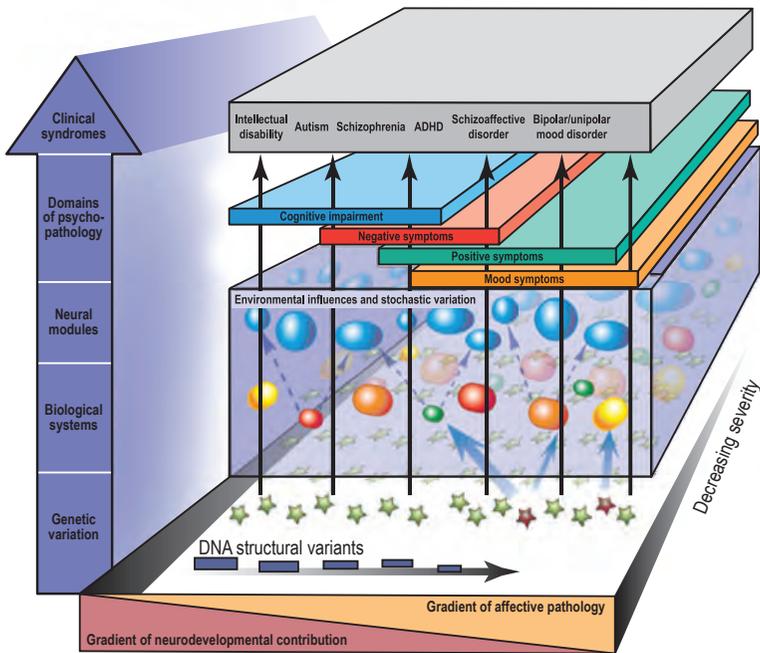
Perhaps more surprisingly, extensive pleiotropy has also been observed in the effects of rare risk alleles that individually confer much larger effects on risk than common alleles. A number of rare, but recurrent, chromosomal copy number variants (CNVs), which typically involve deletion or duplication of hundreds of thousands of bases of DNA sequence, have been found to confer risk of schizophrenia (Malhotra and Sebat 2012; Rees et al. 2014). These are also significantly associated with a range of childhood neurodevelopmental disorders: ASDs, ID, and ADHD as well as other phenotypes such as generalized epilepsy (Owen et al. 2011). Since pathogenic CNVs typically span multiple genes and are concentrated in a relatively small fraction of the genome, it is possible that this may not indicate cross-disorder effects at the level of specific genes. Although support for cross-disorder genetic effects emanates from family studies (Owen et al. 2011), the most compelling evidence comes from a recent large-scale study of small *de novo* mutations that affect one or a few nucleotides. Fromer et al. (2014) found evidence that genes with *de novo* mutations in schizophrenia overlapped those affected by *de novo* mutations in ASD and ID but not controls; loss-of-function (LoF) mutations were enriched even in the very small subset of genes ( $N = 7$ ) with *recurrent* LoF *de novos* in ASD or ID. These findings demonstrate shared etiological overlap between schizophrenia, ASD, and ID at the resolution not just of loci or even individual genes, but of mutations with similar functional (LoF) impacts.

The finding of genetic overlap between schizophrenia and bipolar disorder was hardly surprising, given the frequent difficulties adult psychiatrists have in clinically distinguishing between these disorders (Craddock and Owen 2005). However, the genetic overlap between schizophrenia and childhood neurodevelopmental disorders posed a greater challenge to nosological orthodoxy. Schizophrenia has long been considered to have its origins in neurodevelopment (Weinberger 1987; Murray and Lewis 1987; Owen et al. 2011) but has, in recent years, come to be considered distinct from the neurodevelopmental disorders, which tend to have their clinical presentation in childhood (Rutter et al. 2006). This was largely due to the fact that schizophrenia, unlike the childhood disorders, was seen as a relapsing and remitting illness in accord with the time

course of the psychotic symptoms that tend to result in presentation to clinical services. Many of the clinical features of schizophrenia are chronic, notably the negative and cognitive symptoms, and these often originate in childhood prior to the first psychotic break. There are, in fact, many similarities in phenotype between schizophrenia and the other neurodevelopmental syndromes (Owen et al. 2011). Importantly, all are associated with impairments of cognition. They also tend to be more common in males, and are frequently associated with varying degrees of developmental delay, neurological soft signs, and motor abnormalities. There is also substantial comorbidity among neurodevelopmental disorders, including schizophrenia (reviewed in Owen et al. 2011). As noted above, comorbidity is often obscured in research studies by the use of diagnostic hierarchies or exclusions, but it can also be concealed by developmental change in the predominant symptom type. Current service configurations also impose difficulties due to the administrative split between adult services and those directed toward the treatment of children and adolescents, as well as between psychiatric, ID, and, in the case of epilepsy, general medical services. These service splits have traditionally defined the purviews of researchers, with the result that much research in psychiatric and neurodevelopmental disorders has taken place in silos defined by the existing syndromic categories.

