4

What Does Computational Psychiatry Need to Explain to Capture Mechanisms of Psychopathology?

Facts, Almost Facts, and Hints

Deanna M. Barch

Abstract

This chapter provides specific research examples on the neurobiology of mental illness—using psychosis as a case in point—that may begin to rise to the level of "facts," or at least "almost facts" or strong "hints," about important etiological mechanisms that need to be explained to capture key components of at least some facets of mental illness. These examples are then used to illustrate where computational psychiatry approaches may help. In particular, there is an opportunity to provide links across different levels of analysis (e.g., behavior, systems level, specific circuits and even genetic influences) in ways that can lead to a more unified framework for understanding the apparent multitude of impairments present in psychosis, which may in turn lead to the identification of new treatment or even prevention targets. This chapter also discusses some of the known conundrums about the etiology of mental illness that need to be accounted for in computational frameworks, including the presence of heterogeneity within current diagnostic categories, the vast degree of comorbidity across current diagnostic categories, and the need to reconceptualize the dimensionality versus categorical nature of mental illness.

Introduction

One way to define the field of *computational psychiatry* is to view it as the attempt to *use computational theories of cognition and neuroscience to build*

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

computational models of mental disease and injury. To do this, these theories and models need to capture known features of mental illness at multiple levels of analysis, including information about neurobiological mechanisms, behavior, clinical presentation, course, outcome, and treatment response. This is a tall order, as most psychiatrists and psychologists have a very short list to present when asked to provide the known "facts" about any specific mental illness. Often such facts are at the level of epidemiology or links to specific environmental events (Tandon et al. 2008; Van Os et al. 2008; Brown and Derkits 2010; Vassos et al. 2012); when it comes to neurobiological mechanisms, much less is known. This may, in part, reflect the limits of our currently available technologies, which do not provide the level of *in vivo* examination of neurobiological mechanisms in humans that is achieved in animal models. It may also reflect the real complexity and heterogeneity of the causes of mental illness, and the diversity of pathways that may lead to what appears to be a similar set of outcomes. Further, this state of affairs may arise partly because of our reliance on a set of categories and conceptualizations about the various "types" of mental illness that do not map cleanly onto clear distinctions at the neurobiological level. This latter issue, recognized as a particular crisis point, has led to the emergence of the Research Domain Criteria (RDoC) initiative (Insel et al. 2010; Morris and Cuthbert 2012; Cuthbert and Kozak 2013; Cuthbert 2014a), which is attempting to develop a psychiatric nosology based on variation in known neural systems that link to core aspects of behavior.

In this chapter I provide a few examples of research on the neurobiology of mental illness—using psychosis as an example—that may begin to rise to the level of "facts," though a more conservative stance might frame these as "almost facts" or strong "hints" about important etiological mechanisms that need to be explained to capture key components of at least some facets of mental illness. Following this, I discuss some of the known conundrums about the etiology of mental illness that also need to be accounted for in computational frameworks.

There Is Something Going on with Dopamine in Schizophrenia

The field of psychiatry has long hypothesized a critical role for dopamine in the pathophysiology of schizophrenia, though much of the early evidence for this was based on serendipitous treatment findings and the effects of drugs that stimulate the dopamine system on the emergence of psychotic symptoms. Over the years, numerous researchers have variously argued that dopamine dysregulation is or is not a key feature of the etiology of psychosis. However, in the past several years, the accumulating literature has clearly solidified an important role for dopamine dysregulation in the pathway to psychosis (Howes and Kapur 2009; Bonoldi and Howes 2013; Kambeitz et al. 2014; Howes et al. 2015). It is clear that this is not the only mechanism. It is also clear that there

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

is variability in the degree to which dopamine abnormalities are present across individuals with psychosis and within individuals with psychosis over time. The nature of dopamine dysregulation associated with psychosis is multifaceted. Perhaps the most consistent finding among individuals with psychosis is the presence of increased presynaptic striatal dopamine synthesis capacity (Howes et al. 2012; Fusar-Poli and Meyer-Lindenberg 2013). This increased presynaptic striatal dopamine synthesis capacity is present both in individuals at clinical high risk for psychosis (Howes et al. 2009, 2011b; Allen et al. 2012; Egerton et al. 2013) and in individuals with diagnosed schizophrenia (Lyon et al. 2011), with the most reliable results in the dorsal as compared to the ventral striatum. There is mixed evidence as to whether similar results are present in individuals at genetic high risk for psychosis: at least one study found increases (Huttunen et al. 2008) whereas another did not (Shotbolt et al. 2011).

