Open Issues in Psychiatry

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Complexity and Heterogeneity in Psychiatric Disorders

Opportunities for Computational Psychiatry

Nelson Totah, Huda Akil, Quentin J. M. Huys, John H. Krystal,
Angus W. MacDonald III, Tiago V. Maia,
Robert C. Malenka, and Wolfgang M. Pauli

Abstract

Psychiatry faces a number of challenges, among them are the reconceptualization of symptoms and diagnoses, disease prevention, treatment development and monitoring of its effects, and the provision of individualized, precision medicine. Achieving these goals will require an increase in the biological, quantitative, and theoretical grounding of psychiatry. To address these challenges, psychiatry must confront the complexity and heterogeneity intrinsic to the nature of brain disorders. This chapter seeks to identify the sources of complexity and heterogeneity as a means of confronting the challenges facing the field. These sources include the interplay between genetic and epigenetic factors with the environment and their impact on neural circuits. Moreover, these interactions are expressed dynamically over the course of development and continue to play out during the disease process and treatment.

We propose that computational approaches provide a framework for addressing the complexity and heterogeneity that underlie the challenges facing psychiatry. Central to our argument is the idea that these characteristics are not noise to be eliminated from diagnosis and treatment of disorders. Instead, such complexity and heterogeneity arises from intrinsic features of brain function and, therefore, represent opportunities for com-

putational models to provide a more accurate biological foundation for diagnosis and treatment of psychiatric disorders. The challenges to be addressed by a computational framework include the following. First, it must improve the search for risk factors and biomarkers, which can be used toward primary prevention of disease. Second, it must help to represent the biological ground truth of psychiatric disorders, which will improve the accuracy of diagnostic categories, assist in discovering new treatments, and aid in precision medicine. Third, to be useful for secondary prevention, it must represent how risk factors, biomarkers, and the underlying biology change through the course of development, disease progression, and treatment process.

Introduction

Understanding and treating the enigmatic symptoms of psychiatric disorders has placed the field of psychiatry at an impasse (see Gordon and Redish, this volume). Key issues that must be addressed to advance psychiatry include: highly comorbid diagnoses and heterogeneity of patients grouped under a single diagnostic label; lack of understanding of the causal biological mechanisms, which form the basis of disease etiology and progression, and their impact on treatment decisions; and the absence of biomarkers and clear risk factors that can be used to predict and prevent disease. These challenges likely arise because of the complexity and heterogeneity present in the brain, in the environment, and in our collective attempt to assign patients to diagnostic groups. Moreover, sources of complexity and heterogeneity are dynamic and change over time with natural development and in response to the disease process itself. For instance, the severity of symptoms and the presence of specific symptoms change across various illness stages, which makes diagnosis and treatment decisions difficult. Treating psychiatric disorders will require improving their biological grounding through an understanding of the brain, an organ that is itself a dynamic and complex system. Computational models are well placed to build a bridge between the initial patient self-report and behavioral observations and the complex, dynamic neurobiological and neurocomputational state of the patient.

In this chapter, we propose that computational models can be used for multiple purposes. They can be used as tools of prediction in psychiatry and as as a method for increasing the biological grounding and quantitative, mathematically formalized framework with which disorders can be understood. We begin with an overview of the issues of complexity and heterogeneity that hinder progress in psychiatry. Thereafter we identify opportunities for computational models to address these issues and the data available for use in models. We close by outlining some examples in which computational models may be used as tools or as methods for improving our understanding of the etiology and progression of psychiatric disorders. We will demonstrate how these tools and methods might be used to improve diagnosis, identify biomarkers and risk factors, and prevent disease through treatment or removal of risk factors. By

identifying the sources of complexity and heterogeneity present in psychiatry, we hope to provide a starting point for dialogue between psychiatrists, neuroscientists, and computational scientists. Throughout our overview, we use clinical vignettes to illustrate, from a practical viewpoint, the complexities that challenge the field of psychiatry.

Sources of Complexity in Psychiatry

Clinical Vignette 1: Peter, an 18-year-old high school senior, is brought to the local mental health crisis clinic by his parents. They report that for the past two weeks he has isolated himself in his bedroom, taped up the windows with foil, and refused meals with his family, eating only packaged food that he prepares in the microwave. He has had several angry outbursts when his family has attempted to coerce him to go to school or to get help. The police were called to the house by a neighbor, due to the shouting that occurred, and he reluctantly agreed to come to the clinic voluntarily because the officer told him that he would take him into custody if he did not. Up until about a year ago Peter was performing with average to above average grades in school, playing in his school jazz band, and socializing regularly. At that time, he had an episode of anxiety and depersonalization after smoking cannabis for the first time. The episode lasted for several days and led to a visit to his family doctor. During the visit, he described intermittent feelings of being detached from things, that things were not real, that there were strange shadows outside his windows at night, and that he felt at times as if someone was looking in at him although, when he checked, no one was there. The family physician prescribed an antidepressant for "panic attacks." However, three days after starting this drug he became increasingly irritable, restless, religiously preoccupied, argumentative, and he began to stay up all night playing video games with online partners; this led the physician to discontinue the drug. At that time, Peter's grades started to deteriorate and he became increasingly withdrawn from friends and family. Over the next few months, he spent more time alone in his room and on the Internet. By his report, he was concerned initially that he was being singled out at school by a group of peers with whom he had an argument over rival sports teams. He noticed that his computer became very slow to boot up and was infected by a virus; he became concerned that he had been hacked and that other students in the school, and eventually the teachers, were involved. He began hearing whispers in the background audio of music videos and then, several weeks later, began hearing several voices commenting on his behavior and making derogatory remarks. He stopped showering and his room was piled with dirty clothing. He began to notice that his food smelled different and at one point he had an epiphany: his parents and teachers were illuminati and were trying to poison him. When he was seen in the clinic, he was visibly terrified, scanning the room, trembling and unable to sit still.

Clinicians are confronted by an extremely complex set of variables when they must diagnose a patient and make a treatment decision. One level of complexity is intrinsic to the patient's narrative and the symptoms that they report, and this can lead to comorbid diagnoses. For instance, Peter is irritabile and

restless, staying up all night playing video games; he could be diagnosed with bipolar disorder. But Peter also meets criteria for schizophrenia, with prominent symptoms of social isolation and psychosis. Indeed, one-third of individuals diagnosed with bipolar disorder are also diagnosed with schizophrenia (Gonzalez-Pinto et al. 1998). Yet the psychiatrist must select a diagnosis and this decision will then guide treatment. This complexity that confronts the clinician, therefore, challenges their ability to deliver an accurate diagnosis, predict the time course of disease, select treatment, and monitor treatment response.

In addition to the individualized complexities that arise as a result of each patient's unique narrative, other highly individualized complexities occur at the level of biology and also influence psychiatrists' ability to accurately diagnose and treat the patient. At the level of the individual such complexities include genetic endowment, environmental influences, longitudinal changes in the brain (due to both natural neurodevelopment and neuroadaptation to disease), and interaction with stable traits. At the population level, this overlap between patients leads to comorbidity and to fluctuating diagnoses over time. For example, patients' symptoms will change and cause a diagnosis to fluctuate between, say, a diagnosis of anorexia nervosa and bulimia nervosa (Tozzi et al. 2005). Furthermore, illnesses have temporal components; they can be chronic, relapsing/remitting, or a combination thereof. The onset of an illness can also occur over multiple timescales. It can begin in a punctate manner (e.g., triggered by a trauma) or express itself in a punctant manner (e.g., a suicide attempt or a decision to use a drug), or it can progress longitudinally over a lifetime. Adaptive or nonadaptive processes can alter the course of disease (see chapters by Krystal et al. and Huys, this volume). Differences in treatment history cause diverse disease trajectories, even across patients with the same diagnostic label or underlying disease process. The evolution of Peter's symptoms, from social isolation and weird behavior to frank paranoia, seem to reflect some underlying temporal progression. An additional source of complexity that must be considered is that all of these temporal aspects of illness interact with stable traits and propensities, such as personality, temperament, and genetic endowment.

