What We Know: Findings That Every Theory of Schizophrenia Should Explain

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The article summarizes the process used to distill schizophrenia science into 22 facts. These facts consist of 6 basic facts, 3 etiological facts, 6 pharmacological and treatment facts, 5 pathology facts, and 2 behavioral facts that were critically reviewed by the scholarly community through a special initiative in cooperation with the Schizophrenia Research Forum. A subset of 10 of these facts was selected to form a common set of findings to be explained from the different theoretical perspectives included in this special section of Schizophrenia Bulletin. The rationale for this exercise is to distinguish more precisely the areas of agreement and disagreement between theories of schizophrenia and to highlight where more thought and data can make the greatest impact for understanding this disease.

Key words: Schizophrenia/review/meta-analysis/theory

Introduction: Building a Community Consensus

Japan has a gift for developing crackpot entertainment. Iron Chef is one such show that also amassed a cult following in North America. Week after week the show’s host would challenge chefs from different culinary traditions to create a meal featuring shared ingredients. The show drew viewers because the competing chefs drew their creative end point, their pieces de resistance, from common elements. The current exercise may lack the made-for-TV pyrotechnics and manufactured drama of Iron Chef, but the dynamic spark that comes from using a common set of ingredients will be familiar to its fans. In short, this special section of Schizophrenia Bulletin is designed to set current theories of schizophrenia pathophysiology side by side to highlight their capacity to account for the same body of knowledge. This exercise will hold particular appeal to readers who want to compare modern theories of schizophrenia, but who are concerned that support for such theories suffers from a tendency to self-select the findings to be explained.

The current project drew out of the guest editors’ experiences at the biannual International Congress of Schizophrenia Research. As at any conference of its size, thousands of presentations are made from numerous perspectives and in various formats. Unlike many conferences organized around a methodology or level of analysis, this conference is, like this journal, focused on the problem of schizophrenia. There is an obvious question that comes from attending such a problem-focused conference over time. Does all this research activity contribute to a broader understanding of schizophrenia? This question was very difficult to address without framework on which to organize and integrate the findings that address the question of schizophrenia. If the obvious source of such a framework is a good theory of the disorder, a better framework might be the collection of theories vying to explain schizophrenia.

Just as the task of theorizing about the basis of schizophrenia is not as fanciful as producing a gourmet meal for Iron Chef, so the task of selecting the common ingredients is not as easy as going to the grocer. By their nature, such findings often have a greater affinity for one theory than another. The selection of facts therefore becomes a battleground on which theories vie for the upper hand. This struggle often occurs by the process of embracing convenient findings and disregarding inconvenient ones. A compilation of what is known about schizophrenia risks biasing the observer toward one theory or another. To make this as productive an exercise as possible, we determined to draw from as wide a pool of expertise as possible. Figure 1 describes the strategy we adopted to maximize the likelihood of an inclusive, unbiased compilation of facts drawn from the broadest available scholarship.

To jump start the process, we drew upon the expertise of schizophrenologists at the University of Minnesota and the Veterans Affairs Medical Center, both in Minneapolis. This informal consortium, the Minnesota Consensus Group, was to compile the preliminary list of facts for consideration by a wider audience. One of the first questions encountered by the Group was “How many facts should there be?” A logical response is then “As many as there are things known, beyond dispute, or generally accepted about schizophrenia.” This response provides
The purpose of the compilation of facts was to provide a common set of explananda or features of schizophrenia to be explained by each theory of the disorder included in this special section. To make this exercise interesting, or even feasible, it was determined that this common body of facts should have no more than 10–12 items. Those items could then be selected from a larger list of facts based on their potential for providing insight into the disorder. Because we sought input from the broader scholarly community, who would likely not be able to dedicate a lot of time to consideration of our list, we decided the larger body of items should not be too extensive. We hoped that scholars would be drawn in rather than daunted by the task of reviewing and commenting on such a list. The facts were selected based on a preliminary consensus arrived at through an open discussion of the Minnesota Consensus Group. This was followed up by a literature search, which was then re-evaluated by group. While it was often difficult to word a fact succinctly, consensus regarding the content was not difficult to obtain.

As a result of these considerations, the initial list included 21 items labeled “What We Know” and “What We Don’t Know.” The list was opened on the Schizophrenia Research Forum site in the autumn of 2007. Hakon Heimer also provided a key piece of advice in directing our attention to a similar list on the Alzheimer’s Research Forum site in the autumn of 2007. The Alzheimer’s resource had adapted a convention of indicating, for a given item, what we knew adjoined to what we did not know. This convention allowed us to differentiate between facts that were over our subjective threshold and active areas of research that would eventually augment our knowledge. With the help of the Forum and the national office of the National Alliance for Research in Schizophrenia and Affective Disorders, we solicited input from the broader scholarly community. In this way we hoped to collect the impressions, contradictions, and insights from a group far larger and more diverse than the Minnesota Consensus Group. Of course this was an act of faith; one possible outcome was that the Forum would be bombarded by axe-grinders and partisans with no sense of the broader goals of the project. In the event, we received a multitude of considered and generally balanced perspectives from many of the top scholars in the field. This feedback was in turn posted with an invitation for the community to write about these comments as well.

Eight months after our initial meeting, the Minnesota Consensus Group reconvened to consider the feedback collected through the Forum. A number of changes to the initial list were implemented. For example, it was clear that some of our assertions (such as our endorsement of several genetic loci) overstated our knowledge in that domain. In addition, feedback from prominent epidemiologists drew our attention to recent reviews that allowed us to provide a more nuanced perspective on environmental risk factors. There were a number of specific suggestions that we did not feel met our threshold for inclusion as facts but we agreed were promising avenues of on-going research. In such cases, we made frequent use of the “What We Don’t Know” column to highlight some of these important areas of continuing research. As a result, this column grew to include not only a catalogue of our ignorance but also hints about what might be included as facts in future versions of the table.

