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Clinical Heterogeneity Arising from Categorical and Dimensional Features of the Neurobiology of Psychiatric Diagnoses

Insights from Neuroimaging and Computational Neuroscience

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Abstract

Clinical heterogeneity presents important challenges to optimizing psychiatric diagnoses and treatments. Patients clustered within current diagnostic schema vary widely on many features of their illness, including their responses to treatments. As outlined by the American Psychiatric Association Diagnostic and Statistical Manual (DSM), psychiatric diagnoses have been refined since DSM was introduced in 1952. These diagnoses serve as the targets for current treatments and supported the emergence of psychiatric genomics. However, the Research Domain Criteria highlight DSM's shortcomings, including its limited ability to encompass dimensional features linking patients across diagnoses. This chapter considers elements of the dimensional and categorical features of psychiatric diagnoses, with a particular focus on schizophrenia. It highlights ways that computational neuroscience approaches have shed light on both dimensional and categorical features of the biology of schizophrenia. It also considers opportunities and challenges associated with attempts to reduce clinical heterogeneity through categorical and dimensional approaches to clustering patients. Finally, discussion will consider ways that one might work with both approaches in parallel or sequentially, as well as diagnostic schema that might integrate both perspectives.

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Introduction

> There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know. —Former U.S. Secretary of Defense, Donald Rumsfeld (February, 2002)

The complexity of the neurobiology of psychiatric clinical conditions is sufficiently great, or our knowledge base sufficiently shallow, as to make it impossible to determine with certainty how close we are coming to a precise understanding of any particular symptom or disorder (Wang and Krystal 2014). We lack even a precise understanding of how the brain generates typical adaptive human behaviors, and this undermines our ability to establish reliable and valid psychiatric diagnoses, as reflected in the poor reliability of some psychiatric diagnoses in the initial DSM-5 field trials (Freedman et al. 2013). Yet at the same time, mental health professions are obliged to do all that they can to alleviate the suffering, disability, and mortality associated with psychiatric disorders and to identify new treatments that are safer and more effective than those currently available. Thus, investigators studying the neurobiology of psychiatric disorders in the service of ultimately identifying new treatments are inherently working with an incomplete understanding of the neural processes they are studying or how to fix the relevant aspects of their targeted pathophysiology. To address the limitations in our knowledge, one strategy is to rely on the power of large-scale exploratory or descriptive research in order to map the relevant universe of information, such as sequencing the genomes, epigenomes, connectomes, and microbiomes. These extremely powerful and informative approaches have transformed our understanding of psychiatry (Krystal and State 2014), but they have not yet led to a new treatment. The alternative approach involves informed risk taking through hypothesis building and testing; that is, the development of simplified hypotheses that can be iteratively refined through experimentation. Computational neuroscience may be helpful in this process, as this field of research endeavors to transform conceptual hypotheses about the brain into quantitative models (Sejnowski et al. 1988). In turn, computational psychiatry aims to develop and refine quantitative models to explain the features of psychiatric disorders (Montague et al. 2012; Friston et al. 2014; Wang and Krystal 2014).

The task set before my colleagues and I was to address the question of how computational psychiatry might help to provide insights into the complexity and heterogeneity of psychiatric disorders. This is a wonderful but overwhelming challenge, as there is an enormous body of data but very little insight. In this chapter, we will suggest that biophysically informed computational models can assist in the building of bridges between basic and clinical neuroscience and ultimately shed light on dimensional features within psychiatric disorders, transdiagnostic dimensional characteristics, and categorical features of psychiatric diagnoses. Our discussion focuses on schizophrenia, highlighting both

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dimensional and categorical features of its biology. Lastly, we will consider opportunities and challenges associated with categorical and dimensional approaches to psychiatric diagnosis, particularly with respect to the prospect of developing novel treatments for psychiatric disorders.

Neurodevelopment as a Source of Clinical Heterogeneity: Possible Implications for Illness Phase-Related Aspects of the Neurobiology and Treatment of Schizophrenia

Stable and Evolving Features of Schizophrenia

The presence of a categorical diagnostic system could be viewed as promoting the assumption that the underlying neurobiology of the disorder does not change fundamentally across the course of illness. In the case of schizophrenia, the fact that the same medications are prescribed to patients regardless of their phase of illness would be consistent with this view. However, neurodevelopment has long been thought to play a fundamental role in the neurobiology of schizophrenia, with genetic or environmental etiologic factors early in life giving rise to a complex and evolving illness pathophysiology (Weinberger 1987; Insel 2010; Tebbenkamp et al. 2014; Volk and Lewis 2014). Further, clinical studies have described illness phases that broadly inform current thinking about schizophrenia, including the prodrome, when individuals display subsyndromal features of the illness; the first episode, where full syndromal features of the illness are expressed; the early course of schizophrenia, which is associated frequently with progressive functional decline; and chronic illness, where patients are thought to plateau clinically with episodic exacerbations (Davidson and McGlashan 1997; Lencz et al. 2001; Keshavan et al. 2005; Agius et al. 2010; Insel 2010). Careful study of the chronic phase of illness, particularly in the elderly, reveals that functional impairments and negative symptoms may progress in a subgroup of these patients, associated with reductions in positive symptoms and formal thought disorder (Davidson et al. 1995; Harvey et al. 1997; Harvey 2014). The changes in symptom profiles and functional impairments are thought to have neurobiological underpinnings which might be targeted by novel treatments that might attenuate or even reverse aspects of the underlying biological changes (Breier et al. 1992; Lieberman et al. 2001; Insel 2010). Although there is still a very superficial understanding of the evolving biology of schizophrenia, recent advances suggest some general principles that might inform future studies.

Broadly speaking, schizophrenia appears to be associated with some biological features that do not substantially change with development and others which do. One relatively stable feature, for example, is a disturbance in the functional connectivity of the thalamus. In "high-risk," first episode, and chronic patients, schizophrenia is associated with reduced functional

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connectivity of the thalamus with association cortices and overconnectivity of the thalamus with sensorimotor cortices (Woodward et al. 2012; Anticevic et al. 2014a; Cetin et al. 2014; Klingner et al. 2014; Anticevic et al. 2015b; Tu et al. 2015). Patients with bipolar disorder with psychosis appear to have more disruptions in thalamic functional connectivity than bipolar disorder without this symptom, placing their biology at the boundary of schizophrenia and bipolar disorder (Anticevic et al. 2014b). Figure 16.1 illustrates the dimensional relationship between healthy subjects, people with bipolar disorder, and patients diagnosed with schizophrenia.

In contrast to the relatively stable disturbances in thalamic functional connectivity, schizophrenia appears to be associated with many features of illness that evolve over time (Salisbury et al. 2007; Olabi et al. 2011). For example, various findings suggest the balance of excitatory and inhibitory (E/I) connectivity evolves across the life span. Genetic studies strongly implicate genes associated with the development and function of glutamate synapses in the heritable risk for schizophrenia (Walsh et al. 2008; Malhotra et al. 2011; Gulsuner et al. 2013; Timms et al. 2013). Schizophrenia risk genes appear to be particularly expressed prenatally (Gulsuner et al. 2013). These genetic risk mechanisms may contribute to the deficits in glutamate synapses described in postmortem studies (Black et al. 2004; Glausier and Lewis 2013; Datta et al. 2015; MacDonald et al. 2015; Shelton et al. 2015). Development deficits in NMDA glutamate receptor signaling may stimulate neuroadaptations within pyramidal neurons that restore E/I balance in cortical networks by increasing the intrinsic excitability of pyramidal neurons, such as reductions in GIRK2 (Tatard-Leitman et al. 2015). However, this study suggests that increased basal gamma oscillation power may compromise network function by reducing signal-to-noise balance. Further, animal studies of conditional knockout of the NR1 subunit of the NMDA receptor on forebrain interneurons indicate that early-life deficits in NMDA receptor signaling distort cortical development in ways that result in many neurobehavioral stigmata associated with schizophrenia, whereas the same intervention in adults does not reproduce the same profile of effects (Belforte et al. 2010). Recent studies from the Lewis laboratory further support the hypothesis that GABAergic deficits associated with schizophrenia develop as a consequence of glutamate-signaling deficits and may serve to compensate for deficiency in excitatory signaling (Volk and Lewis 2013; Glausier et al. 2014; Hoftman et al. 2015; Kimoto et al. 2015). It is possible that the developmental proliferation of glutamate synapses throughout childhood (Huttenlocher 1979; Petanjek et al. 2011) also serves to restore, to some degree, E/I balance.

