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Dopamine and Psychosis: Theory, Pathomechanisms and Intermediate Phenotypes

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Abstract

Schizophrenia is a chronic, severe, and disabling brain disorder arising from the adverse interaction of predisposing risk genes and environmental factors. The psychopathology is characterized by a wide array of disturbing cognitive, emotional, and behavioral symptoms that interfere with the individual's capacity to function in society. Contemporary pathophysiological models assume that psychotic symptoms are triggered by a dysregulation of dopaminergic activity in the brain, a theory that is tightly linked to the serendipitous discovery of the first effective antipsychotic agents in the early 1950s. In recent years, the availability of modern neuroimaging techniques has significantly expanded our understanding of the key mediator circuits that bridge the gap between genetic susceptibility and clinical phenotype. This paper discusses the pathophysiological concepts, molecular mechanisms and neuroimaging evidence that link psychosis to disturbances in dopamine neurotransmission.

2 Introduction

Mental illness is a highly prevalent phenomenon in our society that inflicts an enormous burden of distress on the affected individuals and their families. Current scientific evidence suggests that the path to psychopathology is laid by the adverse interaction of multiple risk genes and environmental factors, a constellation that predisposes individuals to the subtle disturbances in brain neurotransmission that ultimately blaze the trail for overt emotional and behavioral symptoms (see figure 1). Among mental disorders, schizophrenia stands out as one of the most severe and disabling conditions affecting roughly 1% of the population worldwide (Sullivan et al., 2000). The hallmark features of the disorder are auditory hallucinations, delusions, and disorganized behavior. Regarding the more proximal mechanisms of schizophrenia, contemporary pathophysiological models assume that psychosis is triggered by a dysregulation

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of dopaminergic activity in the brain, an operational theory that is tightly linked to the fortuitous discovery of the first effective antipsychotic agents in the early 1950s. It has been proposed that dopamine acts on neural circuits that serve as a “filter” for incoming information that competes for processing in the prefrontal cortex, a mechanism that might be impaired in these conditions (Pantelis et al., 1997). This paper reviews the current scientific knowledge on the role of dopamine in the formation of psychosis. In doing so, it attempts to give an overview of the pathophysiological concepts, molecular mechanisms, and neuroimaging evidence that link psychosis to disturbances in dopamine neurotransmission.

3 The dopamine hypothesis of psychosis: historical roots and modern adaptations

The dopamine hypothesis is the oldest neurochemical theory of the pathophysiology of psychosis. Established in the last century based on clinical observations, the theory received considerable scientific attention in past decades. Over the years, the integration of new empirical evidence resulted in a constant refinement of its neurobiological underpinnings, a development that is reviewed here.

3.1 Historical background

Up until the middle of the last century, the condition in mental hospitals was often characterized by long-term hospitalization, overpopulation, and the lack of effective therapies. In 1949, the fortuitous discovery of a new pharmacological treatment set the ball rolling for a development that ultimately transformed the psychiatric discipline. Henri Laborit, a French surgeon, began experimenting with various antihistaminic substances in an attempt to develop a new therapy for shock-related symptoms in injured soldiers. One of these drugs, chlorpromazine (CPZ), induced a noticeable state of mental indifference in his patients which he later described as a state of “sedation without narcosis” (Seeman, 1987). Impressed by this observation, Laborit brought the substance to the attention of his psychiatric colleague Pierre Hamon, who administered CPZ in a “lytic cocktail” with barbiturates and sedatives to a patient who suffered from severe agitation and mania (Hamon et al., 1952). The intervention resulted in a dramatic improvement of the clinical picture, and soon psychiatrists throughout France used the substance to treat patients with various mental ailments (Delay et al., 1952). Chlorpromazine later became the prototype of phenothiazines, a class of first generation antipsychotic compounds with similar pharmacological properties. Although accidental in nature, this discovery opened up a new era of psychopharmacology as it provided the first effective chemotherapy for psychosis that offered more than sedation. Ultimately, the development revolutionized psychiatric healthcare by replacing older invasive procedures and allowing a significant number of institutionalized patients to be discharged and successfully reintegrated into the community.

At the same time, the discovery of antipsychotics sparked considerable interest in the neurobiological basis of psychosis. The earliest formulation of the dopamine hypothesis can be traced to Van Rossum (1966) who surmised that “overstimulation of dopamine receptors could be part of the aetiology” (Van Rossum, 1966, p. 321). Two major lines of evidence supported this assumption. First, the most prominent side effects of phenothiazines involved extrapyramidal symptoms similar to Parkinson’s disease, a motor phenotype that had been previously linked to a central dopamine deficiency by the milestone work of Carlsson (Carlsson, 1964, 1972). Second, early experiments with the dopamine precursor L-Dopa suggested that dopamine agonists relieve drug-induced parkinsonism and may provoke psychotic symptoms (Yaryura-Tobias et al., 1970a, Yaryura-Tobias et al., 1970b). These observations set off a systematic search for the primary site of action of antipsychotic drugs. In 1974, the first direct evidence was established that neuroleptics selectively inhibit dopamine

D₂ receptors and that the clinical efficacy of these agents is directly related to their receptor-blocking potency (Seeman et al., 1975, Seeman, 1987). Over the years, as evidence mounted that not all psychotic symptoms are equally well controlled by D₂ receptor antagonism, the classical dopamine hypothesis was reformulated and integrated into modern neurodevelopmental disease models. One influential hypothesis assumed that psychosis arises from an prenatal disturbance of prefrontal-subcortical network formation (Weinberger, 1987). According to this theory, a dysfunction in the prefrontal cortex (PFC) mediated in part by dopamine D₁ receptors is at the core of treatment-resistant cognitive deficits and negative symptoms. Due to the deficient top-down control of phylogenetically older brain areas the subcortical D₂ receptor function is thought to become disinhibited, thereby raising “the wind of the psychotic fire” (Laruelle and Abi-Dargham, 1999) that promotes the formation of hallucinations and delusions.

