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PSYCHOPATHOLOGICAL ASPECTS OF DOPAMINERGIC GENE POLYMORPHISMS IN ADOLESCENCE AND YOUNG ADULTHOOD

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Abstract

Dopamine hypotheses of several psychiatric disorders are based upon the clinical benefits of drugs affecting dopamine transporter or receptors, and have prompted intensive candidate gene research within the dopaminergic system during the last two decades. The aim of this review is to survey the most important findings concerning dopaminergic gene polymorphisms in attention deficit hyperactivity disorder (ADHD), Tourette syndrome, obsessive compulsive disorder, and substance abuse. Also, genetic findings of related phenotypes, such as inattention, impulsivity, aggressive behavior, and novelty seeking personality trait are presented, because recent studies have applied quantitative trait measures using questionnaires, symptom scales, or other objective endophenotypes. Unfortunately, genetic variants with minor effects are problematic to detect in these complex inheritance disorders, often leading to contradictory results. The most consistent association findings relate to ADHD and the dopamine transporter and the dopamine D4 receptor genes. Meta-analyses also support the association between substance abuse and the D2 receptor gene. The dopamine catabolizing enzyme genes, such as monoamine oxidase A and catechol-*O*-methyltransferase genes, have been linked to aggressive behaviors.

Keywords

ADHD; COMT; DAT1; DRD2; DRD4; MAOA; OCD; polymorphism; substance abuse; Tourette syndrome

1. INTRODUCTION

Family, twin, and adoption studies indicate that a substantial inherited component exists in the background of many psychiatric disorders. Deciphering the specific genetic risk factors of a certain psychiatric disorder is expected to reveal the neurobiology of the disorder and the related atypical behaviors. Analyzing genetic and environmental risk factors and their interactions, which may lead to these complex inheritance disorders, is the aim of many

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psychiatric genetics studies. Despite intense research efforts during the last two decades, understanding the fundamental changes that result in psychopathologies is still a challenge for researchers (Burmeister et al., 2008). Using the dimensional approach seems to be more powerful than using disease categories, and this trend is apparent in the new diagnostic manuals, i.e., in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders 5th edition) and in the ICD-11 (International Classification of Disease 11th edition), that are currently under preparation (Andrews et al., 2009). Disorders can be regarded as extremes of a spectrum, and this view supports the growing importance of using quantitative trait analyses in clinical areas (Plomin et al., 2009). Identifying intermediate phenotypes, termed endophenotypes, is also helpful in the assessment of specific genetic factors in heterogeneous disorders (Almasy and Blangero, 2001).

Epidemiological studies have shown large genetic part in the pathogenesis of many childhood-onset psychiatric disorders. For example, in attention deficit hyperactivity disorder (ADHD), which is one of the most common childhood psychiatric disorders and can persist through adolescence and adulthood, the heritability estimates range from 60% to 90% (Faraone et al., 2005). The picture is complex, however, as the genetic background is polygenic, and genetic factors may interact with each other and with environmental factors. Multifactorial, polygenic inheritance has been proposed for most neuropsychiatric disorders, even for those that have a 90% or higher heritability estimate, such as autism or Tourette syndrome (TS), since no single gene with a major effect has been convincingly identified to date in these disorders (Pauls, 2001; Hapke et al., 2006). Until now, dopamine and serotonin neurotransmitter systems have been studied mainly in child and adolescent psychopathologies; however, novel theories point to the importance of neuroprotective factors, cell adhesion molecules, and components involved in synapse formation (Cichon et al., 2009). To focus our review, only the dopamine system findings will be discussed in detail, because the developmental changes of this neurotransmitter system seem to correspond to the onset of the presented psychiatric disorders. In the primate cortex, dopamine receptor densities peak in childhood and elevated dopaminergic activity is observed during adolescence (Wahlstrom et al., 2010). Dopaminergic pathways affect a range of cognitive and executive functions, such as working memory or behavioral flexibility linked to prefrontal cortex activity (Floresco and Magyar, 2006), as well as positive reinforcement and reward mechanism related to the limbic system (Sesack and Grace, 2010). Among other monoamine neurotransmitters, dopamine also has an important role in impulsive behaviors (Pattij and Vanderschuren, 2008). In this review, we present dopaminergic genetic findings of childhood-onset psychiatric disorders that persist during adolescence (e.g., ADHD, TS) and of psychiatric disorders which are diagnosed later in adolescence (e.g., obsessive compulsive disorder, substance abuse). Quantitative traits, like impulsivity, and objective endophenotypes, like sustained attention performance are also discussed.

2. DOPAMINERGIC CANDIDATE GENES

2.1. Candidate genes vs. whole genome search

Heritability, defining the proportion of the variance explained by genetic factors in certain phenotypes (traits or symptoms), is estimated by comparing the concordance rates of monozygotic and dizygotic twin pairs (Glatt et al., 2008). To identify the specific genes accounting for the heritability, two major methods are currently applied that supplement each other. Candidate gene analyses can reveal the actual genetic variants of the protein-coding genes that are implicated in the pathophysiology of the disorder (Glatt et al., 2008). Based on neurobiological theories, polymorphisms in the monoamine (dopamine, norepinephrine, and serotonin) receptor and transporter genes are the most widely studied candidate genes in psychiatric genetics. The alternative strategy aims to identify specific

chromosomal regions that are related to the disorder by analyzing the whole genome without an *a priori* hypothesis. Linkage studies analyze marker polymorphisms throughout the genome in extended pedigrees of patients to find chromosomal region(s) linked to the disorder. A major genetic effect is identified as a cosegregation of a marker variant (allele) and the disorder with a logarithm of odds (LOD) score of higher than 3 (Lander and Kruglyak, 1995). Whereas this strategy is highly powerful for monogenic diseases, it has proven less effective for complex inheritance disorders in which the individual genetic factors have small effects. Genome-wide association studies (GWAS) are a recent approach of whole genome searches. These studies aim to identify common genetic variants with a relative risk of 1.1 to 1.4 by studying thousands of patients and control subjects (Cichon et al., 2009). Because single studies using either approach cannot identify definite genetic risk alleles unambiguously, meta-analyses combine the samples to gain a higher power of analysis. Among childhood-onset disorders, ADHD and autism have been assessed by GWAS, resulting in numerous novel putative candidate genes (Franke et al., 2009; Weiss, 2009), and the first GWAS in obsessive compulsive disorder (OCD) and TS are presently underway (Grados, 2010). Although the first meta-analysis of ADHD GWAS has not been able to identify any significant genome-wide association (Neale et al., 2010), the conclusion is probably just as important: If common genetic variants account for the majority of the genetic component in the pathogenesis of a disorder, then their effect sizes must be very small. The alternative explanation would be that mostly rare genetic variants (different in every patient but might effect the same neurobiological pathway) account for the heritable component. A new concept for future genetic studies emphasizes the underlying traits in psychiatric disorders which can be expressed as variations in brain functioning. Certain gene variants influence the traits and not the disorder. The risk to develop a disorder comes from the combination of these traits (Hudziak and Faraone, 2010). Therefore, in this review, we mention not only the categorical, psychiatric disorder based association studies (third section), but also those genetic association studies which used quantitative traits (fourth section). Wherever possible, gene $\times$ gene interaction findings are indicated, to illustrate the complexity of the genetic background in more details.

Among the candidate gene analyses of childhood-onset psychiatric disorders, family-based studies are preferred over the simple case-control design, because these methods are devoid of population stratification problems (Schulze and McMahon, 2002), and biological parents are often easily accessible. For example, the Transmission Disequilibrium Test measures the transmission rates of two different alleles from heterozygous parents to the affected offspring; if a significant over-transmission of an allele is observed, that genetic variant can be linked to the disorder. Most of the family-based studies apply diagnostic categories, usually by the DSM-IV (American Psychiatric Association, 1994), which is used in the United States, and sometimes by the ICD-10 (World Health Organization, 1993), which is used in the clinical practice of European countries. At the early onset disorders (ADHD, TS, and OCD sections) we mention specifically whenever family-based association tests were used. At the other sections, the conducted studies follow either the case-control design (categorical approach, third section) or the dimensional approach (fourth section).

In this review, we focus on functional polymorphisms, where the different alleles have been shown to have altered molecular functions. Hitherto, mostly common genetic variants (minor allele frequency higher than 5%) have been studied in psychiatric genetics. To achieve a high frequency in a certain population, a genetic polymorphism needs to either be neutral or favorable in the actual environmental circumstances. Because the surrounding environment can change rapidly, favorable genetic variants might become unfavorable ones. An interesting example is the widely-investigated 7-repeat allele of the dopamine D4 receptor gene that was reported as a young genetic variation, which increased to high frequency in human populations by positive selection (Ding et al., 2002). However, this

allele is now implicated as a genetic risk factor for dopamine-related psychiatric disorders. This example underlines the importance of talking about gene variants influencing certain traits (e.g., impulsivity), and not genetic risk factors for psychiatric disorders (e.g., ADHD or substance abuse).

Another important issue worthwhile mentioning is that certain genetic constellations can make individuals more susceptible or more resilient to environmental factors. Mostly prenatal, postnatal, and childhood adverse effects of the physical and social environment have been implicated in gene $\times$ environment interactions leading to development of psychiatric disorders (Wermter et al., 2010). Although the majority of these interaction results have not been convincingly replicated, we mention them at the genetic finding sections, because this type of analyses will gain increasing significance in future genetic studies.

2.2. Dopamine systems and their involvement in psychopathology

Most of the dopaminergic neurons in the brain originate from the mesencephalon and project to other brain regions. These projections are organized into the following three main pathways: nigrostriatal (or, more correctly termed nowadays as mesostriatal, see Björklund and Dunnett, 2007), mesolimbic, and mesocortical pathways. The mesostriatal system projects mainly from the substantia nigra pars compacta to the dorsal striatum (i.e., the caudate nucleus and putamen) and is responsible for motor control; degeneration of this system is responsible for the motor defects in Parkinson's disease (Smith and Villalba, 2008). The mesolimbic system projects from the nucleus paranigralis of the ventral tegmental area (VTA) to the limbic structures, such as the amygdala and the ventral striatum (i.e., the nucleus accumbens and olfactory tubercle). The mesolimbic dopaminergic innervations have an important modulating role in motivated behaviors, which include behavioral activation, exertion of effort in reward-seeking behavior, and maintenance of motivated behavior over time; dysfunctions in this system can contribute to depression, schizophrenia, and drug abuse (Salamone et al., 2005). The mesocortical dopaminergic neurons originate from the nucleus parabrachialis pigmentosus in the VTA and project to the frontal and anterior cingulate cortex, affecting working memory (planning, monitoring, and organizing goal-directed actions based on short-term memory, especially in the face of distractions), cognitive flexibility (the ability to switch task rules), and attentional set shifting (Seamans and Yang, 2004; Robbins and Arnsten, 2009). Within the prefrontal cortex (PFC), there is an optimum concentration of dopamine to perform working memory tasks. This finding is illustrated by the inverted U-shaped response curve showing that an intermediate level of dopamine leads to optimal cognitive performance. This observation is based on animal and human studies demonstrating that excessive dopamine level (acting on D1 receptors) in the PFC leads to impairments in cognitive performance (Robbins and Arnsten, 2009). Dopaminergic axon terminals form inhibitory synapses on the dendritic spines of pyramidal cells in the PFC and exert a gating function on the information flow via the D1 receptors. A very high dopaminergic tone blocks excitatory inputs onto pyramidal cells, whereas too low of a dopaminergic tone facilitates interference between the different inputs. Both of these mechanisms lead to disruptions in cognitive performance. Cortical D2 and D4 receptor functioning has been indicated in cognitive flexibility, attentional set shifting, and decision-making processes (Floresco and Magyar, 2006; Robbins and Arnsten, 2009). In stressful situations, the increased cortical catecholamine (dopamine and norepinephrine) levels impair cognitive functions through network collapse and decreased PFC neuron activity (Arnsten, 2009).

