Part I Neuroscience

Chapter 1

The Story of Schizophrenia

Liberty or Life

Katherine Warburton and Stephen M. Stahl

Why We Created This Book

KW

John C. was a remarkably nice person. He would greet me every morning after my mile-long journey through parking lots, sally ports, and many locked doors. I tended to arrive at my unit at around the same time, and when I approached the final locked door I would see his smiling face in the small square window. As soon as I stepped onto the unit he would exclaim, "Good Morning Doctor!" He would then update me about his prior evening, before politely inquiring as to how I was. One morning he complimented my pants, asking, "Did you make those yourself?" (I never wore them again.) Despite my young age, he had a strong maternal transference to me – not atypical for a long-term therapeutic relationship. It only gave me brief pause that he'd killed his mother several years earlier by cutting open her stomach and pulling out her internal organs. I wasn't worried because John C. had schizophrenia, which was now well controlled with medication, so the risk of him hurting me or anyone else was quite low – as long as he stayed on his medication.

Originally, I wanted to be a rural family doctor in the osteopathic tradition: a humane, holistic, cradle-to-grave kind of doctor in the Maine woods where I grew up. When I got my third-year rotation schedule in medical school and saw that my requisite psychiatry rotation was at the state forensic hospital, I was terrified. Images from old movies coursed through my mind. I went to the dean and strongly requested an outpatient setting, arguing that as a family doctor I would need skills more consistent with outpatient practice. As with everything at my traditional osteopathic medical school, the answer was: "Suck it up, do it, and stop complaining."

The state hospital infrastructure turned out to be everything I'd feared: decrepit buildings, razor wire fences, and a definite vibe that some very bad things had happened on these grounds. I hadn't felt so uncomfortable since my surgery rotation, in which some rough hazing from the scrub nurses had me throwing up behind the parking garage every morning. But something unusual happened when I walked through those two locked doors and onto my assigned unit: I sensed an unmistakable surge of empathy and kindness coming from the myriad patients wandering the day hall. A very large and tall woman approached me. She'd shaved off her eyebrows and painted them back on with hot pink nail polish. She wore her hair in a bleached blond afro, and her makeup heavily encircled her eyes. In other words, she looked bizarre. Being a relatively small person and knowing that this woman had to have been locked in this "back ward" for something quite violent, I should have felt fear or anxiety in her looming presence. But she immediately put me at ease with a kind smile, before stating, "Oh, you must be the new girl. I can tell you come from the light. We will take good care of you here."

Intrigued, I spent the morning reading through volumes of her records. You could do that on a state hospital rotation, during which you were assigned to a back ward. None of these patients were going anywhere, so the workload was light. I found out that the tall woman's name was Gretchen, and she'd shot her husband and children at close range while they'd slept. All she would say about it after that was that she'd saved their souls.

I found myself captivated by the stories of these patients. I also felt like I'd found my home. There is something about the disease of schizophrenia that strips away any pretense, any superficiality, and renders a person profoundly authentic. As an introvert, small talk and social artifice exhausted me. Spending the day sharing space with 45 people who were struggling to maintain their grasp on reality, sliding back and forth between delusions ("I'm the female Jesus, here to save you") and unit

life ("What time is sick call today, my allergies are acting up?") left little room for the unessential of human interaction. And my need to feel needed, to find meaning by helping, was immediately satisfied. Within a week of starting that rotation, I went to the dean to rearrange my fourth-year schedule. I was going to be a psychiatrist.

Five years later, I was nearing the end of my residency in adult psychiatry, and the work remained fascinating. Reading Freud and being able to detect defense mechanisms felt like a form of magic. Learning about neurobiology was challenging but satisfying. I had a dog-eared first-edition copy of Stahl's *Essential Psychopharmacology* that I'd purchased during that first psychiatry rotation. Stahl was already very famous in my circles; he had an uncanny ability to take the most complicated and poorly understood area of the human body – the brain – and break it down with simple language and cartoon drawings to make it understandable. I'd read this book cover to cover many times. What I failed to appreciate then was that I was coming of age as a psychiatrist at a breakthrough moment in neuroscience. In my lifetime, people like Dr. Stahl had developed medications that actually worked to combat the deterioration in perception experienced by many of these patients. It was remarkable to see someone pull back from the edge of reality and at last be able to function simply after taking a small pill.

I had enjoyed my entire residency: working overnight in the ER and assessing those patients who had finally dragged themselves in from within the deep hole of depression; working in my therapy clinic once a week with the worried well and watching them take better control of their own lives; and doing outpatient medication management. But my favorite times were on the locked psychiatric units, helping my fellow human beings escape the torture of persecutory delusional systems, coaxing them back to reality with medication and compassion. These were my people, this was my calling, so I attended a conference of public psychiatrists and sat in on a lecture about schizophrenia. I thought we'd be talking about the newest therapies, but instead the presenter looked out at us and gravely intoned, "If you are a resident thinking about working with patients who have schizophrenia, you'd better go do a forensic fellowship because they are locking them all up." She then presented alarming statistics about these increasing rates of incarceration and arrest.