The heterogeneities that we have identified have real-world implications for both basic research and practical matters of effective diagnosis and treatment by clinicians. For instance, comorbid and temporally fluctuating diagnoses result in heterogeneous patient populations, which present a challenge to discovering common biological correlates and risk factors. Jonathan Flint has compared the search for genetic risk factors in psychiatry with searching for a genetic risk factor for a diagnosis of fever, which would sample a disease-predisposing genetic makeup from a highly heterogeneous group of patients with autoimmune disease, various infections, cancer, and many other conditions (Ledford 2014). What can be done to improve the accuracy of diagnosis? Clearly, we need a greater understanding of the biological ground truth underlying psychiatric

disease. The lack of correspondence between diagnostic labels and biology has hindered the search for biomarkers, etiological mechanisms, and risk factors that can be mitigated through preventative medicine. In fact, a recent attempt at discovering genetic correlates for depression was successful, whereas others have not been, because the study was designed to reduce heterogeneity across the population of subjects which shared the common diagnostic label of depression (CONVERGE Consortium 2015).

Treatment decisions are also hindered by the mismatch between diagnostic labels and the underlying biology. For example, clinical trials designed to test existing and novel therapies typically fail to take into account differences across subjects that are due to the biological stage of the illness or the biological effects of treatment history. For Peter (the patient in the clinical vignette who early on seems to have met criteria for both mood and psychotic disorders), the clinician must decide whether to either administer an antidepressant for a mood disorder, a mood stabilizer for bipolar disorder, or a preventative treatment for prodromal schizophrenia. His initial treatment by his family doctor was an antidepressant, which unfortunately precipitated his symptoms of mania and hypomania. Could this have been avoided had the physician taken into consideration the complex temporal progression of his disease? There is an emerging recognition that schizophrenia can be conceived of as having "predromal," "prodromal," and "syndromal" phases (Lieberman et al. 2001; Fusar-Poli et al. 2014; Krystal et al., this volume). Given that there are biological differences at each disease stage, a greater understanding of disease stage could lead to better treatments and, perhaps, even prevention. There is also evidence that treatment history, itself, can alter the biological factors underlying disease and must, therefore, be taken into account during diagnosis, treatment decisions, and clinical trial design. For example, patients enrolled in clinical trials for schizophrenia treatment may have already received dopaminergic antipsychotic drug treatment, which could alter the efficacy of the novel treatment being tested. Importantly, basic experiments performed in animals have provided direct support for this hypothesis by demonstrating that long-term administration, and then subsequent withdrawal of antipsychotics, affects the behavioral and neurophysiological response to a novel GABAergic treatment (Gill et al. 2014).

Next we will outline the current state of knowledge about the biological factors underlying psychiatric disease. Central to our proposal for the usefulness of a computational framework in meeting the challenges that face psychiatry is the idea that, although the complexity of the underlying biology leads to inaccurate diagnoses and treatment decisions, it reflects the intrinsic nature of the biology and this "noise" must be harnessed rather than avoided. We believe that a computational framework provides the ability to make sense of the noise. We begin by illustrating the biological complexities present at the genetic level, and their intraction with environmental and stable trait factors, using another clinical vignette.

Genetic Complexity

Clinical Vignette 2: Wendy's first stint in rehab was at the age of 26. She began drinking at age 12 when her mother, a heavy drinker, was diagnosed with breast cancer and died. Having initially surreptitiously sampled unfinished drinks at her parents' parties, she started sneaking drinks from the liquor cabinet before going to sleep at night. This became a habit during her college years, when she would come home after studying or social activities and have several drinks before going to sleep. During exams she would use Adderall to overcome the effects of the night before. She graduated from college with excellent grades and began working as a clerk in a law firm while preparing to take the qualifying exam for law school. She was punctual, courteous and managed to perform her duties in a manner that was satisfactory to the attorneys for whom she worked. She was in a long-term relationship with her boyfriend who occasionally binge drank with her at parties, but he was unaware of her nightly drinking. At times she felt that she had problems with her memory, and she was frequently hung over in the morning. She often thought about quitting drinking. Each day, as her workday wore on, she would begin to think about what she would drink that night and plan her social activities such that she would be able to get back to her apartment and drink. She would often decide that she was not going to drink after all, just as she entered her apartment, but would later abruptly decide to go to the store to buy alcohol. Her alcohol use dramatically increased after her father received a cancer diagnosis. She called in sick for several days and was then arrested driving her car erratically in the early hours of the morning. She had no recollection of how she got there; she had a blood alcohol level four times the legal limit along with amphetamines in her system. On her way home from her court-mandated treatment, she felt ashamed and determined to confront her substance use problem before it cost her lifelong dream to attend law school and become an attorney. As she passed her local supermarket she decided to stop and purchase nonalcoholic beer. She left the store with three bottles of her favorite wine.

Wendy's story illustrates many of the complexities inherent in psychiatric disease. There are often clear predisposing factors, such as, in this case, genetic endowment and family history (her mother was a "heavy drinker") that help explain why she might be more susceptible to addiction than others, such as her boyfriend, who "occasionally binge drank with her at parties." Wendy's alcohol consumption increased during times of stress. Stress is often thought to play a role in precipitating psychiatric symptoms. Might also more stable traits, such as her gender or personality, be additional risk factors? A synthesis of research demonstrates that these factors all contribute and interact. Drug consumption in males tends to be driven by the hedonic, reward-related aspects of the drug, whereas in females it is driven by negative hedonic states and stress (Li et al. 2005; Fox et al. 2006; Hyman et al. 2008; Potenza et al. 2012). These data may explain why her boyfriend binge drank at parties, whereas she consumed larger amounts during times of stress. Such observations about human behavior are bolstered by gender differences in reward-related neurophysiological activity. In comparison to women, alcohol administration increases

striatal dopamine release to a greater extent in men, which may drive increased appetitive reward-seeking behavior in men (Berridge 2006; Urban et al. 2010). Finally, both gender-specific hormones and genetic endowment make independent contributions to drug/reward consumption and habitual drug-seeking behaviors (Quinn et al. 2007; Barker et al. 2010; Seu et al. 2014). These data indicate that genetic endowment, stable traits, hormones, and environmental factors may all interact to contribute to the expression of psychiatric disorders.

Even if we solely look at genetic factors, the picture remains quite complex. In general, psychiatric disorders are known to be highly heritable. Schizophrenia, for instance, is thought to be 70% heritable (Lichtenstein et al. 2009). Familial inheritance studies and twin studies have encouraged decades of research into genetic risk factors and their potential as causal pathophysiological mechanisms (LaBuda et al. 1993; Sullivan et al. 2003; Mitchell et al. 2011). Puzzling out the nature of genetic risk, however, has proved formidable, in part because there are multiple kinds of genetic risk factors and multiple genes of each kind. Copy number variants (CNVs), which are deletions or duplications spanning multiple genes, appear prevalent in schizophrenia, autism, and attention-deficit/hyperactivity disorder (Sebat et al. 2007; Abrahams and Geschwind 2008; Walsh et al. 2008; Xu et al. 2008; Gilman et al. 2011; Levy et al. 2011). Dozens of CNVs have been identified, each accounting for a relatively small proportion of patients with a given disorder, but each having a relatively large effect on risk (on the order of 5- to 30-fold increases). On the other end of the spectrum, genome-wide association studies have provided a list of hundreds of common single nucleotide polymorphisms (SNPs) for schizophrenia. Each of these common risk alleles are seen in large numbers of patients (and healthy controls), and all have small effect sizes (typically much less than 1.5-fold increases in risk) (Raychaudhuri et al. 2009; Stefansson et al. 2009). Similar risk structures may underlie autism (Wang et al. 2009; Gaugler et al. 2014).

Adding to this complexity, even a single one of these hundreds of risk genes can be associated with multiple psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium et al. 2013; Zhu et al. 2014) (Figure 3.1). For example, the translocation of DISC1 is highly hereditary (although it has irregular expression and affects carriers' phenotypes to different degrees) and strongly predicts a number of psychiatric disorders including schizophrenia, bipolar, and depression (St. Clair et al. 1990; Millar et al. 2000; Blackwood et al. 2001; Chubb et al. 2008; Jaaro-Peled et al. 2009). Similarly, several CNVs predispose to both schizophrenia and autism.