Through the course of revision, the number of facts contracted and expanded. Table 1 reports the final list of 22 solid findings about schizophrenia derived through this process. The table divides these facts into what is known, what remains to be known, and where possible a short summary of the relevant effect size reflected as either an odds ratio (OR) or a Cohen’s effect size (d). While the selection of effect sizes from competing reviews has the potential to be a thorny problem for a review of reviews such as this, in practice this arises less frequently than feared. For some observations, effect size estimates were not available. Where present, our approach favored reviews that were more specific, comprehensive and recent, traits which often went together. While this had the negative externality of not acknowledging many foundational papers in the field, it provided extra reassurance that the most recent work had been incorporated into a final parameter estimate. Where comprehensive-ness, recency and specificity did not adjudicate between effect size estimates, we erred on the side of citing a range of effect sizes. It is useful to note that to the extent to which schizophrenia patients are heterogeneous, it is
Table 1. What We Know, Revised List

<table>
<thead>
<tr>
<th>What We Know</th>
<th>What We Do Not Know</th>
<th>Impact in OR Or Effect Size</th>
<th>Additional Cite</th>
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<tbody>
<tr>
<td><strong>Basic facts</strong></td>
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<tr>
<td>1 Schizophrenia has a heterogeneous presentation, with disorganized, positive, and negative symptoms having different levels of prominence across time and across individuals</td>
<td>What causes some symptoms to be more expressed in one patient and a different subset in another? Are other factors (eg, mania, depression, cognitive function) also independent components of schizophrenia? Are there valid subtypes, such as a deficit syndrome or 22qDS that can establish more homogeneous groupings</td>
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<tr>
<td>2 Schizophrenia is relatively common, affecting approximately 0.7% of the world’s population (CI 95% 0.3%–2.7%)</td>
<td>What are the sources of variation in prevalence across the world? Across populations, what is the rate of remission and relapse?</td>
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<tr>
<td>3* Prevalence is greater in men throughout most of adulthood, but is equal by the end of the risk period</td>
<td>Are the relevant differences between men and women cultural, behavioral, biological, or an ascertainment bias? Is schizophrenia equally prevalent in both sexes by age 50 or 60, and if so why? Why are identical twin concordance rates similar for men and women?</td>
<td>OR = 1.4 (male)³</td>
<td>4</td>
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<tr>
<td>4* Schizophrenia has a peak of onset in young adulthood and is rare before adolescence or after middle age. Onset also interacts with sex, such that men are likely to become ill earlier in life than women.</td>
<td>Is psychosis that appears early (before age 14) or particularly late (after age 40) similar to cases in adolescents and younger adults? How should diagnostic criteria adapt to differences in symptoms with age?</td>
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<td>5</td>
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<tr>
<td>5* Liability to schizophrenia is highly heritable (about .81), and concordance between identical twins is almost 50%, suggesting a role for environmental or stochastic influences as well</td>
<td>Do the same genes account for the disorder in different populations? What are the relevant environmental factors, and are they shared or unshared?</td>
<td>OR = 99 (identical twin of patient)⁶</td>
<td>7</td>
</tr>
<tr>
<td>6* All drugs with established anti-psychotic effects block dopamine D2–like receptors, but antipsychotic drugs are not effective for all schizophrenia symptoms. Among available agents, the atypical antipsychotic Clozaril is the most effective; however, it carries unique risks for some.</td>
<td>Why are not the most effective dopamine antagonists also the most effective for reducing symptoms? What is the most cost-effective way to treat schizophrenia? How do effects at other receptors (eg, 5HT2c, mGlu) and pharmacologically induced changes in gene expression influence efficacy?</td>
<td>—</td>
<td>8, 9</td>
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<tr>
<td><strong>Etiological facts</strong></td>
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<tr>
<td>7 Linkage studies (which identify regions of the genome where schizophrenia genes might be found) suggest a number of regions that show genome-wide significance (8p and 22q), with several other regions also receiving strong support (1q, 2q, 3p, 5q, 6p, 11q, 13q, 14p, 20q)</td>
<td>Should we expect different populations to have schizophrenia genes in the same locations? How many genes should we expect? Will studies that identify particular genes, known as association studies, show reliable effects? How should research proceed in the face of large numbers of potential interactions?</td>
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<td>10</td>
</tr>
<tr>
<td>What We Know</td>
<td>What We Do Not Know</td>
<td>Impact in OR Or Effect Size</td>
<td>Additional Cite</td>
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<td>8 The unexpressed genetic liability to schizophrenia affects cognitive and brain functioning and brain structure. The most prominent impairments in individuals with heightened genetic liability, such as patients’ nonpsychotic relatives, have been measured on executive functioning. Overall gray matter and hippocampal volume are also slightly smaller in the relatives of patients with schizophrenia.</td>
<td>Will these “endophenotypes” that reflect the unexpressed genetic liability to schizophrenia help to identify risk genes? Can such behavioral data inform efforts to understand variability in patients?</td>
<td>Continuous performance tasks in relatives $d = 0.56–0.66^{11}$; trail-making tests $0.43–0.50^{11}$; total grey matter decrease in relatives $d = 0.18^{12}$; hippocampus reduction in relatives $d = 0.31^{12}$</td>
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<td>9* Several early neurological insults, later life stressors, and nonhereditary genetic risk factors confer additional risk. These include (in order of impact): migrant status, older fathers, <em>Toxoplasmosis gondii</em> antibodies, prenatal famine, lifetime cannabis use, obstetrical complications, urban rearing, and winter or spring birth.</td>
<td>Are these independent or related risk factors? How do they interact with genetic risk, and to what degree are they specific to schizophrenia? In other words, what is the causal path between each factor and the illness outcome?</td>
<td>OR = 4.6 (migrant status)$^{13}$; OR = 3.8 (older fathers)$^{14}$; OR = 2.73 (<em>T. gondii</em> antibodies)$^{15}$; OR = 2.3 (prenatal famine)$^{11}$; OR = 2.1 (lifetime cannabis use)$^{16}$; OR = 1.79 (obstetrical complications)$^{27}$; OR = 1.72 (urban)$^{1}$; OR 1.07 (winter/spring birth)$^{28}$</td>
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<tr>
<td>Pharmacological and treatment facts</td>
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<tr>
<td>10* While antipsychotics can lead to immediate improvement for some individuals, the time course of medication effects varies widely with some patients showing responses to medication more than a month after beginning treatment.</td>
<td>Is receptor occupancy only one of several ways in which antipsychotics produce therapeutic effects?</td>
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<tr>
<td>11* Exposure to amphetamine, a dopamine agonist, can result in schizophrenia-like symptoms in some individuals. This effect may interact with liability, such that a single dose can trigger relapse in patients, but more chronic use is usually needed to induce psychosis in low risk populations.</td>
<td>Why is this effect observed in chronic, but not acute, amphetamine use?</td>
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<tr>
<td>12* A single exposure to phencyclidine and other NMDA receptor antagonists (such as ketamine) can result in schizophrenia-like symptoms in some individuals.</td>
<td>Are NMDA receptors a useful target for new antipsychotic agents?</td>
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<tr>
<td>A number of psychosocial treatments, including social skills training, family interventions, cognitive behavioral therapy, and cognitive training have been found to be effective for a number of psychotic symptoms.</td>
<td>To what extent do these treatments have specific effects? How can positive outcomes be sustained over time? How can barriers to implementing these treatments in the field be addressed?</td>
<td>$d = 0.23–0.77$ (social skills training); $d = 0.22–0.71$ (family interventions); $d = 0.20–0.49$ (cognitive training); $d = 0.39–0.47$ (cognitive behavioral therapy)$^{24}$</td>
<td></td>
</tr>
<tr>
<td>Longer duration of untreated psychosis is associated with a poorer treatment response.</td>
<td>Can prodromal and early intervention programs alter long-term outcomes on a widespread basis?</td>
<td>$d = 0.50$ (increased symptoms in untreated patients)$^{25}$</td>
<td></td>
</tr>
<tr>
<td>Patients have a 4.9% rate of suicide, which is far greater than the average risk in the United States.</td>
<td>Can suicide-prevention interventions directed at patients early in their illness help to reduce this risk and save lives?</td>
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</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Pathological facts</th>
<th>What We Do Not Know</th>
<th>Impact in OR Or Effect Size</th>
<th>Additional Cite</th>
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</thead>
<tbody>
<tr>
<td>16* Pathological facts</td>
<td>Are reduced arborization and migration causal or epiphenomenal in the schizophrenia disease process?</td>
<td>Prefrontal cell abnormalities $d = 0.87–1.12$; hippocampal cell abnormalities $d = 0.36–0.90$</td>
<td>27, 28</td>
</tr>
<tr>
<td>17* GAD67, that converts glutamate to GABA, is reduced in schizophrenia patients. Reelin, an important factor involved in synaptic plasticity which colocalizes to GABAergic interneurons, is also reduced.</td>
<td>What is the role of GABAergic interneurons in the symptoms of schizophrenia? Are they amenable targets for new anti-psychotic agents?</td>
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<td>30</td>
</tr>
<tr>
<td>18 Even in first-episode patients, the lateral, and third ventricles are somewhat larger, whereas total brain volume is slightly smaller</td>
<td>Given the great degree of variability in brain size in the general population, how is such a subtle change related to risk?</td>
<td>$d = 0.24$ (about 2.7%, total brain volume decrease); $d = 0.32$ (lateral ventricle increase); $d = 0.59$ (third ventricle increase)</td>
<td>31</td>
</tr>
<tr>
<td>19 Medial temporal lobe structures such as the hippocampus, superior temporal, and prefrontal cortices as well as the thalamus tend to be smaller in patients with schizophrenia</td>
<td>What is the relationship between volume reduction, function and symptom expression?</td>
<td>$d = 0.55$ (hippocampus reduction in patients); $d = 0.40$ (superior temporal gyri); $d = 0.39–0.41$ (prefrontal cortex); $d = 0.30$ (thalamus)</td>
<td>33</td>
</tr>
<tr>
<td>20 Functional abnormalities occur in a number of brain systems, including prefrontal and temporal cortices and subcortical structures</td>
<td>Is this a general feature of patients’ brain or are functional abnormalities in certain regions more closely linked to symptom expression?</td>
<td>$d = 0.99$ (reduction in MMN); $d = 0.87$ (reduction in P300); $d = 0.20$ (decrease in dorsolateral prefrontal cortex activity with performance as a significant moderator)</td>
<td>35</td>
</tr>
</tbody>
</table>

