Psychotic Disorders ("Schizophrenia")

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In this chapter, the psychotic experience is presented using paranoid schizophrenia as an example.

Learning Objectives

After reading the chapter, the reader should be able to name the symptoms of schizophrenia as well as its treatment options and to classify different neurobiological explanations.

► **Example**

A 22-year-old mechanical engineering student, accompanied by his flatmates, presents at the emergency department. They had persuaded him to do so because they were increasingly worried about his changed behaviour. About one and a half years ago, after he had passed the first phase of exams, he had let the university slide. In the last two semesters he had not gone at all and had withdrawn more and more. The reasons he gives for this are concentration problems and lack of interest. His flatmates report that there was a clear change 6 weeks ago. He had hardly come out of his room, had neglected eating and personal hygiene. In addition, he had repeatedly said strange and sometimes incomprehensible things. For example, he reported that he could sometimes clearly hear neighbors in his room making nasty comments about him, speaking directly to him. He had noticed suspicious black cars outside the house, indicating the machinations of the neighbours, and was convinced that they had accessed his smartphone to use it to manipulate his thoughts. Finally, he turned off the TV in a rage today, because the anchorwoman of the daytime news was constantly making allusions to him.

Lately he had hardly drunk alcohol and had not used drugs. Only at the end of his school years had he occasionally smoked a joint. Once he had had "strange" experiences (everything around him had felt strangely changed and threatening), whereupon he had decided to "keep his hands off the stuff". His mother had recurrent depressions and a paternal uncle suffered from schizophrenia.

The patient is offered inpatient admission for psychiatric diagnosis and treatment. He is initially ambivalent, but allows himself to be persuaded with the offer of a thorough medical clarification. Laboratory tests of blood and cerebrospinal fluid (CSF) as well as magnetic resonance imaging of the brain remain without pathological findings.

After initial mistrust, the patient agrees to drug treatment with an antipsychotic (aripiprazole) and receives group psychotherapy with a psychoeducational focus as well as metacognitive training and occupational therapy. The fears described on admission increasingly recede into the background and the perceptual disturbances cease within a week. After 3 weeks, the patient can be discharged home. At this time, he still states that he is suspicious of the neighbours, but is now more relaxed in this respect. He wants to spend a few weeks with his parents in Bavaria first and then resume his studies in the next semester. ◄

11.1 Psychotic Disorders: Overview and Incidence

Nowadays, the diagnosis of "schizophrenia" follows operationalized criteria that describe the occurrence of certain symptoms of thinking, self-reference and emotional experience and behavior over a defined period of time while organically tangible causes have been excluded. The focus is on a disorder of thinking with false perceptions (hallucinations), fixed beliefs (delusions) and often disorganised thought processes. Such psychotic experiences, i.e. those associated with a loss of the previously self-evident "reality", were already described in various traditions before the introduction of our current psychiatric classification systems.

The **concept of schizophrenia** on which today's classification systems (ICD and

DSM) are based represents a mixture of various historical concepts and draws on different theories. Important influences can be traced back to Hecker (1871) and his concept of "juvenile insanity" (hebephrenia) as well as to Kahlbaum (1874) with his description of motor phenomena in the form of "Spannungsirresein (tension insanity)" (catatonia). Emil Kraeplin (1856–1926) established the dichotomy that has persisted to this day, although he incorrectly formulated it as a distinction between "manic-depressive insanity" (today's bipolar disorders), which has a cyclic and more benign course, and "dementia praecox", which develops progressively and less favourably, as a premature loss of cognitive abilities in early adulthood (as mentioned in ▶ Sect. 11.3, and in contrast to Kraepelin's postulation, the courses are very heterogeneous). Accordingly, Eugen Bleuler (1857–1939) already distanced himself from Kraepelin's classification with regard to the unfavourable prognosis in his paper "Dementia praecox or the group of schizophrenias". Bleuler postulated instead a disturbance in the association of thoughts as the central characteristic of schizophrenia and contrasted the so-called basic symptoms such as association looseness, affect disorders, autism and ambivalence ("the four As") with what he regarded as more marginal (accessory) symptoms such as perceptual disturbances, delusions and catatonic symptoms. Important for today's concept of schizophrenia were Kurt Schneider (1887–1967) and his emphasis on symptoms based on the phenomenal experience of the patient, such as commenting voices or thought insertion. The variety of phenomena subsumed under the term "schizophrenia" is thus on the one hand historically determined and on the other hand due to the symptom variablility in the course of the illness—from the prodromal stage over the florid psychotic episode to the possible residual state. In the following, we will concentrate on paranoid schizophrenia.

Info Box Schizophrenia

Annual incidence[a]	**15/100.000**
Lifetime prevalence[a]	1%
Gender ratio	w = m
Age of onset	Mean age of first episode in men 21 years, in women 26 years 90% before the age of 30 First manifestation after 40 years of age rare
Major psychiatric comorbidities	Dependence on nicotine, alcohol or illicit drugs (lifetime prevalence 50%) Depression Obsessive compulsive disorder
Hereditary factor	Concordance in monozygotic twins 40–60%.

[a] Average information

11.2 Epidemiology, Symptoms and Diagnosis

11.2.1 Epidemiology

Schizophrenia is a mental disorder which occurs worldwide. The lifetime prevalence, i.e. the proportion of people suffering from schizophrenia in the lifetime up to the time of the survey, is given on average as 1% and ranges between 0.7% and 1.4% in the 15–60 age group worldwide—depending on the breadth of the diagnostic criteria. Approximately 19 new cases are diagnosed per 100,000 inhabitants per year in Germany, so that with a population of 82.3 million in Germany, approximately 15,600 newly diagnosed schizophrenia cases can be expected each year (Gaebel 2010). Recent epidemiological studies suggest that there are significant variations in incidence (McGrath et al. 2008). According to this study, the global median annual incidence is 15.2 per 100,000

persons with a range from 7.7 to 43.0 per 100,000 persons. Increased incidence rates have been described for people with a migration background and low socioeconomic status, as well as in urban settings (Heinz et al. 2013). Interestingly, in epidemiological studies, individual psychotic symptoms are found significantly more frequently than the disorders from the schizophrenia spectrum itself. The prevalence of single psychotic symptoms such as delusions or hallucinations is estimated at 7.2% in the general population and the annual incidence rate at 2.5% (Linscott and van Os 2013). In the vast majority of individuals, such psychotic symptoms are transient and have no medical significance; in approximately 20% of individuals, symptoms may persist and be associated with psychiatric disorders.