3.2 Psychosis as a state of aberrant salience

Although disturbances in dopamine neurotransmission have long been postulated, a comprehensive model that links the phenomenology, pathophysiology, and psychopharmacology of psychosis has long been missing. Shitij Kapur (2003) integrated the dopamine hypothesis of schizophrenia with data on motivational salience in a powerful heuristic framework that explains both the neurobiological foundation of psychosis and the patient’s subjective experience of symptoms (Kapur, 2003, Kapur et al., 2005). The term “motivational salience” refers to the process by which an external stimulus comes to awareness and drives the goal-directed behavior of an individual due to its association with reward or punishment. Previous scientific work has shown that the prediction of rewarding events and the coding of expectancies about behavioral outcomes are critically linked to the firing of dopaminergic neurons in the mesolimbic and mesostriatal system (Schultz et al., 1992, Richardson and Gratton, 1996, Schultz et al., 1997). In this context, the role of dopamine is best described as the neurochemical switch that converts the neural representations of a neutral stimulus into motivationally meaningful (“salient”) experience (Berridge and Robinson, 1998). Kapur translated this concept into the psychiatric field by extending the role of dopamine from a pure motivational cue to a potential mediator of “aberrant salience”. According to this concept, the formation of psychotic symptoms is linked to the chaotic and stimulus-independent release of dopamine in the brain. The untimely firing of dopaminergic neurons to trivial everyday events results in an increased attention and attribution of excessive motivational significance to these stimuli. This explains why a random everyday occurrence, e.g. the statement of a TV anchorman on the earth’s ozone layer, can be assigned with inadequate significance (e.g., is attributed to the own person in the case of delusions of reference), and might even gain the motivational power to drive the most bizarre behaviors (e.g., shielding of the apartment walls with metal panels). In this framework, the psychopathological phenomenon of “delusion” is best described as a top-down cognitive explanation of the individual in an effort to make sense of these odd experiences. Similarly, the emergence of hallucinations can be conceptualized as the attribution of abnormal salience to the internal representations of perceptions and memories. The efficacy of antipsychotic agents to relieve psychotic symptoms and some of their bothering side effects (e.g., anhedonia) are in line with the idea that the dopamine blockade “dampens” the motivational salience of external and internal stimuli. The heuristic power of this framework stimulated the field considerably as it provided a comprehensive molecular explanation for the pathophysiology, phenomenology, and therapy of psychotic symptoms. Recent neuroimaging evidence supports the main tenets of this model by showing that the formation of context-inappropriate associations in schizophrenia is related to a dysfunction of the main target area of dopaminergic neurons in the reward circuitry, the ventral striatum (Juckel et al., 2006, Corlett et al., 2007, Jensen et al., 2008, Murray et al., 2008).

3.3 Neural network models of frontal lobe (dys)function

Schizophrenia patients exhibit a wide array of persistent neuropsychological deficits in cognitive domains that are known to be dependent on the efficiency of the PFC, such as working memory, cognitive flexibility, attention, and interference control (see also the contributions of M. Luciana and M. Frank in this issue). Among these domains, working memory, a cognitive function that involves the maintenance and active manipulation of memorized items, has been examined most extensively in schizophrenia patients. In test settings, schizophrenia patients typically exhibit significant capacity constraints of the working memory buffer, as indicated by a significantly enhanced rate of omissions and false positive responses (Krieger et al., 2005). Several other studies have shown that patients with schizophrenia also perform poorly on the Wisconsin card sorting test (WCST), a popular measure that challenges working memory functions, abstract reasoning and cognitive flexibility (Meyer-Lindenberg et al., 2002, Prentice et al., 2008). A large body of evidence suggests that these performance deficits relate to anomalies in DA signaling and functional impairments of the PFC (Callicott et al., 1999, Manoach, 2003). Single-cell recordings in animals provided insights into the decisive role that mesocortical dopaminergic projections play in the modulation of these functions, especially working memory (Fuster, 1990, Goldman-Rakic, 1995). One key finding of this research is that both working memory performance and task-dependent neuronal firing rates in the PFC are highly susceptible to dopamine D₁ receptor challenge (Sawaguchi and Goldman-Rakic, 1991, Seamans et al., 1998). A large body of evidence has established an “inverted u” shaped relationship between dopamine signaling and working memory capacity (Williams and Goldman-Rakic, 1995, Goldman-Rakic et al., 2000, Mattay et al., 2000). According to this concept, dopamine critically determines the ratio of task-related to task-unrelated neural firing (‘tuning’) of PFC neurons, with the maximum signal-to-noise ratio and task performance being achieved at intermediate levels of dopamine D₁ receptor stimulation. At the cellular level, the dopamine D₁- and D₂-class receptor interaction is highly complex, and the net effect is difficult to study in vivo. In recent years, sophisticated neural network models have been developed that mimic the summed effect of various receptor subtypes and neural currents on the dynamical properties of the frontal lobe (Rolls et al., 2008). These approaches provided a detailed mechanistic picture of the impact of dopamine on the signal to noise ratio of PFC networks, and gave valuable clues to the pathophysiology and therapy of cognitive deficits in schizophrenia.