Support for shared neurodevelopmental etiology and pathogenesis across psychiatric disorders does not come solely from genetics. Obstetric complications and other factors (e.g., maternal infection, poor prenatal nutrition) associated with early cerebral insult have been consistently implicated as environmental risk factors for a range of neurodevelopmental disorders, including non-syndromal ID, ASD, ADHD, epilepsy as well as schizophrenia (Owen 2012a, b). The similarity between this range of outcomes and that seen in association with pathogenic CNVs is striking. In the 1950s, Pasamanick et al. (1956) proposed that a “continuum of reproductive causality” exists, consisting of brain damage incurred during pregnancy, or during or around birth, leading to a gradient of injury that extends from fetal and neonatal death through cerebral palsy, epilepsy, ID, and behavioral disorders, including schizophrenia. Given recent genetic findings, it seems reasonable to modify this concept to encompass a gradient of genetically *and* environmentally induced neurodevelopmental causality along which lie what we currently define as ID, epilepsy, ASD, ADHD, schizophrenia, and possibly the major affective disorders (Craddock and Owen 2010; Owen et al. 2011). This view recognizes the degree of etiological and symptomatic overlap between diagnostic groups as well as the lack of clear diagnostic boundaries. It also perceives the major clinical syndromes as reflecting, in part, the severity as well as the predominant pattern of abnormal brain development and the resulting functional abnormalities and modifying effects of other genetic and environmental factors (see Figure 3.1).

We have emphasized genetic findings that suggest common susceptibility across traditional diagnostic categories, implying that the underlying biology is not specific, at least at the level of current diagnoses. It is, however, important



**Figure 3.1** Hypothesized model of the complex relationship between biological variation and some major forms of psychopathology (adapted from (Craddock and Owen 2010)). One axis depicts the relative contribution of type of pathology, and another (orthogonal) relates to clinical severity. The following description refers to the pathology axis. Starting at the level of genetic variation (lowest tier in figure), DNA structural variation (blue rectangles) has been represented as contributing particularly to neurodevelopmental disorders and associated particularly with enduring cognitive and functional impairment. Single gene variants, of which there are many, are shown as stars. In general, even single base-pair changes in a gene may influence multiple biological systems because genes typically have multiple functions and produce proteins that interact with multiple other proteins. For simplicity, we have shown one example of a variant that influences two biological systems and another that influences only one system (reddish stars and light blue arrows). Variation in the relevant biological systems (colored solid figures) is influenced by genotype as well as by environmental exposures/experiences and random stochastic processes, both historically during development and currently, and this, in turn, influences the dynamic short-term state of the systems. The relevant biological systems influence the neural modules that comprise the key relevant functional elements of the brain (solid light blue figures). Typically, multiple biological systems influence each neural module. The (abnormal) functioning of the neural modules together influences the domains of psychopathology experienced and ultimately the clinical syndromes. Some important clinical syndromes are ordered along a single major axis with a gradient of decreasing proportional neurodevelopmental contribution to causation and reciprocal increasing gradient of proportion of episodic affective disturbance. The single axis is a simplifying device: there is substantial individual variation and it is not uncommon, for example, for individuals diagnosed with autism to experience substantial mood pathology. Other features of the model are described within the text.

to recognize that relatively nonspecific risk factors, which apply to a wide variety of cases, will be easier to identify than those associated with more specific outcomes. Both family and genomic studies provide evidence for risk alleles with differential effects on schizophrenia and bipolar disorder (Lichtenstein et al. 2009; Ruderfer et al. 2013) as well as for alleles that have a degree of specificity to more “refined” clinical phenotypes that do not necessarily relate well to traditional diagnostic categories (Craddock and Owen 2010). Another example comes from the mounting evidence that large, rare CNVs, which are more prevalent in schizophrenia, are actually underrepresented in bipolar disorder (Grozeva et al. 2010; Grozeva et al. 2013). Given that large CNVs have adverse consequences on brain development and cognition, these findings are consistent with the view that a diagnosis of bipolar disorder is unlikely to be made in the presence of cognitive and other sequelae of neurodevelopmental impairment, and that what we refer to as schizophrenia has a stronger neurodevelopmental component than bipolar disorder.