The term "forensic psychiatrist" brought to my mind Jodie Foster, fava beans, and a nice Chianti, and not much more. I'd rotated through a forensic hospital in another state as a medical student, but I'd never put it together that most of the patients in that state hospital had been confined there after committing a violent crime. This focus on patients with criminal legal involvement was what rendered the hospital "forensic." After conducting further research I learned that forensic psychiatry related to the practice and science of my profession at any point where it intersected with the law. Most state hospitals now are largely forensic in nature due to the increasing numbers of people with schizophrenia becoming entangled in the criminal legal system.

During the forensic fellowship that followed my residency, I studied the two primary legal pathways that many people with schizophrenia ended up traversing. The first is implemented before someone is convicted of a crime if they are too delusional or disorganized to stand trial after an arrest. These individuals are deemed Incompetent to Stand Trial (IST) and generally end up in state hospitals for treatment. People found IST are returned to court when their psychosis is under control. The second pathway is implemented after trial. Some states call it "Not Guilty by Reason of Insanity," others "Guilty Except Insane." In any case, this is a legal mechanism to divert people away from prison and into a state hospital if they can prove they were so delusional at the time of the crime that they did not know what they were doing, or did not know that it was wrong.

I was spending a day a week at a very large state hospital interacting with people who were on both legal pathways, and their stories were both bizarre and fascinating. I'd seen complicated schizophrenia before, but nothing on this scale. I decided that if I wanted to be a competent doctor for this population, I would need to be able to work with these most difficult and complicated cases, so I took a job there. I was assigned to a back ward of patients who had been found Not Guilty by Reason of Insanity. I had 36 patients and the luxury of plenty of time to get to know them and understand their long histories of hospitalization. One of my patients had been locked in that hospital longer than I'd been alive.

I loved my work, and my patients – with one exception. I really didn't care for Ellen M., probably because she would scream obscenities at me while referring to me, inexplicably, as Vivian. She was

trapped in a delusional system, and she believed herself to be a prison warden. She thought I was a particularly naughty inmate. And by the time I got to sorting through her case files, I realized she was woefully undertreated. She hadn't had a medication change in the 10 years she'd been at the hospital because her previous doctor had believed her psychosis was due to a neurological condition. From a case review, however, it was clear she had a classic paranoid schizophrenia. Her paranoid delusions caused her to fear that aliens had infested the Earth and were waging an apocalyptic battle between good and evil. She believed that she herself was a warrior, advised by unseen generals. So, when these generals ordered her to run a red light into a crowd of people, she'd complied.

I started titrating Ellen up on a standard antipsychotic called Risperdal and moved on to the next case. Sometime later, she sheepishly approached me.

"Hello, excuse me, are you my social worker?" she asked.

"No, Ms. M., I am your doctor," I told her, then gestured to the clinician standing next to me. "But Penny here is your social worker."

"Thank you so much," Ellen answered politely. "Penny, can you please help me? I'm not sure what I'm doing here in the hospital, but I'd really like to call my husband and children to let them know where I am."

Penny and I stared at each other in shock. Ellen was clear as a bell, with no sign of any remaining psychosis. After 10 years of being trapped in an alternative reality, Ellen emerged as the kind, funny, and delightful woman she'd been prior to the development of the disease. A particular highlight of my career was the family meeting where I witnessed Ellen's two now-grown children emotionally reunite with the mother who'd been absent from their lives for well over a decade. I'd had my first "awakening" experience with these new-generation medications, and I now knew beyond a doubt that, under the right circumstances, they could be miraculous.

As I worked my way through the cases of all 36 patients on my ward, it was also becoming clearer to me that all of them would have escaped the fate of long-term state institutionalization if they'd received treatment earlier in the disease. Before their crimes, their records indicated that they all had loved ones who had been trying to get them into care. The kicker: They were invariably so delusional that they did not realize they were ill. In colloquial terms we refer to this as a "lack of insight." This also goes by a fancy Greek word: "anosognosia." Anosognosia roughly translates to "without disease knowledge." It is extremely common for people with schizophrenia to refuse treatment because they don't believe they are ill. Still, it came as a shock to recognize that every single one of my patients had been experiencing anosognosia at the time of their crimes.

Take Joe P. He himself was a licensed mental health professional, as were all his siblings. He was a middle-aged man from a close-knit, affluent family when he developed a psychotic depression, which can cause symptoms identical to schizophrenia. His family, some of whom were doctorate-level experts in this disease, repeatedly sought help for him. And every time they were turned away because, convinced that he did not have a mental illness, Joe refused treatment. Instead, he believed that imposters had invaded the bodies of his loved ones, and with each day that passed without treatment he grew more paranoid. He lost his job, and he lost his home. His father took Joe in despite his son's growing agitation and suspicions. One night, Joe beat him to death with a sledgehammer. The only way to save his father – to free him to reemerge, Joe had reasoned – was to beat the imposter to death. Joe was found Not Guilty by Reason of Insanity and quickly responded to the same medication as Ellen. That was the easy part. The hard part was helping him through his horror and grief at what he had done while he was out of his mind. His family forgave him and understood, but they railed against a system that had refused to treat Joe against his will. That system, they believed, was responsible for the murder. We tried to discharge Joe back to the community; he was no longer a danger. But the judge made it clear that he would never order a community release given the notoriety of the crime. I began to have questions about such a system that values autonomy so highly yet allows people to get so sick that they are institutionalized for life.