One influential network model is the dual-state theory of prefrontal cortex dopamine function established by Jeremy Seamans and Daniel Durstewitz (Seamans and Yang, 2004, Durstewitz and Seamans, 2008). Based on neurocomputational simulations of the currents resulting from the interaction of dopamine D₁- and D₂-class receptors, the authors predicted the formation of sustained and noise-resistant neural states from optimum-range extrasynaptic (i.e. tonic) D₁-receptor stimulation. This network dynamic has been interpreted as a neural basis for the active maintenance of memory items during the delay periods of working memory tasks, as they seem to “lock working memory buffers into a single mode of action, such that one or a few representations completely guide action at the expense of response flexibility” (Seamans and Yang, 2004, p. 41). Under physiological circumstances, this dynamic is regularly reset by high levels of intrasynaptic (i.e. phasic) dopamine. In the dual-state model, phasic dopaminergic firing is thought to promote the establishment of a more transient, D₂-dominated network state that is characterized by a net reduction in inhibition. This dynamic leads to an increase in the number of low-gain network representations and promotes the access of new information to prefrontal networks. On the behavioral level the D₂-dominated state supports the integration of multiple behavioral options and facilitates cognitive functions like set shifting and flexible problem solving. These benefits, however, come at a price as the resulting network dynamic is also less stable and more susceptible to interfering neural noise. In the healthy brain, the overall network dynamic is balanced, i.e. the pure D₁- and D₂-dominated network states

represent the two extreme endpoints of a continuum. However, in the case of dopamine disturbance the dynamic of prefrontal networks is thought to be skewed towards one of the extremes, which promotes the development of psychotic symptoms. Several core phenomena of psychosis are in line with this model. Deficits in working memory and selective attention may arise from a predominantly D₂-controlled network state that disrupts the formation of coherent trains of thoughts, favors distractibility, and promotes the emergence of inadequate neural representations like hallucinations and delusions. On the other extreme, a very strong D₁-state with an overly high energy barrier might be at the roots of the development of negative symptoms, especially perseverative thinking, avolition, and deficits in cognitive flexibility (Tost et al., 2006). Since positive and negative symptoms usually coexist, this interpretation based on the extremes of cortical network states must be complemented by a model that takes the temporal development and potential superposition of such states into account. Further empirical studies will be necessary to evaluate the potential of this model to identify promising routes for new drug developments.

3.4 Beyond dopamine: dopamine-glutamate interaction and NMDA receptor hypofunction

Glutamate is the most abundant excitatory neurotransmitter in the cerebral cortex. Although the common antipsychotics act on dopamine receptors, the hypofunction of the ionotropic glutamate N-methyl-D-Aspartate (NMDA) receptor has been proposed as a complementary pathomechanism in schizophrenia. This idea is supported by several lines of evidence, especially the psychotomimetic effect of non-competitive NMDA receptor antagonists like phencyclidine (PCP) and ketamine. Moreover, allelic variation in a metabotropic receptor modulating synaptic glutamate (GRM3) has been associated with increased risk for schizophrenia and prefrontal cognitive deficits (Egan et al., 2004). In recent years, the field has been characterized by efforts to integrate both transmitter systems into a comprehensive pathophysiological framework (Carlsson et al., 2004, Stone et al., 2007). Dopaminergic and glutamatergic projections converge and interact on multiple levels of the brain. On the one hand, dopamine optimizes the signal to noise characteristics or “fine tuning” of neural networks in the PFC and hippocampus by modulating the excitability of glutamate and γ -aminobutyric acid (GABA) neurons (Seamans et al., 1998, Seamans et al., 2001). Conversely, the activity of dopamine neurons in the midbrain is under both excitatory and inhibitory control of the PFC (Vollenweider et al., 2000, Strafella et al., 2003, Aalto et al., 2005). The complexity of this interaction extends the scope of the original dopamine hypothesis by suggesting that the antipsychotic mechanism of dopamine-blocking agents involves the modulation of the excitability of prefrontal glutamatergic microcircuits by dopaminergic function. From a pharmacological standpoint, this raises the question of whether or not the development of a primarily glutamatergic substance might be a promising route for a new antipsychotic treatment strategy. This notion is encouraged by the fact that lamotrigine, an anticonvulsant drug that modulates the presynaptic release of glutamate, is known to effectively reverse ketamine-induced psychosis and to augment the efficacy of the atypical antipsychotics (Hosak and Libiger, 2002, Heck et al., 2005, Zoccali et al., 2007). In a recent milestone work, Patil and coworkers (2007) demonstrated the antipsychotic efficacy of LY2140023, an agent that modulates glutamate neurotransmission by selective agonism of the mGlu2/3 receptor. Although the final relevance of this substance for clinical practice is undecided, this finding generated considerable enthusiasm in the field as the development of this new substance class was based on the thorough understanding of the pathomechanisms of psychosis and not “scientific serendipity” as in the case of chlorpromazine (Weinberger, 2007).

4 Dopamine disturbance in psychosis: scientific evidence

Although the dopamine hypothesis of schizophrenia was established in the 1950s, the nature of the presumed dopaminergic abnormality remained elusive for decades (Davis et al., 1991).

It was not until the mid-1980s that the availability of modern nuclear imaging radioligands allowed for the non-invasive examination of the dopaminergic system in patient populations. Similarly, neuropathology has been revitalised over the past decades by adopting techniques from molecular biology that allow for the examination of genes and their expression in post mortem brain tissue (Harrison, 1996).