However, deficits in GABA signaling may also render cortical networks hyperexcitable (Lazarus et al. 2015) and vulnerable to dysfunction (Krystal et al. 2003; Gonzalez-Burgos et al. 2015), suggesting that the reductions in E/I imbalance are allostatic rather than homeostatic. By allostatic, we mean that the compensation for disturbances in synaptic connectivity may serve to

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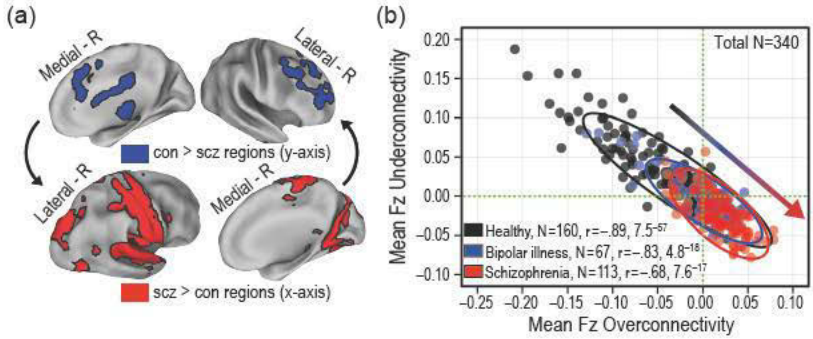

Figure 16.1 Relationship between thalamic over- and underconnectivity across subjects with schizophrenia. (a) Regions showing reduced (blue, top panel) and increased (red, bottom panel) thalamic connectivity for the original discovery sample ($N = 90$) compared to results from healthy comparison subjects. (b) The *x*-axis depicts the extent of functional connectivity of the thalamus and sensorimotor regions where increases are seen in schizophrenia (Fz overconnectivity) and the *y*-axis depicts the functional connectivity of the thalamus with regions in the executive control network where reductions are seen in schizophrenia (Fz underconnectivity). Along each axis, a positive value indicates a positive covariance of thalamic activity and the relevant target regions (*x*-axis: sensorimotor cortex; *y*-axis: prefrontal, cerebellum), whereas negative values reflect negative covariance. A significant negative relationship evident across all healthy controls (gray-black data points, $N = 160$; $r = -0.89$, $P < 7.5^{-57}$) collapsing across three samples (discovery, replication, and healthy subjects matched to patients with bipolar disorder). The same pattern was evident for bipolar patients (blue data points, $N = 67$; $r = -0.83$, $P < 4.8^{-18}$), whereas an attenuated and shifted correlation was found for schizophrenia patients (red data points, $N = 113$; $r = -0.68$, $P < 7.6^{-17}$, collapsing across both discovery and replication samples). Vertical/horizontal green dotted lines mark the zero points. Schizophrenia patients showed a "shift" across the zero lines, indicative of weaker prefrontal-cerebellar-thalamic coupling, but stronger sensorimotor-thalamic coupling. Bipolar patients showed an intermediate degree of disruption, suggesting a "gradient" (inset arrow for qualitative illustration). Ellipses for each group mark the 95% confidence interval. From Anticevic et al. (2014a), reprinted with permission.

restore E/I balance in some contexts, but it renders the network vulnerable to dysfunction, much as adaptations to stress may be successful in the short term but render the organism vulnerable to disease (McEwen and Stellar 1993). We do not mean to imply that GABA deficits necessarily overshoot the extent of glutamate synaptic dysfunction. Instead, we hypothesize that GABA reductions partially compensate for glutamatergic-signaling deficits, but that this adaptation renders the network vulnerable to dysfunction when the network is activated by extrinsic inputs, particularly inputs that are themselves disinhibited and therefore might otherwise be of lower intensity or filtered out (i.e., now are inappropriate to functional context). These extrinsic inputs could be corticocortical (Anticevic et al. 2015a, c) or thalamocortical (Ferrarelli and Tononi 2011; Lisman 2012; Duan et al. 2015). Nonetheless, there are emerging signs of intrinsic abnormalities in GABA systems that might make GABA deficits

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overshoot excitatory deficits, including copy number variants in GABA genes (Pocklington et al. 2015), and deficits in tonic GABA signaling which might augment phasic-signaling reductions (Maldonado-Aviles et al. 2009).

GABA signaling performs essential functions beyond the regulation of cortical excitability, including the optimization of cortical activity to enable precise spatial working memory (Rao et al. 2000) or olfactory memory (Lin et al. 2014). Computational models support the hypothesis that reduced glutamatergic drive to interneurons could impair the ability to suppress task-irrelevant cortical activity (noise) during working memory (Anticevic et al. 2012b; Murray et al. 2014) and compromise the functional antagonism between the executive and default mode networks at rest (Anticevic et al. 2012b). This work is summarized in Figure 16.2. From another perspective, the loss of adequate noise suppression within local networks could serve to impair memory precision and capacity by compromising the sparse coding of information within local networks (Lin et al. 2014). Network disinhibition in the prefrontal cortex, arising as a consequence of a primary glutamatergic-signaling deficit, could also have important downstream consequences for schizophrenia, such as activating dopamine neurons at the level of the midbrain (Lodge and Grace 2011b; Kim et al. 2015) or perhaps by activating dorsal striatal dopamine terminals directly (de la Fuente-Sandoval et al. 2011). The possibility of increased excitatory drive directly to associative striatum might explain why this region alone shows increased dopamine release in schizophrenia, unlike ventral striatum, cortical regions, limbic regions, and midbrain (Kegeles et al. 2010; Kambeitz et al. 2014; Slifstein et al. 2015; A. Abi-Dargham, pers. comm.).

Evidence for GABA-related pathophysiology in schizophrenia comes from many sources. Increased cortical excitability has been described in the form of short-interval intracortical inhibition in individuals at increased risk for schizophrenia, first episode patients, and patients with chronic illness (Rogasch et al. 2014). Other signs of increased cortical excitability also appear to evolve with the progression of illness. For example, cortical glutamate levels measured with spectroscopy are elevated during the schizophrenia prodrome (Stone et al. 2009) or early in the course of schizophrenia, but decline with illness progression (Marsman et al. 2013). In addition, resting functional connectivity as measured with fMRI appears to be increased early in the course of illness but shows some regional decreases with progression of illness across groups of patients, and perhaps even within patients during treatment (Anticevic et al. 2015a, c). It is possible that the "hyperconnectivity" associated with the early course of schizophrenia arises, at least in part, from deficits in a specific role that subpopulations of GABA neurons play in gating or "filtering" inputs to pyramidal neurons. In particular, somatostatin interneurons, which are compromised in schizophrenia and schizoaffective disorder (Lewis et al. 2008b; Morris et al. 2008a), gate the excitability of distal dendrites of cortical pyramidal neurons in an input-specific manner and may serve to shift the balance between long-term potentiation and depression at dendritic spines