How did this come to be, I wondered? In that moment I became a student of the history of mental illness in general, and psychiatry in particular. An illustrious history it is not. Suffice it to say that because the brain was so poorly understood, the experimental treatments that fill the historical record are horrifying, among them induced insulin comas and frontal lobotomies. A patient on my locked psychiatric unit, Jorge C., was a survivor of that era. Jorge was an elderly man and the first patient to greet me when I started on the unit.

I'd barely stepped inside when he ran up and screamed, "Fuckyoufuckyoufuckyoufuckyou" in my face until a psych tech redirected him back to his room. I followed him, and I was overwhelmed by the smell of urine. The lack of sanitary conditions alarmed me, but the tech – who adored Jorge, and vice versa – explained that Jorge would store his urine in his room despite all staff efforts and interventions to prevent him from doing so. I'd never seen a patient present like this before. And when I got around to looking through his chart later that day it became clear why: In the 1960s Jorge had undergone experimental psychosurgery.

Jorge's ill-fated operation occurred in the mid-twentieth century, when state institutions were riddled with experimental, ineffective treatments, abysmal funding, and astonishing overcrowding. Human beings were involuntarily committed with no clear due process or thoughtful consideration. People were locked up for everything from sexually transmitted diseases to alcoholism to tuberculosis. A process called "deinstitutionalization" began in response to these horrific conditions, and such individuals were released to the community. Many scholars attribute a poorly planned process of deinstitutionalization with the later increases in homelessness and criminal legal involvement experienced by people with schizophrenia.

Several years after that back ward of 36 patients captured my heart, I'd been promoted to be the clinical leader of a large forensic hospital system with seven institutions, 6,500 patients, hundreds of doctors, and thousands of clinical staff. I had no idea what to expect, but I can tell you that low on my list of expectations was Stephen M. Stahl, MD, PhD, deciding that he wanted to come in and help. It seemed like a good idea: I would try to manage what had to be an enormous ego and, in turn, be able to leverage his expertise in psychopharmacology. He requested a weekly meeting with me, which seemed reasonable. These meetings would inspire and sustain me throughout a decade. Our first conversation began with a bang.

"You may not realize this, but I'm going to be mentoring you," he told me in a hypomanic but matter-of-fact manner. "You're pretty smart, and you seem to have some good ideas, but no one understands what the hell you're talking about half the time. You need to organize your thoughts. You need to ground your thoughts in the existing literature. You need to write them down; that's the only way you will be able to slow your brain down. And you need to stop apologizing for being ambitious, stop apologizing for being a young woman in your position, dammit. You are in that role because you earned it, and until you own that, you will not be effective. You need to lean in!"

For over a decade, Dr. Stahl and I worked through the problems facing our hospitals. We did it by using the methodology he'd laid out for me: mastering the literature, developing our own studies, and conferring with other states and countries. In time, the daily challenges we faced were eclipsed by an overwhelming increase in the number of patients with schizophrenia that county jails were sending us as IST. We engaged our research partners and sought to figure out the reasons for these increases in arrests of people with active psychosis. These were people with schizophrenia like John, Ellen, and Joe. But, we learned, they were only showing up at our doors after *years* of untreated disease. The overwhelming majority were homeless. Most had been incarcerated many times before. They had extensive underlying untreated medical problems. The trend of criminalization that I first heard about at that public psychiatry conference and saw on my own unit was getting worse – horribly worse.

It didn't help that the hospitals couldn't handle this influx. That meant that individuals with serious mental illness were trapped in county jails on long waiting lists to get into state hospitals. These waits got substantially longer during the COVID-19 pandemic, when we had to cease admissions during lockdowns. Judges and jail officials were understandably frustrated. As was I. As I sorted through the paperwork of the people on our waiting list, what I read broke my heart. Many had been arrested on felony charges for actions that spoke to untreated disease and pure survival: homeless people taking refuge in abandoned buildings or starting fires to stay warm; paranoid people throwing rocks through windows; starving people stealing food. And they were locked away in jails, untreated and at highest risk for a deadly virus that preyed on individuals with the types of medical conditions most people with schizophrenia experience.

As we dug deeper, it became clear that the massive challenges facing forensic state hospitals were not the fault of the hospitals; they were the result of large-scale policy failure. As we chewed on the bitter reality of the increasing incarceration, homelessness, and

trauma experienced by our ballooning hospital population, the answers seemed obvious. But existing policy and legal structures guiding mental health treatment were nonsensical and entrenched. My Friday calls with Dr. Stahl turned into ranting sessions. Why hadn't certain laws passed? Why was funding being held up? We came up with grandiose ideas, ranging from forming a political action committee to beseeching the pope to help us.