4.1 Post-mortem studies

The dopamine D₂ receptor family is expressed at highest concentrations in the striatum and to a much lesser extent at the cortical level, where the distribution follows a rostral-to-caudal gradient of decreasing density (Farde et al., 1988, Lidow et al., 1989). Despite their low concentration, D₂ receptors are ubiquitously present in the cortex and impact on a wide range of brain functional systems. In the late 1970s, the close correlation of clinical efficacy and D₂ receptor affinity of antipsychotics encouraged researchers to seek post-mortem evidence of D₂ overactivity in psychosis. The first series of studies in the 1980s used the D₂ receptor ligand [³H]Spiperone, and yielded conflicting results with respect to the striatal D₂ receptor status in schizophrenia (e.g., increased D₂ receptor binding: (Mjorndal and Winblad, 1986, Hess et al., 1987); no difference: (Mita et al., 1986). Using the ligands [³H]Raclopride and [³H]SCH23390, a later work by Knable and co-workers (1994) failed to define differences in striatal D₂ and D₁ receptor densities in patients that had previously received medication (Knable et al., 1994). The disappointing results of this early research prompted a series of more detailed, region-specific analyses that produced several interesting findings. Among others, anomalies in the modular and laminar arrangements of D₂ receptors in the temporal cortex (Goldsmith et al., 1997), elevated D₃ receptor levels in ventral forebrain and striatum (Gurevich et al., 1997, 1997), and decreased D₃ but normal D₁ and D₂ mRNA expression levels in the PFC have been reported (Meador-Woodruff et al., 1997).

Other post-mortem approaches focused on the examination of the D₁ receptor family. Dopamine D₁ receptors are found throughout the human brain with high levels of expression in the amygdala, putamen, caudate, hippocampus, and PFC. Although not always consistent, several studies reported anomalies in D₁ receptor binding in schizophrenia. In a series of studies performed with [³H]SCH23390 autoradiography, Knable and co-workers detected a higher D₁ receptor binding in the frontal cortex (Knable et al., 1996) but not the striatum (Knable et al., 1994) of previously medicated schizophrenia patients. However, as noted by the authors, the study outline prevented any sound conclusion about whether these findings relate to the pathophysiology of the disorder or its treatment. In a follow-up study, Domyo and colleagues (2001) demonstrated a significant increase in [³H]SCH23390 binding in the inferior temporal and superior parietal cortex in schizophrenia patients who had not received antipsychotic drugs for more than 40 days before death (Domyo et al., 2001). This suggested that the observed changes in D₁ receptor functioning in schizophrenia are inherent to the pathology, and not a mere treatment artifact.

4.2 Nuclear neuroimaging findings

In 1986, the dopamine hypothesis was undergoing a revival when Wong and coworkers found an increased striatal density of dopamine D₂ receptors in neuroleptic-naïve schizophrenia patients in one of the first PET¹ imaging studies in the field (Wong et al., 1986). Unfortunately, subsequent studies were not able to replicate this finding (Farde et al., 1987, Farde et al., 1990), an incongruity that was addressed in a series of discussions (Chugani et al., 1988, Young et al., 1991, Zawarynski et al., 1998, Abi-Dargham et al., 2000). Ten years later, Laruelle and colleagues used [¹²³I]IBZM SPECT² to show that acutely psychotic patients release excessive

¹Positron Emission Tomography
²¹²³I-Iodobenzamide Single Photon Emission Computerized Tomography

striatal dopamine in response to an amphetamine challenge (Laruelle et al., 1996). A follow-up study of the same group demonstrated that the acute depletion of intrasynaptic dopamine was associated with a disproportionately high D₂ receptor availability in unmedicated first-episode schizophrenia patients (Abi-Dargham et al., 2000). In both studies, the striatal D₂ receptor binding profile was predictive of the clinical outcome, in particular the severity of positive symptoms and treatment response. This research provided the first direct evidence that psychotic symptoms are promoted by excessive dopamine D₂-receptor stimulation, a finding that is suggestive of an increased phasic activity of dopaminergic neurons in the subcortex. An own prior study used [¹⁵O]H₂O- and 6-[¹⁸F]DOPA PET to test the hypothesis that prefrontal dysfunction and excessive subcortical dopamine synthesis are related pathophysiological phenomena (Meyer-Lindenberg et al., 2002). We confirmed increased dopamine synthesis in striatum and found that in unmedicated schizophrenia patients, measures of PFC hypoactivation during cognitive performance were predictive of the presynaptic dopaminergic dysfunction in the striatum. This result supports the hypothesis that a top-down control deficit of the PFC is at the root of the observed subcortical disinhibition of dopamine transmission. Moreover, a recent study examined the question of whether or not this dopamine dysregulation relates to the genetic risk for psychosis (Hirvonen et al., 2005). Using [11C] raclopride PET, Hirvonen and colleagues (2005) observed a significant higher caudate D₂-receptor density in unaffected monozygotic co-twins of schizophrenia patients when compared with unaffected dizygotic co-twins and healthy control twins. This finding suggests that the subcortical dopamine dysregulation is a trait phenomenon that is related to the disease vulnerability.