11.2.2 Symptoms

The symptoms of schizophrenic disorders affect areas of thinking, self-reference and emotional experience and behaviour. A common classification is that of positive symptoms, which are added to normal experience, and negative symptoms, which describe a pathological loss of mental functions. Positive symptoms, which describe florid psychotic experience, include delusions, formal thought disorder, perceptual disturbances, and self-disturbances.

Delusion is defined as a false fixed belief and refers to thought content. A delusional belief represents a rigid misjudgment of reality that is held to with subjective certainty, even when the beliefs contradict observations that refute the belief. Delusional interpreted events are experienced as "centered" on the affected person, who sees herself at the center of the imagined events. Typical delusional contents are ideas of reference, for example that television news refer to one's own person, or persecutory delusions, where the patient experiences himself as the target of hostility or surveillance.

Various symptoms associated with delusional experience can be distinguished. Before delusions are fully developed a so-called delusional mood is often observed, which is characterized by an unspecific feeling of being alarmed and the experience that something unusual and threatening is going on. Delusional beliefs may occur suddenly (delusional idea) or perceptions of environmental events may be misinterpreted (delusional perception). Delusional thoughts can greatly determine the patient's experience and develop into a system where different areas of experience are linked. The emotional involvement associated with the delusional experience is referred to as delusional dynamics and can vary profoundly during the course of the disorder as well as through antipsychotic therapy.

Self-disturbance refers to the loss of ego boundaries and thus to the self-reference of the affected person. Patients experience their own thoughts as coming from outside and being manipulated (thought insertion) or describe that other persons would have access to their thoughts and could, for example, read them (thought broadcasting) or take them away (thought withdrawal). Self-disturbance is conceived in the Anglo-American tradition as specific delusional content (*delusions of control*) rather than as a discrete symptom complex, ignoring the fundamental difference between self-disturbance and delusional symptoms: Self-disturbance refers to the experience of one's own thoughts, delusions to the external world. Delusional systems can then connect all these phenomena by complex explanations and secondarily "rationalize" them, for example by explaining that they are technically complicated interventions and manipulations of a secret service.

Formal thought disorders, on the other hand, describe the process rather than the content of thought and manifest themselves,

among other things, as disorganized speech. Disorganized thinking is a condition in which the logical coherence and coherence of thought or verbal utterances no longer exist and other people can no longer follow the patient's train of thought. Other formal thought disorders include the interruption or blocking of the train of thought or the use of terms in other meanings up to the formation of new words (neologisms).

Hallucinations are perceptions without a corresponding stimulus source and are therefore also called "objectively false" perceptions. Hallucinations can affect all sensory qualities. In schizophrenia spectrum disorders, auditory hallucinations are most common, followed by tactile hallucinations. Visual hallucinations are rare and if present should give reason to rule out an acute brain disorder such as delirium.

For schizophrenia the hearing of voices (phonemes) are characteristic, which often comment on the patient's actions or talk about the patient in dialogue form.

Negative symptoms refer to a reduction in functioning such as a general reduction in motivated and goal-directed behavior, social contact, or emotional experience and expression. Avolition refers to a reduction in goal-directed activities and in efforts to carry out a resolution, and anhedonia refers to a reduction in positive emotional experience and/or decreased interest in activities that are perceived as pleasurable. In addition, there are symptoms that also affect emotional expression, such as affective flattening or decreased speech production. Negative symptomatology contributes strongly to impairments in social and occupational functioning and quality of life.

Cognitive symptoms include disturbances in cognitive performance and are an important feature of schizophrenic psychosis, described by Bleuler and Kraeplin (Green and Harvey 2014). Neuropsychological testing procedures allow for measurement of various cognitive domains, with many of the tests used capturing more than a single isolated domain. However, a substantial proportion of patients exhibit only minor impairments at best. The affected cognitive domains include: Working memory, processing speed, attention, verbal as well as visual learning and memory, problem solving, and social cognition. Both chronic schizophrenia patients and patients with a first psychotic episode may exhibit cognitive deficits. In fact, cognitive deficits are often detectable in the prodromal stage (before the onset of full-blown disorder), and their magnitude may be predictive of the transition to psychosis. Although cognitive deficits are not part of the diagnostic criteria, they are important for prognosis and level of functioning (Kahn and Keefe 2013). Since chronic neuroleptic administration may contribute to a low-grade reduction in brain volume, drug effects should be ruled out (Aderhold et al. 2015).

Furthermore, the symptoms of schizophrenia include disorganized behavior and psychomotor symptoms, which are referred to as catatonia. Catatonic symptoms are very diverse. Both hyperkinetic and hypokinetic states can occur. In a characteristic catatonic state, patients fall completely silent (mutism), while speaking abilities are preserved, and may take on bizarre-looking postures, sometimes for hours.

11.2.3 Diagnostics

The **diagnosis of schizophrenia** is made using operationalized criteria according to ICD-10 or DSM-5. As shown in ◘ Table 11.1, a minimum number of certain symptoms is required for a specified time. The two systems are largely in agreement. Differences between the classification systems include the required symptom duration, which is only 4 weeks in ICD-10 but 6 months in DSM-5, and the emphasis on specific symp-

Table 11.1 Diagnosis of schizophrenia according to ICD-10 and DSM 5

ICD-10 (F20)	DSM 5 (295.90)
1. Thought echo, thought insertion, thought withdrawal, thought broadcasting 2. Delusions of control, influence or passivity, delusional perception 3. Commenting or dialoguing voices 4. Persistent delusion 5. Persistent other hallucinations 6. Formal thought disorders 7. Catatonic symptoms 8. Negative symptoms Symptoms: 1 from 1 to 4 2 from 5 to 8 Time criterion: >1 month	1. Delusions 2. Hallucinations 3. Disorganized speech 4. Severely disorganized or catatonic behavior 5. Negative symptoms (e.g. reduced emotional expression, avolition) Symptoms: 2 out of 5 (including 1, 2, or 3) Time criterion: >1 resp. 6 months

toms. In ICD-10, eight symptom groups are distinguished, with the first four being considered particularly characteristic. Thus, only one of these symptoms is sufficient for the diagnosis, such as ego disturbances (which, according to Kurt Schneider, belong to the so-called first-rank symptoms). In contrast, the DSM-5 distinguishes only five psychopathological domains: Delusions, hallucinations, disorganized thinking and speech, abnormal psychomotor behavior, and negative symptoms. At least two symptom domains are required for diagnosis (one of which must involve domains 1–3).

