# Schizophrenia as the Prototypical Psychotic Disorder

Schizophrenia is the prototypical psychotic disorder since it is the most common and best known and expresses prototypical psychotic symptoms. Delusions and hallucinations are the hallmarks of schizophrenia and are often called the "positive symptoms" of psychosis. Delusions are fixed beliefs—often bizarre—that have an inadequate rational basis and can't be changed by rational arguments or evidence to the contrary. Hallucinations are perceptual experiences of any sensory modality—especially auditory—that occur without a real external stimulus yet are vivid and clear, just like normal perceptions, but not under voluntary control. Schizophrenia can also include other symptoms like disorganized speech and behavior and the so-called "negative symptoms" of psychosis, including diminished emotional expression and decreased motivation (American Psychiatric Association, 2022).

Both disease pathophysiology and novel treatments are pivoting from the postsynaptic dopamine D2 receptor to the presynaptic dopamine terminals of overly-active dopamine fibers that drive positive symptoms. High levels of dopamine in presynaptic terminals of psychotic unmedicated patients have been documented and replicated with in-vivo human neuroimaging (Brugger et al., 2020; Weinstein et al., 2017). Emerging genetic research shows this is likely due to aberrant presynaptic D2 receptors being inadequately sensitive and thus unable to turn off dopamine release (Benjamin et al., 2023). Mechanisms whereby upstream modulation of dopamine by various neurotransmitters may treat symptoms of psychosis are presented.

## Schizophrenia Phenotype: Positive and Negative Symptoms

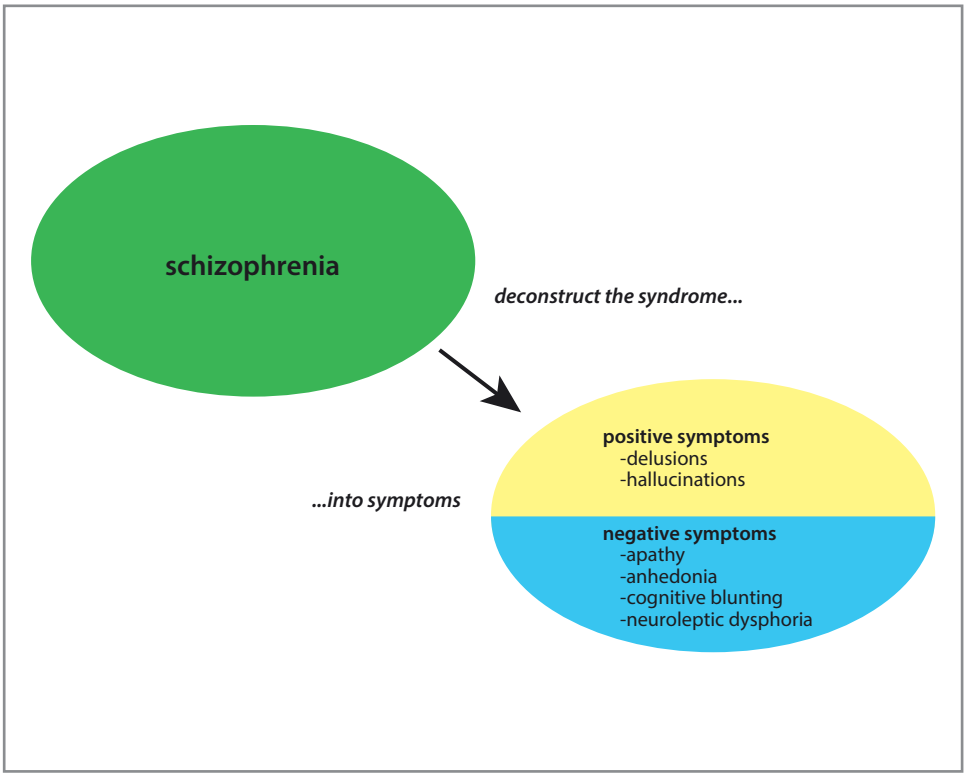



**FIGURE 1.1.** The syndrome of schizophrenia consists of a mixture of symptoms that are commonly divided into two major categories, positive and negative. Positive symptoms, such as delusions and hallucinations, reflect the development of the symptoms of psychosis; they can be dramatic and may reflect loss of touch with reality. Negative symptoms reflect the loss of normal functions and feelings, such as losing interest in things and not being able to experience pleasure (Stahl, 2021).

