Summary

Schizophrenia remains a major burden on patients and society. The dopamine hypothesis attempts to explain the pathogenic mechanisms of the disorder, and the neurodevelopmental hypothesis the origins. In the past 10 years an alternative, the cognitive model, has gained popularity. However, the first two theories have not been satisfactorily integrated, and the most influential iteration of the cognitive model makes no mention of dopamine, neurodevelopment, or indeed the brain. In this Review we show that developmental alterations secondary to variant genes, early hazards to the brain, and childhood adversity sensitise the dopamine system, and result in excessive presynaptic dopamine synthesis and release. Social adversity biases the cognitive schema that the individual uses to interpret experiences towards paranoid interpretations. Subsequent stress results in dysregulated dopamine release, causing the misattribution of salience to stimuli, which are then misinterpreted by the biased cognitive processes. The resulting paranoia and hallucinations in turn cause further stress, and eventually repeated dopamine dysregulation hardwires the psychotic beliefs. Finally, we consider the implications of this model for understanding and treatment of schizophrenia.