I got myself onto state and federal committees, where we blandly discussed anemic and tangential attempts to fix the system. At the end of these meetings, members of the public were invited to comment. Like clockwork, the parents of people with schizophrenia stepped up, begging for help, because their children were incarcerated, untreated, and/or homeless, tortured by delusions and refusing help.

One day, I attended a public meeting for California's CARE Court, implementing a new law designed to compel care for people with schizophrenia who were at risk for homelessness and incarceration. During the comments from the public, a mother called in to speak. At her urging, her daughter had checked in to a homeless shelter. She was experiencing delusions and, as a result, had begun yelling, so the shelter had kicked her out. She'd taken a blanket and walked into the night, settling down to sleep in the dirt and refuse on an empty lot next door. The following morning, the unsuspecting driver of a delivery truck ran over her head, killing her. I found myself crying uncontrollably while listening to this story, one so similar to others I'd heard before.

I had heard so many horror stories by this point in my career, but this one got to me. I think it was the raw pain in the mother's voice. That Friday morning, at my rant session with Dr. Stahl, after asking how policymakers, advocates, and elected officials could be so unwilling to change the system, it finally dawned on us: People simply didn't understand this disease. They didn't understand that it was no different from Alzheimer's disease in terms of a person's inability to make decisions for themselves. The horrible history of psychiatric abuses, combined with the relative newness of promising scientific advances, had left gaping holes where misunderstanding, propaganda, politics, and ideology took root to prevent change.

Someone, we decided, needed to tell the story of schizophrenia. And who better than us?

SMS

My career can be described through three paradigm shifts, the final one relating to this book and our current project. My journey into psychiatry began with a first paradigm shift, namely entering psychiatry only after a detour into neurology, until I realized that with my MD–PhD in pharmacology that medications were much more effective in psychiatric disorders than in most neurological disorders, and that the future held more promise for new innovations in psychopharmacology treatments than in neurology. The decades since the beginning of my career have proven this to be true. Thus, I pivoted to psychiatry and developed my career in the midst of the serotonin selective reuptake inhibitor (SSRI) and atypical antipsychotic era, first as an academic with a lab and a research ward for schizophrenia at Stanford, then with a stint overseas to work for a brain research institute funded by the pharmaceutical industry in the UK, targeting brain disorders for new drug development, and finally back to the USA as a research professor at the University of California, San Diego.

The second paradigm shift occurred after years of doing psychopharmacology research, both basic and clinical, when I realized that it was a very long slog to "invent/discover" new drug treatments that were, in fact, usually just marginal improvements over what already existed, whereas teaching practitioners to close the gap between ideal psychiatric practice and actual practice, utilizing current drugs optimally, would potentially impact the field much more than many new "copycat" drugs. Thus, my era as a textbook author and international lecturer/symposium organizer began. This was and continues to be very gratifying, but I also experienced a blazing glimpse of the obvious: namely, that no matter how ideally drugs for psychosis were prescribed, "they didn't work if you didn't take them." Hard to believe!

I came to realize that there were radically different problems in the treatment of psychosis at the two ends of the spectrum of severity of this illness. On one end of the spectrum were the sickest of the sick, many of those in forensic hospitals like those described by Dr. Warburton, with a lifetime of nontreatment, intermittent treatment, and undertreatment. It struck me that this was analogous to what would have happened if I were in the field of oncology and the system in that field worked the same way as in my field: namely, that no one got effective cancer treatment

until the terminal stage of the disease. Because schizophrenia is a progressive illness involving neurodegeneration of gray matter, especially when not treated, this would mean that untreated psychosis, once such an individual has been criminalized and institutionalized, especially for decades, would result in patients presenting in the late stages of psychosis. And indeed these patients would get treatment, but there were no guidelines on how to treat them with the antipsychotics developed while studying moderately ill patients able to give consent to participate in such research! It dawned on me that these forensic patients at the severe end of the spectrum were in the "top 1% of the 1%." Not economically, certainly, but a bit of math on the back of an envelope told me that if California has a population of 40 million, and 1–2% (or about 700,000) have serious mental illness, and the population of state hospitals was 7,000, this meant that state hospitals housed a population severely skewed to the severe end of the spectrum, and we really did not have guidelines for how to treat them with antipsychotics, especially if they were treatment resistant and violent. Thus, I embarked on a project in the state hospital system that Dr. Warburton runs to capture the collective experience of the experts who had "practice-based evidence" rather that the "evidence-based practice" that dominated my academic life. We developed and published guidelines for treatment resistance, violence, and how to dose guided by plasma antipsychotic drug levels, and we increased the number of experts in the use of clozapine and long-acting injectable antipsychotics. And, lo and behold, despite greatly improving the outcomes of these patients, I watched as hospitals began to overflow with patients at the other end of the spectrum.