### Behavioral facts

| 21 Cognitive tests are challenging for many, but not all, patients even during remission. The greatest deficits appear on tasks such as verbal memory, performance IQ, and coding tasks. | To what extent are cognitive deficits general (that is affecting all functions) or specific (ie, concentrated in a particular function)? For example are executive control functions and early perceptual functions more compromised than other functions? | $d = 0.90$ (overall cognitive performance); $d = 1.4$ (verbal memory); $d = 1.4$ (performance IQ); $d = 1.57$ (coding) | 28, 39, 40 |
| 22 The extent of patients’ cognitive deficits generally predicts functioning in work, social interactions, and independent living perhaps even more than symptom expression | What treatment modalities are best suited to improve cognitive functioning and everyday living? Are there some treatments that work for some patients but not as well for others? | $d > 0.50$ (performance predicting outcome) | 41 |

*Note: *indicates 1 of the 10 facts to be explained by theories in this special section.

OR, odds ratio; $d =$ Cohen’s $d$; NMDA, N-methyl-D-aspartic acid; MMN, mismatch negativity.
important to consider that these estimates will underestimate the true parameter for the relevant group and overestimate the parameter for the irrelevant group or groups. Of these 22 facts, 10 were selected by the group as facts that had the greatest potential to discriminate between modern theories of the etiology and pathophysiology of schizophrenia. As described below, the authors of the subsequent sections were then supplied with both the full table and the subset of 10 items that they were asked to account for (or object to) within their theoretical perspective.

**Results: The 2008 Consensus Report**

The results of this process are summarized on Table 1.

**Basic Facts**

The review process yielded 6 established or “basic” facts about schizophrenia. The first fact is that schizophrenia is known for its variety of symptoms such as hallucinations, delusions, disorganized thinking, and cognitive dysfunction. These symptoms vary between individuals with some having predominantly deficit symptoms from the onset of their illness to others who have predominantly paranoid delusions without significant symptoms in other domains. One approach to heterogeneity has been to describe schizophrenia as a collection of discrete subtypes. For example, the type I/type II subtyping of schizophrenia, which integrated symptomatic, biologic, and outcome heterogeneity generated a great deal of research and may still offer strategies for approaching heterogeneity. Other neurological illnesses that have high rates schizophrenia-like psychosis include 22q deletion syndrome and late-onset Tay Sachs disease, which may provide other valid subtypes and clues to the heterogeneity of schizophrenia and its genetic underpinning (eg,). An alternative to subtyping that is now widely embraced is the investigation of symptom dimensions as a way to organize patient heterogeneity. Lately articles describing the “deconstruction” of psychosis have posited that symptom heterogeneity may be a broader psychiatric phenomenon. These authors suggest that psychosis is the superordinate category with subtypes such as schizophrenia and bipolar illness. In addition to between-patient differences, there are within-patient changes in the level of symptoms over time. For example, in the years before the introduction of antipsychotic medications, assessment of the Iowa 500 demonstrated a significant progression of negative symptoms over time. While it remains unknown what causes patients to have different symptoms across time and across individuals, recent work examining genes and environment or the relationship of genes to cognitive function may eventually shed further light. The field has also not fully accommodated the occurrence of mood and cognitive symptoms into the nosology of schizophrenia. These observations leave open the possibility that new answers might arise from examining dimensions or syndromes associated with schizophrenia or from examining schizophrenia as just one kind of psychotic illness.