Research has also shown that this increased presynaptic striatal dopamine is associated with the severity of symptoms during the prodromal phase (Howes et al. 2009), that individuals who go on to develop manifest psychosis had greater presynaptic striatal dopamine availability at baseline (Howes et al. 2011b), and that the severity of increased presynaptic striatal dopamine availability deteriorates as individuals worsen in their psychotic illness (Howes et al. 2011a). Interestingly, there is also evidence that individuals who respond to antipsychotics are more likely to have increased presynaptic striatal dopamine availability than those who are treatment resistant, again pointing to potential heterogeneity in causal pathways (Demjaha et al. 2012). Importantly, this increased presynaptic striatal dopamine availability has been indirectly linked to altered salience attribution and increased attribution of motivational salience to irrelevant features of stimuli (Roiser et al. 2013).

In addition to the evidence for increased striatal dopamine availability, there is also evidence for increased striatal dopamine release following amphetamine administration (Kambeitz et al. 2014). This is present in both medication naive (Abi-Dargham et al. 2009) and unmedicated individuals with schizophrenia (Laruelle et al. 1996, 1999), as well as in individuals with other clinical manifestations related to schizophrenia, such as schizotypal personality disorder (Abi-Dargham et al. 2004). However, these dopamine alterations may no longer be present in individuals in remission (Laruelle et al. 1999). There is also some evidence of increased occupancy of D2 receptors by synaptic dopamine, again with the most robust evidence for dorsal versus ventral striatum (Kegeles et al. 2010).

Dopamine Dysfunction, Behavior, and Brain Function

There is now a robust behavioral, neuroimaging, and computational literature in healthy individuals that provides strong links between various aspects of dopamine function and a number of different components of cognition, learning,

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

motivation, and effort- and value-based decision making (Hazy et al. 2006; Niv et al. 2007; Schultz 2007; Dayan 2009; Samson et al. 2010; Aarts et al. 2011; Cools 2011; Dayan and Walton 2012). As such, one would expect to find evidence that dysregulated dopamine function in psychosis is directly related to impairments in one or more of these aspects of behavior and function. However, it is not clear exactly what one would predict in terms of the direction of these impairments, given the nature of the dopamine dysfunction present in this illness, in that it is less clear how one would expect the interaction of enhanced dopamine availability, increased dopamine release, and increased D2 receptor occupancy to combine to change behavior. As such, this is a domain in which formal modeling could help to make principled predictions and to link across levels of analysis in a way that might clearly point to novel treatment targets. Surprisingly, there is essentially no research that has provided a *direct* link between any measure of learning, motivation, or decision making in humans with psychosis and indices of either increased presynaptic dopamine availability, increased dopamine response to amphetamine, or increased D2 receptor occupancy in schizophrenia. There is, however, indirect evidence that can inform modeling efforts.

Dopamine, Reward Learning, and Motivation in Schizophrenia

There is, of course, evidence that individuals with schizophrenia show impairments in reward processing, learning, and motivation domains that have been strongly associated with dopamine function, though, as discussed in more detail below, it is not clear whether there is a core mechanism that provides a unified account of these impairments. Further, some of the evidence is mixed in terms of impaired versus intact behavior and, as noted above, it has not been directly linked to dopamine function. For example, one might predict that individuals with schizophrenia should show impairments in learning mechanisms supported by dopamine in the striatum, such as the ability to learn what cues predict reward and to update stimulus response associations via striatal-learning mechanisms. However, the evidence suggests surprisingly intact performance on a range of tasks in which learning is either relatively easy or relatively implicit (Elliott et al. 1995; Hutton et al. 1998; Joyce et al. 2002; Turner et al. 2004; Tyson et al. 2004; Jazbec et al. 2007; Waltz and Gold 2007; Ceaser et al. 2008; Heerey et al. 2008; Weiler et al. 2009; Somlai et al. 2011), though with some exceptions (Oades 1997; Pantelis et al. 1999). Further, for the most part, individuals with schizophrenia show intact learning rates on the weather prediction task, a probabilistic category-learning task frequently used to measure reinforcement learning, though with overall impaired performance (Kéri et al. 2000, 2005a, b; Weickert et al. 2002; Beninger et al. 2003; Weickert et al. 2009). There is some evidence that reinforcement learning may be more intact