# Localization of Symptom Domains

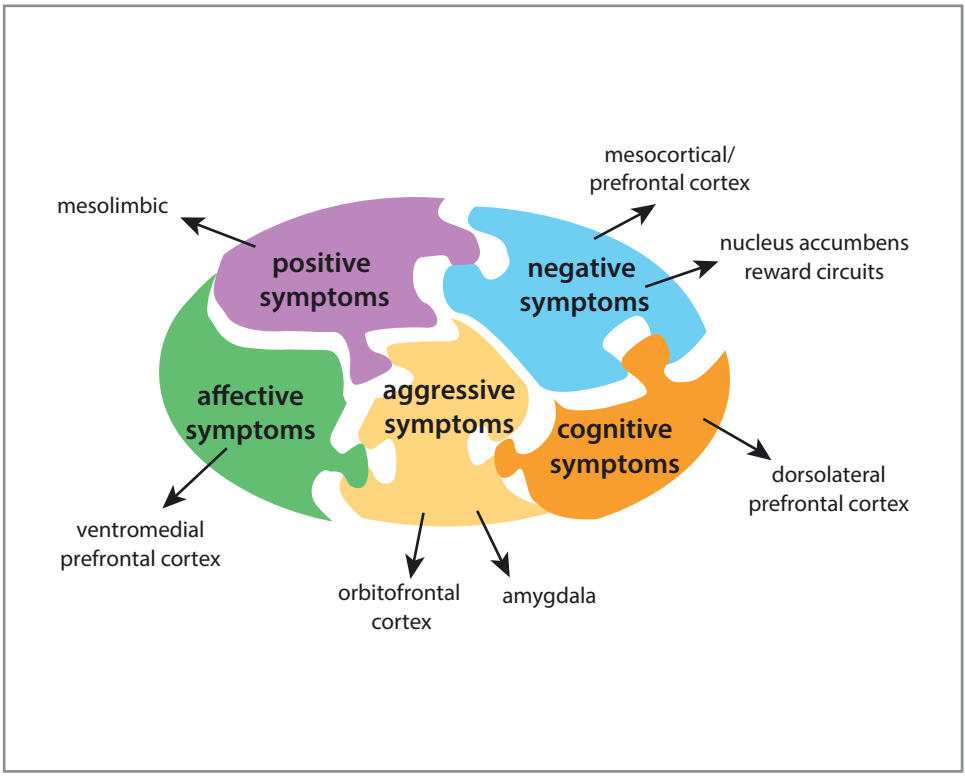
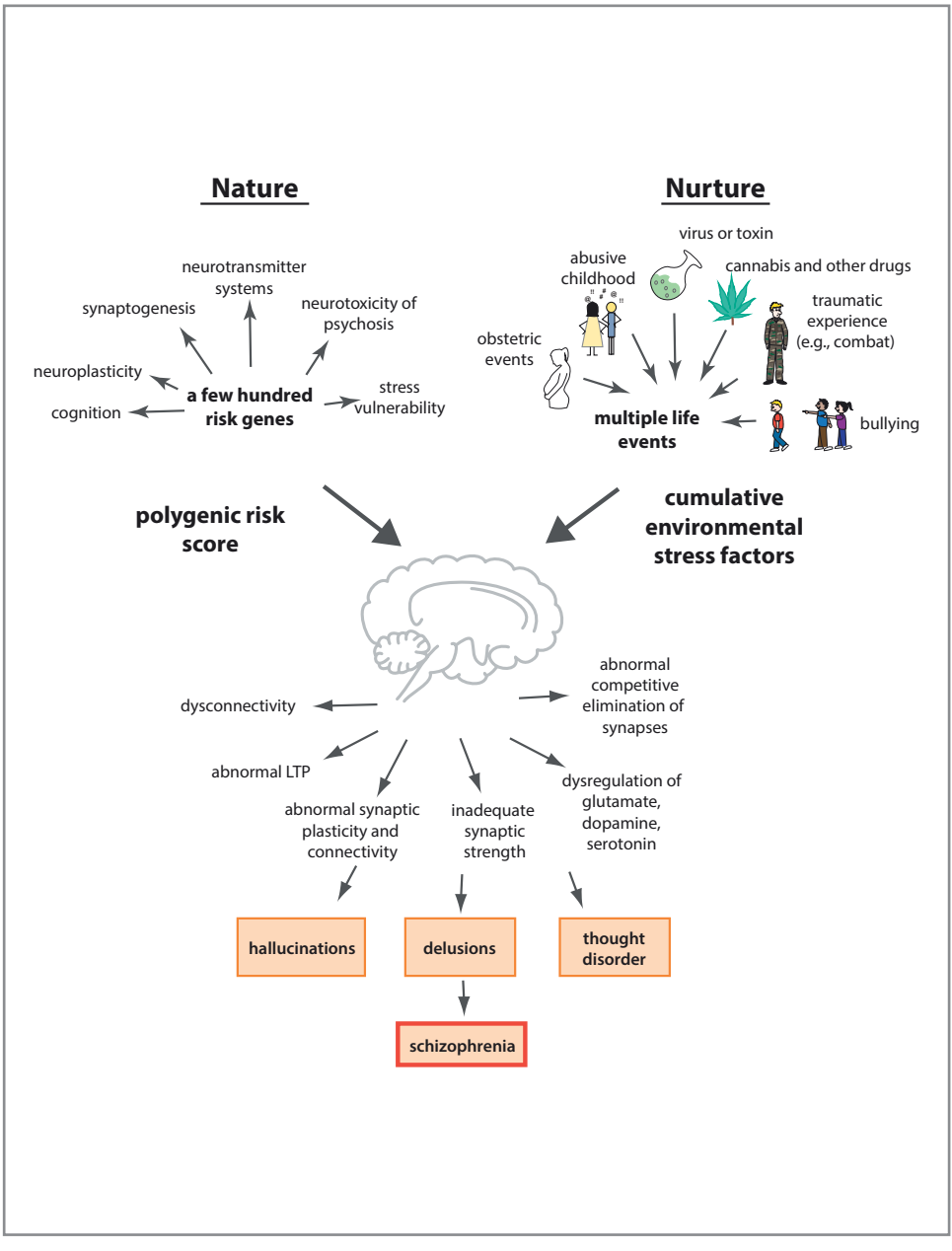