Therefore, multiple types of genetic variation—from hundreds of SNPs, each with a minor effect, to CNVs or other mutations of large effect size, and likely gray areas in between—can interact to give rise to psychiatric phenotypes, and any given gene can raise the risk for multiple different phenotypes. From this perspective, it is clear that genes must be considered part of a network with multiple, interacting genetic pathways to a disorder. It may be
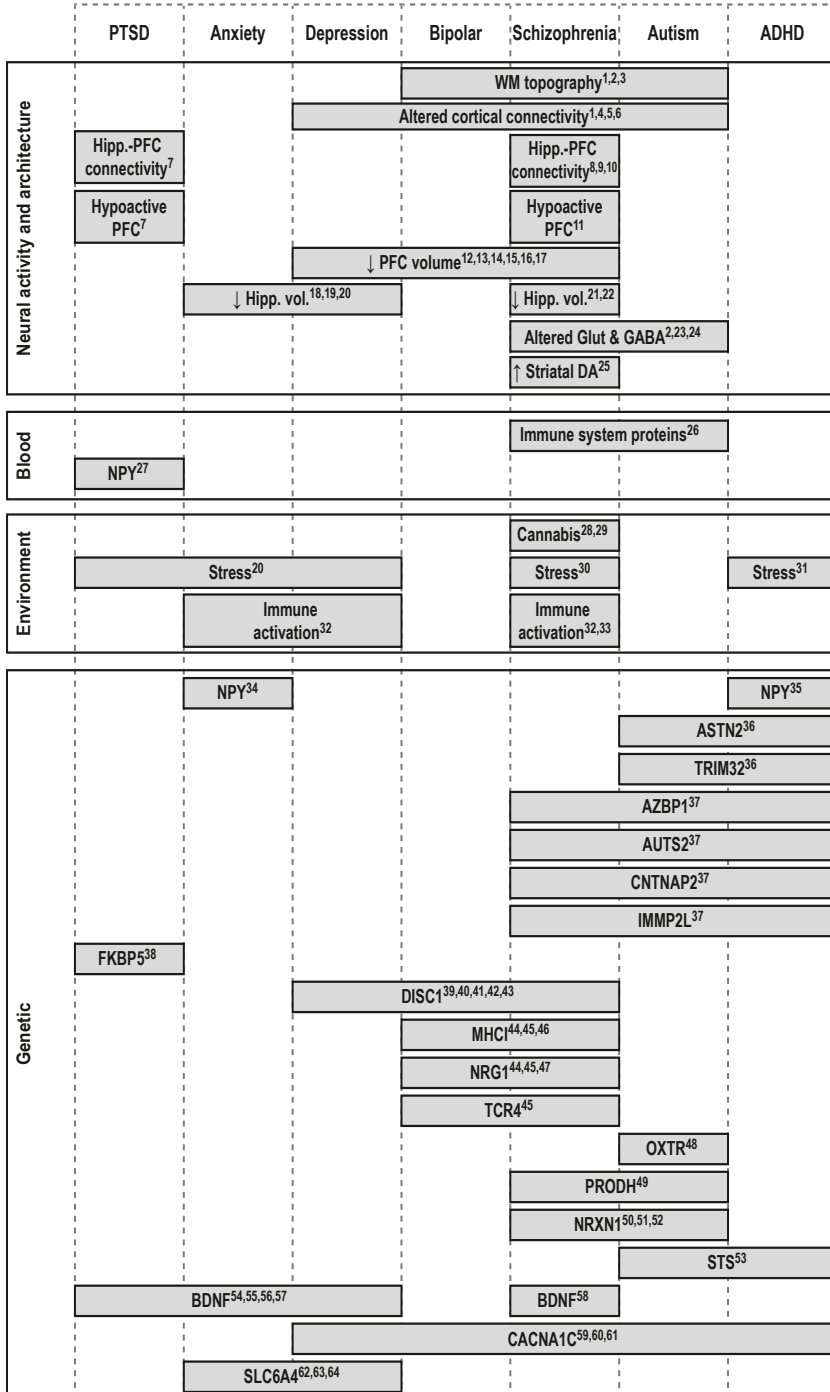
Columns: PTSD | Anxiety | Depression | Bipolar | Schizophrenia | Autism | ADHD

Neural activity and architecture

- WM topography[1,2,3]
- Altered cortical connectivity[1,4,5,6]
- Hipp.-PFC connectivity[7]
- Hipp.-PFC connectivity[8,9,10]
- Hypoactive PFC[7]
- Hypoactive PFC[11]
- ↓ PFC volume[12,13,14,15,16,17]
- ↓ Hipp. vol.[18,19,20]
- ↓ Hipp. vol.[21,22]
- Altered Glut & GABA[2,23,24]
- ↑ Striatal DA[25]

Blood

- Immune system proteins[26]
- NPY[27]

Environment

- Cannabis[28,29]
- Stress[20]
- Stress[30]
- Stress[31]
- Immune activation[32]
- Immune activation[32,33]

Genetic

- NPY[34]
- NPY[35]
- ASTN2[36]
- TRIM32[36]
- AZBP1[37]
- AUTS2[37]
- CNTNAP2[37]
- IMMP2L[37]
- FKBP5[38]
- DISC1[39,40,41,42,43]
- MHCI[44,45,46]
- NRG1[44,45,47]
- TCR4[45]
- OXTR[48]
- PRODH[49]
- NRXN1[50,51,52]
- STS[53]
- BDNF[54,55,56,57]
- BDNF[58]
- CACNA1C[59,60,61]
- SLC6A4[62,63,64]

Figure 3.1   The genetic, environmental, anatomical, and physiological factors that are associated with a variety of psychiatric disorders. This non-exhaustive list conveys the breadth of factors and their overlap across disorders. References are numbered.

1. Bernard et al. (2015)	33. Brown and Derkits (2010)
2. Nelson and Valakh (2015)	34. Kaabi et al. (2006)
3. Sussmann et al. (2009)	35. Lesch et al. (2011)
4. Downar et al. (2014)	36. Lionel et al. (2011)
5. Just et al. (2004)	37. Elia et al. (2010)
6. Koshino et al. (2008)	38. Binder et al. (2008)
7. Fani et al. (2012)	39. St Clair et al. (1990)
8. Meyer-Lindenberg et al. (2005)	40. Millar et al. (2000)
9. Lawrie et al. (2002)	41. Blackwood et al. (2001)
10. Ford et al. (2002)	42. Jaaro-Peled et al. (2009)
11. Weinberger and Berman (1996)	43. Chubb et al. (2008)
12. Pantelis et al. (2003)	44. Intl. Schizophrenia Consortium et al. (2009)
13. Smieskova et al. (2010)	45. Stefansson et al. (2009)
14. Wright et al. (2000)	46. McGuffin (1979)
15. Ward et al. (1996)	47. Harrison and Weinberger (2005)
16. Rajkowska et al. (1999)	48. Gregory et al. (2009)
17. Drevets (2000)	49. Guilmatre et al. (2009)
18. Phillips et al. (2002)	50. Autism Genome Project Consortium (2007)
19. Velakoulis et al. (2006)	51. Walsh et al. (2008)
20. Sapolsky (2000)	52. Rujescu et al. (2009)
21. Bois et al. (2015)	53. Kent et al. (2008)
22. Nelson et al. (1998)	54. Felmingham et al. (2013)
23. Lewis (2014)	55. Soliman et al. (2010)
24. Volk and Lewis (2014)	56. Verhagen et al. (2010); *males only
25. Howes et al. (2009)	57. Tocchetto et al. (2011)
26. Chan et al. (2015)	58. Neves-Pereira et al. (2005)
27. Morgan et al. (2000)	59. Cross-Disorder Group of the Psychiatric Genomics Consortium et al. (2013)
28. Moore et al. (2007)	60. Green et al. (2010)
29. Semple et al. (2005)	61. Ferreira et al. (2008)
30. Anda et al. (2006)	62. Lesch et al. (1996)
31. Van den Bergh and Marcoen (2004)	63. Hariri et al. (2002)
32. Markham and Koenig (2011)	64. Caspi et al. (2003)

necessary, then, to analyze genetic factors as a causal network, rather than as direct causes (Raychaudhuri et al. 2009; Barabási et al. 2011; Gilman et al. 2011). Computational methods for analyzing effects in complex networks may be helpful in this area of research (Boccaletti et al. 2006; Bullmore and Sporns 2009; Barabási et al. 2011). Other work has used computational methods, such as machine learning, to demonstrate that schizophrenia is predicted by inter-acting combinations of genes that affect multineuron population activity as-sociated with working memory, an impaired cognitive function in individuals diagnosed with schizophrenia (Nicodemus et al. 2010). This finding highlights the importance of considering the effects of *interacting* genetic mutations at the level of neural circuit function.