Psychotic symptoms such as delusions and hallucinations may also be present in other psychiatric and neurological disorders, for example, autoimmune disorders and affective disorders with psychotic symptoms, as well as schizoaffective disorder (► Chap. 12). Schizophrenia must be distinguished from brief psychotic disorders that do not meet the required time criteria, from delusional disorder in which other psychotic symptoms are absent, and from schizotypal personality disorder in which symptomatology is less severe and personality traits are enduring. In severe forms of obsessive-compulsive disorder, differentiation can be difficult. Psychotic experiences may also occur in the context of post-traumatic stress disorder. Autism spectrum disorders are characterized by early onset and are not characterized by marked delusions or hallucinations. Psychotic experience may also be due to acute drug effects. Drug-induced psychosis resolves after abstinence, but a clear distinction may be difficult in some cases because of the high comorbidity between schizophrenia and addiction.

The currently available diagnostic systems follow a categorical approach. However, as can be seen from the brief description of symptoms above, the clinical presentation of schizophrenia is very heterogeneous. This is true between individual patients cross-sectionally as well as intra-individually in terms of the clinical course.

A better understanding of the underlying neurobiological mechanisms might be promoted by a dimensional approach. Thus, it has been proposed to describe symptomatology along eight dimensions to map the individual symptom constellation (Heckers et al. 2013). In addition to the five psychopathological domains of the DSM-5, these dimensions include impaired cognition as well as depressive and manic symptoms.

11.2.4 Exclusion Diagnostics

The diagnosis of a schizophrenic disorder requires to exclude brain-organic diseases such as inflammatory processes (e.g. encephalitis, syphilis, multiple sclerosis, Huntington's disease, etc.), epilepsy, delirium or drug intoxications. In addition to a physical examination, necessary additional diagnostic procedures include structural brain imaging by means of magnetic resonance tomography, electroencephalography, and cerebrospinal fluid analysis.

Patients with schizophrenia often have other mental illnesses (comorbidity) such as addiction, depression or obsessive-compulsive disorders. About half of those with schizophrenia meet diagnostic criteria for dependency on alcohol or illicit drugs such as cannabis at some point in their lives (lifetime prevalence), and about 80% of schizophrenia patients are smokers.

11.3 Therapy and Prognosis of "Schizophrenia"

The treatment of schizophrenic disorders is based on the interaction of different therapeutic approaches and is multimodal and multiprofessional. In principle, treatment should be relationship-oriented and adapted to the needs of the patient. The involvement of relatives and participative decision-making play an important role. Stability and consistency of therapeutic relationships with good networking between outpatient and inpatient settings with a preference for outpatient treatment approaches should be of high importance. Therapy is essentially based on three pillars: pharmacotherapy, psychotherapy and sociotherapy.

A basic component of every therapy and an important link between the medical-psychotherapeutic treatment and the social environment is sociotherapy. Sociotherapeutic approaches include measures of structuring the social environment, occupational and work therapy, as well as occupational and social rehabilitation. An important role play integrated treatment concepts aimed at establishing long-term treatment continuity and avoiding or shortening hospitalization.

The importance of **psychotherapy** for schizophrenic disorders was neglected for a long time, but has increased significantly in recent years. In particular, the effectiveness of cognitive behavioural therapy and psychoeducational oriented family interventions is very well documented and has now found its way into most guideline recommendations (National Collaborating Centre for Mental Health 2014).

Pharmacotherapy is mainly based on antipsychotics, the efficacy of which has been well documented in randomized controlled trials, particularly for positive symptoms in all phases of the disease. In addition, depending on individual symptoms and comorbidities, other psychotropic drugs may be indicated, such as anxiolytic agents or antidepressants. The antipsychotic drugs represent a chemically heterogeneous group of substances with different side effect profiles. They influence a variety of neurotransmitter systems, so that it is assumed that clinical efficacy results from an interplay of different mechanisms of action. The antipsychotic mechanism of action is essentially related to the blockade of postsynaptic dopamine receptors of the D2 type. All currently approved neuroleptics block these D2 receptors to a greater or lesser extent. Receptor occupancy of 60–80% is thought to be therapeutically effective. This degree of receptor occupation is already achieved with relatively low dosages (e.g. 3 mg haloperidol per day; Farde et al. 1992; Heinz et al. 1996). Consistent with these findings, higher dosing is not more effective for treating positive symptomatology, but only increases the risk of side effects (Donnelly

et al. 2013). Daily doses of 10 mg haloperidol or more, which were commonplace practice in psychiatric emergency treatment for many years, are no longer justifiable in light of these findings. In particular, D2 receptor blockade frequently leads to undesirable extrapyramidal motor side effects such as parkinsonian symptoms, dyskinesia, and agitation (akathisia). These side effects are particularly pronounced with first generation antipsychotics, as their action is mainly due to D2 blockade. Many second generation antipsychotics (also called "atypical antipsychotics") act more strongly by blocking the receptors of other neurotransmitter systems, such as serotonergic, noradrenergic, histaminergic, and muscarinic acetylcholine receptors. Second generation antipsychotics have fewer overall extrapyramidal motor side effects than first generation antipsychotics. They have also been attributed superior antipsychotic efficacy as well as better efficacy on negative symptomatology, although this superiority is controversial and has not been convincingly demonstrated (Lieberman et al. 2005). In particular, the metabolic side effects of some second generation antipsychotics, such as obesity and an increased risk of diabetes mellitus, should not be underestimated and should be taken into account when choosing an antipsychotic.

A major challenge in the treatment of people with schizophrenia is that psychotic symptoms are often not interpreted as symptoms of illness by those affected, and medical concepts are not perceived as helpful without a detailed explanation and the establishment of a relationship of trust. Even if affected persons are assessed as incapable of giving consent, i.e. the nature, significance and scope of a medical measure (or the omission thereof) cannot be properly grasped due to the mental illness, even medically justified treatment against the will is not lawful in most cases. Such compulsory treatment would constitute a serious violation of the fundamental right to physical integrity. Under German law, it is only possible in exceptional situations, namely when there is an acute or chronic danger to life or health.

The course of schizophrenic disorders is very heterogeneous. About 20% of patients experience only one episode and 30% several episodes with complete remission (reduction of symptoms) in the interval. In about half of the patients, the course is unfavorable with incomplete remission between episodes and increasing social and occupational limitations (Watts 1985). People suffering from schizophrenia die on average about 15 years earlier than healthy comparison persons, which is a particularly high mortality compared to other mental disorders. Approximately 5–10% of patients take their own lives. Other reasons for the increased mortality are somatic comorbidities such as metabolic and cardiovascular diseases, which are partly related to the adverse side effect profile of antipsychotic drugs.