### **A Simple Model**

A simple conception that integrates recent findings is that severe mental illnesses occupy a gradient with the syndromes, ordered by decreasing relative contribution of neurodevelopmental impairment as follows: ID, ASD, schizophrenia, ADHD, schizoaffective disorder, bipolar disorder (Craddock and Owen 2010). Elaborating on this view (Figure 3.1), the key variables are the particular constellation (i.e., number and nature) of disrupted neural circuits, which determine the type of syndrome that results (mental retardation, autism, or schizophrenia, etc.), and the severity (degree of disruption to individual circuits) of the syndrome (severity of ID, severity of ASD, severity of schizophrenia spectrum disorder, etc.). Of course this is a gross oversimplification. The precise nature and timing of critical events also plays a role as well as the modifying effects of genetic and environmental influences on factors such as the brain’s capacity to buffer the effects of early damage, personality, and propensity to affective disturbances. Key features of the model can be described as follows:

- Dimensions or continua are preferred over categories to conceptualize the major clinical syndromes.
- There is broad organization along a major axis according to a gradient of increasing relative neurodevelopmental contribution to illness in one direction and increasing relative episodic affective contribution in the opposite direction, with syndromic severity represented orthogonally.
- Multiple domains or dimensions of psychopathology contribute to the major clinical syndromes in varying proportions, and these may relate more closely to dysfunctional brain systems than categorical diagnoses.

- States of relevant brain systems depend crucially on environmental influences and stochastic variation (both developmentally and dynamically over the short term).
- Brain systems are complex, interdependent, and modular in nature; modules are functionally discernible, not necessarily temporally or spatially stable subunits that are interconnected in complex, often multilayered networks of neuronal circuits.
- One-to-one relationships do not exist. The concept of “a gene for schizophrenia” or even “a gene for auditory hallucinations” is not plausible (Kendler 2006). Instead, sets of many one-to-one or one-to-many relationships are involved.

This simple model proposes an order for biological similarity of some of the major phenotypes, which can be tested empirically.

### Recent Support for the Model

We have recently tested the predictions of this model by comparing *de novo* mutations in schizophrenia with those found in ID and ASD (Fromer et al. 2014). As noted already, we found evidence that genes with *de novo* mutations in schizophrenia overlapped with those affected by *de novo* mutations in ASD and ID, but not controls. We also observed that the genes hit by *de novo* mutations and the mutation sites themselves showed the highest degree of evolutionary conservation (a proxy measure of functional importance) in ID, then ASD, with schizophrenia least conserved. These findings suggest that highly disruptive mutations play a relatively lesser role in schizophrenia, and that the disorders differ by severity of functional impairment, consistent with the hypothesis of an underlying gradient of neurodevelopmental pathology indexed by cognitive impairment, with ID at one extreme.

### Implications of Recent Findings for Basic and Clinical Neuroscience

Thus far, genetic studies have identified specific genetic risk variants that account for only a very small proportion of risk. However, it is now possible to discern the approximate shape of the genetic architecture of psychiatric disorders, and the potential complexity of the relationships between genetic risk and clinical endpoints. The implications for neuroscience are profound.

#### Genetic Complexity

The first key message is that a very large number of genes are involved. In schizophrenia, where the largest samples have been studied and our understanding is

therefore greatest, over 100 distinct genetic loci harboring relatively common alleles of small effect (ORs < 1.3) have been identified to date at robust levels of statistical significance (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Furthermore, it is estimated that relatively common small effect alleles of this kind account for about 25% of total liability to schizophrenia (about 33% of genetic liability) (Lee et al. 2012) and that there are many thousands yet to be identified (Ripke et al. 2013). Presumably, the remaining genetic burden reflects alleles that are insufficiently frequent to be detected by GWAS, and some of these will have sufficiently large effects to be detected in realistically sized studies. As new generation sequencing (NGS) technology is applied, some of these rare variants are being identified at least at the level of specific gene sets (Fromer et al. 2014; Purcell et al. 2014). This complexity means that individuals, even those without the disorder, will carry a large number of risk alleles and that levels of genetic heterogeneity among those affected will be high: individuals with the same disorder, even those that are closely related, will be likely to have a different complement of risk alleles.