Neurobiological Complexity

Clinical Vignette 3: Jennifer woke up in the intensive care unit of a regional medical center. She had been in the hospital for three days following an acet-aminophen and benzodiazepine overdose that had caused some liver damage but was not going to be life threatening. At 36 years, this was an unfamiliar, shock-ing, and embarrassing experience. Since the economic downturn six years ago, she and her family had struggled financially. Her marriage of 13 years had been stressed and her school-age children were having academic and other problems at school. Her oldest son (aged 12) had been suspended for fighting with class-mates. Always a worrier, over the past months she had increasing difficulty get-ting to sleep and staying asleep, leaving her tired and irritable during the day. She ruminated constantly about her family problems and blamed herself for them. She felt increasingly irritable, sad, and empty. She also felt tired and disinter-ested in pleasurable experiences, including food and sexual activity. Initially, she recognized that she was depressed and sought self-help on the Internet; however, over time she increasingly felt that there would be no help for her, that she was a burden on her family, and that they would be better off without her. During the two weeks before her suicide attempt, she saw her family doctor to complain about fatigue and insomnia and was prescribed the benzodiazepine. She also researched suicide on the Internet, including the potential lethality of the medica-tion on which she overdosed. She left a note apologizing to her family for letting them down, stating that they would be better off without her.

Jennifer clearly suffered from depression, but the causes of her depression are, well, complex. Were there genetic factors? Probably. But whatever genetic predisposition to depression lay in her genes, this predisposition was filtered through multiple downstream events: economic troubles and stressful family issues seemed to play a grave role in her illness, which progressed slowly over months but was then punctuated by a terrible event—her suicide attempt. How do we understand her illness at a biological level?

We must start with a fundamental understanding about brain disease: what-ever the fundamental causes, genetic or environmental, these precipitants contribute to behavioral phenotypes only when filtered through neural circuit

development, cellular physiology, and neural circuit activity, each of which adds further complexity to the picture. Thus, for causal events to be useful as biomarkers or etiological mechanisms in psychiatry, they must be integrated with information about gene expression, cellular physiology, and neuronal circuits.

Once again to simplify, consider the case of a disease gene. One recent study has demonstrated that the number of neurons expressing a disease-related mutation is surprisingly low (Cai et al. 2014). This critically important result demonstrates that a mutation can affect the cellular physiology of a relatively confined group of neurons. Well, then, might we just study the small number of cells that are affected directly by this mutation? This approach will probably not be fruitful. Buzsáki and Mizuseki (2014) have proposed that behavior, cognition, and perception depend not only on an active minority assembly of neurons, but on their coordination with a global majority, in order to provide the optimal tradeoff between fast, yet accurate thought and behavior. Multiple neurophysiology studies have demonstrated that a small group of neurons can easily affect a large population of neurons (Cardin et al. 2009; Li et al. 2009; Thiagarajan et al. 2010; Kwan and Dan 2012; Logothetis et al. 2012; Olsen et al. 2012; Beltramo et al. 2013). For instance, a single mouse visual cortex neuron can drive spiking of other neurons within a 100 μm radius with different degrees of drive on different cell types (Kwan and Dan 2012), giving rise to complex, nonlinear dynamics in large networks of neurons. In other words, complex genetic networks (operating within neurons) impact similarly complex neural networks (operating between neurons). The challenge is to build a mechanistic bridge between these genetic and neural networks that offers insight into human thought, mood, perception, learning, and memory (Figure 3.2).

Given that multiple genetic pathways can converge at the level of particular cell types or neuronal circuits, it is imperative that we increase our understanding of how behavior and cognition arise from the activity of these neuronal networks. Neural activity and neurotransmitter systems have been tied to many cognitive functions and behaviors that are impaired in disorders, such as impulsivity (Robbins 2002), working memory (Goldman-Rakic 1996; Arnsten 2011), reward expectation and value (Schultz 2007; Roesch et al. 2010), and fear extinction (LeDoux 2000; Letzkus et al. 2011). In some cases, the neuronal activity underlying these behaviors has been further focused on various cell types interacting as microcircuits or broadened to examine macrocircuit interactions across brain regions. Based on knowledge gained from animal neurophysiology and neuropsychopharmacology studies, testable hypotheses about human neural circuit dysfunctions have been proposed and tested in animals. For example, Homayoun and Moghaddam (2008) have suggested that the orbitofrontal cortex (OFC) is a site of convergence for both dopaminergic antipsychotics (established schizophrenia treatments) and metabotropic glutamate agonists and positive allosteric modulators (novel treatments) to normalize OFC activity that has become aberrant via altered excitatory-inhibitory
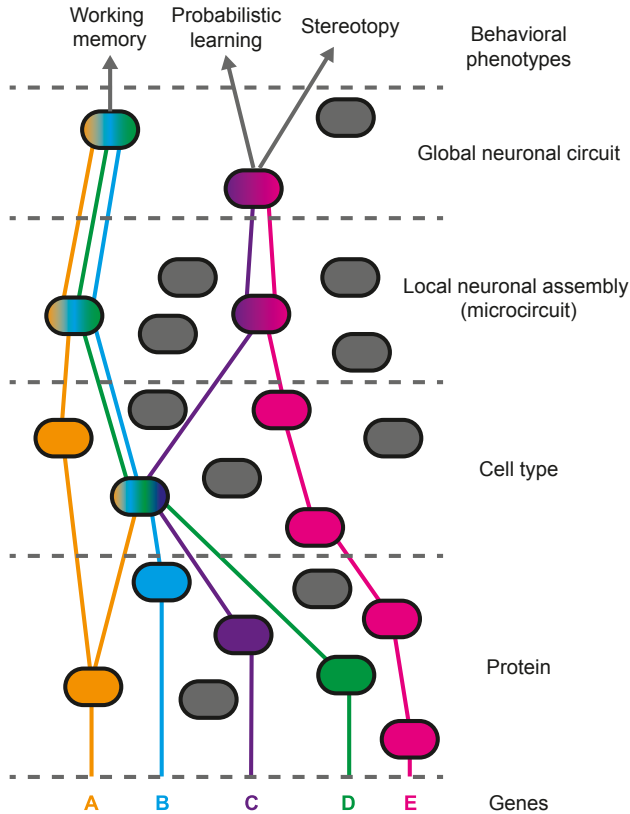
Figure 3.2 Multiple, interacting pathways to disease span biological levels. Each level provides unique pathways to disease. Genes A and C are part of the neuroligin family, which is associated with autism and schizophrenia (possibly through interaction with neurexin) (Carroll and Owen 2009; Sun et al. 2011; Kenny et al. 2014). Gene A is neuroligin-2, which drives changes in the synaptic targeting between excitatory, glutamatergic cortical pyramidal neurons and inhibitory, parvalbumin-containing interneurons (Gibson et al. 2009). Gene C is neuroligin-3, which affects excitatory, glutamatergic synaptic formation on D1 dopamine receptor expressing nucleus accumbens neurons that are involved in learning-motivated behaviors (Rothwell et al. 2014). Gene B effects cell division cycle 42 (cdc42) mRNA expression, which is reduced in schizophrenia and has been shown to reduce dendritic spines on layer 3 prefrontal cortex (PFC) pyramidal neurons, thus effecting prefrontal cortical excitatory-inhibitory balance in a layer-specific manner that is critical for cognitive faculties such as working memory (Goldman-Rakic 1995; Hill et al. 2006; Lewis et al. 2012). Gene D is neuregulin 1 (NRG1), which is associated with bipolar disorder and schizophrenia and is associated with PFC activation during working memory tasks (Nicodemus et al. 2010). Its effects are mediated by interaction of its protein product with an enzyme (γ-secretase), which further regulates gene expression via intracellular signaling. Gene D highlights an example of genes interacting with genes. One consequence of this pathway is altered excitatory synaptic transmission (Fazzari et al. 2014), Finally, Gene E is the dopamine transporter (DAT) gene, which affects dopamine neurotransmission in striatum by altering reuptake.

balance. In other circuit models, Grace (2006, 2010) has suggested that aberrant interaction between the prefrontal cortex (PFC), limbic subcortical areas, and neuromodulatory brainstem structures during stress could provide the basis of comorbid mood disorders, schizophrenia, and addiction. Dysfunctional circuits have, to some degree, also been discovered in humans. A hyperactive subgenual cingulate leads to dysregulation of a network of brain regions associated with numerous symptoms of depression and direct electrical stimulation of this cingulate node normalizes activity in the rest of the network and can cause remission or lessen symptoms (Mayberg et al. 2005). Additionally, individuals with posttraumatic stress disorder are thought to have inadequate PFC excitatory control over inhibitory interneurons in the intercalated nucleus of the amygdala, which provides local inhibition of the amygdala neurons that trigger automatic expression of behavioral responses to fearful stimuli. A lack of PFC excitation to the locally inhibitory cells of the intercalated nucleus removes the internal dampening of fear-related amygdala activity that occurs during learning to extinguish stimulus-evoked fear responses (Parsons and Ressler 2013).