Dopamine elimination is different in the PFC compared to other brain areas (Figure 1). Dopamine transporter (DAT) density is the highest in subcortical regions, such as the dorsal striatum, globus pallidus, substantia nigra, and subthalamic nucleus (collectively termed the

basal ganglia). In these brain regions DAT is localized at synaptic structures and removes dopamine rapidly from the extracellular space after its release (Figure 1A). In contrast, DAT density is comparatively low in human PFC (Sekine et al., 2001; Tupala et al., 2006), similarly to rat and monkey PFC (Sesack et al., 1998; Lewis et al., 2001). Animal studies also showed that DAT is located at a distance from synaptic sites in the PFC, increasing the probability of substantial extracellular diffusion and dopaminergic transmission at extrasynaptic sites (Sesack et al., 1998; Lewis et al., 2001). Dopamine can be taken up by the norepinephrine transporter in the PFC (Figure 1B), as indicated by animal studies conducted on dopamine and norepinephrine transporter knockout mice (Moron et al., 2002) or by pharmacological evidence with selective norepinephrine transporter blocker atomoxetine (Bymaster et al., 2002). In addition, experiments conducted on catechol-*O*-methyltransferase (COMT) knockout mice show that this metabolizing enzyme has a major role in dopamine clearance in the PFC (Käenmäki et al., 2010). COMT has a relatively high expression in the human PFC (Matsumoto et al., 2003), although on the protein level it is not well documented (Robinson et al., 1977). However, the observed effects of COMT inhibitor tolcapone on working memory tasks related to PFC function in normal human subjects (Apud et al., 2007; Giakoumaki et al., 2008) supports the importance of COMT in humans as well. It is also important to emphasize the gradually increasing dopaminergic innervation of the PFC during primate development (Wahlstrom et al., 2010), which can be likewise observed in the developmental increase of cortical COMT enzyme activity in humans (Tunbridge et al., 2007).

2.3. Functional polymorphisms of dopaminergic genes

The two types of the most frequently studied genetic polymorphisms in candidate gene analyses are the variable number of tandem repeats (VNTR) and the single nucleotide polymorphism (SNP). Figure 2 presents schematically the functional polymorphisms discussed in this review.

2.3.1. Dopamine receptor genes—Dopamine receptors belong to the seven-transmembrane receptor family that couple to G proteins. The two main types of dopamine receptors have opposite functions in signal transduction; activation of D1-like receptors (D1 and D5) activates adenylate cyclase, whereas activation of D2-like receptors (D2, D3, and D4) inhibits adenylate cyclase. In addition to the cAMP dependent signal transduction pathway, other mechanisms such as modulation of the intracellular calcium level by inositol 1,4,5-trisphosphate or activation of potassium channels are also involved in the activation or hyperpolarization of the postsynaptic neuron (Romanelli et al., 2010). The presynaptic localization of D2 and D3 receptors suggests that they are also important in controlling dopamine release. The D1 and D2 receptors are the most widely expressed dopamine receptors throughout the brain, whereas the D3, D4, and D5 receptor expression is limited to specific brain regions (Missale et al., 1998). The chromosomal localizations of the five dopamine receptor genes and their polymorphisms are summarized in Figure 2A.

Dopamine D1 receptor gene (DRD1): The D1-receptor family genes do not contain introns; therefore, they are less variable than the D2-receptor family genes (Missale et al., 1998). The DRD1 gene does not have many common variants within the coding region, and association studies have used SNPs from the 5' and the 3' non-coding regions (e.g., the rs4532 C/T (also called -48 G/A) and the rs686 A/G SNP, respectively). Recent studies have reported that the rs686 A/G SNP influences miRNA binding and modulates translation in an *in vitro* reporter gene model (Huang et al., 2008; Huang and Li, 2009). Haplotypes of the rs686 and rs4532, and further three SNPs (rs265973, rs265975, rs2168631) from the non-coding regions near to the DRD1 gene were studied in alcohol and nicotine dependence, respectively (Batel et al., 2008; Huang et al., 2008).

Dopamine D2 receptor gene (DRD2): The D2-receptor family genes contain introns that can give rise to alternative splicing and other protein sequence variations in these receptors. For example, DRD2 has two alternative splicing forms (short and long), which differ in 29 amino acid sequence in the third cytoplasmic loop of the protein and show slight differences in signal transduction efficiency (Fraeyman and Vermis, 2003). Based on different subcellular localization of the two DRD2 splice forms at specific neurons in the monkey brain (Khan et al., 1998), as well as on DRD2-long knockout mice experiments (Usiello et al., 2000), the DRD2 short form is proposed to act as autoreceptor, whereas the DRD2 long form acts primarily as postsynaptic receptor. Interestingly, intronic SNPs (rs2283265 in intron 5 and rs1076560 in intron 6, which are in strong linkage disequilibrium) have been shown to affect the expression of the DRD2 short splice variant relative to DRD2 long one: The minor T alleles of these SNPs favor inclusion of exon 6 (the grey box on the DRD2 gene picture at Figure 2A), resulting in a significant reduction of the DRD2 short splice form, compared to the G alleles (Zhang et al., 2007). Other known functional polymorphisms of the DRD2 gene involve rare SNPs in the coding region, like Pro310Ser and Ser311Cys (Cravchik et al., 1996), but synonymous SNPs and non-coding polymorphisms are used more often in association studies.

Several restriction fragment length polymorphisms (RFLPs) located in non-coding regions of the DRD2 gene have been used as markers, such as TaqIA and TaqIB, which were genotyped with the TaqI enzyme. Because DRD2-specific ligands allow for *in vivo* DRD2 analyses, the gene expression effect of these SNPs can be demonstrated in neuroimaging studies. The most widely studied TaqIA SNP (rs1800497) was identified during the chromosomal localization of the gene. Recently, it became clear that this SNP, which is 10 kb downstream from the DRD2 gene, is located in the neighboring ANKK1 gene where it causes an amino acid substitution (Glu713Lys) (Neville et al., 2004). Nevertheless, independent studies have reported reduced D2 receptor density in the minor A1-allele carriers in SPECT (single photon emission computed tomography) or PET (positron emission tomography) studies. Four studies showed significant differences, and one study showed a trend towards a reduction of striatal DRD2 binding in A1-allele carriers compared to subjects with the A2/A2 genotype (reviewed by Noble, 2003). Therefore, it seems that the DRD2/ANKK1 TaqIA SNP is either in linkage with another functional DRD2 SNP or that it is indirectly involved in DRD2 gene expression. Data exist supporting both possibilities.

On the one hand, the TaqIA SNP is in linkage with the TaqIB SNP (rs1079597) and the C957T SNP (rs6277, Pro319Pro) within the DRD2 gene, and these SNPs have also been associated with altered striatal DRD2 density: The minor B1-allele (in linkage with the A1-allele) has been repeatedly shown to be associated with a low DRD2 density (Jonsson et al., 1999; Ritchie and Noble, 2003). As for the C957T SNP, a detailed PET study showed that the increased binding potential of the 957 T-allele was more pronounced than the slightly increased DRD2 density, making the striatal DRD2 availability of the T-allele higher compared to the C-allele (T/T>C/T>C/C for the 3 genotype groups) (Hirvonen et al., 2009a). The authors also reported that the 957 C-allele carriers had a significantly higher A1-allele frequency, which is in accordance with the notion that A1-allele carriers have lower striatal DRD2 availability. Haplotype analyses also showed that subjects with the A2/A2 and 957 T/T genotypes had the highest DRD2 availability, whereas A1-allele and 957 C-allele carriers had the lowest DRD2 availability, subjects with the A2/A2 and 957 C/C or C/T genotypes had intermediate levels (Hirvonen et al., 2009a). It is important to mention that a recent PET study reported opposite effects for the TaqIA and C957T SNPs in extrastriatal DRD2 availability (Hirvonen et al., 2009b). In this PET study, the 957 T-allele was associated with lower DRD2 availability in a step-wise fashion (T/T<C/T<C/C) throughout the cortex, thalamus, amygdala and hippocampus. The A1-allele carriers had similar, but only marginally, higher extrastriatal DRD2 availability when compared to the A2/A2 group. This

finding illustrates the importance of variations in brain region-specific dopamine transmission. Interestingly, the TaqIA SNP is also in linkage with the intronic SNPs, which were shown to affect the DRD2-short isoform expression (Zhang et al., 2007).

On the other hand, the TaqIA SNP shows strong linkage disequilibrium with several non-synonymous SNPs of the ANKK1 gene. An *in vitro* study demonstrated that a neighboring ANKK1 SNP (rs273849, Arg490His) altered NF- κ B function, which in turn may affect DRD2 expression (Huang et al., 2009). Therefore, ANKK1 SNPs might indirectly influence DRD2 function. Interestingly, the ANKK1 protein has been recently detected in human astrocytes and in mouse radial glial cells. The peak mRNA expression of ANKK1 corresponded to that of DRD2 in mouse embryonic brain samples, suggesting that the interaction of ANKK1 and DRD2 may be relevant in brain development (Hoenicka et al., 2010). This workgroup also showed that a non-synonymous ANKK1 polymorphism (rs7118900, Ala239Thr), which is in strong linkage disequilibrium with TaqIA, had an impact on the ANKK1 protein level (Garrido et al., 2010).

In addition to the previously mentioned SNPs, the DRD2 promoter -141C Ins/Del polymorphism has been also frequently studied; however, the functional role of this polymorphism is less clear. The results of an *in vitro* reporter gene experiment showed a lower expression for the -141C Del-allele compared to the -141C Ins-allele (Arinami et al., 1997), whereas *in vivo* studies could not detect any significant differences in striatal or extrastriatal DRD2 availability (Ritchie and Noble, 2003; Hirvonen et al., 2009b). In contrast to these results, a higher striatal dopamine receptor density was shown for the Del-allele in a SPECT study (Jonsson et al., 1999).

Genetic association studies variably used the above mentioned DRD2 polymorphisms with other, mostly non-coding variants from the 11q chromosomal region (containing not only the DRD2 gene but the ANKK1 and other neighboring genes as well). The SNP combinations used in haplotype analyses conducted by different workgroups are also diverse (Xu et al., 2004; Yang et al., 2007; Huang et al., 2009; Kraschewski et al., 2009).

Dopamine D3 receptor gene (DRD3): Among the DRD3 polymorphisms, convincing functional data exist only for the Ser9Gly SNP (rs6280) that is located in the N-terminal extracellular domain of the receptor. The Gly-variant showed gain-of-function properties in three *in vitro* studies. This variant had a higher affinity for dopamine (Lundstrom and Turpin, 1996) and increased dopamine-mediated signal transduction (Jeanneteau et al., 2006). Interestingly, this variant also caused a shift in the signaling pathways from cAMP level reduction to prostaglandin E2 level reduction (Hellstrand et al., 2004). This polymorphism is sometimes referred to as Ball or MscI, corresponding to the RFLP technique applied for genotyping.

Dopamine D4 receptor gene (DRD4): The DRD4 gene, which is predominantly expressed in the PFC, has been studied very frequently in the field of psychiatric genetics. This gene contains a 48 bp VNTR in the third exon (repeat numbers ranging from 2 to 10, with the 4-repeat as the ancestral allele), expressed as a 16 amino acid repeat in the third cytoplasmic loop of the protein. This protein region is thought to alter the coupling of the receptor to the G_i protein. The first molecular biological study found that the 7-repeat allele exhibited a reduced inhibition of the forskolin-activated cAMP stimulation compared to the 4-repeat allele (Asghari et al., 1995). However, the molecular characteristics of the various lengths of the cytoplasmic loop are still not clear, because subsequent studies did not find a proportional difference in the G protein coupling that was related to the number of repeats (reviewed by Oak et al., 2000). Recent studies by the same group suggested a possible role of the DRD4 VNTR in gene expression and demonstrated that the 7-repeat allele resulted in

reduced RNA stability *in vitro* (Schoots and Van Tol, 2003). In the association analyses, subjects are grouped according to the presence of the 7-repeat allele or the long allele (with a repeat of more than 4 or 5).