A number of prognostically relevant factors have been identified, although individual parameters hardly allow a reliable prognosis of the course in individual cases (Moller 2004). Male gender, positive family history, early first manifestation and comorbid substance use or dependence are associated with a rather unfavourable course. Psychopathological predictors of an unfavorable course include marked negative symptomatology, cognitive deficits, residual delusions after treatment, and the presence of auditory hallucinations or obsessive-compulsive symptoms. Regarding the course, a long prodromal phase, long untreated episodes, an insidious onset, and a slow response indicate an unfavorable prognosis. Prognostically unfavourable social factors include, above all, a low level of education and functioning and the absence of a partnership.

11.4 Emergence of "Schizophrenia": A Spectrum of Theories

Today, it is assumed that schizophrenia is a brain development disorder with multifactorial etiopathogenesis, in which there is an increased vulnerability to environmental influences according to a **vulnerability-stress model** based on genetic factors. The genetic basis for the development of schizophrenia is considered certain due to the familial clustering of schizophrenia with concordance rates of 40–60% in identical twins, which has been proven in numerous studies (Häfner 1995). Genome-wide association studies (GWAS), which have now identified over a hundred genetic risk variants for schizophrenia, suggest a polygenetic etiology (Ripke et al. 2013). The so-called "three-hit" hypothesis specifies the vulnerability-stress model in that genetic predisposition results in increased vulnerability during particularly critical periods of brain development (Keshavan 1999). Harmful influences during early brain development, such as viral infections during pregnancy and perinatal hypoxia, lead to changes in brain development that contribute to an increased risk of disease (*first hit*). However, if detectable at all, such neuropathological findings are very heterogeneous and do not provide a diagnostically useful picture. Environmental factors that exist during childhood also increase the risk of developing schizophrenia (*second hit*). These include early separation from parents, childhood abuse or neglect, and probably also a family communication style with *High-Expressed Emotions*, characterized by strong criticism, hostility, and overprotectiveness (Cechnicki et al. 2013). Under the influence of further factors such as drug use (especially cannabis) or psychosocial stress (e.g. due to migration) in adolescence or early adulthood (*third hit*), the disorder then manifests. While the influence of each of the above-mentioned psychosocial risk factors on their own is relatively small, it is now assumed that these factors together play a significant role (Kirkbride et al. 2010).

Some influential earlier theories on the etiopathogenesis of schizophrenia are no longer considered relevant today. Not least due to the influence of Emil Kraepelin, who coined the term "dementia praecox", a progressive brain disease was long assumed to be the basis of schizophrenic disorders, which is characterized by progressive neurodegenerative processes comparable to dementia. However, neither longitudinal imaging or neurocognitive studies nor clinical outcome studies have provided clear evidence for the hypothesis of a progressive brain disease (Zipursky et al. 2013).

A central question in contemporary **schizophrenia research** is how the now well-documented genetic and psychosocial factors are reflected in neurobiological changes that underlie schizophrenic disorders. An important clue is provided by findings that point to a neuro-developmental dysregulation in the balance between excitatory and inhibitory neurotransmitter systems (excitation-inhibition balance or "E/I balance") as early as adolescence (Rapoport et al. 2012). Genetic and epigenetic factors are thought to cause changes in glutamatergic neurotransmission early in brain development, which in turn, together with other mechanisms, such as immunological ones, influence further brain development. Such changes could lead to homeostatic adjustments in the finely tuned interplay of neuronal systems. For example, it has been proposed that hypoactivity of (excitatory) glutamatergic neurotransmission counterregulates a reduction in (inhibitory) GABAergic activity (Krystal and Anticevic 2015). The balance between excitation and inhibition that is thus restored could be the reason why schizophrenic disorders manifest with a delay, despite the presumably early onset of the brain developmental dis-

order. However, reduced activity of GABAergic interneurons will lead to long-term disinhibition of both cortical glutamatergic neurons and subcortical dopaminergic neurons in the mesolimbic system. Under the influence of stress, such disinhibition could contribute to the increased dopaminergic neurotransmisison in the striatum, which is directly related to the development of psychotic symptoms. This brief summary illustrates that the different neurotransmitter hypotheses of schizophrenia—glutamate, GABA and dopamine—are not incompatible with each other, but can be embedded together in an overarching theory about the disruption of mechanisms at the level of neuronal regulatory circuits (Fig. 11.1; Heinz and Schlagenhauf 2010).

Theories about the role of neuronal control circuits raise the question of how their disturbances are related to altered subjective experience and observable symptoms of schizophrenic psychoses. The methods of **computational neuroscience** offer a promising possibility to relate changes at the level of behavior and experience not only qualitatively-descriptively, but also quantitatively with specific neuronal processes. This still young scientific discipline deals with the information-processing properties of the nervous system and uses mathematical modelling to describe and simulate neuronal processes. Such modelling can describe processes on different levels. Thus, individual subprocesses on the level of local neuronal control circuits (e.g., E/I balance in the prefrontal cortex) or on the level of cognitive functions (e.g., reward learning) can be captured in mathematical models. The individual estimation of model parameters offers the possibility of assigning disease-