The challenge of understanding how neurons and neural circuits give rise to behavior will require not only acquiring additional data, but interpreting data from a computational perspective. Rieke et al. (1997) have described the computations performed by neurons that encode perception. According to their overview, the neuron's only glimpse of the world that we perceive, a world which is full of random and dynamic stimuli, comes from discrete spikes emitted by sensory receptors which must be continuously decoded by neuron upon neuron (and so on) to provide a continuous readout of the world. The authors describe the computations that neurons could perform to represent the world using single, discrete spikes. *One challenge for computational neuroscience is to translate ideas such as these beyond perception and into how neurons represent mood, memories, values, and so on. Further, these ideas must be*

Figure 3.2 (continued)   Note the overlap between the pathway formed by gene B and gene D, which both effect PFC working memory related neuronal activity, possibly by both effecting a common microcircuit parameter (cortical pyramidal neuron dendrite formation). Moreover, note that gene A also effects synaptic targeting, albeit in a different class of cell types, thus modulating microcircuits in a different manner. Finally, there is overlap between gene C and gene E, which may both affect glutmatergic input to nucleus accumbens and its modulation by dopamine, which is a critical component of learning from positive reinforcement (impaired in schizophrenia; Strauss et al. 2011) and controlling goal-directed movements (impaired in autism; Rothwell et al. 2014). Note that the striatal microcircuit affected by genes C and E differ from the prefrontal microcircuit affected by genes A, B, and D, although they may all contribute to symptoms of schizophrenia by affecting different global neuronal circuits. Fault tree analysis (see MacDonald et al., this volume) might be helpful in organizing these data. Tools of studying complex, nonlinear dynamic systems may also be useful in interpreting these data (see text).

integrated with our understanding of the genetic networks that regulate the neurophysiological characteristics of a neuron and how neurons wire together.

Finally, we must of course recognize that the brain is not static: it evolves over time, through neural development as well as through experience. Genes can raise the risk for illness by conferring susceptibility to environmental risk factors, which are experienced at particular points in time, like the polymorphisms in the serotonin transporter promoter that raise the risk for depression only within the setting of early childhood stress (Caspi et al. 2010). Other environmental events only raise the risk for psychiatric phenotypes when they occur at particular times in development, presumably during critical periods of growth and change in the physiology and anatomical connectivity of the brain (Lodge and Grace 2008; Hradetzky et al. 2012). Similarly, the treatments that reverse the effects of time-sensitive insults can have greater effects if they are administered during specific time windows (Du and Grace 2013). These findings have been interpreted within the familiar concept of developmental critical periods, namely, by proposing that genetic factors interact with developmental changes to increase susceptibility to stress-induced psychiatric disorders (Lodge and Grace 2008). In summary, neurodevelopmental trajectories are yet another source of complexity in the etiology of psychiatric disorders.

An additional type of trajectory, which we call "neuroadaptive," is derived from the disease process itself and is thought to contribute further temporal complexity to the etiology and primary prevention of psychiatric disorders. For example, perinatal gene–environment interactions during development might shift the normal gene-guided pruning of excitatory glutamate synapses into a presyndromal disease state of overly reduced glutamate synapses (Feinberg 1982; Weinberger 1987; Lieberman et al. 2001; Lewis and Levitt 2002; Fusar-Poli et al. 2014). This disease state of hypoexcitation will, itself, evoke neuroadaptive changes, such as the reduction of inhibitory GABA that serves to rebalance the reduced excitatory glutamate synapses (see Krystal et al., this volume; Volk and Lewis 2014). These types of neuroadaptive changes—driven by the disease process itself—will also have a trajectory that affects genes and brain circuits throughout the course of the disease. Thus, there are complex gene–gene, gene–environment, and brain circuit interactions that dynamically change in relation to the timing of both neurodevelopmental periods and neuroadaptive periods. Moreover, neuroadaptive processes occur in the context of treatments that are provided to the patient. Recall, for example, that administration of an antipsychotic dopamine antagonist alters the subsequent response to novel antipsychotic medications that primarily affect GABA in animal models of schizophrenia (Gill et al. 2014). It is highly likely that treatment alters the course of neuroadaptive processes during disease. *Methods are needed for representing these complex data sets and their interacting temporal dynamics.* Computational models are appropriate for addressing this complexity by functioning as tools to identify fundamental factors (or combinations of factors) that contribute to disease.

Summary of the Complexity Challenging Psychiatry

Psychiatry must confront these sources of complexity and heterogeneity in its attempt to become ever more biologically grounded. Psychiatric disease is due to the dysregulated function of neural circuits, and this disruption arises from the temporally dynamic interplay of genetic, environmental, developmental, and neuroadaptive factors. Each of these factors, rather than being viewed as noise to be eliminated from psychiatry, are opportunities to provide a more biological foundation to psychiatry. The missing piece is a framework—perhaps probabilistic or mathematically explicit—that represents this complexity in a way that benefits psychiatry. In the next section, we turn to the potential for computational approaches to provide this much needed framework.

How a Computational Approach Can Be Useful

Psychiatry desperately needs greater neurobiological understanding, better diagnostic accuracy, and improved treatment and prevention strategies. Here we discuss how computational approaches might be used to address these challenges because they are suitable for representing and drawing inferences from the complexities discussed above. We outline two potential ways that computational psychiatry can be useful: (a) by providing a sophisticated set of tools and techniques (from fields such as machine learning and nonlinear dynamical systems) to analyze data in ways that are more powerful than customary statistical approaches, and (b) by providing a formal framework for theory and model development in psychiatry (Maia 2015).

Reducing Complexity of Presentation: Improving Diagnoses

Diagnosis in psychiatry is based on clustering enigmatic symptoms, rather than biological ground truths. This diagnostic framework unfortunately lends itself to symptoms that span multiple disorders, which produces a large amount of comorbid diagnoses. A second consequence of this diagnostic framework is that the label given to a group of patients may cluster patients with different disorders, which have different biological causes or risk factors. Computational approaches clearly have a role in helping to construct more useful diagnostic symptoms (see Flagel et al., this volume).

One approach to improving diagnoses is to ground observations in a more objective framework. Some objectivity may be obtained by simply reconceiving enigmatic, self-reported symptoms (e.g., delusions) as objective cognitive variables that can be measured in behavioral tasks. For instance, computational methods have been used to reconceptualize anhedonia, which is present in both schizophrenia and depression and contributes to comorbid diagnoses between these disorders. Theoretical models of reinforcement learning have been used

to place anhedonia into a biological framework by relating it to underlying cognitive processes. Viewing anhedonia from the perspective of reinforcement learning has shifted the emphasis of study away from the severity of anhedonia and toward the cognitive operations that might be associated with the experience of pleasure. For example, these models have suggested that anhedonia in schizophrenia should be reconceived as dysfunction of the cognitive process by which subjects decide to explore their environment (Strauss et al. 2011). In this interpretation of schizophrenia symptoms, anhedonia is actually a reduced tendency to explore actions that could improve their status quo, rather than an altered experience of reward or reward learning. Similiarly, an important meta-analysis of studies has also reconceived of anhedonia within a framework of cognitive operations during major depression (Huys et al. 2013). This work has revealed that major depression and anhedonia were more strongly associated with the appetitive aspects of reward (i.e., the experience of reward) than with reductions in the rate of reward-related learning. Reductions in other dimensions of reward were also noted and have been studied computationally using reinforcement theory models (Chen et al. 2015). As a whole, consideration of the work by Strauss et al. (2011) on schizophrenia and Huys et al. (2013) on depression suggests that patients with a comorbid diagnosis who self-report anhedonia might be diagnostically reclassified using the model parameters derived from fitting their behavior on computerized tasks that dissociate exploration, appetitive behaviors, and learning rate. Indeed, there is growing evidence that these models of reinforcement learning apply to anhedonia as a transdiagnostic dimension of psychiatric disorders (Whitton et al. 2015).