These were patients in the earlier stages of their illness, homeless, receiving no treatment, getting arrested for their illness on the streets, and IST for their charges. They didn't lack effective and available treatments but rather did not want treatment, not recognizing that they were ill or that such treatments would work. The system allowed patients unable to make health care decisions for themselves due to illness – who had anosognosia and a lack of insight into their illness – to refuse treatment, all supposedly because of their rights and for liberty's sake. Of course, a patient with Alzheimer's disease eating out of a dumpster and wandering the streets would be rapidly taken into care no matter how much they protested, but for some reason the system decides that schizophrenia is different. This propelled me to join Dr. Warburton in the third paradigm shift of my career: namely, one toward the implementation of policies that allow humane treatment of psychosis before a patient enters the forensic/criminal justice system.

I specifically came to realize that the system allowing patients to live horrible, unhoused, exploited lives without treatment was based largely on outdated – or frankly wrong – information. The concepts that there is no such thing as schizophrenia and, furthermore, that antipsychotics don't work are prime examples. Liberty over life was a recurring value justifying these tragic outcomes. To counter this nonsense, as a psychiatrist who understood well the exploitation of such patients in asylums of the past, I recognized that we needed help in assessing the dilemma of treating patients who did not want treatment because they did not know that they were sick. So, I consulted a distinguished neuroethicist, the Vatican priest Father Alberto Carrara, dean of the school of neuroethics at the Vatican University of Rome, about the ethics of treatment and nontreatment. After Dr. Warburton and I took him to see the fate of patients with schizophrenia in the USA, to Skid Row in Los Angeles to see homeless psychotic patients in tents eating out of dumpsters, and to a notorious jail housing thousands of psychotic individuals under arrest basically because of their psychotic symptoms, he began to ponder the question of how to consider these issues within a neuroethical framework. He finally figured out that in an untreated psychotic state, the patient has lost a certain amount of freedom, including the freedom to make rational health care decisions. In a stunning statement summing this all up, he found that what was happening was "abandonment dressed up as autonomy." Wow.

So, off we go – to help implement the treatment of psychosis across the spectrum, and especially to get psychotic individuals into housing with treatment that includes programs that provide their lives with meaning. The individuals writing the chapters in this book are all fellow warriors in this fight for justice and humane treatment – such as we have seen in Europe, especially in Italy – and we all know we can do this. The tools are all there, the housing can be found, the medications do work – we just need to put it all together! Our goal is nothing short of revolutionizing the treatment of psychosis in America! Please join us.

Chapter 2

What Is the Neurobiology of Schizophrenia?

Michael A. Cummings, Ai-Li W. Arias, and Stephen M. Stahl

Schizophrenia spectrum disorders are a cluster of psychotic brain diseases that afflict approximately 0.4% to nearly 2.0% of persons in various worldwide populations.[1,2] In 2019, the direct and indirect annual costs of schizophrenia were estimated at $343.2 billion in the United States alone.[3] Moreover, in addition to a substantial economic burden on society as a whole, the schizophrenia spectrum disorders impose a variety of devastating personal and familial burdens, including but not limited to social isolation, disruption of education, unemployment, homelessness, intrafamilial violence, entanglement in the legal system, incarceration, increased injury and illness, and a shortened life span.[4,5] Given the costly and disastrous effects of the schizophrenia spectrum disorders, Emil Kraepelin, who first characterized these psychotic disorders, described them as dementia praecox or early dementia.[6] In the remainder of this review, we will consider the neurobiology underlying a cluster of brain diseases that can be conceptualized under an umbrella as a group of developmental dementias with similar core pathologies but heterogeneous variations in clinical detail.

The human genome was first published in 2001.[7] Since then, researchers have been working to identify protein-coding genes. The number of such genes is presently estimated at between 19,000 and 20,000.[8] Within the human genome, some 270 gene loci have been associated with schizophrenia spectrum disorders, with 108 risk genes being identified as single nucleotide polymorphisms.[9] The most obvious genetic associations have been with genetic variations in the major histocompatibility complex. Besides polymorphisms, structural variants in the form of copy number variants, such as microdeletions and microduplications, have a very high impact in a subset of patients. These variations are mainly microdeletions on 1q21.1, 2p16.3, 3q29, 15q13.3, and 16p11.2, as well as a large deletion on 22q11.21 and a microduplication on 16p11.2.[10] Importantly, many of the genes and gene loci implicated in schizophrenia are involved in areas such as cell differentiation, cell regulation, cell maturation, cell migration, orientation of cells, the structure of cell receptors, cell adhesion, and, in the case of neurons, development of neural networks.[11,12] Additionally, those gene foci that are part of the histocompatibility complex play critical roles in immune identity and control of inflammatory processes.[8,13,14]