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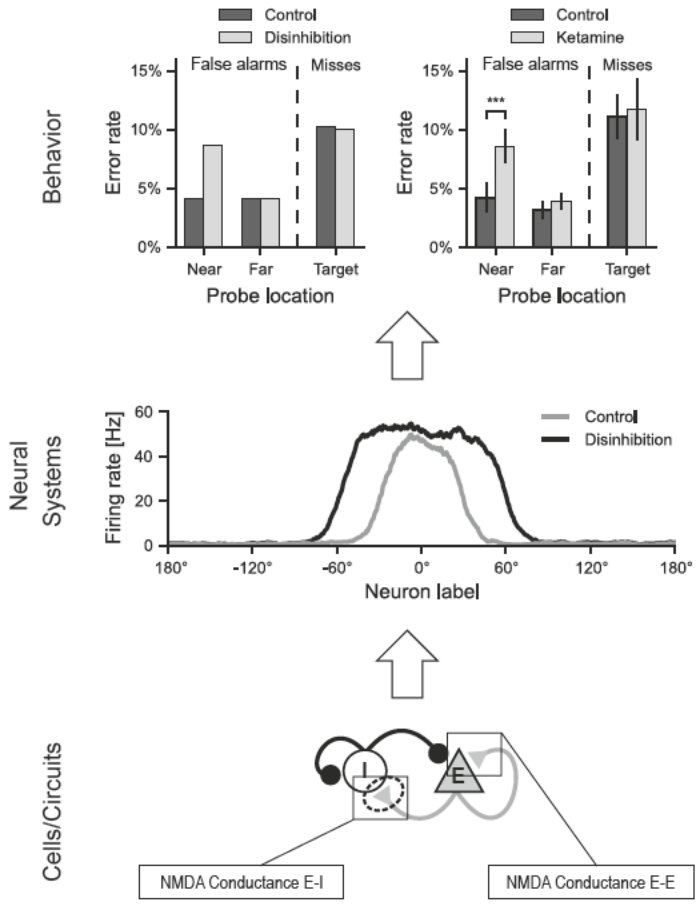

Figure 16.2 Schematic of highlighted findings from a recent computational modeling investigation. The bottom panel shows the manipulation of the NMDA receptor conductance on excitatory (E) and inhibitory (I) cells within a biophysically realistic computational model of working memory (for complete details, see Murray et al. 2014). Because the model is able to capture effects at the microcircuit level (i.e., via firing traces), it generates a specific set of predictions that can be tested at the level of regions or neural systems. As shown in the middle panel, the specific prediction is a broadening of the working memory profile after decreased inhibitory drive onto E cells. This prediction could be tested with electrophysiology (Wang et al. 2013) or BOLD functional MRI at the level of neural systems (Anticevic et al. 2012a, b). The top panel shows how the model generates a behavioral readout such that a specific profile of errors is predicted (top left); this can then be tested with carefully optimized behavioral experiments (top right). Collectively, this approach has the potential to inform across-level understanding disturbances in schizophrenia from receptor to behavior. Nonetheless, this approach is limited because at present it can only be extended to a few well-characterized computational and behavioral processes, such as working memory (see text for further discussion). Asterisks indicate significance (***$p < .001$). From Anticevic et al. (2015d), reprinted with permission.

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(Chiu et al. 2013; Higley 2014; Stokes et al. 2014; Sturgill and Isaacson 2015). Breakdown in this function would be expected to allow a much greater range of cross-talk among pyramidal neurons, contributing to "noise" in cortical activity. Schizophrenia also may be associated with increased resting high-frequency cortical activity (Spencer 2011; Gandal et al. 2012; Hirano et al. 2015), as might occur if parvalbumin-containing basket cells were released from inhibition by somatostatin-containing interneurons (Cottam et al. 2013; Pfeffer et al. 2013) or perhaps vasoactive intestinal polypeptide interneurons (Hioki et al. 2013; Pfeffer et al. 2013), which are not yet well characterized in schizophrenia. This increase in resting gamma activity is sometimes referred to as "background noise" in the EEG. The increase in "noise" is thought to compromise cortical signal processing, defined as the ratio of evoked gamma signal (gamma activity evoked by cognitive tasks or 40 Hz auditory clicks) over the resting gamma power.

A central unresolved question in schizophrenia is whether any of the various forms of E/I imbalance described above trigger their own allostatic responses. Over the past twenty years, scientists described homeostatic mechanisms that are engaged by cortical hyperexcitability and downregulate both the presynaptic (Davis 2006a) and postsynaptic (Turrigiano et al. 1994; Lambo and Turrigiano 2013) compartments of glutamate synapses and upregulate GABA synaptic efficacy. There is growing evidence that synaptic homeostatic mechanisms involve proteins implicated in schizophrenia, such as dysbindin (Dickman and Davis 2009). Consistent with this notion, in cross-sectional or longitudinal studies, schizophrenia is associated with an accelerated age-related reduction in both gray and white matter measured with MRI or DTI (Thompson et al. 2001; Vidal et al. 2006; Mori et al. 2007; Nugent et al. 2007; Andreasen et al. 2011; Zhang et al. 2014), cortical glutamate levels measured with MRS (Aoyama et al. 2011; Marsman et al. 2013), and functional connectivity as measured with resting state fMRI (Anticevic et al. 2015a, c). One study directly linked network disinhibition to reduced structural connectivity. Here, patients at high risk for psychosis with hippocampal hypermetabolism on FDG-PET scans showed hippocampal atrophy with longitudinal follow-up (Schobel et al. 2013). In parallel, the study showed in mice that repeated doses of NMDA receptor antagonists also produced hypermetabolism followed by hippocampal atrophy. The authors implicated GABA neuronal deficits in the network disinhibition produced by NMDA receptor antagonist administration by showing that interneuron precursor transplants attenuated the hippocampal hypermetabolism and related physiologic and behavioral phenotypes (Gilani et al. 2014).

Illness Progression and Compounded Neural Allostatic Adaptations

The preceding would suggest that the biology of schizophrenia may evolve throughout the life span and that illness phases may be distinguished by the

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recruitment of successive allostatic mechanisms that are expressed concurrently with earlier pathological processes (see Figure 16.3). In a gross oversimplification of the complexity of the heterogeneity and progression of schizophrenia, one could build on a prior schema (Insel 2010) and imagine a provisional framework of developmental phases through which schizophrenia might progress. For the purposes of this discussion, we will focus on the interplay of glutamate, GABA, and dopamine signaling.

1. *Predrome*: an early developmental phase where no gross phenotypic alterations arise from the expression of antenatal genetic and environmental risk factors to compromise glutamate synaptic connectivity. This does not preclude the possibility of subtle cognitive or neurophysiologic deficits, as early-life adaptations are not expected to be completely successful.
2. *Prodrome*: the most severe aspects of cognitive and behavioral expression of glutamate synaptic deficits are still largely compensated for by the proliferation of glutamate synapses in childhood combined with deficits in GABA signaling that serve to restore E/I balance. Allostatic adaptation comes at the cost of phenotypic consequences of GABA signaling deficiencies, such as the progressive emergence of cognitive impairments and symptoms. As noted above, dopaminergic activation may be one negative consequence of glutamatergic disinhibition, consistent with recent data in high-risk populations (Bonoldi and Howes 2013). Also, the GABA signaling deficits early in this phase of illness

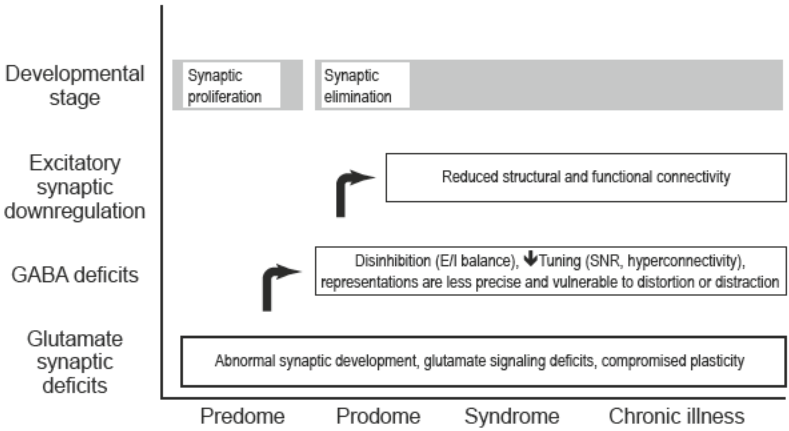

Figure 16.3 A simplified model showing how sequential allostatic neuroadaptations triggered by genetic abnormalities in glutamate synaptic function might interact with programmed synaptic proliferation and elimination, and give rise to an evolving neurobiology of schizophrenia across the life span. SNR: signal-to-noise ratio; see text for description of stages.