Another tandem repeat polymorphism is located in the 5' promoter region that is 1.2 kb upstream of the transcription start site of the DRD4 gene. An *in vitro* analysis of this 120 bp duplication showed that the duplicated form had a lower level of transcriptional activity compared to the single-copy form (D'Souza et al., 2004). The promoter SNPs that are located in the 5' non-coding region might also influence DRD4 gene expression. For example, the -521 C/T (rs1800955) SNP was shown to influence promoter activity *in vitro*; the T-allele had reduced activity relative to the C-allele in a reporter gene analysis (Okuyama et al., 1999). Our results supported that the 120 bp duplicated form had a lower level of transcriptional activity (Kereszturi et al., 2007), but we did not find any difference between the -521 C- and T-alleles in their *in vitro* promoter activity (Kereszturi et al., 2006). Haplotypes of the DRD4 polymorphisms probably better capture the dopaminergic genetic effect, as it has been shown in ADHD studies (Barr et al., 2001; Mill et al., 2003; Lowe et al., 2004; Kereszturi et al., 2007).

It is important to note that norepinephrine has a high affinity for the D4 receptor (Lanau et al., 1997; Newman-Tancredi et al., 1997); therefore, it should be considered as a catecholamine (dopamine and norepinephrine) receptor.

Dopamine D5 receptor gene (DRD5): Although several amino acid substitutions with different agonist binding capacities have been described for the DRD5 (Cravchik and Gejman, 1999, also see Figure 2A), investigations of the coding-region SNPs have been hindered by two pseudogenes (Housley et al., 2009). Therefore, a marker dinucleotide repeat polymorphism located 18.5 kb from the 5' end has been studied most often in relation to psychiatric disorders. This polymorphism was identified at the time the gene was cloned (Sherrington et al., 1993), and the 12 alleles were named based on their length, which ranged from 134 to 156 bp, with the most common allele being 148 bp. To our knowledge, no functional study on this polymorphism has been published yet.

2.3.2. Dopamine synthesis: the tyrosine hydroxylase gene—The rate-limiting step of dopamine biosynthesis is the conversion of tyrosine into dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (TH), which is then turned into dopamine by aromatic amino acid decarboxylase (Figure 1). A 4 bp repeat sequence (TCAT tetranucleotide repeat) in the first intron has been thoroughly investigated by Meloni's laboratory. Their latest *in vitro* study showed a quantitative silencing effect of the TCAT-repeat on TH gene expression, with the 3-, 5-, 8-, and 10-repeat alleles exhibiting a step-wise inhibition on transcriptional activity (Albanese et al., 2001). Association studies refer to these intronic microsatellite alleles as K1–K5, numbering them in a decreasing order, i.e., from K1 = 10-repeat to K5 = 6-repeat (other alleles are rare). Dopamine is converted to norepinephrine by dopamine beta hydroxylase (DBH) in the synaptic vesicles of noradrenergic neurons; therefore, polymorphisms of the DBH gene belong to the noradrenergic system. Interestingly, the DBH enzyme can be measured in the plasma, which allows for *in vivo* measurements of its genetic variants (reviewed by Gizer et al., 2009).

2.3.3. Dopamine clearance: the dopamine and norepinephrine transporter genes—Dopamine neurotransmission is efficiently terminated via dopamine transporter (DAT) in subcortical regions by taking back dopamine from the synapse to the presynaptic neuron (Figure 1A). DAT is the site of action of stimulant drugs such as cocaine, amphetamine, and methylphenidate, which is used in ADHD treatment. Coding region variants of the DAT gene (DAT1, official symbol SLC6A3) are rare; therefore, VNTRs and

SNPs of the non-coding regions have been studied in association studies. There is a common 40 bp VNTR in the 3' untranslated region (UTR) with repeat numbers between 3 and 13. The most frequent allele has 10 repeats, followed by the 9-repeat allele; the others are rare variants. The results of comparative studies of the most frequent variants are controversial using either reporter gene assays (Fuke et al., 2001; Miller and Madras, 2002; Mill et al., 2005a) or post-mortem brain expression data (Mill et al., 2002a; Wonodi et al., 2009). SPECT analyses appear to have more congruent results: Two independent studies have reported a similar difference in striatal transporter density when studying large (N = 96 and N = 79), healthy populations. Participants with at least one copy of the 9-repeat allele (9/9 and 9/10 genotype) had a significantly higher transporter density compared to the 10/10 genotype group (van Dyck et al., 2005; van de Giessen et al., 2009). Studying a 30 bp VNTR in intron 8 (the most frequent alleles were originally named as 2-repeat and 3-repeat, but recent association studies refer to them as 5-repeat and 6-repeat), Guindalini et al. (2006) showed that the 3-repeat allele had a reduced basal expression compared to the 2-repeat allele, however, this allele had a 3-fold higher induction compared to the 2-repeat allele in response to a KCl and forskolin challenge. The higher level of transcriptional activity of the 3-repeat allele was also demonstrated in post-mortem midbrain tissues (Brookes et al., 2007). Constructing haplotypes from the two DAT1 VNTRs are preferred in recent ADHD studies (Asherson et al., 2007; Rommelse et al., 2008; Stevens et al., 2009; Franke et al., 2010).

As mentioned in the previous section, cortical DAT availability is very low compared to that of the striatum, however, dopamine can be taken up by the norepinephrine transporter (NET) in the cortex, resulting in a different dopamine elimination in this brain region (Figure 1B). Similarly to the DAT1 gene, the NET gene (official symbol SLC6A2) does not contain many common non-synonymous polymorphisms, therefore, synonymous SNPs from exons (e.g., rs5569, also called as G1287A from exon 9) and intronic SNPs (e.g., rs2242447 from intron 13) have been selected to cover the whole gene in comprehensive association studies. Unfortunately, the different workgroups did not select the same sets of SNPs, making the comparison of single marker and haplotype analyses hard (Gizer et al., 2009). The only SNP indicated to have functional relevance is located 3081 bp upstream from the transcription start site (−3081 A/T, rs28386840). The −3081 T-allele showed decreased promoter activity compared to the A-allele (Kim et al., 2006).

2.3.4. Dopamine inactivation: the monoamine oxidase and the catechol-O-methyltransferase genes—The monoamine oxidase (MAO) together with the aldehyde dehydrogenase and the COMT enzymes convert dopamine into homovanillic acid (HVA) in two consecutive steps (see Figure 1 legend). MAO is localized in the outer mitochondrial membrane in monoaminergic neurons and glial cells (Shih, 2004), while COMT is localized mainly in the rough endoplasmic reticulum in postsynaptic neurons and glial cells (Männistö and Kaakkola, 1999).

There are two MAO isoforms (MAOA and MAOB) that are encoded by different genes in the central nervous system, and both of these isoforms can degrade dopamine. The specificity of these enzymes is based on differential expression. MAOA is predominantly found in catecholaminergic neurons, whereas MAOB is more abundant in serotonergic and histaminergic neurons and glial cells. Data from studies using knockout mice suggest that MAOA is also important for serotonin breakdown. Increased levels of norepinephrine and dopamine were accompanied by increased serotonin level in MAOA knockout mice compared to wild-type mice, whereas MAOB knockout mice showed only increased phenylethylamine level compared to wild-type mice (reviewed by Shih, 2004). The MAOA and MAOB genes are closely aligned on the X chromosome; therefore, males have only one copy of these genes. For the association studies using females, it is important to note that the

MAOA gene likely has a monoallelic expression (Hendriks et al., 1992; Nordquist and Orelund, 2006; Stabellini et al., 2009), although data arguing for an escape from inactivation have been also published (Carrel and Willard, 2005; Pinsonneault et al., 2006).

A 30 bp VNTR in the 5' UTR of the MAOA gene, located 1.2 kb upstream from exon 1 (therefore called upstream VNTR or uVNTR), has been widely studied and has been repeatedly shown to affect gene expression. The most common alleles contain 3 or 4 repeats, and the less frequent variants are the 2-, 3.5-, and 5-repeat alleles. The 3-repeat allele had a lower transcriptional activity compared to the 3.5- and 4-repeat alleles in the *in vitro* experiments (Sabol et al., 1998; Deckert et al., 1999) and in fibroblasts (Denney et al., 1999). In post-mortem brain samples, a tendency towards the same difference between the 3- and 4-repeat alleles was observed in the level of enzyme activity (Balciuniene et al., 2002). Since there is a controversy about the activity of the 5-repeat allele (Sabol et al., 1998; Deckert et al., 1999), it is advisable to leave out the rare variants from the analyses, however, most genetic association studies refer to the 3.5- and 4-repeat alleles as “high activity”, whereas the 2-, 3-, and 5-repeat alleles are grouped together as “low activity” according to the first *in vitro* study (Sabol et al., 1998).

The availability of the COMT enzyme in cortical areas makes its gene a first-choice candidate gene for neuropsychological studies. COMT also has two isoforms, but these are coded from the same gene by two alternative promoters. The longer, membrane-bound enzyme differs from the shorter, soluble form by 50 additional amino acids forming a hydrophobic, membrane-spanning region. In addition, a human post-mortem study identified two variants of the membrane-bound COMT which probably differ in post-translational modifications (Tunbridge et al., 2006b). The membrane-bound form is expressed predominantly in the brain (Tenhunen et al., 1994; Tunbridge et al., 2007). A human specific G/A SNP (rs4680) in the 158th codon of the membrane-bound form causes a valine-methionine substitution (Val158Met), whereas in the soluble COMT form, the same polymorphism is located in the 108th codon. The Met-form (A-allele) has a lower stability at 37°C resulting in a 20–25% reduction in enzyme activity compared to the Val-variant that is coded by the G-allele (Lotta et al., 1995; Lachman et al., 1996; Chen et al., 2004). Significantly lower protein level and 30–40% lower enzyme activity was measured in postmortem PFC tissues and lymphocytes in Met/Met homozygotes compared to Val/Val homozygotes, whereas heterozygotes had intermediate level of activity (Chen et al., 2004). Significant difference in protein levels (but not in enzyme activity) was confirmed between the Val/Val and Val/Met genotypes (Tunbridge et al., 2007). Since COMT is one of the major determinants of dopamine action in the PFC (Käenmäki et al., 2010), the Val158Met polymorphism might cause significant differences in the cortical dopamine level. Based on the above data, Met/Met homozygotes likely have the highest dopamine levels in the PFC compared to the Val/Met and Val/Val genotypes, and this level seems to be the optimal level for cognitive functions under normal conditions (Tunbridge et al., 2006a). One workgroup showed that the Met-form was associated with better performance of PFC functions (Egan et al., 2001), and after amphetamine treatment, which elevated the dopamine level, cognitive functioning in the Met/Met homozygotes decreased (possibly as a result of too high dopamine level in the PFC), whereas this treatment was beneficial for the Val/Val homozygotes in the same experiment (Mattay et al., 2003). Taking into account the elevated dopamine concentration in stressful situations (Arnsten, 2009) and the association of COMT Val158Met genotypes with PFC-mediated cognitive functions (reviewed by Dickinson and Elvevag, 2009), it is probable that the effect of COMT genotypes on cognitive functions depends on various factors influencing the actual dopamine level in the PFC. In certain circumstances, it is the Val-form which is associated with better cognitive flexibility (Bilder et al., 2004).

Recently, other non-coding and synonymous SNPs of the COMT genes are advised to be investigated in addition to the Val158Met (rs4680), because an *in vitro* study indicated reduced protein translation efficiency due to secondary mRNA structure (Nackley et al., 2006). The rs6269A-rs4633C-rs4818C-rs4680G(Val) haplotype showed significantly reduced COMT protein level and enzyme activity compared to the rs6269G-rs4633C-rs4818G-rs4680G(Val). The third most frequent haplotype rs6269A-rs4633T-rs4818C-rs4680A(Met) had normal protein level but reduced enzyme activity (probably due to the cMet-allele), and hence referred to as intermediate-activity haplotype.