Although schizophrenia spectrum disorders are heavily genetically determined, it is thought that about 20% of the risk for overt illness is determined by environmental factors such as maternal stress during pregnancy, in utero infection exposure, childhood illnesses, childhood adversity, and childhood or adolescent exposure to drugs such as methamphetamine or cannabis.[1,15] Many of these environmental risk factors may influence the occurrence and phenotypic development of schizophrenia via epigenetic processes, such as gene promotion or inhibition of other genes using small peptides or short ribonucleic acid (RNA) sequences, methylation of deoxyribonucleic acid (DNA), or modulation of the acetylation of histone (protein involved in the winding and unwinding of DNA strands for copying).[16,17] Moreover, while no gene therapies currently exist for schizophrenia spectrum disorders, interventions in selected environmental risk factors hold promise for altering the phenotypic presentation of schizophrenia, as well as risk of overt illness in both present and future generations.[18,19]

The human central nervous system begins as a simple tube formed from neural crest cells. This relatively simple structure, however, then undergoes a complex and elegant series of steps to become the brain and spinal cord.[20] The brain is formed by overfolding of the cephalad portion of the neural tube with glial cells laying down the structural form of the brain and providing trails of chemical markers for motile neuroblasts to follow to their cortical and subcortical positions.[21] During the second

trimester of pregnancy, neuroblasts (immature motile forms of later neurons) undergo rapid mitosis deep in the forming brain near the lateral ventricles. These neuroblasts then crawl to their later positions following neurotrophic markers and organize themselves into orderly neural assemblies.[20] They then form neural networks by sprouting axons and dendrites. Initially, the number of connections is 2 to 5 times greater than the connections present in the mature brain. That is, exposure to the environment and the process of learning selects those pathways that will be reinforced and those that will be allowed to atrophy as the brain matures.[22–24] The primary visual cortex is the first to mature at about 1 year of age, while the last areas to mature are the frontal and temporal lobes at between 18 to 25 years of age. Thus, the roughly 100 billion neurons of the central nervous system, along with their associated astrocytes, oligodendrogliocytes, and microglia, as well as other cell types, become the adult brain and spinal cord.[21,24,25]

In contrast, brain development and maturation in schizophrenia spectrum disorders is clearly abnormal. To begin, many of the neuroblasts produced during the second trimester of pregnancy fail to reach their correct positions, instead being found in postmortem studies isolated deep within the white matter of the brain.[26,27] Then, across childhood and adolescence individuals in the premorbid phase of schizophrenia exhibit excessive loss of neurons and synaptic connections, such that by the onset of overt psychosis some one-third to one-half exhibit clear atrophic changes and enlargement of the lateral ventricles on brain imaging.[28,29] Ventricular enlargement, reflecting loss of brain tissue in schizophrenia, is illustrated below (Figure 2.1).

Following the onset of overt illness, loss of brain mass continues and appears to be correlated with the duration of untreated illness and the number of psychotic exacerbations.[1,29,30] At least a portion of the brain tissue loss associated with psychotic exacerbations or longer durations of untreated active psychosis appears to be mediated by inflammatory processes, including activation of microglia and invasion of the brain by macrophages.[14,31,32] Interestingly, treatment of high-risk children (i.e., having two parents with schizophrenia spectrum disorders) with low-dose antipsychotic medications may reduce the rate of conversion to overt illness in adolescence.[33] Nevertheless, it should be noted that some subsequent studies have failed to find evidence that antipsychotic treatment during the premorbid phase of schizophrenia is protective with respect to later development of overt schizophrenia.[34] Better established appear to be observations that consistent antipsychotic treatment

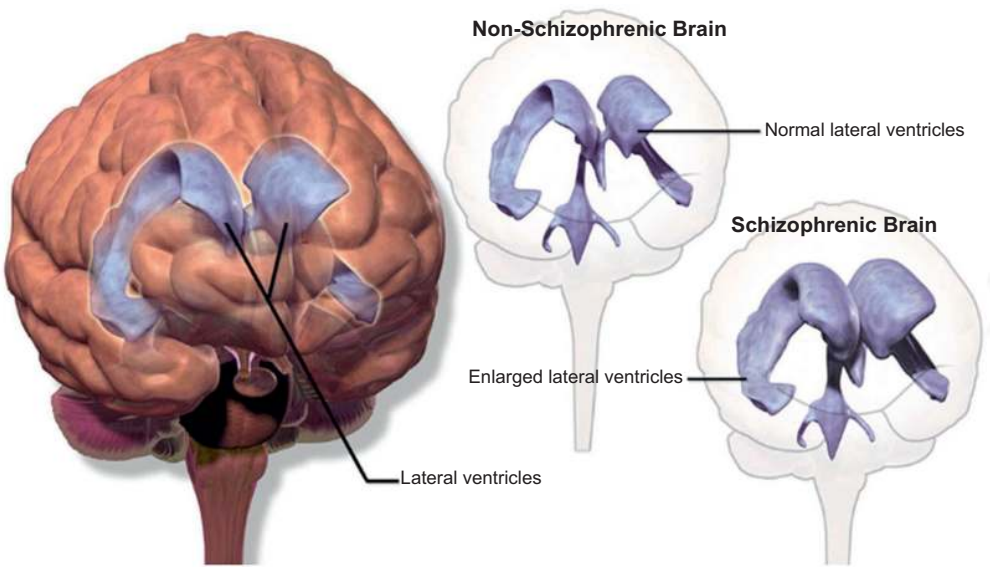

Figure 2.1 Ventricular enlargement/brain atrophy. openbooks.lib.msu.edu (open access).