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

for patients on atypical than typical antipsychotics, though it has been found in those on typicals as well (Beninger et al. 2003; Kéri et al. 2005b). Of course, people can accomplish tasks in many different ways, and intact performance at the level of broad behavioral metrics might arise from varying strategies. Again, this is a domain in which formal modeling might be able to help clarify whether performance is indeed intact using metrics that presumably index a particular approach to performing the task.

In contrast, when the reinforcement-learning paradigms are more difficult and require the explicit use of representations about stimulus-reward contingencies, individuals with schizophrenia show more consistent evidence of impaired reinforcement learning (Waltz et al. 2007; Morris et al. 2008b; Koch et al. 2009; Gold et al. 2012; Yilmaz et al. 2012; Cicero et al. 2014). Interestingly, these impairments may be greater when individuals with schizophrenia must learn from reward versus from punishment (Waltz et al. 2007; Cheng et al. 2012; Gold et al. 2012; Reinen et al. 2014), though some studies also find impaired learning from punishment (Fervaha et al. 2013a; Cicero et al. 2014). Further, recent work suggests that working memory impairments may make a significant contribution to reinforcement-learning deficits in schizophrenia (Collins et al. 2014). Such findings are consistent with the larger literature, which suggests altered cognitive control function in schizophrenia, and are also consistent with the growing basic science literature that suggests important interactions between what have been referred to as "model-free" learning systems (e.g., dopamine in the striatum) and "model-based" learning systems that engage prefrontal and parietal systems, which support representations of action-outcome models (Gläscher et al. 2010; Daw et al. 2011; Doll et al. 2012; Lee et al. 2014; Otto et al. 2015). Given the large body of evidence for altered dopamine function in the striatum in schizophrenia, it is quite puzzling as to why, at the behavioral and functional neuroimaging level, the deficits appear to be more in the realm of the model-based components of learning, which are thought to be supported by cortical systems. This is precisely an area where formal modeling may help us to understand this apparent conundrum.

One might also predict alterations in schizophrenia in the neural signals thought to reflect dopamine-mediated functions, such as reward anticipation or reward prediction error responses. Again, it is not entirely clear what direction of alteration one might predict in schizophrenia, given the nature of the dopamine abnormalities found in this illness. A number of studies have reported reduced ventral striatum activity to reward cues in schizophrenia, both in unmedicated (Juckel et al. 2006b; Schlagenhauf et al. 2009; Esslinger et al. 2012; Nielsen et al. 2012b) and in medicated individuals (Juckel et al. 2006a; Schlagenhauf et al. 2008; Simon et al. 2009; Walter et al. 2009; Grimm et al. 2012). There are some hints that these deficits might not be present in individuals on atypical medications, but these data are from small samples (Kirsch et al. 2007). Some work has found reduced ventral striatal responses to anticipation cues in antipsychotic-naive schizophrenia patients, which improved following

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

atypical treatment (Nielsen et al. 2012a, b). Further, there is evidence that the magnitude of these impairments may vary as a function of the severity of specific types of symptoms in schizophrenia, such as negative symptoms (Juckel et al. 2006a; Simon et al. 2009; Waltz et al. 2010).