Previous nuclear imaging studies of dopamine functioning in schizophrenia have usually been confined to the striatum. Only a few PET or SPECT studies in the field have examined D₂-receptor densities in the cortex, a fact that is largely explained by the low extrastriatal D₂-receptor concentration and the associated need for novel high-affinity radioligands (e.g., [¹⁸F] Fallypride, [¹²³I]Epidepride). Two previous studies reported a significant decrease of D₂-receptor binding in the anterior cingulate (Suhara et al., 2002) and temporal cortex (2003) in neuroleptic-naïve schizophrenic patients. In both cases, the evidenced alterations of cortical dopamine D₂ receptor binding predicted the severity of the clinical picture (cingulate: positive symptoms; temporal: negative symptoms). Likewise, only a few nuclear imaging studies examined the density of cortical D₁ receptors in schizophrenia (Okubo et al., 1997, Abi-Dargham et al., 2002). The reported receptor alterations and their association to cognitive performance are largely contradictory, presumably due to the different radioligands employed. The first PET imaging of D₁ receptors by Okubo and co-workers (1997) used the radioligand [¹¹C]SCH 23390, a less sensitive marker for the quantification of D₁ receptors in low density regions like the prefrontal cortex. In this study, the authors observed a reduction in D₁ receptors binding in the PFC of schizophrenia patients that correlated with the severity of negative symptoms and cognitive deficits (Okubo et al., 1997). Using the high-affinity radioligand [¹¹C]NNC-112, a later study by Abi-Dargham and colleagues (2002) found that increased prefrontal D₁ receptor binding in schizophrenia is strongly correlated with the working memory deficits of these patients (Abi-Dargham et al., 2002). This finding was interpreted as inefficient compensatory upregulation of D₁ receptor density in the PFC secondary to a sustained deficiency in mesocortical dopamine signaling. The complexity of the functional interaction of dopamine receptor subtypes highlights the need for a conjoint assessment of D₁ and D₂ receptor status in future nuclear imaging studies. Chances are that alterations in the density of one dopamine receptor subtype are offset by alterations in density and/or location in other subtypes, a compensatory mechanism that might relate to some of the previously conflicting findings in the field.

5 Dopaminergic susceptibility genes

Data from previous twin, adoption and family studies show that schizophrenia is a predominantly genetic disorder with heritability estimates up to 80% (Sullivan et al., 2003). In the last decades, several risk gene variants have been identified that seem to promote the emergence of psychotic symptoms. In general, previous linkage data do not support the idea of a single causative gene or simple pattern of inheritance. Like diabetes or cancer, schizophrenia is conceptualized as a complex genetic disorder with multiple interacting risk alleles, each accounting for only a small increment in risk (Weinberger, 2005). It is important to note that these variants do not encode for what we consider to be “psychopathology”. Instead, they interfere with the regular functioning of brain systems that mediate the emergence of such complex behavioral phenotypes like hallucinations or delusions (Meyer-Lindenberg and Weinberger, 2006). Not all identified susceptibility genes are clearly functional. The known gene products however regularly interfere with biochemical cascades related to dopamine and glutamate neurotransmission. The following section mainly focuses on candidate genes related to the dopaminergic system (see Harrison and Weinberger, 2005, for a comprehensive review on other susceptibility genes).

5.1 Catechol-O-methyl transferase (COMT)

In past years, the gene encoding for the enzyme catechol-O-methyl transferase (COMT) attracted considerable attention as a promising candidate gene for both cognitive function and mental illness. In the nervous system, COMT mediates the extraneuronal degradation of the catecholamines dopamine, norepinephrine and epinephrine through 3-O-methylation of the benzene ring. Several lines of evidence make the *COMT* gene an attractive schizophrenia susceptibility gene. First, since dopamine transporters are scarce in prefrontal cortex (Lewis et al., 2001), COMT is a particularly critical determinant of dopamine flux in this area (Tunbridge et al., 2006). Second, the *COMT* gene is located at 22q11.2, a chromosomal region that has been implicated in schizophrenia by linkage (Owen et al., 2004, Stefansson et al., 2008). Third, a microdeletion syndrome in the region of the *COMT* gene, velo-cardio-facial syndrome (VCFS), is known to be associated with a high rate of psychosis (Murphy, 2002). Previous studies have shown that a common single-nucleotide polymorphism (SNP) in the *COMT* gene (Val¹⁵⁸Met) affects the thermostability of the protein, resulting in a 3–4 fold reduction in enzyme activity in Met allele carriers (Chen et al., 2004) that relates to changes in prefrontal cognitive functions (Mattay et al., 2000, Goldberg et al., 2003). This suggests that the *COMT* Val allele might increase risk for schizophrenia by enhancing dopamine catabolism, which in turn impairs the functional efficacy of the PFC (Egan et al., 2001, Chen et al., 2004). However, despite the fact that this polymorphism has been consistently linked with measures of prefrontal efficacy, previous data on the association of this particular coding variant with schizophrenia have been rather inconclusive (Egan et al., 2001, Mattay et al., 2003, Fan et al., 2005). This inconsistency might be related to the fact that additional genetic variability is important. In line with this notion, newer scientific evidence indicates that the analysis of *COMT* haplotypes, i.e. specific combinations of risk alleles in closely linked marker regions of the gene, yields a stronger association with the disorder than the analysis of single markers (Shifman et al., 2002, Meyer-Lindenberg et al., 2006). Moreover, a recent statistical meta-analysis suggests that epistasis between *COMT* and other schizophrenia susceptibility genes is a crucial factor in determining the risk for schizophrenia (Nicodemus et al., 2007).