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may be partially compensated for by an adolescent phase of GABA neuronal proliferation and maturation.

3. *Syndrome*: the full spectrum of symptoms and cognitive dysfunctions emerge as neurodevelopmental trajectories shift from synaptic proliferation to synapse elimination. It signals the end of the production of large numbers of new mature GABA neurons (Kilb 2012; Caballero et al. 2014) and the emergence of a new allostatic adaptation, that is, the downregulation of glutamate synapses in response to altered and hyperconnectivity. The functional downregulation of glutamate synapses during adolescence would be expected to augment the impact of the earlier preprogrammed process of synapse elimination. Neuroimaging studies suggest that the rate of cortical volume loss is greatest early in the course of schizophrenia (Thompson et al. 2001; Andreasen et al. 2011), which may be consistent with the notion that allostatic reductions in functional connectivity may be greatest early in the course of schizophrenia in association with the peak levels of E/I imbalance.
4. *Chronic illness*: deficits in structural and functional connectivity progress throughout the syndromal phase, with current treatments having only limited impact. During this phase, age-related deficits in glutamate synaptic connectivity are expected to be compounded by the intrinsic heritable synaptic dysfunction, the failure to tune synaptic activity optimally, and the compensatory downregulation of structural and functional connectivity.

This model makes predictions related to sources of heterogeneity in schizophrenia. For example, it predicts that the interaction of synaptic proliferation in childhood and the hyperconnectivity arising from GABA deficits, presumably in childhood and early adolescence, serve to delay the expression of schizophrenia symptoms from childhood, when abnormalities in glutamate synapses are already present, to adolescence, when tuning deficits may be more severe and glutamate synaptic deficits are compounded by programmed synaptic elimination. Since some of the same synaptic genes are implicated in the risk for autism and schizophrenia, it is possible that these disorders are distinguished, in part, by the relative success of the neural allostatic adaptations in schizophrenia relative to autism. Further, the model suggests that childhood onset of schizophrenia could be distinguished from typical schizophrenia by the greater severity of the initial glutamatergic synaptic dysfunction, failure in allostatic adaptations, or disturbances in synaptic proliferation or elimination. It supports the observation that females might have a later onset (Szymanski et al. 1995; Lindamer et al. 1997), better treatment response (Szymanski et al. 1995), or perhaps lower incidence of schizophrenia (Kendler and Walsh 1995) than males, perhaps as a consequence of the synaptogenic effects of estrogen (Woolley and McEwen 1994). It is also consistent with the increased risk for schizophrenia by prenatal environmental factors that disturb normal

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synaptic development (Insel 2010). Further, it suggests that drugs which compromise the integrity of GABA neuronal function, such as CB1 agonists (Hajos et al. 2008; Eggan et al. 2010; Volk and Lewis 2015), might worsen symptoms (D'Souza et al. 2004; 2005) and perhaps even promote the transition from subclinical to clinical symptoms of psychosis (Wilkinson et al. 2014), although this remains to be clearly demonstrated (van der Meer et al. 2012a).

Toward Illness Phase-Specific Treatments for Schizophrenia

If the pathophysiology of schizophrenia progresses through predictable illness phases, then treatments which target distinct neurobiological mechanisms may have their greatest impact at particular phases of illness. Dopamine D2 receptor antagonists, for example, would be corrective for psychosis in illness phases where dopamine release is increased (Frankle et al. 2004), but they would not be expected to be effective in hyperglutamatergic patients who do not have dopaminergic hyperactivity (Demjaha et al. 2014). These drugs would not be expected to prevent the onset of the schizophrenia prodrome nor reverse the consequences of synaptic pruning in chronic schizophrenia, although they might blunt the severity of symptoms and, in so doing, delay the point where patients met diagnostic criteria for schizophrenia (van der Gaag et al. 2013).

The efficacy of drugs targeting features of glutamate signaling may be particularly affected by the evolving biology of schizophrenia. For example, drugs enhancing the stimulation of the glycine/D-serine co-agonist site of the NMDA receptor might be expected to treat symptoms of schizophrenia attributable to deficits in glutamate synaptic signaling. Indeed, meta-analyses suggest that in chronic schizophrenia, glycine and D-serine may have some modest adjunctive therapeutic value (Tuominen et al. 2005, 2006; Singh and Singh 2011), although this efficacy has been questioned (Iwata et al. 2015). Perhaps, though, these medications are more effective early in the course of schizophrenia, when glutamatergic synaptic elimination has not been fully expressed or perhaps GABA neuronal function may be rescued by enhanced glutamatergic input. Consistent with this view, tantalizing preliminary data raise the possibility that glycine, D-serine, and glycine transporter-1 inhibitors may be effective as a monotherapy in prodromal or patients early in their course of illness (Lane et al. 2008; Woods et al. 2013). These studies need definitive rigorous replication.

Metabotropic glutamate receptor 2 (mGluR2) agonists may also show illness phase-specific efficacy for the treatment of schizophrenia. Preclinical and clinical studies suggest that mGluR2/3 agonist drugs reduced the physiologic and behavioral consequences of acute NMDA receptor antagonist effects by reducing glutamate hyperactivity (Moghaddam and Adams 1998; Cartmell et al. 1999; Krystal et al. 2005), thus raising the possibility that this class of medications could treat symptoms of schizophrenia arising from disinhibition of cortical networks (Krystal et al. 2003). The initial mGluR2/3 agonist trial in schizophrenia was positive (Patil et al. 2007); however, efforts to replicate

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this result as monotherapy or adjunctive therapy did not yield positive results (Stauffer et al. 2013; Adams et al. 2014; Downing et al. 2014). Based on the illness phase model presented above, one might hypothesize that patients early in the course of schizophrenia might benefit from an mGluR2/3 agonist because it would reduce cortical network disinhibition. However, in patients with chronic illness, one might hypothesize that the benefits of modest levels of cortical inhibition would be to halt illness progression, and that higher doses would exacerbate the negative impact of growing deficits in synaptic connectivity. This hypothesis was explored in a secondary analysis performed by investigators at Lilly Research Laboratories in schizophrenia clinical trials of their mGluR2/3 agonist prodrug, LY2140023 monohydrate (Kinon et al. 2015). Their analysis reported that a low dose, 40 mg, of LY2140023 monohydrate was more effective than an 80 mg dose of this drug and comparably effective to risperidone in early course schizophrenia patients. However, in patients with long-standing illness, the 40 mg dose was no better than placebo and the 80 mg dose significantly worsened symptoms relative to placebo (Figure 16.4).

Other medications could be tested for illness phase-specific effects in schizophrenia. mGluR2 agonists were first tested in schizophrenia because they reduced the effects of NMDA receptor antagonists on glutamate release and cognition in animals and humans (Moghaddam and Adams 1998; Krystal et al. 2005). However, other drugs that reduce cortical excitability have been shown to reduce ketamine effects in animals or humans, including AMPA receptor antagonists (Moghaddam et al. 1997), lamotrigine (a drug that blocks several voltage-gated ion channels) (Anand et al. 2000a), alpha7 nicotine receptor agonists (Castner et al. 2011), dopamine-1 receptor agonists, glycine transporter-1 receptor antagonists (Castner et al. 2014), AMPAkines (Roberts et al. 2010), and subtype-selective $GABA_A$ receptor facilitators (Castner et al. 2010). It remains to be seen whether any of these drugs or mechanisms exhibits illness phase-dependent efficacy.

Phase-specific pharmacotherapies may create opportunities for disease-modifying treatments. For example, to the extent that glutamate synaptic deficits contribute to deficient maturation of GABA neurons, early remediation of these signaling deficits might promote normal GABA neuronal development and prevent the emergence of hyperglutamatergic states, and in turn might attenuate the subsequent decline in synaptic connectivity. Reductions in cortical E/I balance might not salvage early synaptic connectivity or the emergence of GABA neuronal deficits, but they may attenuate allostatic loss in synaptic connectivity in response to glutamatergic hyperactivity.