This genetic complexity poses challenges for basic neuroscientists as current methods only allow them readily to study the disruption of a single gene, or at most several at a time. Current translational paradigms aiming to understand the functional consequences of disease risk alleles were developed to study Mendelian disorders; however, we need to find new approaches if we are to translate findings from complex, polygenic genetic disorders into biological and therapeutic insights. Some traction from traditional methods might come from their application to rare high-penetrance risk alleles, and it is likely that more of these will be implicated as NGS technology is applied to larger samples (Fromer et al. 2014; Purcell et al. 2014). Clearly, multiple small effect risk alleles account for a substantial proportion of the heritability of psychiatric disorders, and thus it remains a major challenge to understand how to take these findings forward toward mechanistic insights. It is encouraging that the latest large GWAS data from schizophrenia have implicated a number of already known therapeutic targets, such as the dopamine D2 receptor and several proteins involved in glutamatergic neurotransmission (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). This suggests that we can be optimistic that data of this kind will open up new therapeutic opportunities. However, it seems that it will be necessary to focus translational research on the function of gene and protein networks rather than on single genes. The identification of the key networks will require access to transcriptomic, methylomic, and proteomic data from the brain. Here, there is a need to develop resources initially across brain regions and developmental stages, but ultimately at a single cell level. The question of how to model network biology in experimentally tractable systems is beyond the scope of the present discussion, but it seems obvious, even to the nonspecialist, that this will require larger-scale, more quantitative approaches than are currently in general use. It should also not be forgotten that GWAS signals do not necessarily identify the

key functional alleles, or even the gene or regulatory element that is affected. The research required to resolve these issues is labor intensive and often difficult, and there is an important question concerning the extent to which it will be necessary or even feasible to undertake this work for many hundreds of loci before undertaking the systems biological analyses that will come next.

The emerging evidence for a high degree of complexity also has important implications for clinical and basic neuroscience. The lesson from genomics is clear; the only way to render these complex disorders tractable is through adequately powered studies, and this requires both collaboration and methods that are scalable and standardized across many centers. Concerns have already been expressed about the low power and poor reproducibility of much neuroscience research (Button et al. 2013), and it seems inevitable that a culture change similar to that which took place in psychiatric genetics will be required in psychiatric neuroscience. Funders and journals will need to require adequately powered studies with robust statistical evaluation, data sharing, and an increased emphasis on replication.

### **Pleiotropy**

The second key message is that there is a high degree of pleiotropy, at least at the diagnostic level, with even relatively high penetrance alleles and environmental risk factors being associated with a wide range of clinical outcomes. These findings reinforce the view that we should be seeking new ways to stratify patients for research that go beyond the descriptive clinical phenotypes inherent in DSM and ICD and that use markers of likely pathophysiological relevance (often termed endophenotypes, or intermediate phenotypes). These will include neurobehavioral, neuroimaging, and electrophysiological measures and should be based on current understanding of brain-behavior relationships rather than relying on clinical syndromes as enshrined in DSM-5 and ICD-10 (Craddock and Owen 2010). This philosophy is articulated, developed, and acted upon in the RDoC project of the U.S. National Institutes of Medical Health (Cuthbert and Insel 2013). The implications for clinical neuroscientists are clear: work should not be based on the assumption that current diagnostic categories delineate distinct disorders or even distinct groups of disorders with distinct pathogenic mechanisms. Instead, work should focus increasingly on identifying the mechanisms that underlie specific functional abnormalities, and we should expect these to cross current diagnostic boundaries. Researchers should stop organizing themselves by traditional phenotype and increase the level of interaction, discussion, and collaboration between clinical researchers and neuroscientists.

The requirements noted above for both adequately powered studies and new, more sophisticated ways of stratifying patients for neuroscience research brings a further challenge: if we are really serious about taking this agenda forward, then we need to study very large and deeply phenotyped cohorts. This,

in turn, will require greater collaboration and data sharing between neuroscientists. However, some measures (e.g., neuroimaging measures like fMRI) will be difficult to apply to samples containing thousands of patients. Having said this, other behavioral, cognitive, symptomatic, or electrophysiological measures might well be sufficiently scalable. One explicit subgoal of RDoC is to foster new methods of measurement, and these could be tailored to the goal of feasible deeply phenotyped cohorts.