The second fact is that epidemiologic studies utilizing objective diagnostic criteria have demonstrated that schizophrenia is a relatively common illness affecting approximately 0.7% of the world’s population. The principal thrust of World Health Organization’s work was the relative consistency of this prevalence rate in countries around the world. However, a number of more recent large and carefully designed studies have demonstrated that there are some pockets of lower and higher risk—such as northern Sweden. In addition, the course of remissions and relapses appears to differ across cultures. For example, some Indian and African sights have noted a somewhat milder course with less relapse than in industrialized nations. The sources of this variation in prevalence remain largely unknown, and there is very little information about whether these differences in outcome are related to the biology of the illness or a perception of decreased stress.

The third and fourth facts address the sex ratio of the illness and its age of onset. Schizophrenia appears in males and females at a similar rate until the ages usually associated with puberty. From the age of puberty onward, males have an earlier age of onset than females by between 3 and 5 years, which is also the period at which incidence peaks. New cases then taper off but do not disappear by any means; after the age of 45, or about the usual time for menopause, there may be a period in which women have greater onset of schizophrenia than men (but see ). There is also substantial evidence that women have a less severe course of the illness, eg women are more responsive to antipsychotic agents. It bears mentioning that prevalence differences are common in other psychiatric disorders as well—attention deficit hyperactivity disorder is more common in males, and borderline personality disorder is more common in females. What we do not know about the greater prevalence of male onset in schizophrenia from early teenage years through to mid-40s is what is the nature of these gender differences. Some have hypothesized the protective potential of estrogens or effects related to gender-specific brain development. One might expect that if the threshold for the disorder is different for men and women that twin concordance rates would be different across sexes. While this may be the case for fraternal twins, there does not appear to be a sex difference in concordance among identical twins (eg,), the importance of which is the topic of our next fact. Also, it remains unclear whether developmental changes should be taken into account in the diagnosis of schizophrenia, eg by using different criteria for the disorder for young or elderly patients.
The fifth fact summarizes findings from genetic epidemiology, which uses family, adoption, and twin studies to examine how illness risk changes for individuals depending on the proportion of genes they share with a schizophrenia patient. Twin studies in particular led to our most stark causal finding, that being a 99-fold increase in the odds of being diagnosed with schizophrenia if one’s identical twin is ill relative to the risk in the general population. While this is more than 20 times greater than the OR associated with any “measured” environmental factor, the twin concordance is still only 50%. This suggests that many people with an increased risk for the disorder never fully manifest the illness\(^7\) and that unmeasured, nongenetic factors also play an important role. Large-scale family studies have reported somewhat lower estimates of heritability (eg, 64%\(^8\), 54\(^5\)), perhaps because identical twins share epistatic similarities (gene by gene interactions) to which family studies are less sensitive. One recent meta-analysis of the twin literature also suggests common environmental factors, events that twins share by virtue of growing up under the same circumstances irrespective of whether they are identical or fraternal twins, may account for up to 11% of variance in symptom onset.\(^6\) However, the nature of these events more specifically is only just beginning to be explored within epidemiological studies (fact #9). Another important question that remains to be answered is whether the same genes (and presumably the same regions of the chromosome) are associated with illness risk in different human populations.

The sixth fact addresses what we can infer from pharmacotherapy. It has been noted that all the Food and Drug Administration (FDA)-approved medications for schizophrenia are substantially active at the dopamine D2 receptor. The first medication to demonstrate antipsychotic activity—in both schizophrenia and bipolar disorder—chlorpromazine was later found to have significant dopaminergic activity leading to the dopamine hypothesis of schizophrenia.\(^5\) Later work demonstrated the activity of chlorpromazine at the D2 receptor.\(^5\)\(^5\) This basic fact regarding schizophrenia has been addressed through the testing of numerous medications acting on neurotransmitters or receptors in the brain that do not involve the D2 dopamine system. For example, opiate antagonists, propranolol, serotonin antagonists, and D4 antagonists have all been examined in careful studies and have not had significant or long-lasting effects. Other interventions for schizophrenia with transient effects include electroconvulsive therapy and high-dose benzodiazepines, likely because they address other brain functions to reduce psychosis or indirectly diminish dopamine neurotransmission. Another fact about the psychopharmacology of schizophrenia is the unique usefulness of clozapine as a treatment of last resort. Early studies of clozapine demonstrated an advantage over placebo but also chlorpromazine. The landmark study by Kane et al\(^5\) demonstrated clozapine’s usefulness in the treatment refractory patient group. Clozapine became the first “atypical” antipsychotic medication to be approved by the FDA and led to the exploration of possibilities for decreasing psychosis with an emphasis on low movement disorder side effects. However, clozapine and other second-generation antipsychotic medications are also active in blocking dopamine D2 receptors and therefore conform to the rule. What remains mysterious then is why the most specific and potent D2 receptor-blocking agents are not the most effective for treating schizophrenia. For example, although clozapine has D2 receptor-blocking properties, it affects many neurotransmitters. This leaves open the question of the role in psychosis of other receptors and neurotransmitter systems such as serotonin. Further, the effectiveness of antipsychotic medications which statistically significantly reduce symptoms of psychosis comes at a price. There is the initial cost of the medication, issues related to relapse and costly rehospitalization, and the impact of some antipsychotic medications on cognition, which diminishes the opportunity for the patient to return to work. It is also interesting to note that accepted knowledge about this basic fact may have to be revised in light of recent evidence suggesting that an mGlut 2/3–activating compound may also be more effective than placebo.\(^5\)\(^8\) The glutamatergic-acting compound was also compared with olanzapine, a D2 receptor-blocking atypical antipsychotic medication, and there was no statistical difference between the 2 medications. Current replication studies are underway, and substantial interest is focused on the potential of the first non-D2 receptor treatment for the psychotic symptoms of schizophrenia.