2.4. Neurobiological hypotheses

The inability to suppress inappropriate behaviors or thoughts is the common core deficit in ADHD, TS, and OCD, which are often present as comorbid conditions. Impulsivity in ADHD, involuntary movements and vocalizations in TS, and obsessions or compulsions in OCD might reflect a common immature inhibitory control of the basal ganglia thalamo-cortical circuits, as proposed by Casey et al. (2001). Several parallel frontal-subcortical circuits have been described, which originate from different frontal cortical areas and control different sets of behaviors (Tekin and Cummings, 2002). The motor circuit originates from the premotor cortex, supplementary motor areas, and primary motor cortex, whereas the oculomotor circuit starts from the supplementary eye fields and frontal eye fields, these circuits subserve voluntary skeletal and eye movement control. The dorsolateral prefrontal circuit and the lateral orbitofrontal circuit (originating from the dorsolateral and inferior lateral PFC, respectively) are involved in executive functions, such as action planning and decision-making. While the medial orbitofrontal circuit and the anterior cingulate circuit (collectively termed as the limbic circuit, because they project to limbic structures, such as the nucleus accumbens) regulate actions influenced by emotions. The basal ganglia thalamo-cortical circuits project back to their respective areas of origin in the frontal cortex, forming closed loops (Figure 3). The anatomical definition of the basal ganglia can be strict, meaning only the striatum (i.e., the caudate nucleus and putamen together) and the globus pallidus. In the present paper, we use the functionally related basal ganglia system definition that also incorporates the substantia nigra and the subthalamic nucleus (Bentivoglio and Morelli, 2005). The basal ganglia circuits are composed of a direct (excitatory) pathway facilitating cortically mediated behaviors and an indirect (inhibitory) pathway inhibiting conflicting behaviors (Figure 3). Recently a hyperdirect pathway, which bypasses the striatum by connecting the motor cortex to the subthalamic nucleus, is also included in the model (Nambu et al., 2002). In the proposed model, the frontal cortical areas plan the actions, then – through the sequential information processing of the three pathways in the basal ganglia – the competing actions are inhibited and the desired motor program is selected. Afterwards, the relevant information is relayed to the primary motor cortex, from where the commands for the actual movements go to the brainstem or spinal motor neurons. A hypofunctioning direct pathway may result in interrupted behaviors (problems with sustaining attention and impulsive actions) that are characteristic of ADHD, whereas a disruption of the indirect pathway may cause irrepressible repetitive behaviors and thoughts, such as those observed in association with TS and OCD. Alternatively, a hyperactive direct pathway may lead to repetitive behaviors and thoughts, and an overactive indirect pathway may cause interrupted behaviors. The results of neuroimaging studies have illustrated the involvement of the motor, orbitofrontal, and limbic circuits in ADHD, of the motor and limbic circuits in TS, and of the dorsolateral prefrontal and limbic circuits in OCD (Sheppard et al., 1999). More recent review papers that summarize brain imaging studies have indicated a reduction in the right cerebral volume, the right caudate nucleus, and the cerebellum in ADHD (Valera et al., 2007), whereas only a reduced volume of the caudate nucleus has been convincingly shown for TS (Albin and Mink, 2006).

The dopaminergic innervations of the mesocortical, mesolimbic, and mesostriatal systems modulate cognitive functions (information processing and planning), reinforced behaviors, and locomotion. Animal studies showed that dopamine neurotransmission is heightened in the adolescent period, because the number of cortical and striatal dopaminergic innervations increase during development until adolescence (Wahlstrom et al., 2010). Dopamine receptor levels reach their peaks in adolescence and then decrease over time in the synaptic pruning process (reviewed by Ernst et al., 2009). The prolonged maturation of the dopaminergic systems in ADHD, TS, or OCD children (which occurs more frequently in boys than in girls) can explain the decrease in the number and frequency of symptoms after adolescence.

3. DOPAMINERGIC GENETIC FINDINGS OF DIAGNOSTIC CATEGORIES

3.1. Attention deficit hyperactivity disorder

ADHD is one of the most prevalent childhood-onset psychiatric disorders, affecting 5.3% of children and adolescents worldwide (Polanczyk et al., 2007). The rising rates of ADHD diagnosis and the accompanying rise of stimulant drug use have led to a public debate over the validity of the diagnosis. This problem is now being addressed by a multidisciplinary approach involving natural scientists, clinicians, social scientists, and ethicists (Singh, 2008). It is important to mention that the prevalence rate of ADHD is highly affected by methodological variables (i.e., diagnostic criteria, definition of impairment, source of information) and moderately affected by the geographic location (lower prevalence rate is reported in Africa and the Middle-East compared to North America or Europe, but no significant differences were found in prevalence rates between North America, Europe, South America, Asia, or Oceania) (Polanczyk et al., 2007). The prevalence of ADHD decreases with age, but this disorder still affects approximately 3% of adults, with male predominance in every age range (Faraone, 2004). The characteristic inattention and impulsivity/hyperactivity problems can be present together or separately in the diagnostic subtypes of the DSM-IV (combined, inattentive, and impulsive/hyperactive subtypes, American Psychiatric Association, 1994), symptoms are also listed in the review by Castellanos and Tannock (2002). In the ICD-10 Classification of Mental and Behavioural Disorders, the diagnosis of hyperkinetic disorder is divided to subtypes based on the presence or absence of conduct disorder (CD), listing the disturbance of activity and attention and hyperkinetic conduct disorder separately (World Health Organization, 1993). There are many other frequent comorbid conditions beside CD in ADHD children, such as oppositional defiant disorder (ODD), learning disorders, mood disorders, and anxiety disorders (Biederman, 2005). In adults with ADHD antisocial personality disorder (APD) and substance abuse have also high prevalence besides mood and anxiety disorders (Biederman, 2005). However complex and heterogeneous this disorder might seem, ADHD is still among the best validated diagnoses in child psychiatry. The 76% heritability estimate (Faraone et al., 2005) prompted researchers to reveal the underlying specific genetic factors of this disorder.

The dopamine hypothesis of ADHD is based on data from pharmacological and neuroimaging studies, and from animal models (Madras et al., 2005). The most frequently used drug in ADHD pharmacotherapy is methylphenidate, which blocks DAT and NET, and increases the level of extracellular dopamine. In an elegant SPECT study, Krause et al. (2000) showed that four weeks of methylphenidate treatment reduced the striatal DAT density in adult ADHD patients to the level of the control subjects. DAT1 knockout mice have been shown to exhibit hyperactivity, possibly through a hyperdopaminergic state (Gainetdinov et al., 1999). A more recent animal study showed that a targeted overexpression of DAT in the nucleus accumbens did not result in a change of motor activity but increased impulsivity and risk-taking behaviors in delayed reward experiments (Adriani et al., 2009). As a result, the most widely studied gene in ADHD is DAT1. A meta-

analysis of the DAT1 3' UTR VNTR from 2005 revealed a small but significant effect for the 10-repeat allele (OR of family-based studies = 1.13, 95% CI 1.03 – 1.24) (Faraone et al., 2005). The latest meta-analysis of case-control and family-based studies – taking into account the genetic heterogeneity as well – showed similar effect (OR = 1.12, 95% CI 1.00 – 1.27) (Gizer et al., 2009). Two additional DAT1 polymorphisms have been reported to have modest effects in ADHD: The 3- (or 6-) repeat allele of the intron 8 VNTR and the G-allele of rs27072 were indicated as ADHD risk alleles (Gizer et al., 2009). In addition, the 10-3(6) haplotype created from the two VNTRs was shown to be overtransmitted to combined type ADHD children in a family-based study of the International Multicenter ADHD Gene (IMAGE) project (Asherson et al., 2007). In terms of genes coding for synthesizing and catabolizing enzymes (TH, MAOA, COMT) or for the NET, no significant effect has been reported in the pooled analyses (Faraone et al., 2005; Gizer et al., 2009).

For the dopamine receptor genes, a meta-analysis revealed significant associations between the 7-repeat allele of the DRD4 exon 3 VNTR (OR = 1.33, 95% CI 1.15 – 1.54), the DRD4 –521 (rs1800955) T-allele (OR = 1.21, 95% CI 1.04 – 1.41), and the DRD5 148-bp allele (OR = 1.23, 95% CI 1.06 – 1.43) (Gizer et al., 2009). Taking into account the studies in Asian populations, the DRD5 148-bp allele and the DRD4 7-repeat allele were confirmed as risk factors; in addition, the DRD4 5-repeat allele also conferred increased risk in this meta-analysis (Li et al., 2006). Using haplotype analyses of the DRD4 polymorphisms resulted in mixed outcomes, with only the rs747302 C-allele being common in the indicated risk haplotypes (Barr et al., 2001; Mill et al., 2003; Lowe et al., 2004; Kereszturi et al., 2007). Gene × gene interaction findings showing the involvement of the DRD4 7-repeat allele and DAT1 10/10 genotype in ADHD have been reported in South-American populations with small sample sizes (Roman et al., 2001; Carrasco et al., 2006). Larger scale ADHD studies concentrated on gene × environment analyses. The accumulated studies assessing the DRD4 and DAT1 VNTRs in ADHD have not replicated convincingly the original interaction of the DRD4 7-repeat allele with season of birth (Thapar et al., 2007), and the interactions of the DAT1 10/10 genotype with maternal smoking or alcohol consumption during pregnancy (Wermter et al., 2010).

Increasing number of quantitative trait analyses have been reported using inattention or hyperactivity severity scales. In population-based cohorts, the DRD4 7-repeat allele was related to higher ADHD scores when the low-scoring and high-scoring groups were compared (Curran et al., 2001); however, in the Dunedin-study sample (a large, unselected birth cohort), this finding was not supported (Mill et al., 2002b). Later studies of ADHD children linked the DRD4 5' UTR to inattention symptoms (Lasky-Su et al., 2008), whereas the DAT1 10-repeat allele was shown to be related to hyperactivity (Mill et al., 2005b). These results are in accordance with the predominant prefrontal localization of DRD4 (attention) and the key role of DAT in the basal ganglia (locomotion). In terms of gene × environment interaction findings, the association of increased hyperactive-impulsive symptoms with DAT1 10-repeat allele and with exposure to prenatal smoking has not been supported by the most recent studies (Thapar et al., 2007). However, in the English and Romanian Adoptees longitudinal study, the DAT1 high risk haplotype (10/10 and 3/3 genotypes together) and severe institutional deprivation were associated with increased ADHD scores, and a gene × environment interaction was also detected. Among those who experienced extended periods (more than 6 months) of psychosocial and nutritional deprivation in Romanian orphanages, children with the DAT1 high risk haplotype had significantly higher ADHD scores in adolescence compared to those with low genetic or environmental risk (Stevens et al., 2009). Also, COMT genotype was shown to interact with low socioeconomic status in a general population-based study of pre-adolescents: children with the Val/Val genotype showed higher ADHD scores compared to other genotype groups in the low socioeconomic status families (Nobile et al., 2010).

Another useful tool in genetic research is to investigate disorder subtypes. Persistent ADHD has been recently proposed as a specific subgroup because adult ADHD seems to have a higher rate of familiarity (Faraone, 2004). Investigating the genetic risk factors over the course of ADHD showed that by age 25, a larger number of the DRD4 7-repeat allele carriers (7+) had persistent ADHD compared to the 7-repeat absent group (7-) (76% vs. 66%, Biederman et al., 2009). The authors did not observe any genetic effect for the DAT1 3' UTR VNTR. However, a large-scale collaborative European study showed that the DAT1 9/9 genotype of the 3' UTR VNTR and the 9-3(6) haplotype of the two VNTRs were associated with persistent ADHD (Franke et al., 2010). This finding might provide explanation for increased DAT density observed in adult ADHD (Krause et al., 2000) because both the 9- and the 3-repeat alleles have been associated with higher levels of DAT expression (see the functional polymorphism section for more information).

The DRD4 and DAT1 genetic findings can be easily built into neurobiological models, and polymorphisms of these genes have been widely investigated in relation to ADHD endophenotypes. Endophenotypes are intermediate phenotypes between diagnostic classifications and the causative biological factors, representing quantitative and heritable traits that are found in unaffected relatives of the affected individuals (Almasy and Blangero, 2001). As proposed by Castellanos and Tannock (2002), these phenotypes should be related to specific brain processes. These authors suggested locomotor hyperactivity, delay aversion (preference for a smaller but sooner-received reward over a larger but later-received reward), and executive function (e.g., working memory and response inhibition) deficits for ADHD endophenotypes. The characteristic frequent lapses of attention could be measured by intra-individual reaction time variability in tasks that require sustained attention (for example, continuous performance tests, see "Attentional performance" section). The familiarity of the implicated phenotypes can be assessed by comparing affected and unaffected siblings. For example, analyzing reaction-time variability and accuracy parameters during a Go/NoGo test, a collaborative European study reported that unaffected siblings showed intermediate scores between the ADHD children and the controls (Uebel et al., 2010). Interestingly, in the incentive condition, the reaction-time was faster for ADHD children and their unaffected siblings, but not for controls, whereas the accuracy was improved in all of the groups, suggesting a familial motivational dysfunction in ADHD. In terms of the reward processes associated with ADHD, another study reported that ADHD children and their siblings chose smaller, sooner-received rewards over larger, later-received rewards, confirming the familiarity of delay aversion (Marco et al., 2009).