Even without a formal, conceptual model for behavior, more descriptive (yet still quantitative) formalisms (e.g., machine learning or dynamic causal modeling) may be useful. With sufficient data, tools might be developed for predicting the chance of suicide by using data to classify patients into diagnostic groups or dimensional clusters, mapping the landscape of causes and inferring endophenotypes, weighing gene–environment interactions for use in prevention, selecting appropriate treatments, and diagnosing and predicting response to treatment. For instance, a model could predict how the co-occurrence of anhedonia and lack of social support increase the chance of a depressive episode. In addition, by including task performance measures of anhedonia that focus on specific parameters, such as sensitivity to reward or tendency to explore for new rewards, these models may provide more accurate task-based predictors of disease course and treatment response, which are the formal purpose of diagnoses. As noted above, these descriptive models may be combined with theoretical models that quantify task performance and generate parameters, and can then be used as data in descriptive models to predict illness or treatment response.

As a specific example, consider again the clinical vignette illustrating the case of Peter, who expressed symptoms of bipolar disorder and schizophrenia. A clinician would greatly benefit from a single number that would express

the likelihood that Peter had schizophrenia or bipolar disorder. Functional and anatomical connectivity differ between schizophrenia and bipolar disorder (reviewed by Krystal et al., this volume). Connectivity is an example of a complex system, which can be analyzed and quantitatively described using mathematical methods, such as graph theory and information theory (Boccaletti et al. 2006; Bullmore and Sporns 2009; Quian Quiroga and Panzeri 2009). Although mathematical theories of complexity in the brain are extremely nascent, some attempts have been made using these theories to provide a single variable that uses EEG or fMRI signals to quantify arousal or level of consciousness into a single number (Tononi 2004; Gosseries et al. 2011). The same approach could be applied in diagnosis of psychiatric disease. One such study used information theoretic methods to generate a quantification of complexity which was predictive of later development of autism (Bosl et al. 2011). Thus, one could imagine quantifying the complexity of connectivity (or some other predictive measure) in Peter, and determining whether that quantity was more similar to patients with bipolar or schizophrenia, to arrive at the probability of either diagnosis.

An alternative diagnostic approach might be fault tree analysis (FTA) (see MacDonald et al., this volume). One important goal of psychiatry is to integrate data across complexities and make predictions. For instance, changes of small effect size interact and accumulate in ways that are not simple to visualize and quantify. FTA provides a probabilistic framework that can compute the probability that genetic, environmental, and physiological evidence, as well as evidence of stable traits, impacts behavior and symptoms. In the case of suicide, many genetic, environmental, and behavioral/cognitive observations predict suicide. In the FTA framework, these observations can include protective or resiliency factors (e.g., personality traits, being in a romantic relationship). Critically, an emergent property of FTA is that multiple observations can interact in a probabilistic manner to produce dimensional symptoms that overlap across disorders. Three limitations of the FTA framework are: (a) it addresses discrete (categorical) variables, (b) it can only combine variables according to Boolean operators, and (c) it assumes that the relations are known *a priori*. Psychiatry, however, often addresses (a) interval variables that can (b) exhibit complex probabilistic relations for which (c) we do not know the relations *a priori*. Probabilistic graphical models provide an alternative to FTA (Koller and Friedman 2009; Pearl 2009b). These models have a richer framework that can address multiple types of variables (including categorical and interval); this allows different types of conditional probability relations to be specified (i.e., is not limited to Boolean operators) in which the relations between variables can be automatically learned from data. Both FTA and probabilistic graphical models hold the promise of diagnoses that represent breakdowns in specific elements (or combinations of elements) within the complex system that is the brain.

Improving Treatment

Improving how patients are assigned a diagnostic label will also improve treatment selection and monitoring of treatment response. For example, re-conceptualization of anhedonia within a reinforcement-learning model framework has led experimentalists to study the neural mechanisms associated with depression using behavioral tasks that have been informed by these models. These efforts have drawn attention to circuits previously implicated in reward (Pizzagalli et al. 2005; Kumar et al. 2008) and the mechanisms of antidepressant treatment (Herzallah et al. 2013). Subsequently, these circuits have been probed with regard to compromised functional connectivity in depression and response to circuit-based treatments (Downar et al. 2014). Thus, by rendering symptoms into constructs that can be studied with computational and experimental approaches, models of reinforcement learning have provided new windows into studying neurobiological mechanisms and potentially designing new treatments.

Similarly, models might also serve as a way to improve existing treatments. Learning models, for instance, permit one to reverse engineer the causal factors in cognitive behavioral therapy, enabling efficacy predictions of efficacy against depression (see Huys, this volume). Advances in methodology and the increased availability of computer power has allowed increasingly complex models to be tested and validated (Huys et al. 2012, 2015a). The resultant models suggest that specific psychotherapeutic interventions might be efficacious in particular types of patients, classified by their relative impairments in specific processes implicated by these models. Huys (this volume) reviews how these computational approaches have been used for assessing the need for, and response to, cognitive behavioral therapy.

Understanding Neurobiological Complexity

Another component of complexity is the multitude of genetic, environmental, neurodevelopmental, and neuroadaptive factors that cause disease. Here, too, computational models could be tremendously helpful for understanding how these factors dynamically interact and mechanistically cause psychiatric disorders.

Gene–gene interactions are now being studied in the context of complex networks (Barabási et al. 2011). The goal of these computational models is to define simple mathematical rules that describe how components of the network interact and use those mathematical formalisms to predict how perturbations of the network will change it. This type of computational approach has been studied in many different contexts, from gene–gene interactions, to neuronal interactions, to social interactions (Boccaletti et al. 2006; Bullmore and Sporns 2009; Barabási et al. 2011). Future work can build on these gene- and neuron-based networks by integrating them together and including environmental

information. The goal of such network models could be, for example, to predict how perturbations, like stress, occurring at a particular neurodevelopmental period, affect gene expression and neuronal activity.

The above approach will require the integration of large amounts of data that span multiple levels (genes to environment to neuronal circuits). The same approach has been used in the context of computational models of reinforcement learning to improve the accuracy with which they predict behavioral performance (Luksys et al. 2009). In their work, Luksys et al. used a simple reinforcement-learning model that learns the value of various states and actions; however, they insightfully incorporated additional variables that modulated the model's learning. These modulatory variables spanned multiple levels, from genes to neuronal circuits: they reflected changes in arousal, attention and learning rate, and the tendency to explore new choices. Importantly, these modulatory variables were configured using the subject's (mouse) genetic endowment; arousal- and attention-related neurotransmitter (norepinephrine) levels; stable traits for anxiety, responsivity to stress, responsivity to novelty, and arousing situations; and task performance history and experience. Critically, in comparison to traditional reinforcement-learning models, this broader model, which incorporated data from many biological levels, was able to better predict the behavioral task performance. In summary, the biological cause(s) of symptoms and disorders emerge frothe complex and rich interactions between genes, environment, and neural circuits. By incorporating all of these data together into a computational model of reinforcement learning, we may obtain models that more accurately fit human task performance during learning. Moreover, in line with the discussion of diagnoses above, the parameters generated by the model fit may help to reconceptualize some enigmatic symptoms in a cognitive or decision-making framework, which could be useful for splitting patients into different diagnostic groups.

Taking Advantage of Temporal Complexity

One of the needs of psychiatry is the ability to predict the onset and stage of a disease using biomarkers. A wealth of genetic, anatomical, neurophysiological, and behavioral data is available to apply computational approaches to build predictive models. One recent study used machine-learning methods to classify and separate controls from individuals diagnosed with schizophrenia (Pettersson-Yeo et al. 2013). Furthermore, the method was able to distinguish correctly the stage of the disease, in that it separated prodromal individuals from syndromal (first episode psychosis) individuals. The data set highlights the usefulness of combining multiple types of data, including cognitive task performance. In this work, Pettersson-Yeo et al. (2013) used anatomical data obtained using structural and functional MRI, white matter topography data obtained by diffusion tensor imaging, genetic SNP data, and cognitive task performance. The inclusion of cognitive task data in analyses of this type is

critical because other studies have demonstrated improved patient classification when the data set includes parameters derived from fitting theory-driven (e.g., reinforcement-learning) models to the behavioral data (Wiecki et al. 2015). These studies highlight the usefulness of computational methods for determining the onset and stage of disease, specifically, by incorporating a wide range of multilevel genetic, neural, and behavioral data.