However, it is evident that we do not yet understand how to restore deficiencies in glutamate synaptic connectivity, which evidently are more complicated than deficits in stimulation of the glycine/D-serine site of NMDA receptors. It is tempting to think that drugs which enhance synaptic excitability—such as AMPAkines, low- (alpha7 subunit containing) and high-affinity nicotine receptor agonists or positive allosteric modulators, muscarinic cholinergic

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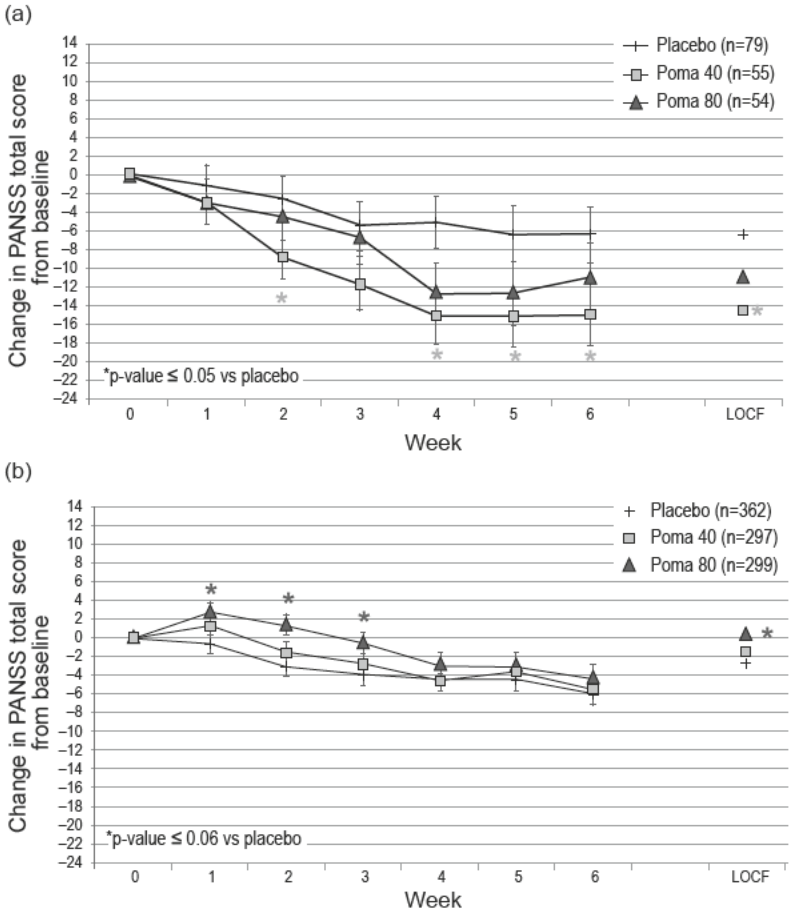

Figure 16.4 Change in PANSS total score with pomaglumetad in Eli Lilly study HBBM illustrates the possibility that mGluR2/3 agonism might treat symptoms in early course schizophrenia patients but worsen them in patients with chronic illness. From Kinon et al. (2015), reprinted with permission. Duration of illness for early-in-disease patients is ≤3 years (a) and for late-in-disease patients is ≥10 years (b). PANSS: positive and negative syndrome scale; Poma: pomaglumetad, an mGluR2/3 agonist pro-drug; RIS: risperidone; SE: standard error.

agonists, and estrogen (in relation to its capacity to stimulate dendritic spine growth) (Woolley and McEwen 1994)—or drugs that enhance neurotrophic factor signaling might play a role in this phase of illness. However, few of these mechanisms have been adequately tested, and evidence is limited to support the efficacy of those mechanisms that have been tested and is generally suggestive of modest effects. It will be important to determine whether these treatments enhance cortical signal processing or merely increase cortical noise. Perhaps one value of viewing the pharmacotherapy of schizophrenia

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in an illness phase-dependent manner is that it may help to focus attention on important gaps in treatments that might get targeted by new treatments.

Summary

Developmental changes in the neurobiology of schizophrenia and other CNS disorders are an important source of clinical heterogeneity that is not addressed adequately in current diagnostic schema. Better understanding of this evolving neurobiology may help guide the development of more effective treatments aimed at addressing aspects of the pathophysiology that give rise to symptoms and functional impairments at the various stages of illness.

Dimensional Properties of Psychiatric Diagnoses and Clinical Heterogeneity

Another source of clinical heterogeneity arises from a "known unknown"; that is, our inability to classify patients on the basis of etiology or pathophysiology. Present diagnostic schemas (DSM, ICD) are based on symptom profiles that are likely to lump together patients with markedly different pathophysiologies and to divide patient groups that share common elements of both etiology and pathophysiology (Wiecki et al. 2015).

There is a high degree of overlap in the common gene variants contributing to the risk for schizophrenia and bipolar disorder (Cardno and Owen 2014; Maier et al. 2015). However, large numbers of both rare and common gene variants contribute to the risk for each disorder. Thus one source of neurobiological heterogeneity may be genetic heterogeneity within a diagnostic category. Further, some neurobiological properties might constitute a dimension of neural dysfunction that could span several diagnoses. This dimensional perspective would be particularly important if an array of distinct abnormalities at molecular and cellular levels produced common disturbances in the function of cortical microcircuits or macrocircuits. Informed by this type of thinking, the Research Domain Criteria (RDoC) incorporate some of the advantages that result from approaching psychiatric pathophysiology from a transdiagnostic dimensional perspective (Cuthbert 2014b; Insel and Cuthbert 2015).

There is some preclinical evidence to support this approach. One recent example of this type of convergence comes from animal models of deficits in NMDA receptor function, where mice with selective knockouts of GluN1 NMDA receptors on forebrain cortical pyramidal neurons and mice with selective knockouts of GluN1 subunits in parvalbumin-containing interneurons resulted in some common cortical electrophysiological and behavioral alterations (Billingslea et al. 2014; Krystal 2015; Tatard-Leitman et al. 2015).

One exemplar where a dimensional approach to diagnosis may yield important insights is in the relationship between schizophrenia and bipolar disorder.

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In many domains of clinical status, including symptom severity, cognitive dysfunction, and functional impairment, patients diagnosed with schizophrenia appear to have similar but more severe problems than patients with bipolar disorder (Badcock et al. 2005; Green 2006; Sanchez-Morla et al. 2009; Brosey and Woodward 2015). A growing number of studies of circuit-based imaging studies have highlighted dimensional relationships between these two disorders (Qiu et al. 2007; Sui et al. 2011; Argyelan et al. 2014; Lui et al. 2015). For example, disturbances in thalamic functional connectivity may be a dimensional trait shared by schizophrenia and bipolar disorder; that is, where schizophrenia appears to express qualitatively similar but quantitatively more severe version of a disturbance found in patients diagnosed with bipolar disorder. As noted earlier, a growing number of studies of schizophrenia have described reduced thalamic functional connectivity with executive control circuits and increased functional connectivity with sensorimotor regions. Thalamic overconnectivity was associated with symptoms of schizophrenia, whereas deficits in association cortex and thalamus were linked to executive cognitive dysfunction. This pattern of alterations is also observed in bipolar disorder but to a lesser degree. The dimensional relationship between the two groups of patients is evident when data from both patient groups are plotted on the same graph (see Figure 16.1).

Therapeutic insights may emerge from dimensional approaches to diagnoses. For example, in the case of the disturbances in thalamic connectivity, one might wonder whether depotentiating (1 Hz) TMS stimulation over sensorimotor cortex (Hoffman et al. 2005) or potentiating (10 Hz) TMS stimulation over executive cortices (Shi et al. 2014; Wolwer et al. 2014; Wobrock et al. 2015) would reduce symptoms or cognitive impairments, perhaps by correcting illness-related alterations in thalamocortical connectivity. Similarly tDCS over association cortices might activate the underlying regions and enhance cortical plasticity (Hoy et al. 2015; Tarur Padinjareveettil et al. 2015). These approaches need to be explored with some care to ensure that increasing cortical excitability did not simply exacerbate cortical E/I imbalances and increase "noise" rather than "signal." It will be important to determine whether neurostimulation treatments, like some pharmacologic ones, show illness phase-dependent efficacy.