Finally, it is important to note an important fact that is often overlooked in clinical research on neurodevelopmental disorders: namely, these disorders manifest differently across the life span. Future research must factor this in and be aware of the possibility that key phenotypes and endophenotypes will change as the individual develops and ages. This will require research to characterize normative as well as pathological developmental trajectories.

### **Biological Convergence**

The third key message is that, despite (a) the large number of genes implicated (a small proportion of the likely total) and (b) the divergent outcomes associated with individual alleles, there is already evidence for some convergence onto specific biological processes. Results from GWAS (Ripke et al. 2013), CNVs (Kirov et al. 2012), and sequencing studies (Fromer et al. 2014; Purcell et al. 2014) of schizophrenia point to highly functionally related sets of postsynaptic proteins involved in synaptic plasticity, learning, and memory. These include L-type calcium channels, postsynaptic scaffolding proteins involved in NMDA signal transduction, and proteins which interact with ARC (activity-regulated cytoskeleton-associated) protein, referred to as the ARC complex (Kirov et al. 2012), and brain-expressed genes that are repressed by fragile X mental retardation protein (FMRP).

A notable feature of these findings is not only their consistency across several studies, but also their convergence onto a coherent set of biological processes involved in the regulation of plasticity, particularly at glutamatergic synapses. These processes have major effects on plasticity in the postsynaptic region, although some implicated genes, including the L-type calcium channels and Neurexin-1 (an associated CNV locus; Kirov et al. 2009), also exert effects on plasticity presynaptically. These synaptic genes have also been implicated in cognition (Grant et al. 2005) as well as a range of neuropsychiatric conditions, including ASD and ID, and there is some support from the exome sequencing data for the notion that these disorders exist along a gradient of neurodevelopmental impairment (Fromer et al. 2014). However, the degree to which the associated pathways cross current diagnostic boundaries remains to be fully established. It is highly unlikely that this will represent the only set of biological processes implicated in the disorder, but the identification of at least one system involved in risk for schizophrenia and related disorders would pave

the way for more detailed mechanistic studies and potentially stratified and novel therapeutic approaches.

While the degree of convergent support for glutamatergic synaptic processes is encouraging, it seems inconceivable that other processes are not involved. There is a highly convincing body of evidence implicating dopaminergic dysfunction in the genesis of psychotic symptoms, which occur commonly in schizophrenia and bipolar disorder but also in other neurodevelopmental disorders as well (Howes and Murray 2014). Indeed, the mechanism of action of antipsychotic drugs is understood to depend largely on the blockade of dopamine D2 receptors. Understanding the relationship between glutamatergic dysfunction, which is closely related to cognitive impairment, and abnormalities of dopamine signalling is likely to be the key focus in understanding how psychosis arises in schizophrenia and related disorders.

Further insights into possible mechanisms come from the observation that a wide variety of environmental mechanisms (e.g., traumatic, infective, inflammatory, toxic) converge on the same spectrum of neurodevelopmental outcomes as relatively disruptive, rare genetic events such as LoF mutations and CNVs. This suggests that genetic factors predisposing to adverse consequences of these environmental insults might play a role in these disorders. There may indeed be as many etiological mechanisms at work as there are ways of disrupting brain development, and it remains to be seen to what extent and how they converge on circumscribed pathogenic processes.