**Etiological Facts**

The review process yielded 3 etiological facts. Thus, the seventh fact on our list dealt with molecular genetic findings in schizophrenia. Through the process of revision, we removed any single-nucleotide polymorphism or specific structural variant from consideration as a solid fact of schizophrenia. There were, however, 2 meta-analyses of generally the same database of linkage studies both of which fingered 2 regions, 8p and 22q as regions with strong linkage to schizophrenia.\(^5\)\(^9\)\(^6\) In addition, these analyses separately implicated 13q\(^6\) and 1q, 2q, 3p, 5q, 6p, 11q, 13q, 14p, and 20q.\(^5\)\(^9\) The relationship between genes and schizophrenia remains one of the most active areas of research in schizophrenia. Of course the main thrust of this literature is to go beyond the limitations of linkage findings, which after all can only identify regions of the genome likely to be implicated in the disorder, and to examine actual genes.\(^10\) As noted above, this effort is ongoing, without any particular gene implicated beyond question (see reference \(^6\)1 for a description
of the Schizophrenia Research Forum’s exhaustive approach to this issue). As technology for genotyping advances, new techniques that examine the whole genome are opening new avenues of research. One result of this work has been the finding that patients may have a different number of copy number variants, or regions where the structure of a gene is altered. While these specific results must still be regarded cautiously, such findings remind us of the possibility that the genetic liability to schizophrenia need not be related to the same portion of the genome across individuals or even across populations. This is a fundamental, outstanding question that will need to inform the methods and procedures used in the coming years.

Despite uncertainty about the role of specific genetics, there is a strong and generally consistent literature on the unexpressed genetic liability to schizophrenia. Thus, the eighth fact on our list drew on such quantitative genetic studies, generally conducted in the unaffected first-degree relatives of schizophrenia patients. Such studies have found that the heightened genetic risk for the disorder in this population is reflected in small changes in cognitive functioning. Although some such studies show inflated differences between relatives and controls based on the nature of the recruitment of control groups,65 small differences between relatives and controls (generally less than \( d = 0.50 \)) have been reported across a wide variety of measures even when correcting for such possible confounds. Differences in brain function66 and structure67 have also been reviewed, with consistent patterns only now beginning to emerge. Interestingly, these brain-related group differences are, if anything, smaller than the behavioral differences reported to date. One implication of this line of evidence is that these more subtle indices of genetic liability, which have been referred to as endophenotypes or intermediate phenotypes,7 may be useful both in finding genes associated with the illness and in understanding the mechanisms through which this liability may become expressed as full-blown schizophrenia.

The last etiological fact, the ninth on our list, subsumes the environmental factors found to be associated with the expression of schizophrenia. The importance of environmental factors has been appreciated for some time. As noted above, genetically identical twins are only 50% concordant for developing schizophrenia.68 However, a number of challenges, including the small effect sizes associated with any given factor, has made it challenging to pin down the particular environmental factors reliably. Now several national epidemiological samples and meta-analytic findings have drawn our attention to the role of several factors with ORs ranging between 4.6 (for increased prevalence in migrants) and 1.07 (for increased risk in winter/spring births, see Table 1).13,14,27 Interestingly, a number of these factors (older fathers, prenatal famine, urban upbringing, and winter/spring birth) might be considered “shared” or “common” environmental influences, suggested by a meta-analysis of twin studies (see fact #5, above). With a collection of strong candidate risk factors, investigators can now address more mechanistic questions that will help us understand the path to schizophrenia. Perhaps most important among these is how the environmental and genetic risk factors work together in manifesting schizophrenia. An understanding of this interwoven pathway may have treatment implications that go beyond understanding the contribution of any one environmental or any one genetic contributor.

Pharmacological and Treatment Facts

The process yielded 6 facts about the pharmacology and treatment of schizophrenia. The 10th fact derives from the observation that although the D2 receptors in the brain are occupied within the first few hours of administration, symptoms of psychosis in schizophrenia often take far longer to resolve—often on the order of several weeks—if they resolve at all. Of note is that psychotic symptoms seen in nonpsychotic people frequently resolve within hours of administration of a single dose of a D2-blocking antipsychotic medication. The timing of response to medications has been the object of recent research in which older “basic facts” of clinical lore indicating that 4–6 weeks is needed for the medications to work have been shown not to be true. Such studies have shown that the greatest symptom reduction occurs within the first 2 weeks of treatment.19 Other studies have shown that patients who do not respond briskly in the first 2 weeks lag behind the treatment-responsive group throughout the length of clinical trials.69 Further, some patients have very little response to traditional or first-line second-generation antipsychotic medications. Such treatment-refractory patient show little change over the first weeks of treatment (eg, 57). What is not known is why D2 receptor occupancy can occur within hours, yet substantial reduction of rating scale scores do not diminish for 2 weeks or longer. Whether these changes are a delayed onset of action or a slowly emerging response, it leads to an important question about other mechanisms for the successful treatment of psychosis. For many medications, examination of other factors such as second messenger effects, effects on genetic aspects of cell function, etc. are being explored.

The 11th fact concerns the psychotomimetic action of amphetamine. With the discovery of chlorpromazine as an effective antipsychotic medication came the exploration of its actions. Studies in normals demonstrated that prolonged and high doses of amphetamine could produce a paranoid schizophrenia-like picture, which was seen as support the dopamine hypothesis. Subsequently, Angrist and Gershon70 found amphetamine exacerbated symptoms of schizophrenia in patients with the illness and that the degree of exacerbation was associated with
What We Know

Antipsychotic medication treatment response. Other work has suggested that response to amphetamines was not always the same and may be related to the phase of illness.71 Recent studies utilizing positron emission tomography (PET) scanning technology have demonstrated that patients with schizophrenia have a greater outpouring of dopamine following an amphetamine challenge compared with controls.72,73 Therefore, the amphetamine group of studies provides interesting facts about the role of dopamine in psychosis. Some work that has been done on dopamine-stimulating agents in other disorders suggests that the psychosis-inducing effects of amphetamine challenges are not specific to schizophrenia.74 Regarding what is yet to be fully explained is why schizophrenic patients are susceptible to psychosis following amphetamine while normal subjects require an extended period of time at very high doses to achieve a similar effect. Also, as we shall see in the next fact, dopamine agonists are not the only class of drugs that can exacerbate psychotic symptoms.