Categorical Features of Psychiatric Diagnoses

Despite the genetic complexity of psychiatric disorders, the extensive progress made in identifying genes associated with traditional categorical diagnoses suggests that these diagnostic entities are linked in ways that are still unclear regarding etiology and pathophysiology (Krystal and State 2014). A critical question is whether dimensional "transdiagnostic" approaches to the neurobiology of psychiatric disorders will replace previous categorical diagnostic

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systems or whether the current emphasis on dimensional approaches will lead to a synthesis of categorical and dimensional approaches to psychiatric diagnosis.

Supporting the importance of categorical distinctions, recent neuroimaging studies provide strong evidence for qualitative differences in the neurobiology of schizophrenia and bipolar disorder. For example, to date increased dopamine release in the associative striatum has been widely demonstrated in schizophrenia (Laruelle et al. 1996; Kegeles et al. 2010) but not documented in bipolar disorder (Anand et al. 2000b). While this difference may reflect inadequate study of the neurobiology of bipolar disorder, other important differences have emerged. Postmortem dorsolateral prefrontal cortex cellular deficits in schizophrenia and bipolar disorder show evidence of qualitative and quantitative differences (Selemon and Rajkowska 2003). Also, as presented in Figure 16.5, schizophrenia appears to be associated with increased signal power in the low-frequency range and increased signal variance in resting-state fMRI data, whereas bipolar disorder is not associated with either of these properties (Yang et al. 2014). Two features of the increase in variance were demonstrated: an increase in the voxel-wise variance across the brain and an increase in the global signal. It would be important to know whether these features, which distinguish schizophrenia from bipolar disorder, contribute to the progressive and persisting cortical volume in schizophrenia. Bipolar disorder, which does not appear to be prominently associated with increased signal power in the low-frequency range or increased signal variance, also does not appear to be prominently associated with persisting enhancements in cortical volume loss after early adulthood (Woods et al. 1990; Blumberg et al. 2006).

To explore mechanisms that might account for the categorical differences between schizophrenia and bipolar disorder, a biophysically based computational model of resting state fluctuations was applied (Deco et al. 2013). In this approach BOLD signals are simulated using mean-field dynamics (Wong and Wang 2006) for each of 66 neural nodes that are coupled following a structure based on diffusion-weighted imaging studies in humans (Hagmann et al. 2008). Key parameters in the model include the strength of recurrent "self-coupling" (w) within nodes and long-range or "global" coupling (G) between nodes. Each of these parameters represents the combination of excitatory and inhibitory connectivity. In this model (Figure 16.6), the local variance of each node increased with increasing values of w and G. Together these data suggest that the functional hyperconnectivity observed in rs-fMRI data might contribute to the increase in the voxel-wise signal variance observed in schizophrenia. This finding provides support for the hypothesis that the increased variance observed in schizophrenia, but not bipolar disorder, has a neural rather than artifactual origin. Further, the similarity in the increases in functional connectivity produced by the NMDA glutamate receptor antagonist, ketamine, in healthy human subjects (Driesen et al. 2013) to the hyperconnectivity documented in association with schizophrenia may suggest that the increases in functional

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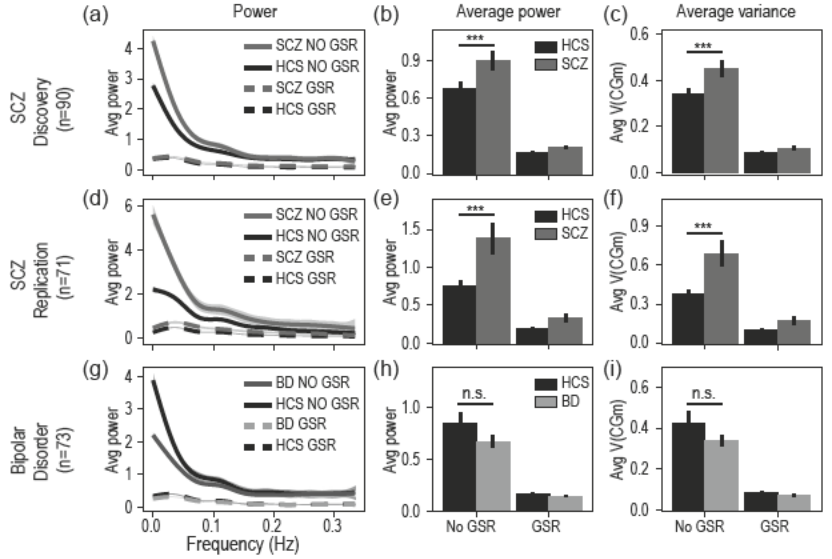

Figure 16.5 Illustration of diagnosis-related disturbances in cortical activity where schizophrenia and bipolar disorder exhibit qualitative differences in relation to healthy subjects; from Yang et al. (2014), reprinted with permission. Power (proportion of the signal power falling within discrete frequency bins) and variance of the cortical gray matter signal in schizophrenia (SCZ) and bipolar disorder (BD). (a) Power of the cortical gray matter signal in 90 SCZ patients (dark gray) relative to 90 healthy comparison subjects (HCS) (black). (b) Mean power across all frequencies before and after global signal reduction (GSR) indicating an increase in SCZ [$F(1, 178) = 7.42$, $P < 0.01$], and attenuation by GSR [$F(1, 178) = 5.37$, $P < 0.025$]. (c) Cortical gray matter variance also showed increases in SCZ [$F(1, 178) = 7.25$, $P < 0.01$] and GSR-induced reduction in SCZ [$F(1, 178) = 5.25$, $P < 0.025$]. (d)–(f) Independent SCZ samples confirming increased cortical gray matter power [$F(1, 143) = 9.2$, $P < 0.01$] and variance [$F(1, 143) = 9.25$, $P < 0.01$] effects, but also the attenuating impact of GSR on power [$F(1, 143) = 7.75$, $P < 0.01$] and variance [$F(1, 143) = 8.1$, $P < 0.01$]. (g)–(i) Results for BD patients ($n = 73$) relative to matched HCS did not reveal GSR effects observed in SCZ samples [$F(1, 127) = 2.89$, $P = 0.092$, n.s.] and no evidence for increase in cortical gray matter power or variance. All effects remained when examining all gray matter voxels. Error bars mark ± 1 SEM. ***$P < 0.001$ level of significance; n.s., not significant.

connectivity observed in schizophrenia have their origins in deficits in NMDA glutamate receptor signaling, hypothesized to contribute to network disinhibition in schizophrenia (Olney and Farber 1995; Grunze et al. 1996; Moghaddam et al. 1997; Krystal et al. 2003).