**FIGURE 1.2.** Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness into five dimensions: positive, negative, cognitive, affective, and aggressive. Each of these symptom domains may hypothetically be mediated by unique brain regions (Stahl, 2021).

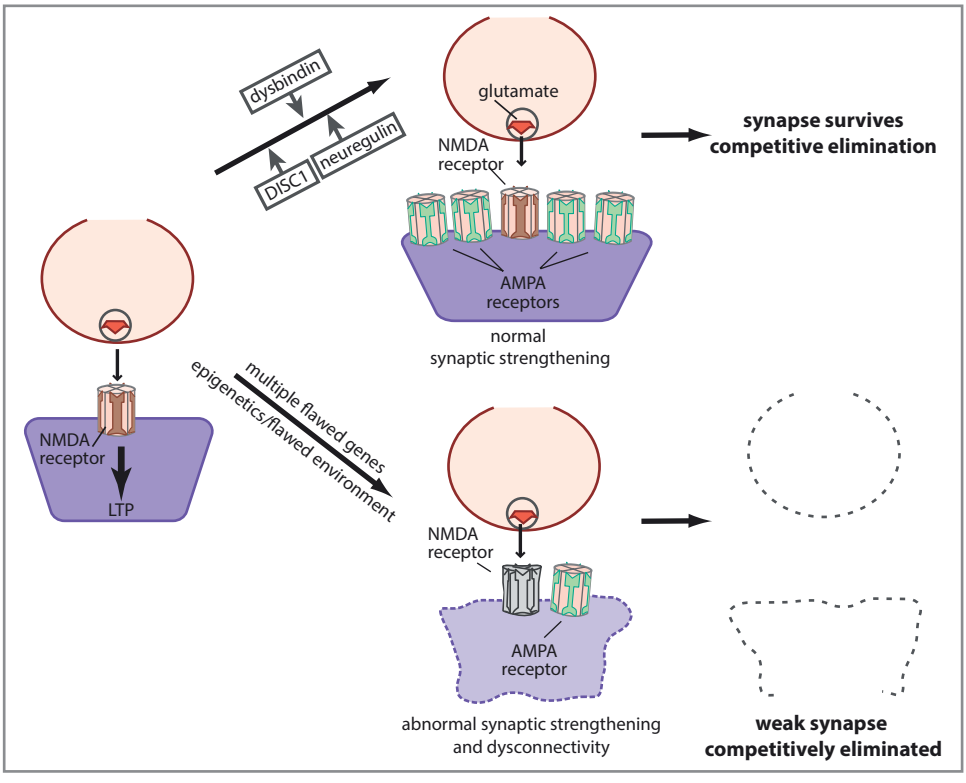
# The Nature and Nurture of Schizophrenia