Other studies in schizophrenia have also examined prediction error responses using functional neuroimaging: an increase in striatal (potentially dopaminergic) responses to unexpected rewards and a decrease in striatal responses when predicted rewards do not occur. Several studies have found altered prediction error responses in schizophrenia, manifesting as either reductions in responses to unpredicted rewards and larger than expected responses to predicted rewards (Murray et al. 2008; Morris et al. 2012; Schlagenhauf et al. 2014). Gradin et al. (2011) found reduced prediction error responses in the caudate, but increases in the ventral striatum. Waltz et al. (2009) found evidence for reduced positive prediction error responses in a range of regions that included the striatum (dorsal and ventral) as well as insula, but relatively intact negative prediction errors in these same regions. In contrast, Walter et al. (2009) found intact prediction error responses in the striatum for both positive and negative prediction errors. Thus, this literature is quite mixed. There is again suggestion that medication may have a key influence. Insel et al. (2014) found that individuals with chronic schizophrenia taking higher doses of medication showed smaller prediction error responses. However, the fact that reduced prediction error responses have also been seen in unmedicated individuals (Schlagenhauf et al. 2014) argues against such abnormalities resulting only from medication effects in schizophrenia. Again, there is evidence that the magnitude of these impairments may vary as a function of the severity of specific types of symptoms in schizophrenia, such as negative symptoms (Waltz et al. 2009).

There is also a growing literature on altered effort-based decision making in schizophrenia, another function often associated with the dopamine system. The animal literature provides strong evidence that dopamine plays a key role in regulating physical effort allocation and vigor (Niv et al. 2007). For example, dopamine blockade, especially in the accumbens, reduces physical effort allocation (Salamone et al. 2009, 2012; Farrar et al. 2010; Salamone and Correa 2012), and increased D2 receptor expression in the nucleus accumbens of adult mice increases physical effort expenditure (Trifilieff et al. 2013). In humans, Treadway et al. (2012) found that increased dopamine release in response to d-amphetamine in the left striatum and the left ventromedial prefrontal cortex (PFC) was associated with increased willingness to expend physical effort. Based on these data, one might predict that individuals with schizophrenia might not show impaired effort-based decision making or that they might even be willing to expend greater levels of physical effort (at least those not on medication) if schizophrenia is characterized by hyperdopaminergic function. Surprisingly, the opposite has been found.

The majority of the literature on effort in schizophrenia has used physical effort tasks that involve finger tapping (Treadway et al. 2009), a balloon-popping

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

task (Gold et al. 2013), or grip strength as metrics of physical effort allocation. Studies of finger tapping have consistently found a specific pattern of reduced effort allocation in schizophrenia: they do not differ from controls at low levels of reward or low levels of probability of receiving the outcome; they also do not show the same increase in effort allocation as either reward or probability increase (Fervaha et al. 2013b; Gold et al. 2013; Barch et al. 2014; Treadway et al. 2015). The two studies using grip strength showed differing results: one found reduced effort allocation in those with schizophrenia rated clinically as having higher apathy (Hartmann et al. 2015), whereas the other study found no significant differences in schizophrenia (Docx et al. 2015). Two studies have also examined cognitive effort. One study used a progressive ratio task and found evidence for reduced effort allocation in schizophrenia, although the design of the task was such that cognitive effort was confounded with physical effort (Wolf et al. 2014). In contrast, Gold et al. (2015) found little evidence of reduced cognitive effort in schizophrenia across three studies, though these studies did suggest that individuals with schizophrenia had difficulty detecting variations in cognitive effect among conditions.

In summary, the behavioral and neuroimaging literatures do suggest some consistent evidence for impairments in reward processing, reinforcement learning, and motivational functions putatively associated with dopamine in schizophrenia. However, it is not clear how easily the observed patterns map to what one might expect, based on the normative literature about dopamine's role in these functions and the impact that one would expect increased versus decreased dopamine metrics to have on behavior or brain function. Further, none of these studies have directly linked such impairments to variations in dopamine function in schizophrenia. As noted above, this is clearly a domain in which formal modeling, which can take into account the complex interactions among different components of the dopamine systems, could help to make rational predictions about behavior and neural activity, and help to bridge the levels of analysis. Some examples of the types of models that could be relevant are nicely outlined by the contribution of Frank (this volume).