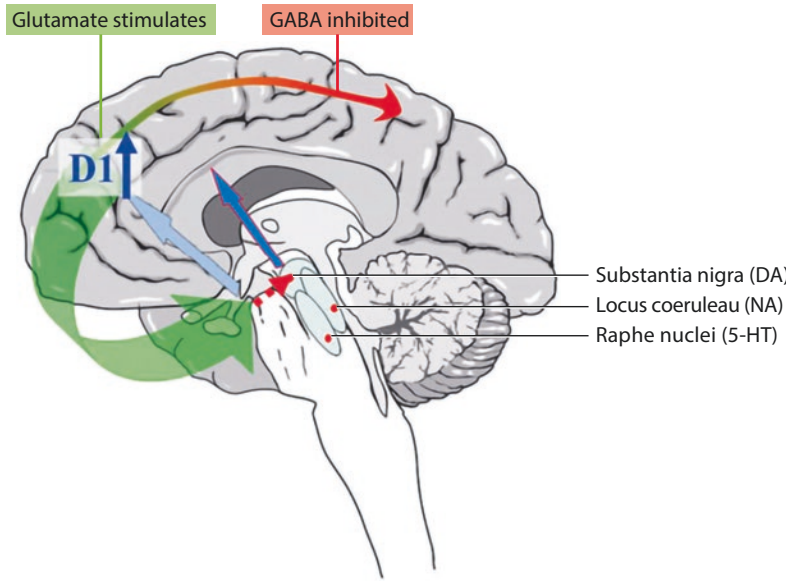


Fig. 11.1 Possible relationship between changes in glutamatergic, GABAergic and dopaminergic neurotransmission according to Heinz and Schlagenhauf (2010). Hypofunction of glutamatergic prefrontal-subcortical projections (green arrow) leads to decreased activation of GABAergic interneurons and thus to disinhibition of dopaminergic neurons in the midbrain. In contrast, there is a decreased dopamine release in the prefrontal cortex with upregulation of dopamine D1 receptors, which in turn results in a disruption of the function of prefrontal glutamatergic neurons (*DA* dopamine; *NA* norepinephrine; *5-HT* 5-hydroxytryptamine). (After Heinz and Schlagenhauf 2010, with kind permission)

relevant behavioral or symptom dimensions to neuronal dysfunctions in a quantitative manner, thus bridging the gap between neurobiological and symptom levels (Friston et al. 2014).

11.5 Neurobiological Foundations

The neurobiological basis of schizophrenia is poorly understood. No circumscribed anatomical or functional abnormality has been identified as specific for this disorder. Serious brain changes, as described in neurological diseases (e.g. dementias, inflammations), do not seem to be associated with the disease (Kahn et al. 2015).

As described in ▶ Sect. 11.4, most of today's explanatory models of schizophrenia assume a complex interplay of genetic factors and environmental conditions that affect brain development and influence the course of neurobiological adaptation processes to further (stressful) life events, which is referred to as the **neurodevelopmental model**. This is matched by the fact that the onset of the disease occurs in early adulthood, but that important risk factors relate to prenatal (e.g. infections) or perinatal events (e.g. hypoxia at birth). Thus, early environmental exposures may increase the risk of developing psychotic symptoms in response to later social stressors. However, the exact molecular mechanisms are not clear.

Subtle changes in specific cell populations, such as GABAergic interneuron populations, are postulated. Most importantly, current theories assume pathological alteration of functional networks. Several of the domains proposed in the RDoC approach (▶ Sect. 9.5.1) and the neural circuits underlying them appear to be involved in schizophrenic disorders. Alterations in perception and cognition in schizophrenia are associated with dysfunctions of fronto-parietal networks as well as fronto-striatal-hippocampal circuits under the influence of neuromodulatory systems.

11.6 Genetics

In genome-wide association studies, schizophrenia has been linked to genes predominantly expressed in the brain and immune system (Ripke et al. 2013). The majority of identified single nucleotide polymorphisms (SNPs) are non-protein coding and appear to be involved in gene regulation. Individually, such SNPs have a negligible effect on schizophrenia risk, and collectively they explain only a moderate proportion. However, these findings are crucial for a pathophysiological understanding of the mechanisms involved in the disease. Thus, associations were found with genes encoding the dopamine receptor (DRD2), or with genes associated with glutamatergic neurotransmission as well as synaptic plasticity and interneuron function.

In addition to the involvement of gene variations frequently found in the population with low impact, rarely occurring gene variants with higher risk are of importance. These include *copy number variances* (CNVs), which are structural variants of DNA where the number of copies of larger DNA segments differs greatly between individuals. A gene can occur more than once (duplication) or be completely absent (deletion). An example is the microdeletion syndrome 22q11, in which changes exist on the long arm of chromosome 22 at position 11, which is associated with a greatly increased risk of psychosis. In addition, some de novo mutations have been identified, but these findings are still inconsistent.

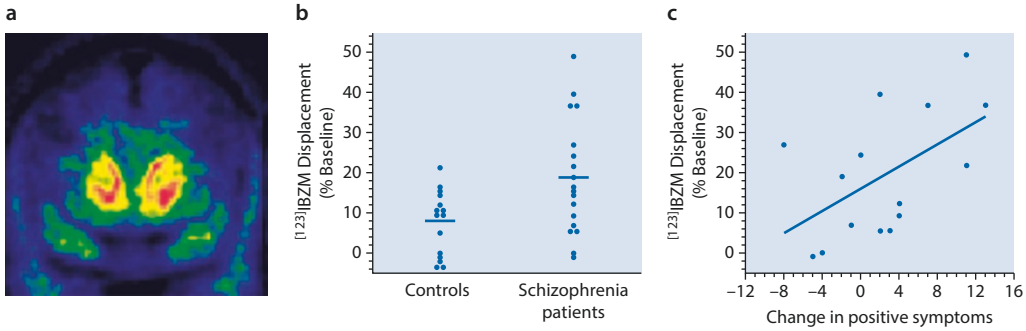
In summary, there are not just a few genes that can be associated with schizophrenia. Rather, the disorder is polygenetic, i.e. it is caused by the interaction of numerous genes. Many of the identified genes are

also involved in the occurrence of other psychiatric disorders and are therefore not specific to schizophrenia (pleiotropic). Many genetic markers for schizophrenic psychosis overlap with risk factors for bipolar disorder. In addition, gene-gene interactions and gene-environment interactions are likely to be crucial for a more detailed understanding of etiopathogenesis.

For further reading, please refer to Psychiatric Genomic Consortium: ▶ https://www.med.unc.edu/pgc/ and Avramopoulos (2018).

11.7 Neurotransmitter

Several neurotransmitter systems are involved in schizophrenia. However, the neuromodulatory dopaminergic system is of particular importance in theories of schizophrenia. The so-called dopamine hypothesis of schizophrenia is based primarily on pharmacological evidence. Initially, a global overactivity of the dopaminergic system was assumed. A modified version of the dopamine hypothesis postulates hyperactivity subcortically and hypoactivity in the mesocortical system. The most important evidence for an involvement of dopaminergic neurotransmission comes from the fact that all currently available drugs have an antagonistic effect on dopamine receptors, especially of the D2 type. D2-antagonistic drugs such as the first, accidentally discovered antipsychotic chlorpromazine act on positive symptoms but not on negative symptoms or cognitive deficits, and antipsychotic medication at very high doses may even increase avolition and apathy. A further argument for involvement of the dopaminergic system is the observation that dopamine agonistic substances such as amphetamine can trigger psychotic experience, i.e. have a psychotomimetic effect. Direct studies of the dopaminergic system in individuals with psychosis are crucial: in humans, in vivo measurements of the dopaminergic system are possible by nuclear medicine techniques. When a weakly radiolabeled precursor of the transmitter such as ^{18}F-fluoro-3,4-dihydroxyphenyl-l-alanine (F-DOPA) is applied, its metabolites accumulate in the presynaptic vesicles of dopaminergic neurons (◘ Fig. 11.2). The emitted alpha radiation can be measured by positron emission tomography to provide a measure of presynaptic dopamine synthesis. A well-