5.2 Protein kinase B (AKT1)

The molecular function of dopamine is mediated by two classes of G protein-coupled receptor subtypes that stimulate (D₁) and decrease (D₂) the intracellular production of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), respectively. D₂ receptors also signal through an AKT1/glycogen synthase kinase 3 (GSK3) pathway via β -arrestin 2, a signaling

cascade that modulates the expression of dopamine-associated behaviors independent of the canonical cAMP/PKA pathway (Beaulieu et al., 2004, Beaulieu et al., 2005). Several converging findings suggest a role of AKT1 in the pathogenesis of schizophrenia. The *AKT1* gene (14q32.32) has been linked to schizophrenia by genetic association (Schwab et al., 2005, Tan et al., 2008) and by its interaction with key environmental risk factors like obstetric complications (Nicodemus et al., 2008). In a series of experiments, Emamian and colleagues provided evidence for a significant reduction of AKT1 protein levels and GSK3 β phosphorylation in postmortem brains and peripheral lymphocytes of schizophrenia patients (Emamian et al., 2004). The same study also reported a pronounced susceptibility of AKT1 deficient mice to amphetamine-induced disruption of prepulse inhibition, a common animal model of sensorimotor gating deficits in psychosis. Moreover, the authors provided evidence that one of the molecular mechanisms of haloperidol, a first generation antipsychotic drug, is to compensate for AKT1 deficiency by increasing the regulatory phosphorylation levels of AKT and GSK3 β (Emamian et al., 2004).

5.3 Dopamine and cyclic AMP-regulated phosphoprotein 32 (DARPP-32)

Dopamine- and cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein of molecular weight 32,000 (DARPP-32) is a key regulator and integrator of neural signals in the dopaminergic system. DARPP-32 is encoded by the gene *PPP1R1B* located in the chromosome region 17q12. The phosphoprotein is expressed in dopaminergic neurons, especially in the medium-sized spiny neurons forming the efferent pathways of the striatum. Stimulation of dopamine D₁ receptors induces the phosphorylation of DARPP-32 via cAMP and PKA, which converts the molecule from its inactive form to a powerful protein phosphatase 1 (PP-1) inhibitor (Fernandez et al., 2006). Inhibition of PP-1 in turn modulates the activity of a large number of other local effectors, i.e. receptors, ion channels, and transcription factors (Svenningsson et al., 2004). Thus, DARPP-32 is a crucial molecular switch that integrates the effects of local dopamine neurotransmission with other converging neural signals such as glutamate, serotonin, neuropeptides, and steroid hormones (Svenningsson et al., 2002). Several lines of evidence suggest an involvement of DARPP-32 in the pathophysiology of psychosis. First, postmortem studies have found a significant reduction of DARPP-32 in the dorsolateral PFC of schizophrenia patients (Albert et al., 2002, Ishikawa et al., 2007). Second, previous animal work has shown that the psychotomimetic effect of amphetamines and phencyclidine is attenuated in mice with a knock-out of the *PPP1R1B* gene or point mutations in the regions encoding for the phosphorylation sites of DARPP-32 (Svenningsson et al., 2003). In addition, the chromosomal region of the *PPP1R1B* gene has been implicated in risk for schizophrenia by linkage (Cardno et al., 2001, Lewis et al., 2003) and association analysis (Meyer-Lindenberg et al., 2007).

5.4 Dopamine D₂ receptor gene (DRD2)

In line with the mode of action of most antipsychotic drugs, the gene encoding for the dopamine D₂ receptor (*DRD2*, 11q23) has long been a prime candidate gene for schizophrenia. An SNP at codon 311 results in a cysteine for serine (Cys³¹¹Ser) substitution that alters the structural and functional properties of the receptor protein (Itokawa et al., 1993, Arinami et al., 1994). Available data from a meta-analysis suggests that the cys allele increases the risk for schizophrenia across populations, although the magnitude of the effect itself seems to be rather small (Glatt et al., 2003, Glatt et al., 2008). On the molecular level, this genetic variant has been associated with a reduced ability of the D₂ receptor to decrease cAMP levels in dopaminergic neurons, which supports the notion that an excess of dopamine activity promotes the emergence of psychotic symptoms. Recent reports indicate that other functional variants in the *DRD2* gene, e.g. functional polymorphism in the 5'-promoter region, may contribute to the risk to develop the disorder (Arinami et al., 1997, Bertolino et al., 2008).

5.5 Proline Dehydrogenase (PRODH)

Proline oxidase (POX), a mitochondrial enzyme encoded by the gene *PRODH*, catabolizes the nonessential amino acid proline into different metabolites including glutamate. In a subset of excitatory neurons, high-affinity proline transporters are expressed in axon terminals and vesicles suggesting an immediate physiological role for proline in glutamatergic neurotransmission (Shafqat et al., 1995, Parra et al., 2008). Several observations support the notion that variation in *PRODH*, POX deficiency, and hyperprolinemia may confer risk for schizophrenia. As in the case of *COMT*, the *PRODH* gene is localized in the chromosomal region implicated in VCFS (22q11.2). Hyperprolinemia has been associated with an increased susceptibility for psychosis (Jacquet et al., 2002, Bender et al., 2005, Jacquet et al., 2005, Raux et al., 2007), and schizophrenia-like behavioral phenotypes are evident in mice with *PRODH* mutations (Gogos et al., 1999, Paterlini et al., 2005). Moreover, several studies provide evidence for an association of schizophrenia with allelic and haplotypic variation in the *PRODH* locus (Liu et al., 2002, Li et al., 2004, Kempf et al., 2008), although conflicting reports also exist (e.g., see Williams et al., 2003, Glaser et al., 2006). While *PRODH* is not a dopaminergic risk gene in the strict sense, recent evidence on mice with *PRODH* mutations shows that COMT is the most dysregulated gene product in these animal models (Paterlini et al., 2005). This suggests a mechanistic link of *PRODH* dysfunction to dopaminergic neurotransmission, a notion that is supported by recent imaging genetics findings that show a convergent effect on prefrontal-subcortical interactions (Kempf et al., 2008).