Dopamine, Cognitive Control, and Working Memory in Schizophrenia

Although much of the literature on the role of dopamine in behavior has focused on reward or motivationally related functions, there is also a robust literature on the role of dopamine in other domains, such as cognitive control and working memory. Such theories have argued that dopamine is critical for modulating active maintenance of representations in PFC, potentially by providing a gating signal that indexes the need to update maintained representations (Braver 1997; O'Reilly et al. 1999; Braver and Barch 2002; O'Reilly and

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

Frank 2006), or to modulate local network activity in a way that regulates the maintenance of representations in PFC (Camperi and Wang 1998; Seamans and Yang 2004; Wang et al. 2004; Vijayraghavan et al. 2007).

There is a huge literature documenting that individuals with psychosis experience deficits in working memory and cognitive control (Barch 2005; Lee and Park 2005; Forbes et al. 2009), with evidence that deficits are present at first episode in unmedicated individuals and in individuals at familial risk for psychosis (Agnew-Blais and Seidman 2013; Bora and Murray 2014; Fatouros-Bergman et al. 2014). Critically, there is also a body of research indicating that cognitive impairment in schizophrenia is a critical determinant of quality of life and function, potentially more so than the severity of other aspects or symptoms of schizophrenia, such as hallucinations and delusions (Nuechterlein et al. 2011; Lepage et al. 2014).

One of the major challenges to understanding the nature of cognitive function in schizophrenia (or psychosis more broadly) is that at least on the surface, individuals with this illness appear to have deficits in a wide array of domains, not just in working memory and cognitive control. These domains include language function, episodic memory, processing speed, attention, inhibition, and sensory processing (Forbes et al. 2009; Mesholam-Gately et al. 2009; Sheffield et al. 2014), with such deficits clearly present even in unmedicated individuals (Fatouros-Bergman et al. 2014). It is unlikely that a single mechanism or model will be able to account for all of these impairments. At the same time, it seems equally problematic, and definitely not parsimonious, to develop different theories or models about the causes of impairments in each of these domains independently. Instead, there are likely several core mechanisms that each contribute to impairments in a number of cognitive deficits in psychosis.

In the spirit of identifying core mechanisms of cognitive dysfunction in schizophrenia, I and others have argued that one such mechanism is a deficit in the ability to actively represent goal information in working memory needed to guide behavior, and that this deficit reflects impairments in the function of the dorsolateral prefrontal cortex (DLPFC), its interactions with other brain regions (e.g., the parietal cortex, the thalamus, and the striatum), and the influence of neurotransmitter systems such as dopamine, GABA and glutamate (Barch et al. 2009; Edwards et al. 2010; Lesh et al. 2011). This framework is based in part on computational modeling work by Cohen and colleagues, which put forth the hypothesis that intact function of dopamine in DLPFC was responsible for the processing of context, and that a disturbance in this mechanism could account for a range of cognitive deficits in schizophrenia (e.g., Braver et al. 1999; Cohen et al. 1999; Barch et al. 2001). We have suggested that impairments in working memory, attention, inhibition, and language processing in schizophrenia can all be understood in terms of a deficit in goal representations, as each of these domains requires the active representation of such context information for effective function (for full discussion, see Braver et al. 1999; Cohen et al. 1999).

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

In more recent years, the role of context processing in cognition and in schizophrenia has been reconceptualized somewhat more broadly as the function of proactive cognitive control (Braver et al. 2007, 2009; Haddon and Killcross 2007; Edwards et al. 2010). This reframing builds upon concepts of context processing to argue for flexible mechanisms of cognitive control that allow humans to handle the range of challenges faced in everyday life. One such theory, termed dual mechanisms of control (Braver et al. 2007, 2009; Edwards et al. 2010), makes a distinction between proactive and reactive modes of cognitive control. Proactive control can be thought of as a form of "early selection," in which goal-relevant information is actively maintained in a sustained or anticipatory manner, before the occurrence of cognitively demanding events. This allows for biasing of attention, perception, and action systems in a goal-driven manner. By goal information, we mean information about what one needs to accomplish in this particular task situation or the intended outcome of a series of actions or mental operations. In real-life settings, such goals may include the main points you wish to communicate in a conversation or the need to organize a shopping trip so that you can make sure to get everything you need. In contrast, in the reactive mode, attentional control is recruited as a "late correction" mechanism that is mobilized only when needed, such as after a high-interference event is detected (e.g., you encounter unexpected distracting stimuli and need to retrieve the topic of your conversation). Thus, proactive control relies on the anticipation and prevention of interference before it occurs, whereas reactive control relies on the detection and resolution of interference after its onset.