◘ **Fig. 11.2** Nuclear medicine techniques for in vivo measurement of dopaminergic neurotransmission in patients with schizophrenia. **a** Imaging of dopamine synthesis in the striatum using positron emission tomography (PET) with ^{18}F-DOPA as the radiolabeled precursor of dopamine. **b** Increased striatal dopamine release after amphetamine administration in schizophrenia patients compared to healthy controls according to Laruelle et al. (1996; © National Academy of Sciences); **c** Correlation between the extent of amphetamine-induced dopamine release and the increase in positive symptoms under amphetamine administration according to Laruelle et al. (1996; © National Academy of Sciences)

replicated finding is that schizophrenia patients show increased subcortical dopamine synthesis capacity primarily in the associative part of the striatum compared to healthy individuals (Howes et al. 2012). An increased striatal dopamine release has also been shown after amphetamine administration (Fig. 11.2a), whereby the extent of the increased release was related to the increase in positive symptoms (Fig. 11.2b; Laruelle et al. 1996).

Pharmaceuticals with antagonistic action at the glutamatergic N-methyl-d-aspartate (NMDA) receptor, such as the anesthetic ketamine or the designer drug phencyclidine, can induce psychotic experience, negative symptoms, and cognitive deficits. Therefore, ketamine is used as a pharmacological model for psychosis, and a deficit in NMDA receptor function is postulated. NMDA receptors are important for synaptic plasticity and learning through processes such as long-term potentiation (LTP). Together with the inhibitory neurotransmitter GABA, glutamate is crucial for the E/I balance of cortical networks that show alterations in schizophrenia spectrum disorders.

There is **no independent serotonin hypothesis** for schizophrenia. However, serotonin agonists such as the hallucinogens lysergic acid diethylamide (LSD) or mescaline can trigger psychotic symptoms, especially perceptual disturbances. However, blocking serotonin receptors alone has no antipsychotic effect. However, many second generation antipsychotics also have an antagonistic effect at the 5-HT2 receptor, which is associated with their better tolerability with regard to extrapyramidal side effects.

11.7.1 Excitation-Inhibition Balance

Neuronal information processing is based on a functional balance of excitatory and inhibitory networks, the E/I balance. At the level of a single neuron, such a balance consists of an appropriate ratio of excitatory glutamatergic and inhibitory GABAergic synaptic inputs. Glutamatergic and GABAergic neurons form most cortical synapses and are targets of cortical and subcortical modulatory connections. When an excitatory synapse is activated by glutamate, this leads to depolarization of the neuron, increasing the likelihood of triggering an action potential, whereas inhibitory GABAergic synapses have an opposite effect (Gao and Penzes 2015). GABAergic interneurons account for approximately 10% of cortical neurons and can be divided into several subtypes. One type of GABAergic neurons expresses the calcium-binding protein parvalbumin (PV+). This class includes basket cells, which inhibit pyramidal cells perisomatically, and chandelier cells, which form their inhibitory synapses at the axon initial segment of pyramidal cells. Therefore, these PV+ interneurons have a central influence on the formation of pyramidal cell action potentials and are crucial for the synchronized activity of neuronal assemblies. Dysfunction of these PV+ interneurons has been postulated in the cortex as well as in the hippocampus of patients with schizophrenia. E/I imbalance could result from hypofunction of NMDA-type glutamate receptors on the dendrites of the inhibitory PV+ interneurons. This would result in less activation of the inhibitory PV+ interneurons, leading to decreased inhibition of the excitatory pyramidal cells (Gonzalez-Burgos et al. 2015). Due to the reduced GABAergic influence, the inhibitory influences on the pyramidal cells are reduced, resulting in their disinhibition and thus increased excitability.

The branched connections of the basket cells lead to a simultaneous, coordinated inhibition of numerous pyramidal cells and thereby enable a synchronized activity of the pyramidal cells. Through synchronized activity, cortical neurons dynamically connect to form functional networks. This

rhythmic activity occurs in different frequency ranges and can be measured electrophysiologically, for example, as temporal coherence between anatomically distributed areas. In schizophrenia patients, impairments of gamma oscillations (frequency range between 30 and 80 Hz) have been repeatedly found and associated with cognitive deficits such as working memory impairment. PV+-GABAergic interneurons are critical for the generation of gamma oscillations and associated synchronized cortical network states. NMDA-R dysfunction could lead to reduced inhibition by PV+ interneurons and overstimulation of excitatory neurons with a reduction in gamma oscillations and dysconnectivity observed in schizophrenia patients (Uhlhaas and Singer 2015, see also there for further information).

11.7.2 Aberrant Salience

The **theory of aberrant salience** relates psychotic symptoms to a stress-related or chaotic hyperfunction of the subcortical dopaminergic system in order to explain the subjective experience of patients (Heinz 2002; Kapur 2003). From a clinical perspective, environmental stimuli that are actually neutral and insignificant often acquire an extraordinary importance and significance for people with psychotic experiences. For example, in the patient description at the beginning of the chapter, the patient notices black cars in front of his house that seem particularly significant and suspicious to him. According to the theory, the patient tries to explain this aberrant salience experience by delusional explanations, for example, the particular importantance of the cars is explained by the thought that the patient is being persecuted, thus forming the starting point for the development of a persecutory delusion.

Salience refers to the property of a stimulus or event to attract attention and *arousal*, which favors its neural processing and a behavioral response to such a salient stimulus. Several properties of salience can be distinguished: the physical properties, the novelty or unexpectedness of a stimulus, and motivational salience. The latter is referred to as *incentive salience* and describes the motivational component in the response to a stimulus, which has been linked to the activity of the dopaminergic system (Berridge 2012; Robinson and Berridge 1993). In the healthy state, context- or stimulus-related dopamine release mediates that motivational salience, and thus meaningfulness, is attributed to that particular context or stimulus. In the context of psychotic experience, dysregulated dopamine release, which occurs independently of stimulus and context due to biological dysregulation, leads to erroneous salience attribution to what should be neutral and insignificant environmental stimuli or internal representations (Heinz 2002; Kapur 2003). Accordingly, a dysregulated, chaotic dopamine release could lead to a subtle change in experience. Its persistence can then lead to the formation of delusional beliefs, through which the constant experience of aberrant salience can be explained away. The administration of antipsychotics then leads to a reduction in the salience experience associated with psychosis, so that a gradual distancing from, for example, the experience of persecution may occur (Fig. 11.3). If antipsychotics are overdosed, however, general motivational aspects of environmental stimuli may also be blocked, and avolition and apathy may result.