6 Intermediate phenotypes: bridging the gap between predisposition and pathology

The path that leads from genetic predisposition to psychopathology is intricate. Multiple gene variants interact with each other and the environment and modulate, each to a varying degree, multiple neural circuitries that shape different behavioral phenotypes. Although several schizophrenia susceptibility genes have been identified in the past, their mechanism of action on the brain system level has been enigmatic. In recent years, a new neuroimaging research strategy ("imaging genetics") has provided valuable insights into the neural pathways that translate genomic variation into complex psychiatric phenotypes and has shaped the way that mental illness is conceptualized.

6.1 Conceptual framework

The search for the intermediate neural mechanisms of psychiatric risk genes has been a complicated endeavor for several reasons. First, the majority of psychiatric risk genes are not "functional" in the traditional sense of a coding variant, and their effect size is rather small. This implicates that very large sample sizes are necessary in order to characterize the associated neural correlates. Second, the operational criteria implemented in modern classification systems are entirely descriptive, but, at the same time, there is no one-to-one mapping between risk gene variants and neural system mechanisms or between neural mechanisms and psychopathology. This implicates that no particular constellation of genes or environmental factors is characteristic for the majority of individuals with the same diagnostic label. In past years, the combination of multimodal neuroimaging and genetic mapping techniques has proven to be a powerful tool in overcoming these obstacles (Meyer-Lindenberg and Weinberger, 2006). This research strategy uses genetic variants or heritable traits known to be associated with psychiatric disorders in order to dissect the underlying neural mechanisms that mediate these complex behavioral phenotypes. The intermediate phenotype strategy takes advantage of the fact that many genetic variants associated with psychiatric disorders are frequently expressed in the normal population. One main postulation of this approach is that the penetrance of gene effects is greater at the neurobiological level than at the level of complex behavior, and that these gene effects can be traced at the neural systems level in risk allele

carriers even when the disease phenotype itself is not expressed (Goldberg et al., 1990). This implicates that risk gene effects can be examined without the confounding factors of illness chronicity or medical treatment, which constitutes a major advantage of the method.

6.2 Neural mechanisms of dopaminergic risk genes

The strongest evidence for the efficacy of the intermediate phenotype approach in psychosis arises from previous studies on *COMT*. Research from our laboratory has demonstrated that the Val^(108/158)Met coding variant in *COMT* impacts on prefrontal activation during working memory performance (Egan et al., 2001), modulates the performance in cognitive tests that challenge prefrontal lobe functions (Goldberg et al., 2003), and influences the cortical response to amphetamine (Mattay et al., 2003). In the latter challenge study, the acute increase in dopaminergic tone led to an improved prefrontal efficiency during working memory performance in subjects with the Val/Val genotype, but deterioration in subjects with the Met/Met genotype, who in turn had the superior baseline function (see figure 2). These data supported the results of previous animal studies suggesting an “inverted-U” functional response curve of dopamine signaling in the PFC (Williams and Goldman-Rakic, 1995). According to this model, the *COMT* genotype places individuals at predictable points along the inverted U-shaped curve that links the dopaminergic tone, neuronal activity, and functional efficacy of prefrontal neural networks. Homozygotes for the Val allele are thought to be positioned to the left of the Met allele carriers at a point of decreased PFC efficiency (COMT efficacy↓, dopamine↓), while the Met allele carriers are located near the peak at the presumed functional optimum of the curve (COMT efficacy↓, dopamine↑). These data illustrated the utility of neuroimaging techniques in pharmacogenomics and validated the concept of PFC inefficiency as key endomechanism of susceptibility to psychosis. The genetic risk associated with the *COMT* Val^(108/158)Met coding variant is thought to be mediated by a reduced signal-to-noise ratio in prefrontal networks that promotes the development of cognitive deficits and positive symptoms in Val-allele carriers. In line with the tuning concept, an own prior PET study (Meyer-Lindenberg et al., 2005) showed that task-unrelated and task-related activation of the prefrontal cortex is inversely related to neuroimaging markers of midbrain dopamine synthesis, which, in turn, is directionally dependent on the *COMT* Val^(108/158)Met genotype. In Val-allele carriers, higher midbrain dopamine synthesis was predicted by lower prefrontal cerebral blood flow, which indicates that the risk for psychosis is mediated by mechanisms of frontal-striatal dysfunction and subcortical dopamine disinhibition. Recent studies extended this view by providing evidence for a statistical epistasis of *COMT* with other schizophrenia susceptibility genes involved in the regulation of glutamatergic and GABAergic neurotransmission (i.e., *GRM3*, *GADI*). This suggests that the neural correlates of psychosis are shaped by the complex synergism of multiple risk gene variants (Straub et al., 2007, Tan et al., 2007).

Other intermediate phenotype studies from our laboratory focused on the neural mechanisms that relate risk for psychosis to genetic variation in *PPP1R1B*, *AKT1* and *PRODH*. Despite the considerable importance of DARPP-32 as an integrator of dopamine and glutamate signals in the striatum, data on *PPP1R1B* variation in humans have been rare. In a translational genetics approach, we investigated the relevance of DARPP-32 for aspects of human brain morphology and function (Meyer-Lindenberg et al., 2007). We identified a frequent *PPP1R1B* haplotype that predicts cognitive function and mRNA expression of *PPP1R1B* isoforms in postmortem human brains. Multimodal imaging revealed an impact of this haplotype on striatal volume, activation, and prefrontal-striatal interactions (see figure 3). Moreover, we provided evidence that the same variants may be associated with risk for schizophrenia. These convergent results indicate that genetic variation in *PPP1R1B* impacts on cognitive performance and the structural and functional integrity of fronto-striatal networks by modulating the expression of DARPP-32. Moreover, the data suggest that *PPP1R1B* might contribute to risk for psychosis

by causing disturbed gating as a result of an impaired striatal-frontal coupling (Swerdlow et al., 2001, Meyer-Lindenberg et al., 2007).