In terms of dopaminergic genetic effects on specific neurobiological endophenotypes, the DRD4 7-repeat allele was associated with poor performance on intelligence measures, interference control, and working memory tasks (Loo et al., 2008), supporting the involvement of DRD4 in executive functions in the PFC. Another interesting result was presented after the analysis of two independent birth cohorts: dopaminergic genetic effect on IQ could be detected only among those diagnosed with ADHD. Carriers of the DRD4 7-repeat allele or the DAT1 10/10 genotype had lower IQs compared to those without either risk genotype, whereas those carrying both DRD4 and DAT1 risk factors had the lowest IQ (Mill et al., 2006). Concerning the DAT1 3' UTR VNTR findings in relation to neuropsychological measures, such as sustained attention and executive functions, mostly negative findings have been reported (reviewed by Rommelse et al., 2008). These researchers also conducted a large-scale neuropsychological study among ADHD patients and their siblings in a wide age range (5–19 years) and assessed many SNPs within the DAT1 gene in addition to the two VNTRs; however, they did not find any significant associations between DAT1 genotypes or haplotypes and neuropsychological performance.

Another type of endophenotypes comes from imaging studies that measure brain region volumes with magnetic resonance imaging (MRI) or that measure brain activity with functional MRI (fMRI). Several structural changes have been described in ADHD children compared to controls, such as smaller total brain volume, a reduction in the size of the cortical lobes and the caudate nucleus (Valera et al., 2007). A large-scale MRI study reported a decreased cortical thickness in the right PFC and in the posterior parietal cortex in ADHD children compared to controls. In addition, this study reported a DRD4 genetic effect in both groups: the ADHD 7+ group had the thinnest cortex, followed by the ADHD 7- group, then by the healthy 7+ group, and finally by the healthy 7- group (Shaw et al., 2007). It is important to note that this regional thinning was most apparent in childhood and largely resolved by late adolescence. Comparative fMRI studies of ADHD patients and controls have shown a reduction in the activity level of the basal ganglia thalamo-cortical circuits (involving the cortical areas, amygdala, hippocampus, and basal ganglia) in the resting state and during neurocognitive tasks, such as the Go/NoGo, stop-signal, or Stroop tests. Whereas, in reward-related settings, a reduction in the level of activity was observed in the nucleus accumbens (reviewed by Durston et al., 2009). A dopaminergic gene effect was observed in ADHD boys and their unaffected male siblings but was not observed in control boys: The DAT1 9-repeat allele carriers showed greater levels of activity in the striatum during cognitive control trials among probands at risk for ADHD (Durston et al., 2008).

3.2. Tourette syndrome

TS is a childhood-onset neuropsychiatric disorder that is characterized by multiple motor tics, i.e., involuntary, rapid, non-rhythmic skeletal movements and vocalizations. The prevalence of TS varies in different age-groups and is presently estimated as 1% of school-age children, whereas the prevalence of tic disorders (chronic motor or vocal tics) vary between 6 to 12% among children (Singer, 2005). Similar to ADHD, TS is more frequent in males (3:1 ratio). Family studies have shown that TS is highly heritable, and small-scale twin studies indicate that TS has 80–90% heritability (O'Rourke et al., 2009). TS is rarely present without comorbid conditions, and most often, it is accompanied by OCD and/or ADHD (Singer, 2005). This pattern of comorbidity indicates that genetic risk factors closely connected with TS may be responsible for a spectrum of disorders, including OCD on one side of the spectrum and ADHD on the other. At the two endpoints of the spectrum, OCD and ADHD can exist separately with unique etiologies (O'Rourke et al., 2009). The most widely studied candidate genes in TS belong to the dopamine system; however, serotonergic genes have also been analyzed because of the frequent comorbidity with OCD.

The dopamine hypothesis of TS is based on pharmacological and neuroimaging evidence. Classic antipsychotic (neuroleptic) drugs, such as haloperidol, can effectively suppress tics through DRD2 antagonism (Singer, 2005). Most SPECT studies have shown increased DAT densities in the striatum of TS patients compared to controls (Albin and Mink, 2006), and post-mortem analyses have revealed elevated DAT and DRD2 levels in the frontal brain regions (Yoon et al., 2007a). In the early 1990s, all of the investigated dopaminergic genes were excluded from TS pathology because of the assumed autosomal dominant inheritance in the linkage studies. Comings et al. (1996) suggested that polygenic inheritance was involved in TS, and subsequent genetic analyses were based on complex inheritance (e.g., by studying allele transmission in families).

The DRD2 TaqI A1-allele has been implicated in TS by a series of case-control association studies (summarized by Comings et al., 1996). To date, only one case-control study from Taiwan supported this finding (Lee et al., 2005), and family-based studies did not observe over-transmission of the A1-allele (Nothen et al., 1994; Diaz-Anzaldúa et al., 2004). For the DRD4 VNTR, case-control studies (Cruz et al., 1997; Comings et al., 1999; Yoon et al., 2007b) and family-based studies (Grice et al., 1996; Hebebrand et al., 1997; Diaz-Anzaldúa

et al., 2004; Tarnok et al., 2007) resulted in contradictory findings. There are only a few published studies that investigated the involvement of the dopamine synthesizing and catabolizing enzyme genes with mostly negative findings for TH and COMT, and positive findings for MAOA (reviewed by O'Rourke et al., 2009). For the DAT1 3' UTR VNTR, the categorical analyses showed a significant association (Comings et al., 1996) and a tendency towards an association with the 10-repeat allele (Diaz-Anzaldúa et al., 2004). Later studies did not observe significant associations with TS diagnosis (Tarnok et al., 2007; Yoon et al., 2007b). However, after applying a dimensional approach, the 9-repeat allele was associated with a greater tic severity (Tarnok et al., 2007). Based on the results of the largest SPECT studies where the 9-repeat allele was linked to a higher DAT density, we may speculate that this gene variant is a risk factor for TS and/or for tic severity. Further studies should apply quantitative trait and endophenotype analyses for TS to yield more consistent results, in a manner similar to that done in ADHD studies during the last decade.

3.3. Obsessive compulsive disorder

OCD is characterized by recurrent, intrusive thoughts (obsessions) that cause marked distress and/or by repetitive behaviors (compulsions) which are aimed at preventing or reducing anxiety. Importantly, the obsessions and compulsions are time consuming, or significantly interfere with the person's normal routine, occupational functioning, or social activities (American Psychiatric Association, 1994). The OCD category is heterogeneous in terms of symptoms, because the obsessions and compulsions can be related to many different dimensions (e.g., contamination/cleaning, hoarding/collecting, checking) as listed in the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989). The most frequent comorbid diagnoses are other anxiety disorders (e.g., social phobia), mood disorders, tic disorders, and substance abuse (Abramowitz et al., 2009). According to an American survey, the lifetime prevalence of OCD is 1.6%, and the median age of onset is 19, with 25% of the cases starting in adolescence (Kessler et al., 2005). Twin studies indicate the importance of separating childhood-onset OCD, because the observed genetic influence on OCD symptoms is much higher in children (ranging from 45% to 65%) compared to adults (ranging from 27% to 47%) (van Grootheest et al., 2005).

Based on the efficiency of serotonin reuptake inhibitors in the pharmacotherapy of OCD, most candidate gene studies focused on the serotonin transporter linked polymorphic region (5-HTTLPR) and serotonin receptor polymorphisms (see review papers by Grados, 2010 and by Walitza et al., 2010). A meta-analysis of the serotonin transporter gene studies reported that the long 5-HTTLPR allele was associated with childhood-onset OCD (Bloch et al., 2008). In terms of dopaminergic polymorphisms, there are fewer candidate gene studies in the OCD literature, although the high comorbidity with tic disorders and the usefulness of additive antipsychotic treatment in serotonin reuptake inhibitor resistant cases point to the involvement of the dopamine system (Abramowitz et al., 2009). A meta-analysis of the COMT Val158Met polymorphism indicated an association of the Met-allele with OCD in men (OR = 1.88, 95% CI 1.45 – 2.44) but not in women (Pooley et al., 2007). Recent studies started to utilize dimensional symptom scales or factors in the COMT candidate gene analyses (Lochner et al., 2008; Katerberg et al., 2010), but these results have not been confirmed by independent workgroups. Of the dopamine receptor polymorphisms, only the DRD4 VNTR showed positive associations: The protective effect of the DRD4 4-repeat allele in OCD was indicated by a case-control study (Camarena et al., 2007) and by a family-based study (Walitza et al., 2008); whereas the increased frequency of the DRD4 7-repeat allele was shown in late-onset OCD group (Hemmings et al., 2004), and in a subgroup of OCD patients with comorbid tics (Cruz et al., 1997). The MAOA genetic findings are less consistent (Grados, 2010). Interestingly, both linkage studies and family-based association analyses indicated the glutamate transporter gene (SLC1A1) on

chromosome 9p24 in the development of OCD (Grados, 2010), which started pharmacological trials of glutamate antagonist riluzole augmentation in treatment-resistant cases (Abramowitz et al., 2009), showing the possible usefulness of genetic study findings.

3.4. Substance abuse

Substance use disorders can be subdivided according to the abuse/dependence state and the type of substance abused. According to the DSM-IV (American Psychiatric Association, 1994), substance abuse is a maladaptive, non-medical use of psychoactive drugs that leads to functional impairments or distress, whereas substance dependence involves tolerance to the effects of the drug and the presence of withdrawal symptoms when the use of the drug is reduced or stopped. In general, drug-seeking and drug-taking behavioral patterns persist despite serious negative consequences. Repeated exposure to addictive substances, such as nicotine, cannabinoids, ethanol, psychostimulants, and opioids can initiate adaptive changes in the central nervous system, causing physical and psychological dependency. The lifetime prevalence of any substance use disorder was 14.6% in an American survey from 2005 with diagnoses starting from late-adolescents (25% of cases at age 18 and 50% of cases at age 20) (Kessler et al., 2005). Epidemiological studies indicate that genetic factors play a significant etiologic role in the development of substance use disorders, estimating a varying (30% to 60%) heritability of heroin addiction and stimulant abuse (Tsuang et al., 1998; Kendler et al., 2003). The heritability is approximately 50 to 60% in alcohol dependence (Gelernter and Kranzler, 2009) and approximately 50% in nicotine dependence (Ho and Tyndale, 2007) and cannabis use disorders (Agrawal and Lynskey, 2009). Neurobiological models emphasize the key role of the reward system in addiction, as the dopaminergic mesolimbic pathway interacts with other stimulatory and inhibitory neurotransmitter systems (Comings and Blum, 2000). Various drugs of abuse act at different points in these systems, but they all lead to an elevated level of dopamine in the nucleus accumbens (Koob and Volkow, 2010). Therefore, genes of the dopaminergic system are logical candidates for association studies of substance use disorders.

Results from the association studies of the dopamine receptor gene variants have been summarized recently and have been supplemented with detailed descriptions of the animal studies that investigated the dopamine models of drug addiction (Le Foll et al., 2009). The most conclusive findings are related to the DRD2 TaqIA polymorphism. Recent meta-analyses of nearly 40 studies confirmed the association of alcoholism with the DRD2 A1-allele, showing a modest but significant effect (OR = 1.22 by Smith et al., 2008 and OR = 1.31 by Le Foll et al., 2009). Additional studies have suggested that the DRD2 A1-allele is associated not only with alcoholism but also with smoking and other type of substance abuse, as well as with pathological gambling. These behaviors are manifested as part of the aptly named reward deficiency syndrome (Comings and Blum, 2000). A meta-analysis of 29 smoking-related studies did not confirm the DRD2 effect (Munafo et al., 2009), whereas a few studies investigating opiate addiction reported a higher consumption of heroin in DRD2 A1-carriers among different nationalities (Le Foll et al., 2009). Studies investigating multiple SNPs of the DRD2 and surrounding genes in haplotype analyses indicated distinct haplotypes in different ethnic populations at alcohol dependence (Yang et al., 2007; Kraschewski et al., 2009), nicotine dependence (Huang et al., 2009), and heroine dependence (Xu et al., 2004). Therefore, the usefulness of haplotype detection needs to be supported by further studies.