The 12th fact concerns the psychomimetic effects of another class of drugs, N-methyl-d-aspartic acid (NMDA) receptor antagonists. Decades ago, clinicians noted that young people would come to emergency rooms with schizophrenia-like symptoms following use of phencyclidine (PCP). Interestingly, this psychotomimetic agent led to symptoms that were not readily reversible with traditional antipsychotic medications. Later investigators noted that a related compound, ketamine, could be used in the laboratory to create symptoms of psychosis in control subjects and could lead to an exacerbation of psychotic symptoms in schizophrenic patients.75 This tool led to another avenue of investigation of schizophrenia that was not based on the dopamine hypothesis. By examining functional brain imaging (PET), investigators demonstrated changes in the brain after ketamine that differed between schizophrenic patients and controls.76 The psychotomimetic properties of PCP and ketamine are leading to new avenues for the treatment of schizophrenia. Glutamate-acting compounds such as N-acetylcysteine may be useful in reducing refractory schizophrenic symptoms when used as an augmenting agent. However, many or even most glutamatergic compounds are ineffective as antipsychotics. What remains unknown is precisely what aspects of the glutamatergic system are the most appropriate treatment targets.

While much schizophrenia treatment research has focused on medicine, the 13th fact is that a number of psychosocial interventions can also help to treat the illness. Overall, the effect sizes associated with these treatments are small to moderate, which is approximately the magnitude of psychosocial interventions for other disorders and for many medications. Trials assessing family interventions, many based on theories of expressed emotion, reduce relapse rates in patients with schizophrenia by focusing psychoeducation, support, and strategies to reduce family conflicts. Social skills training, which focuses on initiating and maintaining interpersonal relationships to better integrate patients into their communities, has also shown ability to improve function in patients with schizophrenia. Cognitive behavioral therapy for schizophrenia adapts cognitive restructuring techniques originally developed for treating major depression. These techniques allow one to challenge, and ultimately shape, the meaning of various negative emotions or aberrant experiences into something less threatening.78 A technique adapted from stroke rehabilitation that has proved to be useful is called cognitive remediation.79,80 Evaluation of these techniques has shown that training specific functions, such as working memory, attention and perception, can increase capacity in these essential domains. It remains to be determined whether direct training is the most useful or whether cognitive support is equally efficacious.81 While there is consistent support for the efficacy of psychosocial treatments for schizophrenia patients, there remain a number of crucial questions about their implementation. For example, when patients received social skills treatment and their families were also in therapy, relapse rates were reduced more than by either therapy alone.52 This finding addresses an issue for future research to establish whether a comprehensive program of psychosocial interventions is better than individual components. Also unanswered is who are the most appropriate candidates for which treatment modalities. In addition, sustaining the positive impact of these interventions is an important question for a persistent illness. Can the psychosocial treatments be modified over the longer period of treatment for the illness to continue to provide benefit?

The 14th fact is that the length of time a person is ill before treatment begins is related to the person’s outcome. Originally suggested by an early intervention study more than 2 decades ago,83 there is now a consensus that the duration of untreated psychosis might be crucial to success of the early stages of schizophrenia treatment. Since that time many, but not all, studies of this issue have shown a relationship of duration of untreated psychosis with poor symptomatic recovery and functional outcome with an overall moderate effect size.25 Additional first-episode research has demonstrated that the length of the prodrome, or the time before full symptoms emerge, may be related to poor outcome. One marked example was a study of early-stage schizophrenic patients randomized to treatment with and without medication for 6 months.84 At the 3-year follow-up, the patients who had received medication for the first 6 months of treatment had nearly half as many hospital days in the follow-up period. Can our understanding of duration of untreated psychosis now be translated for clinical use? One study in this area is illustrative of the issue of feasibility and outcome. Melle et al compared 2 Norwegian towns for outcome of first episode of schizophrenia—one town continued its current practice.
of caring for people who developed schizophrenia and the other had an active program to alert the community to the seriousness of psychosis. The town with the active program was able to reduce the length of untreated psychosis, showing that the people so identified were healthier than in the town that continued treatment as usual. The results of this study bolster the theory of the impact of duration of untreated psychosis on schizophrenia. Another avenue of research that is emerging that supports the idea that early intervention can reduce a poor outcome is the effort to intervene in the ultra high-risk prodromal phase of the illness. It would therefore appear that, as in many fields of medicine, early intervention favors good outcomes.

It is our 15th fact that, in the current environment, the rate of suicide is markedly higher for patients with schizophrenia than is observed in the general population. It is in fact in the range of other serious mental illnesses such as depression, bipolar disorder, and borderline personality disorder. Furthermore, these state and national suicides remain unchanged despite efforts of education and prevention. Research approaching this important fact has utilized epidemiological methods, phenomenology, and psychodynamic formulation. Follow-up studies have noted that the early stage of schizophrenia—within the first 5 years of the onset—is a period of high risk. Several reports suggest that frequent symptoms, such as command hallucinations, may lead some people with schizophrenia to make suicide attempts. After psychotic symptom remission, young patients may feel particularly hopeless about their future. Whether this phenomenon is secondary to the psychological reaction to having a serious illness or the physiology of “postpsychotic depression” will require further study. One thing that is clear is that reducing rate of suicide in people with schizophrenia is an important treatment goal. A large study comparing clozapine to olanzapine with regard to suicidal thoughts and behavior recently led to FDA approval for clozapine for this purpose. Early intervention would also appear to play a role. The Norwegian town that received a public awareness and early intervention program to reduce the duration of untreated psychosis also observed a reduced rate of suicide at the 2-year follow-up. Both of these successes point to a general conclusion that reducing the severity of psychotic symptoms is likely to reduce suicide rates. Further work on phenomenological approaches coupled with prevention strategies will be clinically useful.

**Pathological Facts**

The review process yielded 5 facts about the pathophysiology of schizophrenia, much of which has only emerged in the past decade.