(e.g., with long-acting injectables [LAIs]) slows but does not reverse the deterioration of the brain in schizophrenia spectrum disorders.[35–37]

Clinically, the signs and symptoms of schizophrenia have been divided into positive, negative, and cognitive deficit domains.[1,38] Positive signs and symptoms include hallucinations/illusions, delusional ideation, illogical thoughts and behavior, hyperactivity/agitation, and thought disorder.[1,38] Negative signs and symptoms include apathy, lethargy, abulia, avolition, and social withdrawal.[39] Cognitive deficits in schizophrenia spectrum disorders include deficits in attention, concentration, memory organization and recall, language processing, and executive functions such as self-awareness and social judgment.[38, 40] In addition to the developmental abnormalities and atrophic brain changes described earlier in this article, two neuromodulatory molecules, that is, dopamine and serotonin, appear to play important functional roles in schizophrenia spectrum disorders.[41,42] Below, we consider three neural networks with respect to the positive, negative, and cognitive domains of schizophrenia.

Positive signs and symptoms appear to arise in part from excessive dopamine stimulation of mesostriatal projections to temporal lobe association cortices and related structures (formerly termed the mesolimbic pathway).[41,43] This excessive stimulation of limbic D_2 dopamine receptors, in turn, appears to arise from a failure of inhibition by gamma aminobutyric (GABA) interneurons in the frontal cortex and failure of M_4 acetylcholine receptors on the cell bodies of the relevant mesostriatal dopamine neurons.[41,44] This is illustrated as follows (Figure 2.2).

Excessive serotonin (5-hydroxytryptamine) stimulation of $5HT_{2A}$ receptors may add to positive psychotic signs and symptoms, especially visual hallucinations, in schizophrenia.[41,45] This is illustrated as follows (Figure 2.3).

Finally, it appears that in addition to previously described developmental pathologies and atrophic changes, inadequate stimulation of frontal lobe D_1 and D_3 dopamine receptors contributes to the negative symptoms and cognitive impairments of schizophrenia spectrum disorders, including anosognosia (unawareness of illness).[41,46] This is illustrated as follows (Figure 2.4).

Importantly, all antipsychotic medications appear capable of ameliorating psychotic symptoms, with the

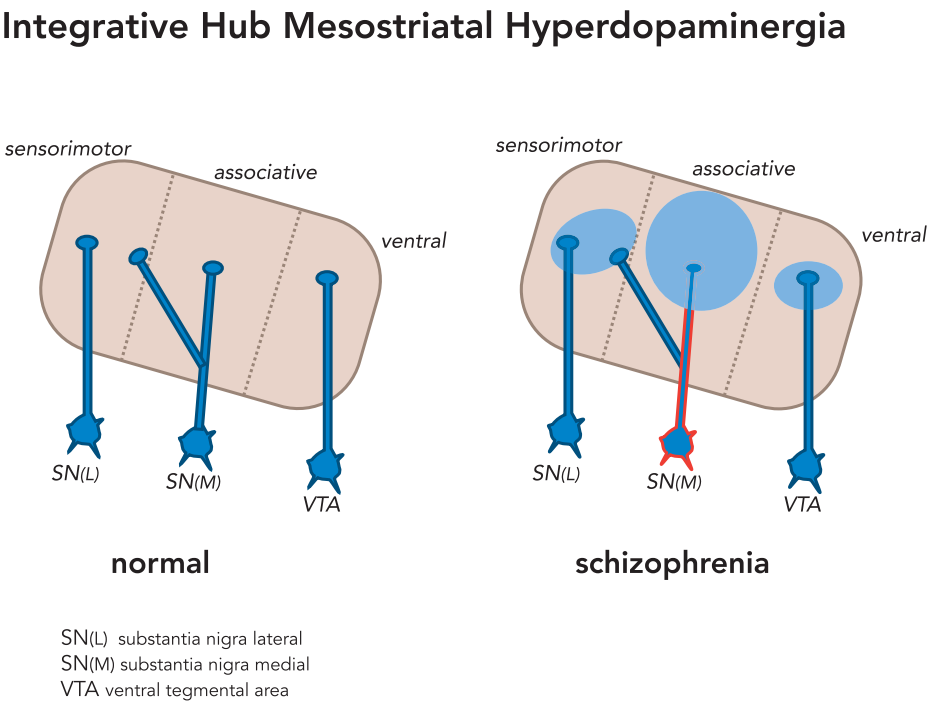

Figure 2.2 Mesostriatal dopaminergic hyperactivity. Stahl, S. Stahl's Essential Psychopharmacology, 5th Edition, Chapter 4, p. 93.