In terms of other D2-like receptor genes, the DRD3 studies resulted in mostly negative findings at alcohol and cocaine dependence, however, two large scale studies showed association of the Ser9Gly (rs6280) SNP with nicotine dependence or heaviness of smoking (reviewed by Le Foll et al., 2009). The DRD4 VNTR findings are also less straightforward. Although the DRD4 long allele was initially associated with alcohol dependence, other

studies failed to replicate this finding (Le Foll et al., 2009). According to a recent study in heavy-drinking college students, a significant association between the DRD4 VNTR and alcoholism was found; however, the association was diminished when the novelty seeking personality trait was included in the analysis (Ray et al., 2009). To date, only the intermediate phenotype approach has resulted in a consistent association. The DRD4 long allele carriers were reported to exhibit a greater urge to drink compared to subjects with short (less than 5-repeat) alleles (reviewed by McGeary, 2009). The quantitatively measured phenotypes have also been used for association studies of smoking behavior: The DRD4 7-repeat allele carriers exhibited higher rates of lifetime smoking, higher smoking cue reactivity, and poorer quit rates compared to subjects without the 7-repeat allele, although, negative results have also been reported (McGeary, 2009). The DRD4 7-repeat or long allele has been associated with a more severe smoking phenotype (heavy smoking), that may influence cessation outcome. In terms of the association between the 7-repeat allele and opiate or psychostimulant use, both positive and negative results have been reported (Le Foll et al., 2009); however, the urge phenotype and a higher quantity and frequency of drug use have been repeatedly linked to the DRD4 long allele (McGeary, 2009).

At the D1-like receptor genes, the DRD1 association results have been positive in relation to alcohol dependence, although only three studies were summarized (Le Foll et al., 2009). Interestingly, DRD1 haplotype analyses resulted in positive findings as well: the rs686A-rs4532C haplotype was associated with alcohol dependence (Batel et al., 2008), and the rs265973C-rs265975T-rs686A haplotype formed by the 3' UTR SNPs was associated with nicotine dependence (Huang et al., 2008). Studies investigating DRD5 polymorphisms are even fewer: only one study resulted in negative findings at nicotine dependence, and one study showed modestly positive association with heroin addiction (Le Foll et al., 2009).

The other frequently studied dopaminergic gene is DAT1, especially among stimulant drug abusers. Recent reviews have not confirmed the association of the DAT1 3' UTR VNTR with methamphetamine use disorders or with nicotine and alcohol dependence (Ho and Tyndale, 2007; Bousman et al., 2009; van der Zwaluw et al., 2009). One study showed the importance of the intron 8 VNTR in the DAT1 gene among cocaine abusers (Guindalini et al., 2006), but no replication has been published yet. Results from the Mannheim Study of Children at Risk provided evidence for the DAT1 3' UTR VNTR: nicotine dependence and alcohol abuse was associated with the 10/10 genotype in subjects who started daily smoking and experienced the first alcohol intoxication earlier in life (Schmid et al., 2009). In addition, the intention to quit smoking was lower in adolescents with the DAT1 10/10 genotype (Laucht et al., 2008). However, these findings have not yet been confirmed. There are also interesting observations about nicotine usage among adult ADHD patients. A decreased striatal DAT availability was detected in smoking ADHD subjects, which was similar to the effect of methylphenidate medication (Krause et al., 2003) and supported the self-medication hypothesis for psychiatric patients. The NET gene polymorphisms were less frequently studied. Negative findings were reported in relation to alcohol dependence in European and Chinese populations (Samochowiec et al., 2002; Huang et al., 2008). In terms of stimulant drug use, only one study reported association of acute response to amphetamine with NET genotypes and haplotypes among healthy young adults (Dlugos et al., 2009).

In terms of dopamine synthesizing and catabolizing enzyme genes, the K4 (7-repeat) allele of the TH tetranucleotide repeat polymorphism has been repeatedly shown to be a protective factor in smoking (Ho and Tyndale, 2007). Positive association findings related to COMT are scarce (Tammimäki and Männistö, 2010), and no consistent MAOA findings have been reported in the substance abuse literature (Ho and Tyndale, 2007; Lachman, 2008; Bousman et al., 2009). A recent approach of genetic association analysis used a set of dopaminergic gene polymorphisms to create high or low activity dopaminergic genetic groups (Conner et

al., 2010). In this way, the hypodopaminergic functioning was shown to be related to drug use in male adolescents among the studied children of alcoholics.

4. DOPAMINERGIC GENETIC FINDINGS USING DIMENSIONAL APPROACH

4.1. Attentional performance

Twin studies and genome-wide association studies indicate that inherited factors have considerable impact on cognitive performance (Plomin, 2001; Butcher et al., 2008). Candidate gene studies have aimed to identify the genetic underpinnings of the different networks of the information processing system by studying healthy individuals and ADHD patients. The most extensively studied cognitive domains are connected to the attention system. The attention network is responsible for many functions, such as focusing attention, maintaining focus, or dividing attention between two or more stimuli. Attention models distinguish these three networks, with three main neurotransmitter systems responsible for alerting (noradrenergic), orienting (cholinergic), and executive control (dopaminergic) (Raz and Buhle, 2006). The alerting network is responsible for maintaining the alert state, allowing one to respond. The process of selecting information between sensory inputs is mediated by the orienting network. The executive control network includes a set of complex operations responsible for mediating stimulus and response conflicts to control behavior.

The Attention Network Test was developed to measure individual differences in alerting, orienting, and executive attention. A small-scale twin study confirmed the heritability of the executive control network (Fan et al., 2001). This workgroup also studied dopaminergic (DRD4, DAT1, COMT, and MAOA) polymorphisms among healthy individuals. Their results highlighted the importance of dopamine catabolizing enzymes in executive attention: The MAOA low-activity (3-repeat) allele was associated with higher executive attention scores; moreover, a comparison of the groups with low vs. high cortical dopamine levels (i.e., COMT Val/Val + MAOA 4/4 vs. COMT Met/Met + MAOA 3/3) showed a significant difference, as the high dopamine group exhibited better executive attention (Fossella et al., 2002).

The COMT Val158Met polymorphism has been shown to modulate attentional control; better performance was reported in Met-carriers among healthy subjects (Egan et al., 2001) and ADHD children (Sengupta et al., 2008). Because of its importance in the PFC (Tunbridge et al., 2006a), this COMT polymorphism has been widely studied during cognitive tasks over the last few years. However, the results from many studies are not in agreement. For example, the high-activity Val-allele was associated with both better and poorer prefrontal functioning, and a recent meta-analysis showed no main effect of the COMT Val158 Met polymorphism on cognitive functions (Barnett et al., 2008). Based on the tonic-phasic dopamine hypothesis, it was proposed that the Met-variant could be beneficial in working memory and sustained attention tasks for which stability is required; in contrast, the Val-variant facilitates the transition between states and enhances flexibility (Bilder et al., 2004). It is important to note that a cortical COMT effect probably depends on many factors, e.g., the level of stress the individual experiences during the task (see the dopamine systems section for more information). Recent genetic studies include other COMT SNPs in addition to the Val158Met (rs4680) polymorphism to access more precise functional variants. For example, a large scale, population-based study showed an inverted U-shaped association between COMT haplotypes with decreasing enzyme activity and working memory performance among 10-year old children (Barnett et al., 2009). In addition, gene $\times$ gene interactions can be also important, as shown by the finding of Reuter et al. (2005): In the Stroop interference test, the COMT Met/Met participants performed significantly better than the Val-allele carriers in the DRD2 A1-allele present group,

whereas in the DRD2 A1-allele absent group, subjects with the Met/Met genotyped performed the worst.

Other groups have used computerized continuous performance tests to study attention endophenotypes by response time variability or the number of omission errors (representing inattention). In this type of test, the number of commission errors can be also recorded (indicating impulsivity). Only the DRD5 148-bp allele was associated with all of the main outcome measures in an Israeli ADHD group (Manor et al., 2004). The MAOA uVNTR was associated with the number of commission errors (Manor et al., 2002b), whereas the DRD4 VNTR was associated with both the number of commission errors and the response time variability in this group (Manor et al., 2002a). The attention-related DRD4 findings in the continuous performance test studies are not always in agreement with one another. In two ADHD studies, the DRD4 4-repeat or short allele was associated with a slower reaction time and variable responses (Swanson et al., 2000; Manor et al., 2002a), and only one ADHD study reported the expected result of the DRD4 7-repeat allele carriers making more errors (Kieling et al., 2006). Our group recently confirmed the association between the DRD4 7-repeat allele and slower responses among healthy young adults during verbal tasks, such as word reading or picture naming, but not during simple choice reaction time tasks (Szekely et al., 2011). The DRD4 7-repeat allele might have a special effect in ADHD groups. A study that included control and ADHD children performing the Sustained Attention to Response Task showed that the ADHD 7+ group performed significantly better compared to the 7-group, whereas this genetic effect could not be detected in the control group (Johnson et al., 2008). Also, the previously mentioned MRI study (Shaw et al., 2007) showed that ADHD children carrying the 7-repeat allele had better clinical outcome and showed normalization of the right parietal cortical region compared to the 7-repeat absent ADHD group.

Besides the dopamine receptor genes, the DAT1 gene has been also implicated in sustained attention in clinical groups, such as ADHD. ADHD children with the 10/10 genotype had higher reaction-time variability and more errors compared to those carrying the 9-repeat allele in some but not all studies (Bellgrove and Mattingley, 2008; Rommelse et al., 2008). Whereas continuous performance test analyses of NET polymorphisms conducted among ADHD children gave contradictory results (Cho et al., 2008; Kollins et al., 2008).

4.2. Impulsive behaviors

Another group of intermediate phenotypes in ADHD, the impulsivity-related behaviors are also associated with substance abuse, antisocial and borderline personality disorder, and impulse control disorders (e.g., kleptomania, trichotillomania, and pathological gambling). Impulsivity is a multidimensional trait, its various aspects are generally divided into two broad categories (cognitive/psychological and motor/behavioral). The cognitive aspects, such as impulsive decision making (the inability to withhold an action for the time needed to estimate consequences) or sensation seeking, are measured by self-report personality questionnaires; whereas the motor aspects, such as disinhibition (the inability to inhibit an unnecessary action) and delay aversion (see ADHD endophenotype paragraph) are assessed by behavioral inhibition and delayed reward tasks (Evenden, 1999). Behavioral inhibition can be measured with neurocognitive tests, such as the Go/NoGo or stop-signal tasks, which are used in endophenotype related genetic studies.

According to twin studies, self-reported impulsivity shows approximately 45% heritability (reviewed by Congdon and Canli, 2008), which prompted candidate gene research using personality questionnaires. The most consistent genetic findings in impulsivity-related studies are connected to the DRD2 gene. The results from studies conducted among healthy, young adults showed an association between the DRD2 A1-allele and impulsive behavior

using a response inhibition test (White et al., 2008) or a delay discounting task (Eisenberg et al., 2007). A significant DRD2 A1-allele $\times$ DRD4 7-repeat allele interaction was observed for delay discounting in the latter study, and a trend towards an association with sensation seeking was also reported (Eisenberg et al., 2007). Our recent study in an at-risk, young adult population revealed an association between the DRD2 gene (A1- and B1-allele) and impulsive self-damaging behaviors that were assessed using borderline symptoms (Nemoda et al., 2010). Other DRD2 SNPs were also associated with impulsivity in healthy individuals. The C/C genotype of the DRD2 C957T polymorphism was associated with a higher reward responsiveness after a psychological stressor (White et al., 2009). In a neuroimaging study, the DRD2 -141C Del carriers exhibited higher reward-related ventral striatum reactivity, which was associated with self-reported impulsivity (Forbes et al., 2009). This neuroimaging study also reported a higher reactivity in the DRD4 7-repeat allele and the DAT1 9-repeat allele carriers. The authors suggested that a connection exists between greater ventral striatum reactivity and hypodopaminergic variants.