Similar approaches on broad data sets that span multiple biological levels may assist efforts toward primary and secondary prevention of disease. For example, machine learning has been used as a tool to produce a potential biomarker that predicts adolescent drug use (Whelan et al. 2014). It is conceivable that this tool could be used to select vulnerable individuals for targeting efforts aimed at primary prevention of disease. Whelan et al. (2014) conducted a longitudinal study that incorporated personality traits, task performance, environment, and genetic endowment. Their work revealed that life experience (e.g., romantic relationships) in combination with neurobiological and personality characteristics can predict the emergence of future adolescent drug use. Therefore, machine-learning methods could be used to screen for vulnerability to future drug use, and primary prevention efforts could focus on removing this risk factor to lower the incidence of mental health disorders in college students.

Another recent study that used a novel computational approach to predict the transition from the prodromal stage to psychosis should be highlighted here: Bedi et al. (2015) note that one of the prominent symptoms of schizophrenia, which begins in the prodromal stage, is aberrant speech. Clinicians often pick up on aberrant speech during patient interviews. Bedi et al. (2015) used computational methods to decode informative patterns in speech from prodromal (ultra high risk) individuals and found that this method predicted transition to psychosis better than a psychiatrist, and better than biological signals obtained from fMRI. Although many computational approaches are focused on the biology (genes, physiology, and neural circuit connectivity and activity), this example highlights some uniquely human symptoms, such as language, which may be particularly amenable to computational approaches that aid in diagnosis or tracking the stage of a disease.

Moving Toward Prevention

A key unmet goal in psychiatry is the transition from treating disease to preventing it. There are two chief forms of prevention: primary and secondary. Primary prevention aims to stop individuals from contracting an illness. Secondary prevention aims to stop an illness from progressing. Neither is currently possible for most, if not all, psychiatric diseases; either would be tremendously beneficial to patients. Computational methods could, in principle, help with identifying methods for either primary or secondary prevention.

To achieve primary prevention in psychiatry is to mitigate the effects of the above-mentioned genetic, environmental, and stable trait-risk factors.

Approaches aimed at understanding the interactions between these factors, therefore, might reveal mechanisms to reverse or compensate for risk. It is important, however, to note that these factors do not always confer "risk." The exact same factor can provide risk in some contexts, whereas it is actually protective against disease in other contexts. For example, animal models have demonstrated that stress can have both maladaptive and protective effects on neural circuits and the propensity to develop psychiatric disorders (Ladd et al. 2005; McEwen 2006). Thus, efforts to prevent psychiatric disorders must take into account the ability of a single factor to have opposing contributions to disease, depending on the other factors that are present.

Efforts toward primary prevention are also stymied by an unclear picture of what constitutes the formal onset of the disease. The onset of anxiety disorders (Beesdo et al. 2009), schizophrenia (Eaton et al. 1995; Levine et al. 2011a), and autism (Zwaigenbaum et al. 2009; Brian et al. 2014) is variable across individuals. In schizophrenia, for example, the predromal (before symptoms) and prodromal (some signs of dysfunction but no frank psychosis) stages could reflect the presence of risk factors which may or may not guarantee development of schizophrenia symptoms. Without an accurate time point for disease onset, it is thus not clear what risk factors should be the focus of primary prevention efforts, nor is it clear when preventative efforts should be made. Here again, computational approaches might be helpful, if formal models, which characterize diease progression from a biological standpoint, can be developed to predict disease stage and progression.

Efforts toward effective secondary prevention will also require understanding how biological systems change with disease onset and progression. The prodromal stage of schizophrenia contains subsyndromal symptoms, such as abnormal thoughts and perceptions, anxiety and irritability, cognitive problems, and social withdrawal (McGlashan 1988; Seidman et al. 2010; Giuliano et al. 2012). This collection of symptoms has been termed "attenuated psychosis syndrome" or APS (Fusar-Poli et al. 2014) and clear biological correlates of APS have been reported (Howes et al. 2009; Egerton et al. 2012; Fusar-Poli et al. 2013a; Bernard et al. 2015; Chan et al. 2015), which suggests that there are biological targets for prevention of continued progression of the disease to the chronic stage. Furthermore, there are other biological changes that occur later in the syndromal and chronic stages of the disease (Krystal et al., this volume).

Although it is a source of complexity, disease stage-specific biology provides an opportunity for secondary prevention efforts that target stage-specific biological processes. Indeed, there is some evidence that stage-specific treatments succeed during the prodromal stage of schizophrenia. For example, cognitive behavioral therapy and omega-3 polyunsaturated fatty acid supplementation appear to be effective interventions precisely during the prodromal stage (Addington et al. 2011; Morrison et al. 2011; van der Gaag et al. 2012). Secondary prevention, using treatments that target stage-specific biological processes, will rely on searching for biological correlates and testing

mechanistic hypotheses about the etiology and progression of disease; for example, animal models can test hypotheses about how perinatal dietary intake of omega-3 polyunsaturated fatty acids affect glutamate synapses (Bondi et al. 2014). In summary, the ability to enact secondary prevention to halt the progression of disease will rely on detecting the onset of disease and determining stage-appropriate treatments.

There are already areas where computational models have suggested therapies aimed at secondary prevention. These computational models fall into two categories: biophysical and theoretical (e.g., reinforcement learning). For example, biophysical models have suggested that mGluR2/3 agonists could prevent the progression of schizophrenia if administered at the right phase of illness (see Krystal et al., this volume). Another example comes from Parkinson disease research, where reinforcement-learning models combined with biophysical models have suggested that adenosine drugs are useful, during the early stage of Parkinson disease, for preventing the aberrant motor learning that underlies some of the chronic motoric impairment (Beeler et al. 2012). In these studies, dopamine D2 antagonists were used to model Parkinson disease by inducing direct motor performance deficits in rodents, but they also induced aberrant learning, which interfered with subsequent performance, even after drug washout. Computational models of the basal ganglia simulated this pattern via biophysical modeling of the effects of D2 antagonists on the excitability and plasticity of neurons that represent action costs, which were modeled by a reinforcement-learning (theory-based) model. The computational modeling study suggested that the blockade of adenosine receptors could reverse the plasticity underlying aberrant learning without affecting direct motor performance. This computational interpretation implies that adenosine antagonists might be fruitfully applied during the early disease stage to prevent further aberrant learning and progression of symptoms. In addition to suggesting biological pathways for secondary prevention, this computational interpretation provides novel testable hypotheses for animal models of action and learning in health and disease.

Finally, we highlight another type of computational approach, a hidden Markov model, which has not been extensively used to model disease progression, but may be useful for predicting the transition from one disease stage to another by taking into account the underlying biological changes. In psychiatry, it would be helpful to predict the transition from abstinence to relapse in addiction or the transition from the predromal, prodromal, syndromal, and chronic stages of schizophrenia. Current data suggests that intermittent and attenuated psychotic symptoms predict psychosis in only 30% of patients, whereas the remaning patients do not transition to psychosis or are subsequently diagnosed with bipolar disorder instead of schizophrenia (Fusar-Poli et al. 2013a). The benefit of hidden Markov models is that they can be used to model states that you cannot directly measure in humans (e.g., glutamate synaptic dysfunction, GABA deficit, synaptic downscaling, and atrophy). These states are assigned

a probability based on what can be measured (e.g., using EEG, MRS). These models may allow inference of the neurobiological states and the corresponding disease stage of the patient.

Predicting Punctate Events

Finally, we wish to draw attention to the potential utility of models that predict punctate events. Such events include taking a drug, self-harm, suicide, sexual offense, and dangerousness to others. Between 1999 and 2009, suicide accounted for an average 34,523 deaths per year in the United States (CDC 2014). Furthermore, while 41,149 deaths occurred due to suicide in 2013, there were 1,028,725 attempts (USA Suicide 2013). Preventing suicides would have a huge impact on society. How accurately might the clinician predict the likelihood of a suicide attempt, based only on the information available in a typical case, as illustrated in the clinical vignette of the patient Jennifer? A decision to release a patient from a secure psychiatric facility is based on predicting whether they will attempt suicide in the next few hours or days, not over the next five years. Yet studies that have estimated the accuracy of suicide prediction suggest that our abilities to predict acute risk are woefully inadequate. Suicide is associated with factors such as psychiatric disorders, history of suicide attempts, insomnia, and self-reports of suicidal ideation (e.g., answering yes to "have you felt that life is not worth living?"). Jennifer meets criteria for diagnosis with major depressive disorder, she has insomnia, and she has suicidal ideations. Furthermore, she appears to have stable traits ("she was always a worrier") that could contribute to her predisposition for mood disorders and suicide. Although a suicide attempt appears likely in the long run for Jennifer, it is extremely difficult to predict the timing of that attempt over the short term. Thus, the decision to release her or not is a seemingly impossible scenario. One study that used the above factors as predictors of suicide attempt had only a 55% sensitivity (Pokorny 1983). Using self-report of suicidal thoughts alone to predict a suicide attempt is also likely inadequate. Approximately 9.3 million adults in the United States reported thoughts of suicide in 2013, yet there were considerably less (approximately 1 million) attempts (USA Suicide 2013; Substance Abuse and Mental Health Services Administration 2014). An alternative approach for prediction is to use biological factors, rather than self-reports and symptoms. Genetic polymorphisms and stress-related hormones (both available in saliva or blood samples) have some demonstrated usefulness as potential biomarkers that predict suicide, but not enough to warrant being used as a decisive criterion for holding a patient (Caspi et al. 2003; McEwen 2015). Here, computational approaches could help weigh various factors and make a prediction. For example, Bayesian methods based on biological factors (immune and inflammatory proteins) have improved sensitivity in comparison to predictions made using self-report and symptoms alone (Amsel and Mann 2001; Mann et al. 2006).