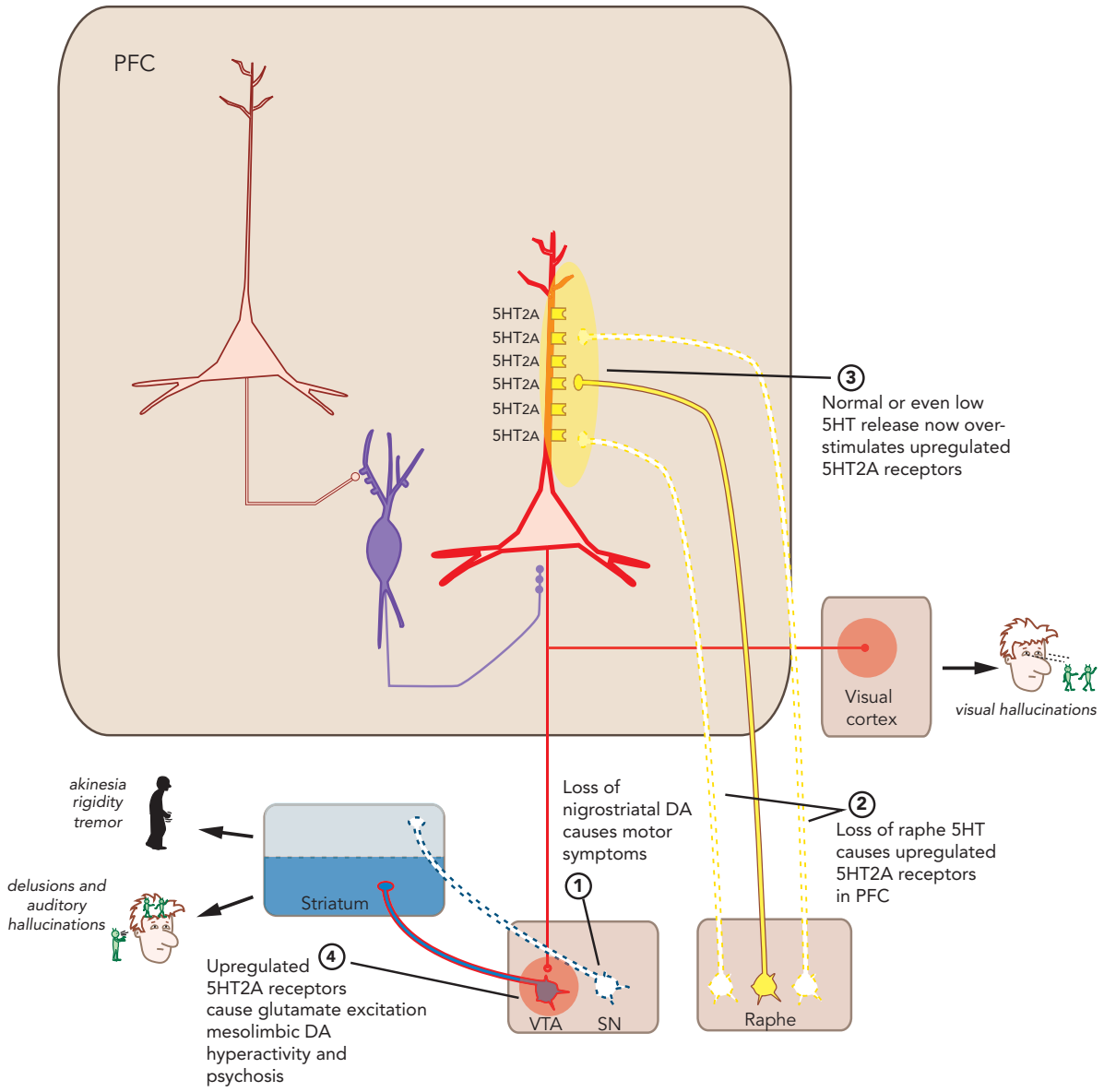

Figure 2.3 $5HT_{2A}$ serotonergic hyperactivity. Stahl, S. Stahl's Essential Psychopharmacology, 5th Edition, Chapter 4, p. 136.

largest effects being on positive signs and symptoms.[47] In particular, LAIs appear superior in preventing relapse and, thereby, illness progression, morbidity, and mortality.[35,48] In the near future, a new class of antipsychotics likely starting with xanomeline/trospium may be able to presynaptically modulate dopamine release in mesostriatal projections by targeting the M_4 acetylcholine auto-receptor.[44] Among the antipsychotics, clozapine remains the "gold standard" of treatment in several areas, that is, management of treatment-resistant illness, reduction of violence, reduction of suicide risk, and enhancement of cognitive executive functions.[49,50] Clozapine also appears to be unique in that it likely acts by exerting effects upstream of the mesostriatal dopamine neurons by improving glutamate signal transduction.[51,52]

Summary: Schizophrenia spectrum disorders are a group of related psychotic developmental