In addition to encoding salience, dopamine is also involved in other functions. Animal studies show that dopaminergic neurons are also activated when an unexpected reward arrives. However, if the reward is predicted as part of a learning process, the dopaminergic signal remains absent and may even decrease if the reward that arrives is less than expected. Accordingly, the dopaminergic signal follows a prediction error that encodes the difference between

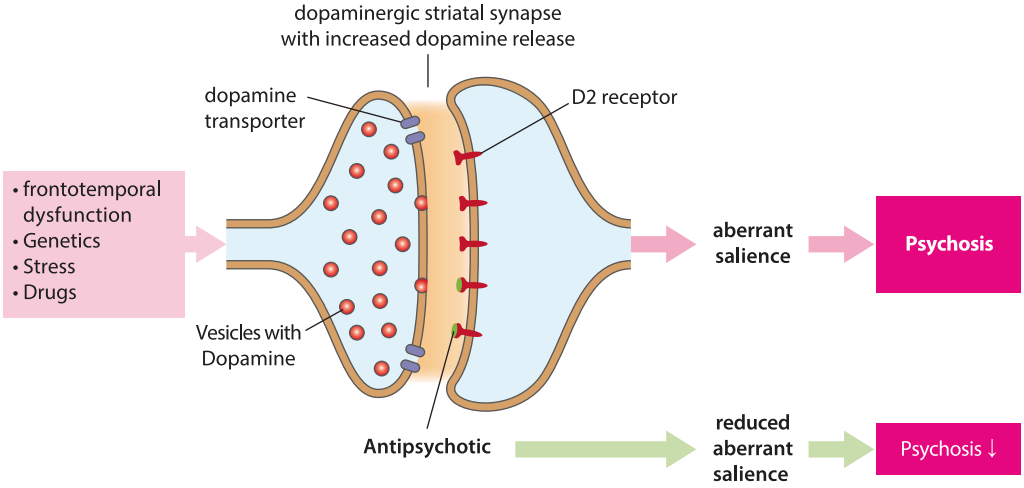


Fig. 11.3 Under the influence of multiple factors (e.g. genetics, stress, drugs), there is an increased striatal dopamine release, which leads to "aberrant salience" as the basis for the development of psychotic symptoms. Most currently available antipsychotics interfere with this process by blocking postsynaptic dopamine receptors. (Adapted from Howes and Kapur 2009)

the expectation and the actual event and can be used to adjust future expectation (Schultz 2017). Accordingly, only an unexpected stimulus that indicates reward leads to a short-term (phasic) dopamine release and thus to the attribution of salience, so again the—in this case temporal—surprise effect and thus a prediction error is crucial. Accordingly, it has been postulated that a reduction in adaptive (dopaminergic) prediction error signals due to disturbed encoding of relevant stimuli and events contributes to the emergence of the motivational negative symptoms, whereas an increase in aberrant, chaotic error signals is involved in the emergence of the psychotic positive symptoms (Maia and Frank 2017).

11.8 The Bayesian Brain and Predictive Processing

An influential general theory about how the human brain works is the "**Bayesian Brain Hypothesis**". This term stands for the idea of inference (Helmholtz 1867), first formulated by Helmholtz, which states that the brain uses learned prior assumptions to infer their causes from sensory input data. This process can be formulated as a Bayesian inference process in which probabilistic predictions (*priors*) are combined with the probability of the presence of sensory data, the sensory evidence (*likelihood*), to calculate an a *posterio* probability (*posterior*) of the cause of a sensory event (Friston 2005). The posterior thus corresponds to the perception that is most likely based on the combination of prior and likelihood (Hohwy 2012). This Bayesian inference might be implemented in the brain in the form of a hierarchical prediction model (*Hierarchical Predictive Coding*), in which increasingly abstract predictions are encoded at higher levels of the cortical hierarchy (Friston 2005; Lee and Mumford 2003). If the predictions do not match the sensory data, prediction error signals are generated to correct the predictive model. The precision with which predictions and sensory data are encoded plays an important role. In the Bayesian formulation, precision corresponds to the inverse variance of the probability distributions representing predictions and sensory

data. If the precision of the sensory data is high, this also results in a stronger prediction error. How much this prediction error in turn corrects the predictions also depends on the precision of the predictions. Imprecise predictions are more strongly corrected by the prediction error than precise predictions.

A leading hypothesis for schizophrenia within this theory is that changes in this interplay of predictions and sensory data lead to erroneous conclusions (inferences) that form the basis for the development of psychotic symptoms (Fig. 11.4). For example, it has been suggested that reduced precision of prior assumptions may lead to sensory data being weighted more heavily, resulting in stronger prediction errors (Adams et al. 2013; Sterzer et al. 2018). This reasoning is based on numerous empirical findings, such as the lower susceptibility of people with schizophrenia to visual illusions (Notredame et al. 2014). An example that well illustrates this putative change in Bayesian inference is the so-called hollow-face illusion. When healthy subjects are shown the mask of a face from the inside, it is not perceived as concave, but erroneously as a convex face, i.e., curved outward. According to Bayesian theory, extensive experience with faces in healthy subjects leads to a very accurate prior about the configuration of faces, namely that they are convex. When the prior is integrated with the sensory evidence (likelihood), the prior is weighted so heavily because of its high precision that the perceptual outcome corresponds to a convex face despite stimulus properties that indicate a concave configuration of the face. In contrast, people with schizophrenia are more likely to actually perceive the concave face as concave (Schneider et al. 2002), indicating a lower precision of the prior and a stronger weighting of the likelihood. These theories may also explain why psychosis is clustered among people with immigrant backgrounds and experiences of social exclusion: Priors may be less precise compared to accurate