The DRD4 genetic effect on neurocognitive tasks is less clear than that of the DRD2 gene. As we mentioned earlier, the commission error rate findings in ADHD children were not in agreement with one another; the DRD4 7-repeat allele was linked to both higher and lower error rates (Manor et al., 2002a, Kieling et al., 2006). During a behavioral inhibition test that was conducted among healthy, young adults, the DRD4 7+ group had longer mean reaction times on the stop-signal task compared to the 7- group. In addition, a DRD4 $\times$ DAT1 interaction was observed: The longest reaction time was observed for the DRD4 7+ and DAT1 10/10 genotype group compared to other genotype combination groups (Congdon et al., 2008). This finding supports the conclusion found in the ADHD literature, namely that the DRD4 7-repeat allele and the DAT1 10-repeat allele are risk factors for ADHD. However, during a similar response inhibition test conducted in a healthy student population, the DRD4 7/7 genotype group performed better on the Go/NoGo task (Kramer et al., 2009). The opposing findings of the two studies might be explained by the observation that the attentional processes involved in detecting infrequent NoGo signals might be involved in the Go/NoGo task (Congdon and Canli, 2008), for which the DRD4 7-repeat allele might not be the risk allele (see the attentional performance section for more information). Further studies using brain activity measurements will hopefully elucidate the underlying processes, as event-related potential differences were also observed in the DRD4 7-repeat allele carriers during the Go/NoGo task (Kramer et al., 2009).

Dopamine synthesizing and catabolizing enzyme genes have not been frequently investigated in relation to behavioral inhibition (Congdon and Canli, 2008). A recent fMRI study conducted among healthy, young adults reported greater brain activity in the right inferior frontal gyrus of the COMT Met-allele carriers compared to the COMT Val/Val genotype group during a stop-signal task (Congdon et al., 2009). Similarly, higher activation was observed in the right supplementary motor area and in the right subthalamic nucleus of subjects with at least one DAT1 9-repeat allele compared to the 10/10 genotype group. According to the authors, the greater activation represented better inhibitory control, therefore, the DAT1 10/10 genotype and the COMT Val/Val genotype were associated with an impaired neural response during behavioral inhibition (Congdon et al., 2009), which is in agreement with ADHD findings (Thapar et al., 2007; Gizer et al., 2009).

4.3. Externalizing behaviors

As mentioned previously in the ADHD section, ADHD is often accompanied by ODD starting in early childhood, and by CD diagnosed in late childhood – adolescence or by APD diagnosed after age 18 (Biederman, 2005). According to DSM-IV (American Psychiatric Association, 1994), ODD is characterized by negativistic, hostile, and defiant behaviors (e.g., actively defying or refusing to comply with adults requests or rules, deliberately

annoying people, blaming others for his or her mistakes or misbehavior). Whereas CD symptoms include aggressive and destructive behaviors (e.g., cruel behavior toward people or animals, destruction of property, stealing), and violations of rules. After the age of 18, CD may develop into APD, which is characterized by the above mentioned aggressive and destructive behaviors with an apparent lack of remorse. APD symptoms can also include recurring difficulties with the law, irresponsible work behavior, and abusive relationships. It has been shown that childhood ADHD predicts adult substance abuse, but it has also been demonstrated that early intervention and treatment in ADHD can prevent later illicit substance abuse during adolescence (Faraone and Wilens, 2003). Externalizing disorders, such as CD, APD, and substance abuse showed 80% heritability in a large-scale twin study conducted among 542 families (the Minnesota Twin Family Study, Hicks et al., 2004). Using a quantitative genetic model, the same workgroup could detect a gene $\times$ environment interaction in the development of externalizing disorders showing that genetic factors exhibited a greater effect under environmental adversity (Hicks et al., 2009). Using candidate gene analyses, a reproducible gene $\times$ environment interaction involving the MAOA uVNTR and childhood adversities has been shown for antisocial behaviors in independent association studies (reviewed by Thapar et al., 2007).

In a large Dutch family study a rare mutation in the X chromosome indicated that MAOA is involved in aggressive behavior, because aggressive and violent behavior was observed in MAOA deficient men (Brunner et al., 1993). Later, an animal study supported this observation as mice lacking the MAOA enzyme also exhibited enhanced aggression during adulthood (Cases et al., 1995). Since the gene encoding MAOA is localized on the X chromosome, robust effects are usually observed in males. In addition, it is not recommended to include heterozygote females in the analyses because of the potential inactivation of one of the X chromosomes; therefore, most association studies included only male subjects. The first study reporting gene $\times$ environment interaction regarding the MAOA uVNTR and childhood maltreatment showed that males with the low-activity MAOA genotype in the severe maltreatment group were more likely to develop CD in adolescence, had more APD symptoms at age 26, and were convicted for violent offence more frequently compared to those maltreated subjects with the high-activity MAOA genotype (Caspi et al., 2002). Although some subsequent studies reported negative findings concerning the interaction between the MAOA genotype and childhood maltreatment, the results of a meta-analysis supported the original finding (Taylor and Kim-Cohen, 2007). A recent study suggested that this interactive effect of MAOA and childhood maltreatment can be observed only at moderate levels of trauma exposure, because extreme levels of trauma appear to overshadow the effects of MAOA genotype (Weder et al., 2009). The underlying neural mechanisms responsible for the MAOA findings have been localized in the limbic system, as low-activity MAOA genotype men had a reduced limbic volume and a higher amygdala responsiveness during emotional arousal (Meyer-Lindenberg et al., 2006).

MAOA metabolizes serotonin and norepinephrine in addition to dopamine, thus the MAOA genetic findings could be attributed to other monoamine theories. For purely dopaminergic genes, the picture is less clear: three longitudinal, general population-based studies and three clinical sample-based studies investigating adolescents with ADHD or CD resulted in contradictory findings for the DAT1 3' UTR VNTR. The 9-repeat allele or the 9/10 genotype (vs. 10/10) was associated with higher levels of externalizing symptoms (Young et al., 2002, Barkley et al., 2006), but this finding was not supported by later studies using either community-based samples (Jorm et al., 2001; Caspi et al., 2008) or clinical samples (Caspi et al., 2008; Schulz-Heik et al., 2008). One possible explanation for these contradictory findings may be the distinct underlying factors for violent, physically aggressive behaviors, and for non-aggressive, rule-breaking antisocial behaviors. This explanation was presented by Burt and Mikolajewski (2008), who reported that more rule-

breaking behavior was observed in male undergraduates with the DAT1 10/10 genotype than those without this genotype. At the dopamine receptor genes, a gene $\times$ gene interaction was described in connection to adolescent CD problems and adult antisocial behaviors in a large, population-based study: males with the DRD2 A1-allele and DRD4 7-repeat allele showed more CD symptoms (Beaver et al., 2007).

In terms of the COMT Val158Met polymorphism, CD and APD were studied in the general population (birth cohorts) and among subjects diagnosed with ADHD. The Val/Val genotype was repeatedly associated with more CD and aggressive symptoms among children with ADHD (Caspi et al., 2008; Monuteaux et al., 2009; DeYoung et al., 2010) but not among children without ADHD (Caspi et al., 2008). In addition to the association of CD symptoms and the COMT Val/Val genotype in ADHD children, there was a gene $\times$ environment interaction described: children with the Val/Val genotype were more susceptible to the adverse effects of prenatal risk as indexed by lower birth weight (Thapar et al., 2007). Other gene $\times$ environment interaction findings in connection to antisocial behavior among ADHD children were also reported in the Cardiff ADHD genetic study, for example between DAT1 and DRD5 polymorphisms and maternal smoking during pregnancy (Thapar et al., 2007). Future analyses from independent studies are needed to support these findings.

4.4. Novelty seeking

One possible dimensional approach to impulsive traits and substance use disorders is the assessment of risk-taking behaviors (defined as high levels of risk-taking, exploration, and novelty or sensation seeking). These behaviors are especially characteristic of adolescence (Romer, 2010), and it would be useful to conduct a longitudinal study related to genetic vulnerability; however, most of the genetic association studies are carried out in young adult (student) populations. Several studies have shown that individuals exhibiting high novelty or sensation seeking personality traits are at an increased risk for using drugs of abuse (Bardo et al., 1996; Zuckerman and Kuhlman, 2000). Studies have consistently shown that polysubstance abusers have particularly high levels of impulsivity and sensation seeking (Conway et al., 2003). In most of the prevailing personality models, one main dimension is novelty seeking or impulsivity or extraversion, which are generally referred to as approach-related traits (Munafo et al., 2008). Novelty seeking is measured using the Tridimensional Personality Questionnaire (TPQ) or the Temperament and Character Inventory (TCI). Extraversion is one of the main dimensions of the Neuroticism Extraversion Openness (NEO) Personality Inventory and the Eysenck Personality Inventory or Questionnaire (EPI or EPQ). Whereas the Karolinska Scales of Personality (KSP) has an impulsivity scale. Association studies typically use only one questionnaire, however, dimensions measuring the same construct are highly correlated. Therefore, comparison of genetic findings is possible with the assumption that all of these interrelated traits reflect a common underlying neurobiological motivational mechanism. Because the psychobiological model of TPQ/TCI provides a well-established theoretical framework for an association between the dopamine system and novelty seeking temperament dimension (Cloninger et al., 1993), the original novelty seeking scores or transformed scores from other impulsivity scales are usually reported in dopaminergic genetic association studies.

A substantial genetic component of personality traits has been demonstrated in twin and adoption studies. For example, a large Australian twin study reported heritability for TCI temperament scales that ranged from 30% to 40% (Gillespie et al., 2003). To investigate the specific genetic factors, several candidate gene studies have been conducted, initiated by the groundbreaking association of novelty seeking and the DRD4 7-repeat (or long) allele (Benjamin et al., 1996; Ebstein et al., 1996). Studies aiming to replicate this association resulted in contradictory findings, probably because the indicated genetic factor has a small

or modest effect size (Ebstein et al., 2000). Therefore, increasing the size of the studied population and/or utilizing published results for meta-analyses may help to settle the contradictions. Based on a recent meta-analysis, the DRD4 VNTR does not seem to have a significant effect on novelty seeking, whereas the -521 C/T (rs1800955) SNP probably affects this trait (Munafo et al., 2008). The DRD4 -521 T-allele carriers had lower scores on approach-related trait scales; interestingly, a significant association could be observed for novelty seeking (TCI/TPQ) and impulsivity (KSP) but not for extraversion (NEO or EPI/EPQ). This finding leads to questioning the basic assumption that these traits assess the same neurobiological mechanism. An early meta-analysis of the other dopaminergic polymorphisms did not show any significant effect for DRD2 or DAT1 polymorphisms, only the DRD3 Ser9Gly SNP was associated with approach-related traits (Munafo et al., 2003). It is important to mention that the social environment might have a significant and possibly interacting effect. In a longitudinal study, for example, higher novelty seeking scores in the DRD2 A1-allele carriers were observed only if participants had a negative, punitive environment in childhood, and the DRD2 genotype had no effect under more favorable conditions (Keltikangas-Järvinen et al., 2009).

There are only a few MAOA and COMT related studies, and their meta-analyses have not yet been carried out. Interesting findings have been reported in regard to the COMT Val158Met polymorphism. A three-way interaction was observed between COMT, DRD4, and the serotonin transporter polymorphism (5-HTTLPR) on novelty seeking. In the absence of the short 5-HTTLPR allele together with the presence of the high-activity Val/Val COMT genotype, the novelty seeking scores were higher in the DRD4 7+ individuals in two independent populations (Benjamin et al., 2000; Strobel et al., 2003). In terms of solely the COMT genetic effect, the results are not in agreement with one another. The low-activity Met/Met genotype was associated with a high level of novelty seeking (Golimbet et al., 2007), whereas the high-activity Val/Val homozygotes were reported to have higher extraversion scores (Reuter and Hennig, 2005).