### **Phenotypic Complexity**

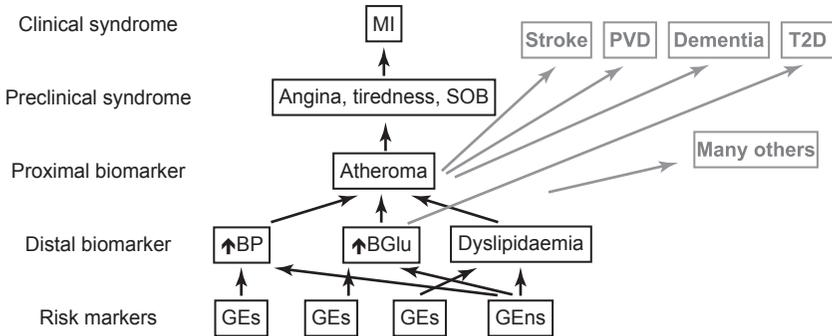
A final important implication for future neuroscience research comes from the fact that neurodevelopmental disorders have multiple domains of function. Whether or not specific abnormalities are included in the definition of the disorder is largely arbitrary and a matter of convention. Kraepelin, for example, saw disorders of cognition as integral to schizophrenia, but over time there was an increasing diagnostic focus on psychotic symptoms and a de-emphasis on cognitive dysfunction. In recent years, as noted above, cognitive impairment has once again been viewed as central to the disorder, though it is possible to receive a diagnosis of schizophrenia without cognitive impairment. Movement disorders are also commonly seen in psychotic disorders but play little part in ICD and DSM definitions, whereas there is a whole tradition of nosology based on the work of Leonhard (e.g., Leonhard et al. 1999) in which psychotic disorders are central together with the course of disorder. In fact, studies of cognition and of brain imaging and electrophysiology in schizophrenia have found dysfunction to be widely distributed over multiple cognitive domains as well as brain regions and functions. This is not to say that all dysfunctions are present in all patients—far from it. There is widespread heterogeneity. Thus the complex constellation of symptoms and syndromes observed in individual patients likely reflects developmental and functional disturbances in a wide

range of brain systems and psychological processes, and this is unlikely to be understandable in terms of a single pathway from pathology to diagnosis. Of course it is to be hoped that in time we will be able to decompose these into different groups of patients with specific constellations of symptoms and impairment, reflecting disturbances in different brain mechanisms and circuits. However, we need to recognize that it is possible for the underlying diathesis to involve the whole brain, or at least multiple, widely distributed systems, rather than reflecting dysfunction in specific brain regions or circuits. This accords with recent findings which implicate genetic abnormalities in the ubiquitous excitatory synapse as well as many hundreds of other risk loci, and the broad impact likely to result from many environmental risk factors.

### **How Do We Integrate Disease Classification with Neurobiology and Genetics?**

The extensive shortcomings of current categorical criteria for research into etiology and pathogenesis have been addressed above and a number of possible ways forward discussed. Even the fiercest critics of DSM and ICD have to admit, however, that we are still some way off having sufficient new insights from genetics and neuroscience to replace current diagnostic approaches in the clinic. It has been argued that clinical practice would be improved by augmenting current categorical approaches with a number of cross-cutting dimensional measures; these, however, would introduce complexities into clinical practice and have not been welcomed sufficiently by practitioners. Attempts to introduce them into DSM-5 failed. Notwithstanding Robins and Guze (1970), there were good reasons for doubting whether genetics would allow us to carve nature at the joints and to map out clinical syndromes on the basis of nonoverlapping genetic etiology (Kendler 2006). This suggestion can probably be discarded once and for all on the basis of recent genetic findings. Given the challenges outlined above, it is probably too early to say what impacts neuroscience will have on classification and diagnosis. Current diagnostic categories are likely to remain clinically useful to the extent that they best inform management and prognosis, but these will require modification, as future research indicates closer relationships of specific phenotypes and endophenotypes to mechanism, and likely need to include both dimensional and categorical entities.

It seems likely, therefore, that the introduction of genetics and neurobiology into the clinic will occur piecemeal as new advances are made. There is probably already a good case to be made for the introduction of testing for rare CNVs in neurodevelopmental disorders, including schizophrenia. Although testing is unable to assist the identification of therapeutic options, it does provide patients and their families a partial explanation of the illness and has some implications for genetic counseling. It also has implications for prognosis, especially if testing is conducted in children, but the counseling



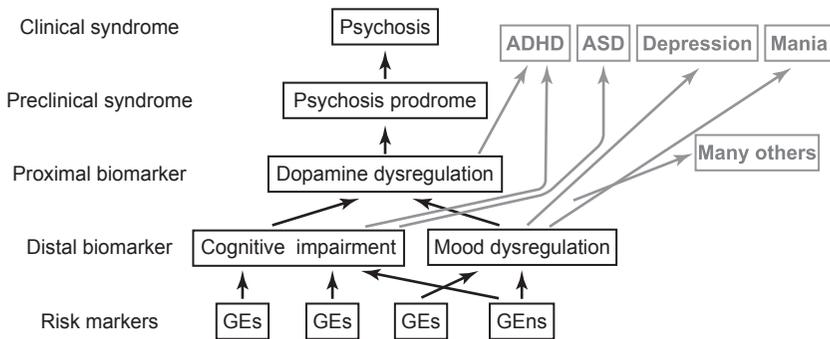
**Figure 3.2** Schematic showing a simplified representation of the etiology and pathogenesis of myocardial infarction (MI). PVD: peripheral vascular disease; T2D: type 2 diabetes; SOB: shortness of breath; BP: blood pressure; BGlucose: blood glucose; GEs: specific genetic and environmental factors; GEnS: nonspecific GEs. Genetic and environmental factors are placed together for simplicity. Associated pleiotropic phenotypes are shown in gray. Diagnosis is multilevel and shown in box for exemplar case.

challenges should not be underestimated given the wide range of possible outcomes (Kirov et al. 2014).