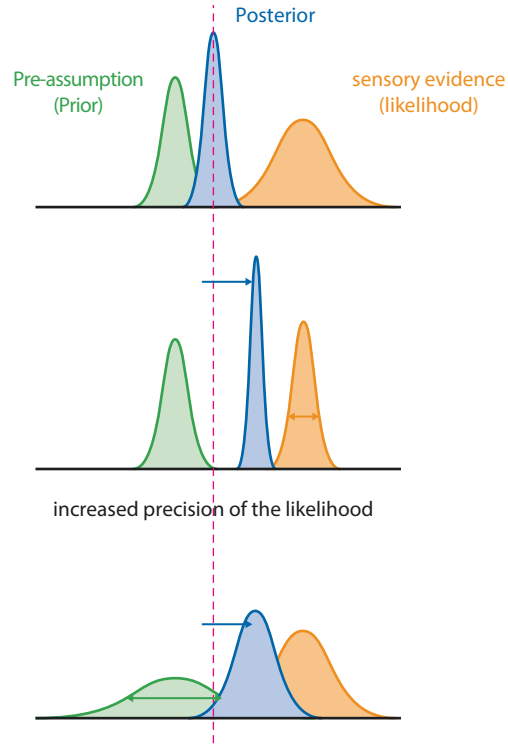


Fig. 11.4 Schematic representation of the changes in Bayesian inference. Prior, likelihood and posterior are shown as probability distributions. The larger the variance of a distribution (the wider it is), the lower its precision. The calculation of the posterior depends on the respective precision of the prior and the likelihood. Both an increased precision of the likelihood (middle) and a decreased precision of the prior (bottom) can lead to a shift of the posterior towards the likelihood. This results in a stronger weighting of sensory evidence over prior assumptions. (Adapted from Adams et al. 2013)

observation of the threat-experienced environment, resulting in clustered dopaminergic encoded prediction errors (Heinz et al. 2018).

The neuronal basis of altered Bayesian inference is currently the subject of research. A central mechanism may lie in the NMDA-R dysfunction discussed above. The NMDA receptor is thought to play an important role in the transmission of excitatory feedback signals (Bastos et al. 2012),

so NMDA-R dysfunction may be a mechanism of the reduced precision of feedback prediction signals (Corlett et al. 2009). In addition, increased dopaminergic neurotransmission could contribute to increased precision (not in the sense of correctness, but in the sense of relevance) of prediction error signals (Galea et al. 2012). As a result of these changes, individuals with schizophrenia experience a greater weighting of sensory information in the context of Bayesian inference, which, similar to the mechanism discussed above, leads to aberrant salience and, subsequently, the development of delusional mood and delusional thoughts. Aberrant salience theory, which in its original form was limited to motivational salience, can thus be embedded in the more general theory of Bayesian inference (Heinz et al. 2018; Maia and Frank 2017; Sterzer et al. 2018).

11.9 Outlook: A Neurobiological Integrative Approach

Neurobiological research on the pathophysiology of schizophrenia has revealed a multitude of findings at different levels of observation. Integrating these findings into a coherent picture that has clinical relevance beyond theoretical insight is a major challenge for current schizophrenia research. As with other mental disorders (► Chap. 12), the vulnerability-stress model described above remains the standard model for the development of psychotic disorders such as schizophrenia. This model has the advantage of establishing a link between the genetic predisposition to psychosis, which is now regarded as undoubted, and the recognition that environmental factors also have a significant influence on the development of the disorder. Thus, on the one hand, the vulnerability-stress model provides a helpful framework, but on the other hand, it must be filled with specific mechanisms in order to fulfill the claim of a neurobiologically integrative approach. At least two major challenges arise: on the one hand, the integration of different psychosocial and neurobiological findings into a comprehensive neurodevelopmental disorder model, and on the other hand, the still existing explanatory gap between neurobiological mechanisms and the subjective experience of those affected.

Currently, we have only a rudimentary understanding of the neurobiological processes and mechanisms underlying disease predisposition and its interaction with environmental factors, and how this might integrate different neurobiological findings into a comprehensive neurodevelopmental disorder model. For example, little is known about how genetic factors are related in detail to neurotransmitter alterations (such as glutamatergic NMDA-R hypofunction or dopaminergic hyperfunction) and what role these relationships play in brain development and vulnerability to stressors occurring later in life. Further neurobiological research using a variety of methodological approaches, from animal models to brain imaging in humans, will be required to address these questions. However, an important step towards an improved understanding will also lie in the mathematical ("computational") modeling of neuronal processes or data measured as proxies (fMRI, EEG, etc.) with regard to their function or dysfunction. Basically, two categories of such computational models can be distinguished (Valton et al. 2017): top-down models provide algorithms for describing behavioral phenomena and then relating model parameters to neural signals. Bottom-up models, on the other hand, describe how computational processes are implemented on the neuronal level and how this results in behavior. Although these two categories involve different approaches, they are not mutually exclusive and can be combined. For example, the Bayesian brain theory described above is a top-down approach, but it can also be combined with models

about implementation at the level of neural control circuits (e.g., Bastos et al. 2012). Such "predictive processing" models therefore have the potential to link different levels of observation, from the dysfunction of specific transmitter systems to psychopathology, and thereby provide the basis for a comprehensive neurodevelopmental disorder model.

With regard to the explanatory gap between neurobiology and subjective experience, previous theories already provide some promising starting points. For example, the theory of aberrant salience (Heinz 2002; Kapur 2003) aimed to establish a link between subcortical dopamine hyperfunction and psychopathological phenomena such as the experience of meaning and delusion via the functional relevance of dopaminergic signals and their stress-related alteration (which may also differ with regard to neurodevelopmental risk factors). This approach offers people with psychotic experiences the possibility of a plausible explanation of their subjective experience, which may well contribute to the depathologization and thereby destigmatization of psychosis, especially when the influence of stressful experiences on dopaminergic transmission is taken into account (Heinz et al. 2018). However, aberrant salience theory, like other previous models explaining psychotic phenomena (see also, for example, the comparator model; Frith and Done 1989), remains limited to a single mechanism for explaining a particular symptom. It is therefore an important task for the future to develop more comprehensive disorder models that allow to derive plausible neurobiological models for the different and variable symptom domains of schizophrenia spectrum disorders and thus make psychotic experience more understandable for the affected individuals and their environment.

The goal of integrating neurobiology into a clinical approach is therefore by no means merely to develop better neurobiological methods (e.g. psychosocial interventions or medications) that act more specifically on certain symptoms and their neurobiological correlates. Rather, a transparently and critically communicated, neurobiologically integrative approach can also lead to a better understanding of the disease and its psychosocial risk factors. On the one hand, this can enable the development of new therapeutic approaches, but on the other hand it can also lead to an open "trialogical" discussion (between affected persons, their relatives and professionals) and thus contribute to reducing the stigmatization to which mentally ill people are still exposed.

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