The implications of deficits in NMDA glutamate receptor signaling and secondary GABA signaling in connectivity disturbances in schizophrenia return the therapeutic focus to the issues raised earlier. Restoration of normal glutamatergic signaling capacity as early as possible in the life span might reduce the emergence or expression of GABAergic deficits and other sources of

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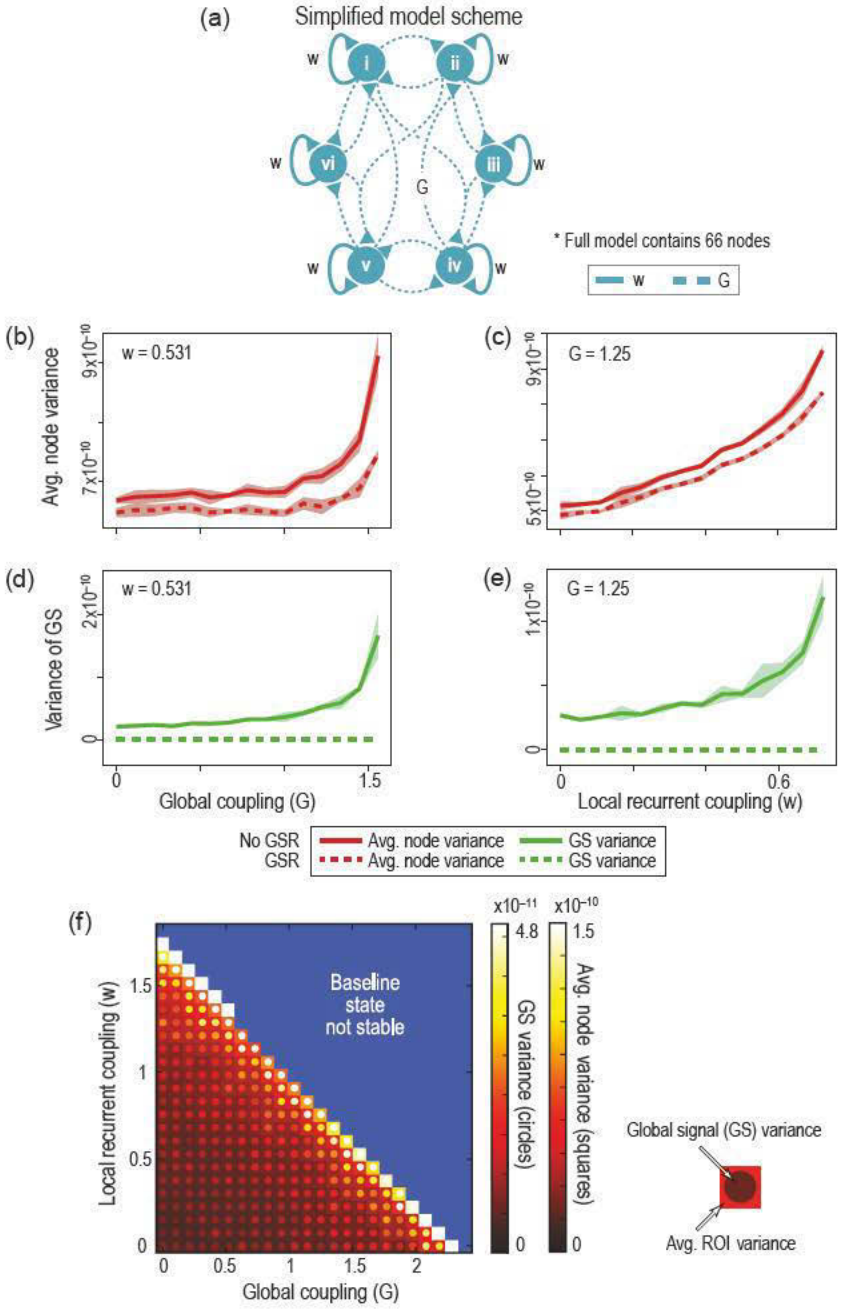

Figure 16.6 Computational modeling simulation of BOLD signal variance illustrates a biologically grounded hypothetical mechanism for increased global and local variance; from Yang et al. (2014), reprinted with permission.

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cortical functional hyperconnectivity and increased signal variance (i.e., "cortical noise") associated with schizophrenia. Similarly, suppression of cortical hyperconnectivity would be expected to reduce the expression of noisy cortical activity, a benefit that must be balanced against the cost of suppressing cortical signals with the progression of illness. The striking prediction of the finding that hyperconnectivity and increased cortical signal variance are features of schizophrenia but not bipolar disorder suggests that diagnosis-specific treatment strategies may emerge from careful study of the categorical features of the neurobiology of psychiatric disorders.

Toward Synthesis: Balancing Categorical and Dimensional Approaches

The preceding discussion suggests that tensions between categorical and dimensional psychiatric diagnoses are unavoidable and that they reflect important contributors to clinical heterogeneity. Thus a critical question at the moment is whether either approach on its own—that is, the categorical approach espoused in DSM-5 (APA 2013) and ICD-10 (1992) or the dimensional approach presented in RDoC (Insel and Cuthbert 2015)—has sufficient explanatory power to guide treatment and stimulate research, so as to serve as the framework for future diagnostic schema. Perhaps, future diagnostic schema will adopt one or the other approach as the backbone for classification and then integrate the other perspective within a hierarchical or matrix model.

As in all models, there may be elements of the organizational structure that arise arbitrarily or from convention. In other words, the same data could be clustered using either dimensional or categorical approaches. For example, as discussed above, schizophrenia and bipolar disorder are associated with some

Figure 16.6 (continued) (a) A biophysically based computational model of resting-state BOLD signals is used to explore parameters that could reflect empirical observations in schizophrenia. The two key parameters are the strength of local, recurrent self-coupling (w) within nodes (solid lines) and the strength of long-range, global coupling (G) between 66 nodes in total (dashed lines). (b) and (c) Simulations indicate increased variance of local BOLD signals originating from each node, in response to increased w or G. (d)–(e) The global signal (GS), computed as the spatial average across all nodes, also showed increased variance by elevating w or G. Shading represents the standard deviation at each value of w or G computed across four realizations with different starting noise, illustrating model stability. Dotted lines indicate effects after *in silico* GS regression. (f) Two-dimensional parameter space, capturing the positive relationship between w/G and variance of the BOLD signal at the local node level (squares, far right color bar) and the GS level (circles in each square, the adjacent color bar). The blue area marks regimes where the model baseline is associated with unrealistically elevated firing rates of simulated neurons. Model simulations illustrate how alterations in biophysically based parameters (rather than physiological noise) can increase GS and local variance observed empirically in schizophrenia. Of note in (b)–(e), when w is modulated, $G = 1.25$. Conversely, when G is modulated, $w = 0.531$.

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qualitative differences in functional connectivity and voxel-based signal variance. These data would tend to support categorical diagnostic approaches, exemplified by DSM-5 (APA 2013). However, having defined their clinical significance, these traits could be used within a dimensional or transdiagnostic approach to group patients based on their biology.

Keeping an open mind with respect to categorical and dimensional features of psychiatric disorders over the course of illness may be important because our current understanding of disorders like schizophrenia is based on data from medicated patients, and it is possible that drug and illness effects are somewhat confounded. Some postmortem studies of schizophrenia have attempted to address these confounding effects by comparing data from patients to medication-treated nonhuman primates (Volk et al. 2013; Georgiev et al. 2014). Careful retrospective comparisons in patients combined with prospective studies in primates suggest that antipsychotic treatment affects glial populations and reduces cortical volume (Dorph-Petersen et al. 2005; Konopaske et al. 2008), among other effects. One could imagine that the differential prescription of antipsychotics and mood-stabilizing medications might have contributed to categorical differences in the neurobiology of schizophrenia and bipolar disorder. However, mood stabilizers are widely prescribed to people with schizophrenia and antipsychotic-resistant symptoms (Meltzer 1992; Wolkowitz 1993), and second-generation antipsychotic medications have emerged as first line treatments for bipolar disorder. Thus, it may be the case that these medications now contribute to dimensional features of the neurobiology of these disorders.

Further, even when diagnostic groups are distinguished by qualitative differences in their underlying neurobiology, as highlighted in Figure 16.5, there may still be dimensional relationships across these diagnoses (i.e., substantial overlap in the biology of individuals across diagnoses). To illustrate this point, we conducted a secondary analysis of data from a subgroup of individuals from the data presented in Figure 16.5. As can be seen in Figure 16.7, even though the groups differ qualitatively in their average power and average variance, there is still overlap of individuals with schizophrenia and bipolar disorder. While it is possible that this overlap simply reflects a failure of symptom-based categorization to adequately separate patients with schizophrenia and bipolar disorder, it is also possible that these disorders intrinsically overlap in their biology even in dimensions where they qualitatively differ as groups.