The 16th fact concerns the patterns within postmortem brain tissues. While difficult to collect and conduct, this work is central to understanding the pathophysiology of schizophrenia because it provides the closest glimpse that is possible of schizophrenia in the brain. This work has generally focused on prefrontal cortex and hippocampus, although other regions have also been explored. One consistent finding in this literature concerns the large, pyramidal neurons in the third cortical layer of dorsolateral prefrontal cortex that are often the targets of afferents from other brain regions, including the thalamus. Schizophrenia seems to affect these neurons by reducing their dendritic spine density by as much as 23%. Abnormalities have been reported in other regions, such as anterior cingulated, although some like Brodmann’s Area 44 appear to be spared. One meta-analysis suggested large effect sizes across a number of measures of neuropathology. In addition, there are signs of abnormal developmental trajectories in the carefully delineated layers of the hippocampus. This structure is known to be vulnerable to early neural insults, such as hypoxia. These effects are somewhat less reliable, but the same meta-analysis suggested small to large effect sizes in this region. While this work utilizes advanced histological techniques, there are important limitations to the sources of the data. Because specimens are perforce collected at the end of life and only after extended exposure to illness-related factors such as chronic medication, such studies are removed from the pathogenesis of schizophrenia. While these concerns can be addressed by examining whether specific factors such as medications affect neural tissue in the same manner in animal preparations, it is not practical to examine all illness-related factors in this manner.

The 17th fact also derives from postmortem methods and highlights recent findings concerning GABAAergic neurotransmitters. Glutamic acid decarboxylase (GAD67 and GAD65) are 2 rate-limiting enzymes that convert glutamate to GABA. GAD67 has been reliably found to be reduced in patients with schizophrenia primarily in prefrontal and temporal cortices, but also anterior cingulate and cerebellum. GAD65 may also be reduced in a subset of these areas. This deficit in GAD67 availability is partially reversed through antipsychotic treatment. The importance of this observation is that these proteins play a crucial role in the oscillatory activity of pyramidal neurons that coordinate cognitive functioning. A related finding concerns the Reelin protein, which regulates neuromigration and is expressed by GABA interneurons. Patients with schizophrenia show a 30%–50% reduction in Reelin levels in a number of cortical regions, and the extent of this decrease appears to be linked to the levels of reduced GAD67 protein. To our knowledge, no meta-analyses summarize the effect size for this abnormality. These findings share some of the same interpretive concerns as the dendritic spine density findings discussed above. There is also concern that these reductions characterize psychotic disorders more broadly rather than schizophrenia.
What We Know

reductions, there have been meta-analytic assessments initial reports regarding regional specificity of structural zophrenic patients compared with controls. Since the early meta-analysis of the thalamic size in schizophrenia found that across the 15 studies assessed, there was a consistent, albeit small, effect. First-episode studies have also suggested ventricular enlargement at the outset of the illness. In terms of total brain size, Friedman et al have demonstrated through meta-analysis that people with schizophrenia have smaller brains, even at the first episode. It remains unclear what is to be made of the large variance in these measures, however. A close examination of scatterplots reveals substantial overlap in many of the above-referenced studies. Thus, the meaning of the enlarged ventricles and smaller brain size associated with the illness is not known. Adding to what we do not know about brain morphology at the outset is recent data describing dynamic changes in structure from the first episode to multiyear follow-ups. More fine-grained neuroanatomical structural differences between the brains of people with schizophrenia and controls constitute the 19th fact. With the increased precision of magnetic resonance imaging scanning as well as more sophisticated and objective measures of specific brain structures, it has become increasingly practical to measure specific brain areas such as the hippocampus, superior temporal and frontal cortices, and the thalamus. Early reports of these areas indicated these areas to be smaller in people with schizophrenia than in controls. For the cortical areas, volumetric reductions were seen in the middle, frontal, and paralimbic brain regions as well as in the anterior cingulate and paracingulate gyri. Cortical thinning in patients with schizophrenia has been reported to be localized to frontal and temporal areas. This suggests that the global measures of ventricular size and brain size may not reflect equal degrees of change across the entire cortex. Also, subcortical structures such as thalamus have been reported to be smaller in people with schizophrenia than in controls (eg). An early meta-analysis of the thalamic size in schizophrenia found that that across the 15 studies assessed, there was a small but consistent reduction in the thalamus of schizophrenic patients compared with controls. Since the initial reports regarding regional specificity of structural reductions, there have been meta-analytic assessments demonstrating that both the frontal and temporal lobe are subtly smaller in schizophrenic patients. In this latter meta-analytic study, functional assessment was also included, indicating regional differences in schizophrenic patients from controls. The effect sizes associated with these structural differences are also small, implying a great deal of overlap between ill and nonill participants. Therefore, it remains quite unclear how these structural differences contribute to brain functioning and the expression of symptoms or even if they do at all.

The 20th fact attempts to encompass the breadth of findings from the past 2 decades that have found a number of brain processes to be abnormal (either unusually high or more commonly unusually low) in patients with schizophrenia. While brain function has long been hypothesized to be awry in schizophrenia, the seminal work of Ingvar and Franzen was the first to implicate more specific brain regions using biological measures, in this case prefrontal cortex. Recent reviews of functional abnormalities continue to implicate prefrontal cortex and more specifically dorsolateral prefrontal cortex as a region that shows reduced activity with adjoining regions showing at times increased activity. Reviewers have been thus far reluctant to summarize this abnormality into a simple pattern of findings due to differences across studies both because of the tasks used and the predictable differences in performance on tasks that tap working memory and executive functions that utilize this region (see fact #21). Sculp recordings have also been used to measure functional abnormalities. One of the most successful paradigms to date has come from the mismatch negativity waveform which occurs, eg, following an aberrant tone within a string of monotonous tones. This signal, thought to have a source within the superior temporal lobe’s primary and secondary auditory cortices, shows a large effect size across more than 32 studies. The P300 signal is similarly reduced in patients across 46 studies that used oddball paradigms, in which an unexpected stimulus occurs within a series of similar stimuli. The P300, which is a positive deflection that occurs approximately 300 ms following the oddball stimulus, is diffusely generated and is generally found to be largest at medial central and parietal sites. Other electrophysiological abnormalities that have received considerable attention in the schizophrenia literature include the P50 (an early response to observing a stimulus), prepulse inhibition or PPI (a change in responsivity to the second stimulus in a pair), and reductions in gamma rhythm synchrony (30–80 Hz electrical activity). Thus, functions subserved by a number of brain regions and a number of neurotransmitter systems are affected by the illness. Although some exceptions have been reported, the pattern of functional neuroanatomical impairments is wide spread and nonspecific. Furthermore, it remains largely unknown which regions are most closely linked to variation in symptom expression (fact #1).
Behavioral Facts