If we wish to speculate how psychiatrists of the future, say in twenty years, will use genetic and neurobiological data in diagnosis and stratification, then it is instructive to consider how similar information is being used in other branches of medicine. Figure 3.2 illustrates how physicians currently approach a diagnosis in a case of myocardial infarction based on a combination of clinical syndromic presentation, biomarkers of underlying pathogenic mechanisms, and presence of environmental risk factors. It also indicates a potential role for genomic profiling for future individualized medicine. Figure 3.3 shows a similar, albeit highly speculative, schema of how psychiatrists of the future might approach a diagnosis of psychosis, integrating information across levels and using neurobiological and genetic markers to target therapies. It seems likely that clinical syndromes will remain useful but be augmented by biomarker and risk factor information in order to target therapies, devise secondary prevention, and inform prognosis. The extent to which a greater understanding of pathogenic mechanisms based on future advances in neuroscience and genetics will allow current clinical syndromes to be refined is unknown.

## Conclusions

There seems little doubt that the widespread and uncritical use of current categorical diagnostic systems has impeded research into the etiology and pathogenesis of psychiatric disorders. Until recently it was high impossible to



**Figure 3.3** Schematic showing a simplified speculative representation of the etiology and pathogenesis of psychosis. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; GEs: specific genetic and environmental factors; GEnS: non-specific GEs. Genetic and environmental factors are placed together for simplicity. Associated pleiotropic phenotypes are shown in gray. Diagnosis is multilevel and shown in box for exemplar case.

publish a paper or obtain grant funding without adhering to either DSM or ICD. Recent findings in psychiatric genetics have contributed to an increased realization that this situation must change, and there are encouraging signs (e.g., the RDoC project) that this is beginning to happen. However, the new findings pose a number of challenges. The genetic complexity of psychiatric disorders means that efforts to translate these findings into new mechanistic insights will require cultural as well as technological changes in the neurosciences. In particular, there will be a need to study networks rather than individual genes and proteins, and to develop experimental systems in which multiple variables can be manipulated and multiple endpoints studied. The complexity and mutability of psychiatric phenotypes also pose challenges for clinical neuroscience, and new ways of stratifying patients in neurobiologically meaningful ways are required, as is a move away from conducting research in diagnostic silos. In both basic and clinical neurosciences, there will need to be an increased focus on large-scale experimentation, collaboration, statistical robustness, and reproducibility.

A brief perusal of Figure 3.2 reminds us that psychiatric disorders are not unique in being genetically and phenotypically complex with extensive pleiotropy and multiple, related pathogenic mechanisms. These are features of common disorders in general. What sets psychiatry apart is the complexity and relative inaccessibility of the diseased organ. The continuing success of psychiatric genetics and the rapid development of new methods for studying the brain in humans and model systems are causes for optimism. The challenge now is to develop new approaches to identify pathogenic mechanisms and to identify the most suitable phenotypes to which these relate.

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The neurodevelopmental gradient model was developed with Nick Craddock, and my work in psychiatric genetics in Cardiff has been conducted in collaboration with Nick Craddock, Mick O'Donovan, Peter Holmans, Valentina Moskvina, George Kirov, and Anita Thapar as well as many excellent junior colleagues. Many of the recent advances in psychiatric genetics have taken place as part of a global cooperative enterprise involving numerous scientists and clinicians from many countries.

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First column (top to bottom): Stephan Heckers, Cynthia Joyce, Bruce Cuthbert,  
Raquel Gur, Andreas Meyer-Lindenberg, Bruce Cuthbert, Steve Hyman  
Second column: Steve Hyman, Michael Owen, Steve Hyman, Matt State,  
Group discussion, Stephan Heckers, Matt State  
Third column: Bruce Cuthbert, Thomas Bourgeron, Cynthia Joyce,  
Stephan Heckers, Raquel Gur, Thomas Bourgeron