Categorizing patients on the basis of particular biological traits is likely to reduce some sources of clinical heterogeneity while increasing other aspects (see Table 16.1). For example, one might cluster schizophrenia and bipolar disorder on the basis of their shared common gene variants, but this would ignore the significant differences between these disorders with respect to the impact of rare gene variants (Cardno and Owen 2014) and fail to capture links between schizophrenia and autism with regards to these rare gene variants (Sebat et al. 2009). There may be a fundamental tension between unidimensional and multidimensional clustering strategies. DSM-5 embraces clinical

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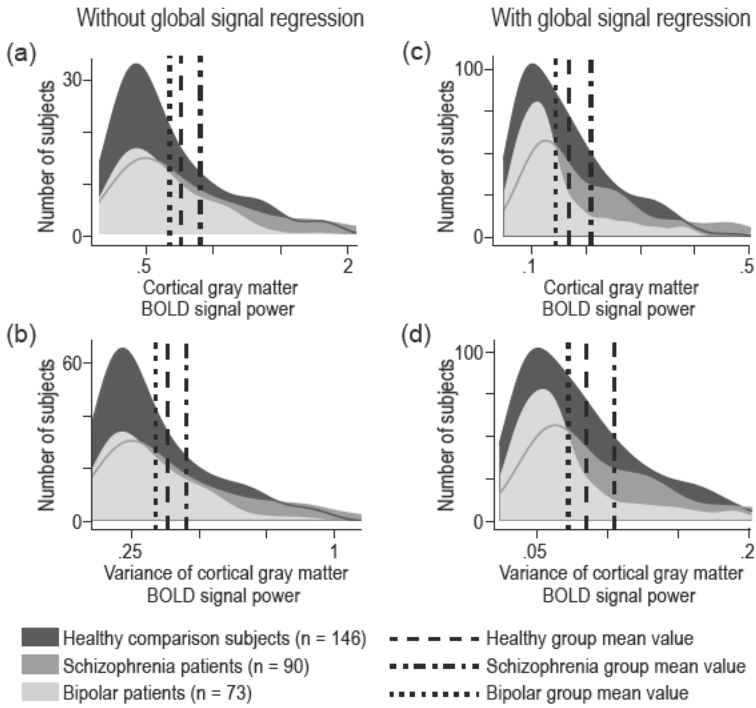

Figure 16.7 Power and variance of cortical gray matter signal in schizophrenia and bipolar disorder. The distribution of the average signal variance and average power of the gray matter signal of individual subjects from a subgroup of the sample presented in Figure 16.5: healthy subjects, n = 146; schizophrenia, n = 90; bipolar disorder, n = 73. Data are presented without and with global signal regression. (a) Group distributions of BOLD signal power averaged across the cortical gray matter for each subject, computed without removing the global mean signal. (b) Group distributions for the variance of BOLD signal averaged across cortical gray matter, computed without removing the global mean signal. (c) Same as in (a), except computed on the BOLD signal after removing the global mean signal through regression. (d) Same as in (b), except computed on the BOLD signal after removing the global mean signal through regression. This figure shows that even though schizophrenia patients increased on these dimensions compared to healthy subjects and bipolar patients were numerically reduced on these dimensions compared to healthy subjects, there was overlap in the values from all three groups.

heterogeneity on any particular dimension, in theory, to reduce the clinical heterogeneity of the overall treatment and clinical course. In contrast, RDoC allows for a greater degree of heterogeneity in clinical presentation in the pursuit of greater homogeneity, in particular prioritized biological or behavioral traits. The benefit of the latter strategy is that it might serve to guide the development of treatments and, more importantly, increase the likelihood of detecting clinical benefits of treatments that targeted that particular dimension of illness. This approach actually validates clinical practice, as clinicians frequently

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Table 16.1 Clinical heterogeneity associated with categorical and dimensional categorization exemplified by DSM-5 and RDoC, respectively.

	DSM-5	RDoC
Type	Categorical	Dimensional
Objective	Guide clinical practice and reimbursement	Advance translational neuroscience and discovery of novel treatments
Strategy for reducing heterogeneity	Optimizing statistical association of clinical features within diagnoses	Clustering patients on the basis of well-defined traits that have emerged from translational neuroscience
Sources of heterogeneity	Syndromes defined very broadly Most syndromes defined without basis in etiology or neural mechanism	Clustering patients with evident heterogeneity in clinical presentation

target specific treatment nonresponsive symptoms using a dimensional approach (i.e., treating residual anxiety in schizophrenia with an anxiolytic rather than antipsychotic). There is, however, no guarantee that this patient clustering strategy will recapitulate the degree of homogeneity of multidimensional clustering strategies with regards to genetics or other dimensions of neurobiology, as endophenotypes (Gottesman and Gould 2003) appear to be associated with many of the challenges in genetic association as traditional psychiatric diagnoses (Krystal and State 2014).

Can computational approaches yield evidence-based schema that would more effectively categorize patients (see Chapters 1 and 2, this volume)? Machine-learning approaches, for example, may make it possible to cluster patients empirically in ways that are both more homogeneous and better predictors of treatment response (Wiecki et al. 2015) than current categorical schema. Further, these approaches may be applied to many types of clinical data so that symptoms; cognitive function; structural, functional, and chemical neuroimaging data; social and vocational function; course of illness; patterns of comorbidity; and other data can be more meaningfully integrated. Computational approaches that employ Bayesian approaches might enable the integration of a wide array of information within a nosological framework and the updating of this framework on an empirical basis when important new data are generated (see Mathys as well as Flagel et al., this volume). This strategy may reduce the appearance of tension between dimensional and categorical features of nosology by incorporating these perspectives in a single schema. The Bayesian approach to diagnosis, which considers multiple potential diagnoses concurrently and updates the prioritization of these diagnoses as new information emerges, is not alien to medical thinking: it is at the core of medical practice.

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Efforts to reduce clinical heterogeneity in the diagnostic schema are irrevocably linked to the search for novel treatment mechanisms. For example, RDoC was introduced to facilitate closer links between neural processes and psychiatric medication development within a translational neuroscience framework (Insel and Cuthbert 2015). The anticipated outcome is that new treatment mechanisms will be identified that "fix" disturbances in these neural processes. When that occurs, it may then become important to assess these neural processes, which may be measured using genomic, epigenomic, neuroimaging, or other approaches in routine clinical practice. This is the natural progression that has emerged in all other areas of medicine. Measuring blood pressure became important when it was appreciated that treating elevated blood pressure reduced risk for cardiovascular and cerebrovascular disease. Measuring the presence of Her2 in breast tumors became important clinically when Herceptin was introduced (Mukerjee 2010). When these measurements become clinically useful, we can expect them to be incorporated, whether as dimensional or categorical traits, within treatment algorithms and diagnostic schema.

Conclusions

In this chapter we have considered sources of clinical heterogeneity related to the effort to understand psychiatric disorders from categorical and dimensional perspectives. Examples from the neurobiology of schizophrenia were used to illustrate several important points. Computational neuroscience approaches help frame the interpretation of neuroimaging findings to illustrate where the biology of schizophrenia appears to be similar but more severe than bipolar disorder (or were qualitatively different from findings in bipolar disorder), highlighting dimensional and categorical diagnostic properties of the neurobiology of schizophrenia.

Important sources of clinical heterogeneity include the evolving neurobiology of psychiatric disorders with development, which may have important treatment implications. The presence of categorical features of neuropsychiatric disorders supports the maintenance of some elements of categorical diagnoses even though current diagnostic schema give rise to clusters of patients who vary widely on any particular clinical or neurobiological dimension. Data supporting transdiagnostic dimensional features of psychiatric disorders reinforce an approach consistent with the RDoC approach of clustering patients, even though it may not conform to traditional diagnostic schema and may thus produce greater levels of clinical heterogeneity in clinical or neurobiological dimensions. Moving fluidly between these two approaches may enable both clinical practice and research to address specific clinical or research challenges. It is possible that categorical and dimensional approaches could be integrated, better than they are currently in DSM or ICD, within future approaches to the classification of patients.

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