# The Nature and Nurture of Schizophrenia

**FIGURE 1.3.** Schizophrenia may occur as the result of both genetic (nature) and epigenetic (nurture) factors. That is, an individual with multiple genetic risk factors, combined with multiple stressors causing epigenetic changes, may have abnormal information processing in the form of dysconnectivity, abnormal long-term potentiation (LTP), reduced synaptic plasticity, inadequate synapse strength, dysregulated neurotransmission, and abnormal competitive elimination of synapses. The result may be psychiatric symptoms such as hallucinations, delusions, and thought disorder (Stahl, 2021; St Clair & Lang, 2021; Wahbeh & Avrampolous, 2021).

# Neurodevelopmental Hypothesis of Schizophrenia: Abnormal Synaptogenesis



# Neurodevelopmental Hypothesis of Schizophrenia: Abnormal Synaptogenesis

**FIGURE 1.4.** Dysbindin, DISC1 (disrupted in schizophrenia-1), and neuregulin are proteins involved in "strengthening" of glutamate synapses. Under normal circumstances, N-methyl-D-aspartate (NMDA) receptors in active glutamate synapses trigger long-term potentiation (LTP), which leads to structural and functional changes of the synapse to make it more efficient, or "strengthened." This process leads to an increased number of α-amino-3-hydroxy-5 methyl-4-isoxazolepropionic acid (AMPA) receptors, which are important for mediating glutamatergic neurotransmission. Normal synaptic strengthening means that the synapse will survive during competitive elimination. If the genes that regulate strengthening of glutamate synapses are abnormal, combined with environmental insults, then this could cause hypofunctioning of NMDA receptors with a resultant decrease in LTP and fewer AMPA receptors. This abnormal synaptic strengthening and dysconnectivity would lead to weak synapses that would not survive competitive elimination. This would theoretically lead to increased risk of developing schizophrenia, and these abnormal synapses could mediate the symptoms of schizophrenia (Bubeníková-Valesová et al., 2008; Stahl, 2021).