A number of prior studies have provided support for these hypotheses concerning context processing, goal representation, and proactive control deficits in schizophrenia using a range of paradigms (for reviews, see Barch and Braver 2007; Barch and Ceaser 2012; Barch and Sheffield 2014, 2016). Further, there is robust evidence that individuals with schizophrenia have difficulty with components of working memory which one might closely link to the mechanisms of proactive control (Barch 2005). Specifically, individuals with schizophrenia show impairments on working memory tasks with all different material types (e.g., verbal, spatial), and there is relatively little evidence for selective deficits with one material type over another (Lee and Park 2005; Forbes et al. 2009). In addition, they consistently show deficits on tasks designed to measure a range of functions ascribed to the "central executive" component of working memory, including manipulation (Kim et al. 2004; Horan et al. 2008), interference control, and/or dual-task coordination (e.g., Smith et al. 2011) as well as information updating and temporal indexing (e.g., Galletly et al. 2007).

Despite this wealth of evidence for impairments in proactive control, working memory, and other "executive" type tasks, there are also some important conflicting data points. First, the literature on task switching is not seamlessly consistent with ideas about proactive control and prefrontally maintained task

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

representations. In task-switching paradigms, people often show worse performance when they have to switch between tasks and update rules. This effect, however, is reduced when they have a longer time between task cues and stimulus, allowing them to use anticipatory mechanisms to reconfigure task sets prior to applying them to a stimulus. In such situations, one might expect that individuals with schizophrenia would show increased "switch" costs and less of a benefit from a longer time between task cue and stimulus. However, only a handful of task-switching studies have shown evidence for increased task- or response-switching costs in schizophrenia (Elvevåg et al. 2000; Meiran et al. 2000; Franke et al. 2007). Many others have not shown any evidence of increased task-switching costs (Barton et al. 2002; Manoach et al. 2002; Karayanidis et al. 2006; Kieffaber et al. 2006; Greenzang et al. 2007; Jamadar et al. 2010; Manoach et al. 2013), at least not when overall longer reaction times are taken into account. Further, individuals with schizophrenia seem to show as much benefit as controls when there is a longer period between the task-switch cue and the trial (Meiran et al. 2000). The fact that individuals with schizophrenia seem able to use this cueing time to prepare in advance is not consistent with a deficit in proactive control. Ravizza and colleagues have shown task-switching impairments in schizophrenia when the task involved more complex rule switching, but not in a more perceptually based task (Ravizza et al. 2010; Wylie et al. 2010). They argue that task-switch deficits will be more apparent when the rule that needs to be updated is the more complex.

A second conflicting data point is that one would predict that individuals with schizophrenia should have challenges using predictive cues to help them select task-relevant versus task-irrelevant information for encoding into working memory. However, studies by both Jim Gold's and Ed Smith's groups found evidence that individuals with schizophrenia had an intact ability to use predictive cues to guide management of the contents of working memory (Gold et al. 2006; Smith et al. 2011). Gold's group, however, has found strong evidence for impaired working memory capacity (Gold et al. 2003, 2010), and robust evidence that individuals with schizophrenia have difficulties inhibiting the impact of salient distractors in working memory (Hahn et al. 2010). As with the task-switching literature, it is not quite clear why there is not more evidence for impaired predictive control over working memory in schizophrenia, though one could again speculate as to whether introducing a prepotency manipulation might reveal susceptibilities in these mechanisms.

As with the literature on reward processing and reinforcement learning described above, there is almost no evidence directly linking specific types of cognitive impairments to dopamine function in schizophrenia, though there is clearly indirect evidence. For example, a number of studies have linked manipulations of the dopamine system to performance on tasks tapping proactive control in both humans and nonhuman animals (Barch 2004; Chudasama and Robbins 2004; Barch and Carter 2005; Barch and Braver 2007; Cools and

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

D'Esposito 2011). This is consistent with the literature discussed above on a potential role for dopamine in gating representations in working memory that are relevant for maintaining cognitive control (Braver 1997; O'Reilly et al. 1999; Braver and Barch 2002; O'Reilly and Frank 2006). Nevertheless, while such evidence is consistent with the idea that there may be a role for dopaminergic abnormalities in cognitive impairment in psychosis, more direct evidence is needed, as well as formal modeling efforts that can link across levels of analysis.