A number of studies assessed personality traits as part of the genetic investigations of substance use disorders. For example, higher novelty seeking score was associated with the DRD4 7-repeat allele among heavy-drinking college students (Ray et al., 2009) and in adolescent boys from a high-risk community sample (Laucht et al., 2007). In addition, two preliminary studies were conducted among methamphetamine dependents. Consistent with previous findings on drug users, methamphetamine users had higher novelty seeking scores than controls in both samples. Within the patient groups, a subgroup of the DRD2 A1-allele carriers (Han et al., 2008) or COMT Met-allele carriers (Hosak et al., 2006) had the highest novelty seeking scores. The COMT genetic finding was supported in opiate dependence by our laboratory. We reported increased novelty seeking scores in the presence of the Met-allele among 117 heroin-dependent subjects that participated in a methadone substitution program (Demetrovics et al., 2010).

The self-report questionnaires have strong limitations in measuring human personality dimensions. To better understand the genetic underpinnings of personality, novel and complex experimental paradigms are suggested for further studies, such as broader personality phenotypes (e.g., altruism and pro-social behavior) or objectively measurable endophenotypes from neurophysiological tests (e.g., event-related potentials and prepulse inhibition) or from computer games (Ebstein, 2006). The latter approach has been successfully applied recently for testing a reward-related endophenotype by the Iowa Gambling Task. The DRD4 long allele carriers had higher novelty seeking scores and showed elevated levels of risk-taking behavior (Roussos et al., 2009). Also, emotional processes were assessed in a subset of subjects by startle reactivity. The DRD4 long allele was associated with constricted emotional responses. Another gambling test study

measuring event-related potentials did not report a DRD4 -521 C/T SNP effect (unfortunately, the analysis of the DRD4 VNTR was not reported) but showed an increased amplitude of the medial frontal negativity (a larger difference between the gain and loss conditions) in COMT Val/Val homozygotes compared to Met/Met homozygotes. The Val/Val group also exhibited greater beta activity during gain trials compared to the Met/Met group (Marco-Pallares et al., 2009). If these genetic findings are replicated, the objective phenotypes that characterize risk-taking behaviors could be helpful in genetic association studies and diagnostic processes. Animal models for risk-taking behaviors are numerous, and they would be useful to elucidate the underlying neurobiological mechanisms of impulsive decision-making. Adolescent rats, like their human counterparts, exhibit increased risk-taking and novelty seeking behaviors and drug use (Laviola et al., 2003). Therefore, animal studies can be used to assess this vulnerable period of development.

5. CONCLUSIONS

We would like to emphasize that genetic association studies do not aim to find good or bad gene variants. Identifying the genetic factors in the background of heritable disorders can help us to better understand the underlying neural mechanisms of the disorder and the related behaviors (e.g., ADHD and impulsive behaviors). Psychiatric disorders can be seen as extremes of certain behaviors. In many cases, a small portion of these extreme behaviors are evolutionarily beneficial in human populations, because they maintain diversity. For example, impulsive risk-taking behavior in a minority of the population can aid survival (Williams and Taylor, 2006). Therefore, gene variants that have been indicated as risk factors in certain psychiatric disorders might have favorable effects under special circumstances.

Since single genetic factors have only small effects on complex inheritance disorders and traits, refining the studied phenotype is necessary. Although heterogeneous disorder categories have been continually replaced by quantitative trait measures in psychiatric genetic studies during the last decade, current parent-rated symptom scales and self-report questionnaires still do not provide the best phenotypes. Objectively measured endophenotypes, such as event-related potentials, fMRI signals that mirror regional brain activity, reaction time measures, or error rates on standardized computerized neurocognitive tests would help us to decipher specific genetic effects. Based on the presented dopaminergic genetic data (summarized in Table 1), we can conclude that dopamine D2 receptors in the subcortical brain regions may be important in reward-related associative learning and behavioral inhibition, as DRD2 gene variants resulting in reduced expression (A1-, B1-, and 957 C-allele) are repeatedly linked to substance abuse and impulsive phenotypes. The widely investigated DRD4 exon 3 VNTR has an influence on PFC-related executive functioning; however, recent results also point out the importance of DRD4 promoter variants. The COMT Val158Met SNP affects cognitive functions by influencing cortical dopamine level. This polymorphism is likely the best example of the good vs. the bad effect of a specific gene variant. The approximate 50–50% frequency of the Val- and Met-alleles of this functional polymorphism shows that both variants can have advantageous effects. It has been proposed that the Val-variant is associated with better cognitive flexibility, whereas the Met-variant has been reported to lead to an advantage on memory and attention tasks which require stability (Bildner et al., 2004). The dopamine transporter is a key component of dopamine transmission in the basal ganglia, and therefore, it is important in inhibitory control. However, specific DAT1 gene variants with convincing functional effects have not yet been confirmed. The low-activity allele of the MAOA uVNTR has been shown to be related to aggressive traits. This association could be explained by dopaminergic or serotonergic pathways because this enzyme converts monoamines (dopamine, norepinephrine, and serotonin). The MAOA effect shows the

importance of gene $\times$ environment interactions. As it can be noticed in recent review papers (Grisham et al., 2008; Nigg et al., 2010), the environmental factors which have been convincingly replicated as risk factors in childhood-onset psychiatric disorders, such as low birth weight and physical or sexual abuse, are not specific to these disorders. Finding specific genetic factors that make individuals vulnerable or resilient to harmful environmental factors is the prevailing approach in present psychiatric genetic research. It is important to note that newer hypotheses refer to the MAOA uVNTR and to the other most commonly researched dopaminergic and serotonergic polymorphisms, i.e., the DRD4 VNTR and the 5-HTTLPR, as plasticity and not vulnerability factors, arguing that the indicated gene variants make individuals more sensitive to environmental influences (to both positive and negative influences) (Belsky et al., 2009). Early adverse environments might exert their effects via epigenetic modulations (Meaney, 2010), which should be taken into account when trying to understand the biological processes leading to disorders and maladaptive behaviors. Longitudinal population-based studies collecting environmental data and animal studies controlling for specific environmental factors would help shed light on the important steps in the development of psychopathologies.

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Highlights

- description of functional polymorphisms in the dopaminergic genes
- dopaminergic genetic findings of psychiatric disorders in adolescence, e.g., ADHD
- genetic findings of quantitative traits, like impulsive and externalizing behaviors
- genetic findings of objective endophenotypes, like attentional performance

Figure 1. Dopaminergic synapse in the caudate nucleus and in the prefrontal cortex

Dopamine biosynthesis involves two steps: tyrosine is converted by tyrosine hydroxylase (TH) into dihydroxyphenylalanine (DOPA), which is then turned into dopamine (DA) by aromatic amino acid decarboxylase (DC). In the axon terminal, dopamine is rapidly taken up by vesicular monoamine transporter (VMAT) into storage vesicles, from which, upon arrival of the action potential, it is released into the synaptic cleft. The neurotransmitter molecules act on postsynaptic dopamine receptors, which belong to two main families (D1-like and D2-like). Dopamine release is controlled by presynaptic DRD2 (or DRD3) receptors. In the basal ganglia, such as the caudate nucleus (1.A.), the neurotransmission is terminated by dopamine transporter (DAT), which pumps back dopamine into the presynaptic neuron. Most of the captured dopamine is recycled into storage vesicles for reuse, whereas some of the free dopamine is catabolized by monoamine oxidase (MAO, presiding in the mitochondria outer membrane) and subsequently by aldehyde dehydrogenase (AD) into 3,4-dihydroxyphenylacetic acid (DOPAC). DOPAC is further transformed into homovanillic acid (HVA) by catechol-*O*-methyltransferase (COMT, dashed arrow). In the prefrontal cortex (1.B.) volume transmission is more pronounced because of the lack of DAT. Dopamine can be transported into noradrenergic neurons by norepinephrine transporter (NET) or into glial cells by Na⁺ dependent and Na⁺ independent transport systems. Here COMT carries out the first catabolism step, 3-methoxytyramine (3MT) is formed, which is converted into the final dopamine metabolite, HVA, by MAO and AD.

2.A. Dopamine receptors

2.B. Enzymes and transporters

Figure 2. Candidate gene polymorphisms

2.A: The dopamine receptor genes are presented according to the two main families (D1-like DRD1 and DRD5, and D2-like DRD2, DRD3, DRD4). 2.B: Abbreviations of the enzymes and transporters are the following: TH: tyrosine hydroxylase, MAO: monoamine oxidase (A and B isoforms), COMT: catechol-*O*-methyltransferase, DAT1 (SLC6A3): dopamine transporter, NET (SLC6A2): norepinephrine transporter, 5-HTT (SLC6A4): serotonin transporter. The chromosomal localization and direction of the genes are indicated by the arrows based on the NCBI Gene database (<http://www.ncbi.nlm.nih.gov/gene>). Black boxes represent exons (if the translation start site is located in the second exon, the first exon is shown by a dotted box), grey boxes show alternatively spliced exons, transparent boxes indicate untranslated regions (5 and 3 UTRs). The SNPs are indicated by stars and the VNTRs are presented by striped boxes. The most frequently studied polymorphisms are highlighted with bold letters.

Figure 3. The frontal-subcortical circuits

Excitatory glutamatergic projections from the frontal cortex reach the striatum (more precisely the putamen in the motor circuit, the dorsolateral caudate nucleus in the dorsolateral prefrontal circuit, the ventromedial caudate nucleus in the lateral orbitofrontal circuit, the nucleus accumbens in the medial orbitofrontal circuit, the ventromedial caudate nucleus and the nucleus accumbens in the anterior cingulate circuit) creating two pathways. The direct pathway consists of inhibitory projections from the striatum (GABA, cotransmitter: substance P, dynorphin) to the inhibitory neurons in the substantia nigra pars reticulata (SNr) and the globus pallidus interna (GPi), resulting in disinhibition of the thalamus. The indirect pathway consists of inhibitory projections from the striatum (GABA, cotransmitter: enkephalin) to the globus pallidus externa (GPe), followed by inhibitory projections from the GPe to the nucleus subthalamicus (STN), which activates the inhibitory neurons of GPi. The net effect of this three-link pathway is the inhibition of the thalamus. Excitatory glutamatergic projections from the motor cortex go directly to the STN, creating the hyperdirect pathway.

The single bolded arrows indicate excitatory glutamatergic projections, and the double arrows indicate inhibitory GABAergic projections. The dashed arrows indicate the modulatory dopaminergic projections from the ventral tegmental area (VTA) to the cortex (mesocortical pathway) and to the nucleus accumbens (mesolimbic pathway), and from the substantia nigra pars compacta (SNc) to the putamen and caudate nucleus (mesostriatal pathway). Note that dopaminergic inputs in the striatum encourage activation of the direct pathway via DRD1 and promote inhibition of the indirect pathway via DRD2.

Table 1

Dopaminergic genetic risk factors of psychiatric disorders and related traits.

genes	ADHD	TS	OCD	subs. abuse	inattention	impulsivity	aggressive behav.	novelty seeking
DRD1	- -	- -	none	++ (alcohol) + (nicotine)	none	none	+	+
DRD2/ANKK1	M -	+/-	- -	M + (alcohol) M - (nicotine) ++ (opiate)	+/-	++	++	M -
DRD3	- -	- -	- -	- - (alcohol) ++ (nicotine)	+	+	+	M +
DRD4	M +	+/-	++	+/- (alcohol) ++ (nicotine) +/- (opiate)	+/-	+/-	+	M +
DRD5	M +	- -	none	-(nicotine) + (opiate)	+/-	none	none	+
TH	M -	-	none	+/- (alcohol) ++ (nicotine)	none	none	-	+
MAOA	M -	++	+/-	+/-	+/-	+	M +	- -
COMT	M -	- -	M + (men)	+/-	+/-	+	++ (in ADHD)	+/-
DAT1(SLC6A3)	M +	+/-	- -	- -	++	+/-	+/-	M -
NET(SLC6A2)	M -	- -	-	- - (alcohol) + (stimulant)	+/-	none	none	+/-

M +: meta-analysis showing positive association, M -: meta-analysis showing negative association, +/-: findings are contradictory, ++: more positive association results compared to the negative results, +: suggestive evidence (no replication yet), - -: more negative association results compared to the positive results, -: single negative study, none: PubMed search did not yield any result in December 2010.