## Elevated DA Synthesis and Release in Schizophrenia

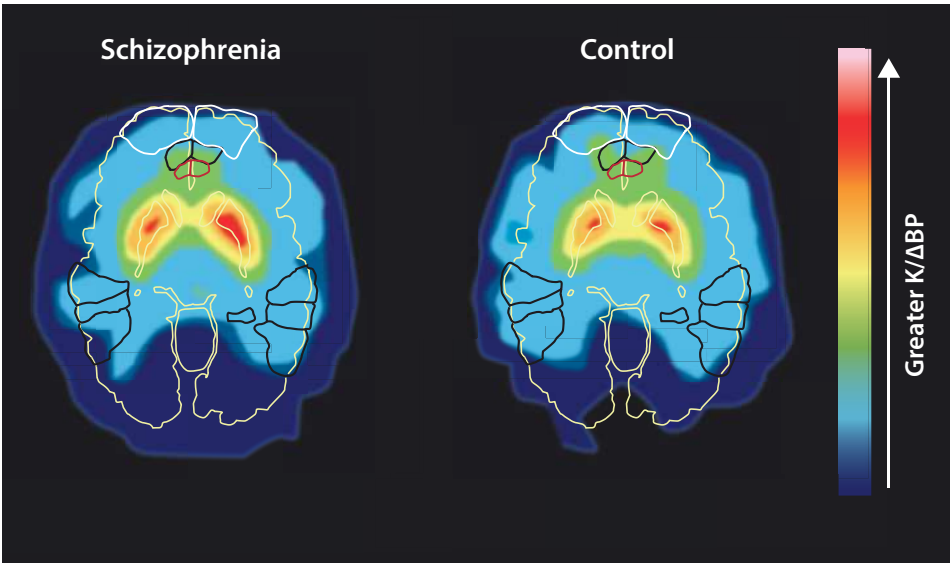



**FIGURE 1.5.** Molecular imaging studies indicate that individuals with schizophrenia have elevated presynaptic striatal dopamine (DA) synthesis and release capacities compared to healthy controls. Dopamine synthesis is measured by the uptake of radiolabeled L-DOPA tracer (K), while dopamine release capacity is measured by a change in tracer binding to the postsynaptic dopamine receptor following a psychostimulant challenge (ΔBP) (Brugger et al., 2020; Howes et al., 2011; Lindström et al., 1999; Weinstein et al., 2017).

# D2 Receptor Short Isoform Is a Risk Factor for Schizophrenia

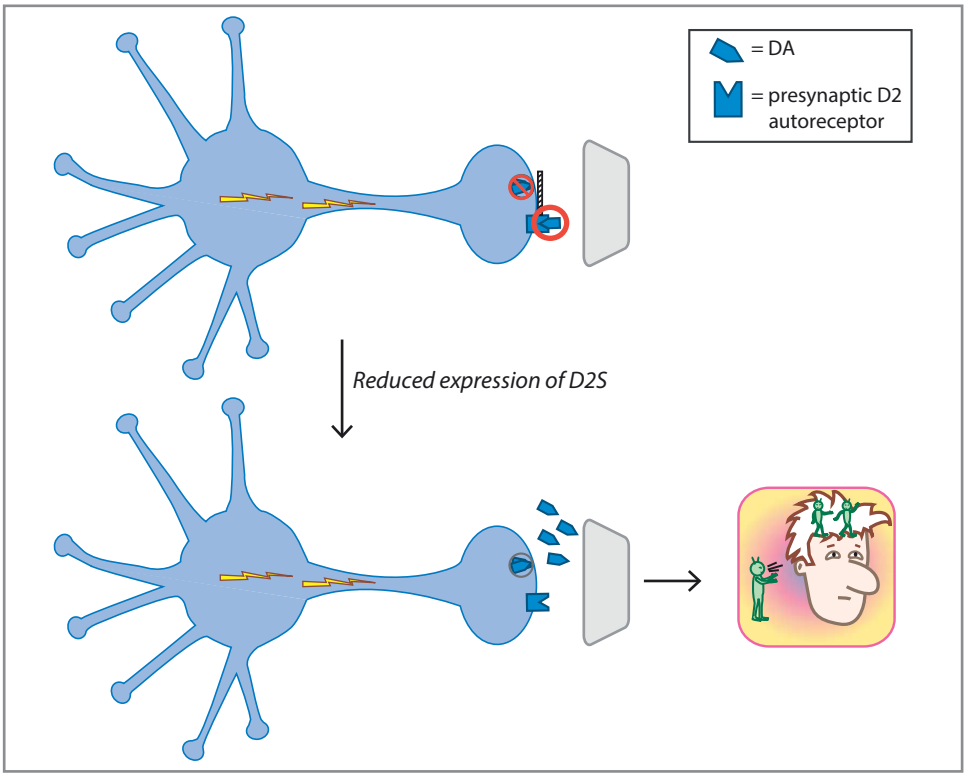



**FIGURE 1.6.** Presynaptic D2 autoreceptors can be located on the axon terminal. When dopamine builds up in the synapse it is available to bind to the autoreceptor, which then inhibits dopamine release. The *DRD2* gene generates two principal receptor dopamine D2 isoforms, D2L (long) and D2S (short). D2L functions as a postsynaptic dopamine receptor, while D2S functions as a presynaptic autoreceptor. Genetic analyses of postmortem brain tissue show reduced expression of D2S isoforms in the caudate nucleus of people with schizophrenia. Consequently, this compromised presynaptic autoregulation leads to increased synaptic dopamine in the striatum that putatively places individuals at risk for schizophrenia (Benjamin et al., 2022).

# The Psychosis Circuit: Upstream Cholinergic Modulation of DA