The process yielded 2 facts about the behavioral impairments associated with schizophrenia. First, since the time of Bleuler, impairments in cognitive functions such as attention have been noted in schizophrenia. Loren and Jean Chapman observed that patients were impaired across a broad swathe of cognitive domains and coined the term “generalized deficit” to succinctly capture this observation. More recently, the independent work of Heinrichs and Dickinson and their colleagues have quantified the behavioral deficits in schizophrenia patients. The 21st fact on our list highlights this observation. These meta-analyses suggest that patients perform about 1 SD worse than controls on clinical neuropsychological tasks. Some tasks show an even greater deficit (up to $d = 1.57$ for coding tasks, which require a combination of speed, working memory, and executive functions). Unfortunately, the generality of this impairment might limit its usefulness for understanding schizophrenia. That is, if all cognitive functions are impaired, no brain system or neurotransmitter system in particular is implicated by these data. Research in this domain may yet find an implicit task demand shared by all such tests that accounts for this common deficit. For example, an important perceptual (eg, gestalt perception), executive control (eg, rule maintenance), or motor function (eg, response threshold) might lead to deficits across many seemingly unrelated tasks. It remains likely, however, that the strong effects associated with cognitive impairments in schizophrenia represent a convergence of many, more subtle, brain deficits.

Irrespective of their specificity or source, cognitive impairments appear to have important implications for patients’ everyday lives. This is the 22nd and last fact on our list. Green et al reviewed 18 studies that used neuropsychological test indices to predict a range of variables, ranging from the total number of hours worked to quality of life, 6 months to 2 years later. These studies are generally consistent in demonstrating medium ($d > 0.50$) to large ($d > 0.80$) effect sizes for these associations. These data are insufficient to confirm a causal relationship. Another explanation of the strength of this relationship is that both cognitive performance and functional outcomes reflect an underlying continuum of severity. However, there is a small but growing body of evidence that targeting patients’ cognitive impairments leads to improvements in functional outcomes, such as the number of hours worked, which is more consistent with a causal relationship. Of course this observation also has a number of important treatment implications. The challenge remains, however, as to how best to match patients to appropriate psychosocial interventions to maximize their potential gains. This is particularly difficult work and requires sample sizes substantially larger than those generally used in such treatment outcome studies.

Conclusion and Preface

The consensus facts reviewed above are by the time of this publication a part of a larger series of efforts to systematize and sort through what we know about schizophrenia. As noted in the introduction, our particular approach to these facts was informed by a desire to see them drawn together into a coherent theory of schizophrenia. In this regard, the Minnesota Consensus Group did not believe that it was either necessary or desirable for the theoreticians to account for every finding in schizophrenia. Among the basic facts, fact #3 (sex differences), fact #4 (age of onset), fact #5 (heritability), and fact #6 (antipsychotic action) were felt to be the most likely to sharpen the differences between theoretical accounts. Among the etiological facts, only fact #9 (environmental risk factors) was incorporated for the sake of this exercise. Three of the pharmacological and treatment facts were highlighted, including fact #10 (medication response), fact #11 (psychomimetic effects of dopamine agonists), and fact #12 (psychomimetic effects of glutamate agonists). And among the pathological facts, fact #16 (reduced dendritic spine density) and #17 (reduced G67 levels) required an account. Interestingly, it was not felt that either of the 2 behavioral facts was likely to distinguish between theories.

To what extent would a different group or a different process have distilled a different set of facts from the schizophrenia literature? A serendipitous point of reference in this regard is the recent work of Tandon et al. Rather than group consensus informed by expert consultation, these reviewers performed a systematic review of 6000 abstracts and over 2000 articles. In many respects, their final list bears a striking similarity to ours. This is likely in large part because both adopted a similar structure (in their case clinical features, epidemiology, neurobiology, and treatment) and both took advantage of the recent proliferation meta-analyses. There are still a number of noteworthy differences that the authors of that work and this project are reconciling. For example, that work highlights as a fact a 2-fold increase in age-standardized mortality beyond the increased risk for suicide. This is a well-supported finding that had so far not come to our attention.

The current set of facts is the product of a number of additional constraints. We have endeavored to make statements that are consistent with the current state of our knowledge, integrate a very large literature into a manageable number of facts, preserve accessibility to a broad audience by avoiding jargon where possible, and be sensitive to the different perspectives of caregivers, patients, and patients’ family members. As the list continues to be refined in the future, it will be useful to keep in mind the importance of falsifiability by tightening the statements and strengthening the parameter estimates.
In this special section, there are 3 accounts by leading theoreticians about how these key facts should be understood from each of their perspectives. First, Drs Stephan, Friston, and Frith (in press) describe how an NMDA-induced failure of synaptic connectivity can give rise to these various phenomena. Next, Drs Howes and Kapur (in press) outline a revised dopamine hypothesis, incorporating recent work on dopamine’s role in ascribing motivational importance, or “salience.” Finally, Drs Fatemi and Folsom (in press) draw attention to neurodevelopmental models of schizophrenia. Such models are informed by changes in the nervous system through embryogenesis and childhood and are conscientious of the kinds of insults that can derail normative developmental trajectories. These 3 papers go far beyond accounting for our 10 test facts, however. For interested readers, they open up the depth of the literature that supports their perspective. The authors also had challenges to address a sticky question: what evidence would cause them to abandon their hypothesis.

The last paper of this special section is contributed by Tyrone Cannon of the University of California at Los Angeles. Dr Cannon’s crucial contribution to this project is to reflect on our state of theorizing and to highlight the challenges of theorizing in a field bedeviled by quasi-experimental data (Cannon, in press). In reflecting upon the theories that can be built around the current set of facts, he notes they are not incompatible. As a result, an important next step is to further draw out the implications of each position to more fully delineate the domains in which they make conflicting predictions. This endpaper is particularly suitable for the current project, which began with the goal of comparing theories on a level playing field of facts. Cannon’s conclusions move the challenge back to theories, by asking that they specify more rigorously the ways in which they differ in their implications and predictions. Of course this is not merely the role of their proponents, but it is a challenge for all of us in the field to strengthen and systematize our thinking about these issues.

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