How Does Dopamine Dysfunction Relate to Other Neurobiological Abnormalities Present in Psychosis?

As described above, there is now consistent evidence for specific types of dopamine abnormalities in individuals with psychosis. However, there is also consistent evidence for other types of neurobiological impairments in psychosis, and it will be important to develop models that allow us to understand the full range of neurobiological factors that may contribute to the emergence of psychosis. As an example, meta-analyses indicate that individuals with schizophrenia show robust evidence for reduced activation in the DLPFC during a range of cognitive tasks, especially those tapping into cognitive or executive control (Minzenberg et al. 2009; Ragland et al. 2009). This consistent meta-analytic evidence for altered activation extends to dorsal parietal and anterior cingulate regions as well, though it is actually increased activity in anterior cingulate (Minzenberg et al. 2009). There is also meta-analytic evidence for a range of alterations in brain structure in schizophrenia, including reduced hippocampal volumes (Vita and de Peri 2007; Adriano et al. 2012), reductions in insula, anterior cingulate, thalamic, and caudate volumes, and increased ventricular volumes (Ellison-Wright et al. 2008; Glahn et al. 2008; Adriano et al. 2010; Bora et al. 2011). There is also some evidence of progression to these brain volume changes, with decreases in whole brain volume and increase in ventricular size over the illness course (Olabi et al. 2011; Vita et al. 2012).

There is also at least some evidence for alterations in other neurotransmitter systems besides dopamine in schizophrenia, with literatures regarding both GABA and glutamate. The evidence for GABA impairment has recently been reviewed by Taylor and Tso (2015) and is nicely articulated by Krystal et al. (this volume). One example provided by the authors was that good data from postmortem studies indicates that certain types of GABAergic interneurons are reduced. Specifically, Taylor and Tso argue that there is consistent evidence from postmortem studies for reductions in 67-kDa isoform of GAD67, localized to parvalbumin (PV)-positive interneurons. This has been found across a number of different brain regions. However, they also note

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

that the *in vivo* studies of GABAergic function in schizophrenia have not yet provided strongly consistent evidence in this regard. Taylor and Tso note that there are at least two types of PV-positive interneurons that could be particularly functionally relevant to understanding cognition and behavior in schizophrenia. One set are the fast-spiking PV-positive basket cells that have been associated with cortical gamma oscillations (Bartos et al. 2007; Sohal et al. 2009), which has in turn been associated with working memory and proactive control (Cho et al. 2006; Lewis et al. 2008a; Minzenberg et al. 2010). The other are chandelier cells, which may play a role in depolarizing and exciting pyramidal cells when they are less active, but potentially inhibiting active ones (Woodruff et al. 2011).

The evidence for glutamate impairment in schizophrenia has recently been succinctly summarized by Howes et al. (2015), with much of the evidence coming from either ketamine studies in healthy adults (which elicit psychotic-like symptoms) or from magnetic resonance spectroscopy studies. Hypotheses around glutamate in schizophrenia tend to focus on hypofunction of the NMDA receptor, though as Howes et al. (2015) note, the evidence for this in postmortem studies is not consistent. A recent meta-analysis examined studies using ^{1}H magnetic resonance spectroscopy (^{1}H-MRS) to examine glutamate and glutamine (precursor to glutamate) (Marsman et al. 2013). This meta-analysis found reduced glutamate in the frontal cortex, but increased glutamine. Marsman et al. suggest that this could reflect a deficit in glutaminase, which normally converts glutamine into glutamate. Howes et al. (2015) also note the growing literature that suggests important links or interactions between dopamine and glutamate dysfunction in the etiology of schizophrenia. The hypothesis is that dopaminergic hyperactivity might be secondary to glutamate dysfunction in regions such as the hippocampus; this, in turn, leads to disinhibition of dopamine neurons in the striatum (Lodge and Grace 2006, 2007, 2011a). As an aside, there is also a literature on modeling of glutamate/GABA interactions with dopamine contributions to working memory that might also inform formal modeling and help us to understand the nature of working memory impairments in schizophrenia (Wang 1999; Seamans et al. 2001; Yasumoto et al. 2002; Lapish et al. 2007; Rolls and Deco 2015).