As pointed out before, the canonical cAMP/PKA pathway is not the only biochemical cascade that integrates neural signals in dopaminergic neurons. This opens up the possibility that multiple risk gene variants impact on the same neural circuitry by interacting with different molecular targets. In line with this assumption, a recent study by Tan and colleagues (2008) provided evidence that genetic variation in *AKT1* is associated with risk for psychosis and alterations of prefrontal-striatal structure and function. These effects are likely to result from disturbances in dopaminergic signaling related to the AKT1/GSK-3 signaling cascade (via β -arrestin 2). Moreover, significant genetic epistasis with the *COMT* Val^(108/158) Met genotype was evidenced, a finding that is consistent with the putative role of *AKT1* in dopamine signaling. The crucial importance of the frontal-striatal circuitry for the pathophysiology of psychosis is also highlighted by another recent study that demonstrated that risk and protective gene variants in *PRODH* are associated with dissociable effects on POX enzyme activity and striatal-frontal structure and function (Kempf et al., 2008). On the neural systems level, the identified risk haplotype predicted decreased striatal gray matter volume and increased striatal-frontal functional connectivity, while the protective haplotype was associated with the opposite structural and functional effects. This data provided evidence that genetic variations in *PRODH* contribute to risk for and protection from schizophrenia by modulating the enzymatic activity of POX and impacting on fronto-striatal neural processing.

7 Conclusions and future perspectives

It has been more than 50 years since the first pathomolecular theory of psychosis was formulated, but patients still continue to face a chronic and debilitating disease that significantly limits their capacity to function in society. Although major progress has been made with respect to the clinical management of symptoms, current treatment options are entirely symptomatic and usually involve recurrent hospitalizations. The resulting financial burden for the health care system is enormous, costing an estimated 65 billion dollars per year in the USA alone (Genduso and Haley, 1997). As a result, basic neuroscience research faces mounting pressure to focus available resources on the pathophysiological mechanisms that will likely lead to the improvement of current treatment options. In the past decade, the availability of modern research techniques has significantly extended our understanding of the pathomechanisms that promote the development of psychosis. In past decades, numerous functional, structural and molecular brain anomalies have been described which have stimulated a continuous refinement of the traditional dopamine hypothesis. Core pathophysiological findings include working memory deficits, functional and structural alterations of the striatal-frontal circuitry, and subcortical dopamine dysregulation. Similar results have been obtained in healthy subjects genetically at risk for schizophrenia, suggesting that these anomalies reflect valid intermediate phenotypes of the underlying disease vulnerability. The main goal of psychiatric research is to improve mental health by translating basic scientific discoveries into practical applications. In recent years, imaging genetics has proven to be a pivotal tool to characterize the neural mechanisms that translate genetic susceptibility into psychopathology. Future applications of this strategy in a multimodal research context will help to unravel the molecular mechanisms of psychosis and stimulate new antipsychotic drug developments by defining rational treatment targets. Specifically, approaches that combine multimodal neuroimaging and genetic mapping techniques may elucidate the neurobiological susceptibility mechanisms that translate unfavorable gene-environment interactions into risk for schizophrenia (e.g. serious obstetric complications and schizophrenia candidate genes regulated by hypoxia).

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Figure 1. Etiology of psychosis: complex interaction of genetic and environmental factors

Figure 2. Effects of COMT Val(108/158)Met polymorphism on prefrontal cortex activity

(a) An inverted u-shaped curve links extracellular dopamine to prefrontal signal-to-noise ratio (top) and working memory performance (bottom): homozygotes for the Val-encoding allele are positioned at the left (COMT efficacy $\uparrow$, dopamine $\downarrow$) while Met homozygotes are near the optimum of the curve (COMT efficacy $\downarrow$, dopamine $\uparrow$). Heterozygotes are intermediate. (b) Increasing synaptic dopamine by the administration of amphetamine dissociates the functional states of Val and Met homozygotes. At medium working memory load level (2-back task), Val homozygotes profit from increased dopamine, whereas Met homozygotes, near the optimum, show little change (left). At high load level (3-back task), dopamine increase by drug intervention pushes Met homozygotes into the suboptimally high range of dopamine

stimulation, leading to reduced prefrontal efficiency (right; localization of activity in the prefrontal cortex is shown on the far right). Reprinted with permission from (Meyer-Lindenberg and Weinberger, 2006).

Figure 3. Effects of genetic variation in *PPP1R1B* on brain morphology and function

Effects of genetic variation in *PPP1R1B* on human brain morphology and function. The top row shows haplotype effects on volume (A) or activation (C and E) in the striatum; the bottom row shows haplotype effects on structural (B) and functional (D and F) connectivity of the striatum to the prefrontal cortex. Voxel-based morphometry: (A) significantly reduced volume in the striatum ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype; (B) greater structural connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. fMRI, N-back task: (C) significantly reduced reactivity in putamen ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype; (D) greater functional connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. fMRI, Face-matching task: (E) significantly reduced reactivity in striatum ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype; (F) greater functional connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. Reprinted with permission from (Meyer-Lindenberg et al., 2007).