Theoretical models based on decision theory and reinforcement-learning models have also been proposed as a means of predicting suicide. For instance, game theoretic models have examined suicide attempts from the perspective of signaling others (e.g., family, physicians, bystanders) and influencing their behavior (Rosenthal 1993). Decision theoretic models can also examine suicide from the reinforcement-learning perspective of death being a "goal" to be obtained by a self-harming action. The goal, albeit an abnormal one, is associated with probabilistic risks, costs, and values, just as any other goal would be; in addition, the actions, in this case self-harming, can be associated with probabilities of obtaining the goal and amount of control over impulsively taking a self-harming action. These types of variables and their ability to predict a decision are commonly used in models of decision making (for a review, see Frank as well as Huys, this volume). Furthermore, these variables are quantifiable using behavioral tasks and have been found to be altered in individuals who attempt suicide. Suicide has been associated with impulsivity (Nock et al. 2009), altered emotional processing (Pisani et al. 2012), and altered valuing of future events (Courtet et al. 2011). We propose that models of reinforcement learning and agent-based choice models, which take these factors into account, could learn to "avoid" the suicidal goal or maladaptively learn that suicide has the highest utility out of all available choices.

How could these reinforcement-learning models be used to predict suicide? Models which "pathologically" learn to choose suicide could be fit to the behavior of patients measured in computerized decision-making tasks. The extent to which a patient's behavioral task performance is fit by a reinforcement-learning model, with the goal of attempting suicide, could provide a quantitative measure for their actual propensity to make an attempt. The model would incorporate the patient's valuation of suicide and other outcomes (such as seeing a loved one) and their ability to control impulsive actions that are self-harming. There is evidence that latent variables, such as impulse control and emotional state, can be measured in behavioral tasks and used to predict suicidality. For example, Nock and Banaji used computerized cognitive tasks to demonstrate that suicidal individuals bias their responses to emotional, suicide-related stimuli, as reflected in reaction times (Nock and Banaji 2007; Cha et al. 2010; Nock et al. 2010). Quantitative measures, such as reaction times, also allow potentially inaccurate self-reports of intent to harm to be avoided. Nock and Banaji have proposed that self-reports are not useful as a clinical criterion of suicidality, because individuals who are suicidal may lack the insight and reflection to report their intentions accurately, or may attempt to conceal their plans. Agent-based decision-making models could be fit to data in tasks using emotional, suicide-related stimuli so as to provide some model parameters that could be predictive of suicide. Bayesian hidden Markov models are another model type that could be used to infer individuals' beliefs about the utility, risk, and probability of a suicide attempt being successful. Models such as these have been used to infer subjects' beliefs about task structure in other

types of decision-making tasks and have accurately predicted reaction times in those tasks (Paulus et al., this volume; Shenoy and Yu 2011; Ma and Yu 2015). Perhaps similar computational methods can be used to infer individuals' beliefs about the utility and cost of a suicide attempt based on reaction time, eye gaze pattern, and autonomic arousal data from tasks using emotional, suicide-related stimuli.

Limitations and Requirements of Models

Computational models provide a substantial arsenal for addressing issues of heterogeneity and complexity that occur in the computations performed by the brain and in the presentation of symptoms and the time course of disorders. For this endeavor to succeed, it is imperative that psychiatrists, researchers who study biology and neuroscience, and computational researchers communicate in a nonexpert manner. To this end, we have set out some requirements of models from the perspective of interactions between computational modeling research and psychiatry.

Successful use of computational approaches will require that behavioral tasks and data collection are designed with a particular computational model in mind. Models intended to disentangle various multilevel factors that could be implicated in mental illness will be far more useful if the data collected are informed by the model in the first place. For example, one might want to know whether a patient's seemingly maladaptive choices reflect changes in decision making or aberrant reward learning (Collins and Frank 2014). For simplicity, consider the most basic reinforcement-learning model that might be used to fit behavioral data collected to answer this question. This model has two parameters:

1. A learning rate that scales the impact of unexpected outcomes on future reward estimates
2. An exploration parameter that scales the degree to which the model either chooses what it perceives to be the best action or engages in some amount of random exploration

Depending on the behavioral task given to the subject, these model parameters can either be separable or colinear. For instance, if the task is deterministic (each choice always leads to the same outcome), a shallow learning curve could be explained by a low learning rate, a low choice exploration parameter, or both. However, if the task includes choices with multiple levels of reward probabilities, and if the task has sufficient duration to allow learning curves to reach an asymptote, then model-fitting task performance can reveal separable influences of learning and choice parameters. The model parameters will then be useful for answering questions about how a patient's choices are reflected in their decision-making and reward-learning processes. Thus, it is

critical that the task manipulates experimental factors that are most identifiable to the model (or preferably, class of model) being employed. Simulations can be run before any data are collected to optimize the task design. Although it is understandable that tasks which accommodate patients can be difficult to design, it is worth increasing our efforts to design tasks in collaboration with modeling researchers. Importantly, this effort should also be made in modeling task performance in animals, since they are often a source of mechanistic insight into disease etiology and treatment. Finally, if models are to be useful for understanding the etiology of disease and developing novel treatments, they must be robust and validated and capable of generating testable hypotheses for experiments.

In the development of computational models, attempts should be made to build on existing models and integrate models of various types (biophysical, connectionist, etc.), which has been done to a great extent already. They should also continue to integrate vertically across levels (e.g., incorporate genes for the dopamine reuptake transporter and dopamine synthesis in reinforcement-learning models). Finally, models should also be user-friendly and the methods communicated clearly. For example, overfitting impacts reliability and should therefore be communicated when the methods used to design the model are explained.

Recommendations

We close with a set of specific recommendations to guide how computational models can address pressing issues in psychiatry. It is crucial that models are used to provide a biologically grounded and formal mathematical framework to our understanding of psychiatric disorders. The goals of this framework must be to identify critical biological factors and risk factors that predict disease risk, to offer differentially diagnostic criteria, and to define treatment and monitor its efficacy. The discovery of critical factors should be used to refine experimental hypotheses about the etiology and progression of disease. In turn, models should accept iterative updating to generate testable hypotheses in the laboratory setting.

As the field of computational psychiatry matures, the tools and novel schemata that it contributes to diagnosis, treatment selection, and evaluation of treatment response must be realized in practice. This practical impact will depend on outreach to health services providers and incorporating models into how mental health services are provided. We recommend focusing outreach, not only on psychiatrists, but specifically on nonmental health service providers (e.g., primary care physicians, school counselors and teachers, social workers) as these people often make the initial identification of mental illness and treatment decisions.

By focusing on practical applications of computational psychiatry, a complementary, but critical need in psychiatry—management and reduction of costs—may be addressed. For instance, a recent study in England found that the total cost to society of only schizophrenia alone amounts to 11.8 billion GBP annually; this equates to 60,000 GBP per person annually (Andrews et al. 2012). One report from England reports that the total annual costs (in GBP for year 2007) for other psychiatric disorders have been estimated as 7.5 billion (depression), 8.9 billion (anxiety), 4.0 billion (schizophrenia), 5.2 billion (bipolar disorder), and 14.9 billion (dementia) (McCrone 2008). The practical impact of computational approaches on mental health services will hopefully address the urgent need to manage ballooning healthcare costs by determining the most clinically and cost-effective interventions. Even a slight improvement in treatments or ability to predict illness emergence and progression would reduce health costs and improve lives.

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