As yet, relatively little work has been done to link the diverse neurobiological impairments found in schizophrenia. However, there are some intriguing hints. For example, presynaptic striatal dopamine availability has been linked to altered PFC activity during cognitive performance in individuals at clinical high risk for psychosis, with evidence for links with both increased inferior prefrontal activity (Fusar-Poli et al. 2011) and decreased middle frontal gyrus activity (Fusar-Poli et al. 2010). In addition, other work has shown a negative correlation between hippocampal glutamate levels and striatal dopamine in individuals at clinical high risk for psychosis (Stone et al. 2010).

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

How Does Dopamine Dysfunction Relate to Other "Facts" about Psychosis?

A number of consistent epidemiological factors have been associated with the development of psychosis. These factors include, among others, the evidence that pregnancy and birth complications with hypoxia are associated with a higher risk of psychosis in the developing fetus (Cannon et al. 2002; Miller et al. 2011). In addition, other prenatal and perinatal adversities (including stress, infection, malnutrition, maternal diabetes, or other medical conditions) have been linked to psychosis (Brown 2011). Work has also linked season of birth to the rates of schizophrenia (Brown 2011), potentially because season of birth marks the potential risk for the exposure to maternal influenza in the fetus. Intriguingly, offspring with older paternal age are at a greater risk for schizophrenia (Malaspina et al. 2001; Stilo and Murray 2010). How does one integrate such factors with the evidence described above for impairments in dopamine function, glutamate, brain activity, or brain structures? An elegant framework for incorporating these factors into a unified understanding has been made available by Howes and Murray (2014), who have used a neurodevelopmental framework to integrate these seemingly diverse factors. More specifically, they have argued that a number of the early childhood factors associated with increased risk for schizophrenia are ones that are also known to lead to alterations in the dopamine system and at least some aspects of brain structure, such as hippocampal volume. This includes evidence that *in utero* inflammation and exposure, as well as a variety of stress and social risk factors, are associated with altered dopamine function, including stress-related sensitization of the dopamine system. Although these links are primarily conceptual at this stage, they do provide an intriguing way to begin to try to unify our understanding of the diversity of impairments present in psychosis, in a way that may be relatively amenable to formal modeling.

Additional Challenges and Considerations for Computational Psychiatry

Above I very selectively reviewed some "facts," "almost facts," and "hints" about impairments that are present in psychosis, and which may be part of the pathophysiology of this illness. While not at the same level of analysis as the types of mechanisms and impairments described above, there are other "facts" about psychiatric disorders and the presence of varying types of neural impairments that need to be taken into consideration when trying to develop and apply computational frameworks to help us understand etiological mechanisms.

The first is something alluded to at the start of this chapter: we clearly do not have our diagnostic categories quite right, or maybe not even close to right.

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.

This is reflected in the fact that there is huge heterogeneity among individuals with the same diagnoses in terms of the types of symptoms with which they present, with accompanying heterogeneity in the severity of behavioral and neural impairments. Further, there is massive comorbidity across psychiatric disorders, with the same individuals often meeting criteria for many different disorders, and with both symptoms and behavioral/neural deficits shared across putatively different diagnostic boundaries.

The second is that the manifestations of psychiatric disorders vary across the lifetime of the individual, even after the development of manifest illness. Some of this may reflect treatment-related changes, but it may also reflect the interaction of illness factors with normal developmental and/or aging mechanisms. If so, then information about developmental changes in neural mechanisms need to be incorporated into our models so that predictions can be made about factors that may influence emergence, presentation, and treatment at different stages of life.

From "Computational Psychiatry: New Perspectives on Mental Illness,"
A. David Redish and Joshua A. Gordon, eds. 2016. Strüngmann Forum Reports, vol. 20,
series ed. J. Lupp. Cambridge, MA: MIT Press. ISBN 978-0-262-03542-2.