To: ***Neuroscience & Biobehavioral Reviews*** *(Life-Span Comorbidity of ADHD Special Issue)*

ADHD co-morbidities: A review of implication of gene × environment effects with dopamine-related genes

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Abstract: ADHD is a major burden in adulthood, where co-morbid conditions such as depression, substance use disorder and obesity often dominate the clinical picture. ADHD has substantial shared heritability with other mental disorders, contributing to comorbidity. However, environmental risk factors exist but their interaction with genetic makeup, especially in relation to comorbid disorders, remains elusive. This review for the first time summarizes present knowledge on gene x environment (GxE) interactions regarding the dopamine system. Hitherto, mainly candidate (GxE) studies were performed, focusing on the genes *DRD4*, *DAT1* and *MAOA*. Some evidence suggest that the *DRD4* exon 3 variable number tandem repeat (VNTR) and *MAOA* uVNTR may mediate (GxE) interactions in ADHD generally, and comorbid conditions specifically. For other polymorphisms, evidence is contradictory and less convincing. Particularly lacking are longitudinal studies testing the interaction of well-defined environmental with polygenic risk scores reflecting the dopamine system in its entirety. Only such an approach would be less susceptible to false-positive findings and provide clues on how genes could interact with non-genetic factors to shape psychopathology over the life span.

Keywords: ADHD; co-morbidity; gene; environment; dopamine

1. ADHD and comorbidity; genes and environments

Attention deficit hyperactivity disorder (ADHD) is a growing public health concern, addressed in multiple genetic studies. This review has the objective to summarize the findings with focus on two aspects: on the dopaminergic system where the culprit of ADHD, according to correlative and experimental studies in animals and humans, is likely to lie, and on the role of environment(s) that may mold the genetic predispositions into pathogenetic process. To that end the major dopamine system shaping genes that encode tyrosine hydroxylase, dopamine receptors of type D_1, D_2, D_4 and D_5, the dopamine transporter, as well as monoamine oxidase A and catechol-o-methyl transferase are considered in detail. This review also aims at a discussion of potential fundamental reasons why the findings to date have often been inconsistent and not yielded a simple and coherent picture.

1.1 ADHD and its comorbidities

ADHD is an often lifelong condition centred around the core symptoms of inability to focus and sustain attention, excessive activity and/or physical restlessness, and impaired impulse control (American Psychiatric Association, 2013). ADHD is a major burden on health. Being the most common neurodevelopmental disorder that in many instances spans throughout life course, it often presents serious co-morbidities that further reduce quality of life (Sobanski et al., 2007; Steinhausen, 2009; Faraone et al., 2015; Franke et al., 2018). It has been estimated that more than 80% of adult ADHD patients suffer from at least one co-morbid condition (McGough et al., 2005; Torgersen et al., 2006; Jacob et al., 2007). One study estimated the ADHD patients to visit doctors

ten times more frequently than the respective control group, and their emergency visits and hospitalization rate were three times higher (Kirino et al., 2015). Besides the early comorbid autism spectrum and conduct disorders (Rommelse et al., 2010) the most common co-morbidities with ADHD include major depression (Angold, 1999; Kessler et al., 2006; Caye et al., 2016), addiction and substance use disorder (Martinez-Raga et al., 2013a; Luo and Levin, 2017), obesity (Nigg et al., 2016), but also headache (Jacobs et al., 2016), anxiety disorders (Spencer, 2006; Steinhausen et al., 2006; Reimherr et al., 2017), personality disorders (Katzman et al., 2017) and sleep disorders (Jacob et al., 2007). Symptoms of co-morbidities may dominate the clinical picture and so ADHD in adulthood can be missed, with resultant under-diagnosis and under-treatment (McIntosh et al., 2009; Ginsberg et al., 2014); on the other hand, it is the co-morbidity that may bring the patient to medical attention. Proper treatment of ADHD can prevent the development or worsening of comorbid conditions or even produce improvement (Spencer et al., 2006; Biederman et al., 2009; Cortese et al., 2016).

It should be noted that ADHD onset precedes the typical age-of-onset of most of these co-morbidities, serving as an early entry point into the cascade of deteriorating health. Substance use disorders appear in adolescence and further in adulthood. School achievement and social/legal functioning suffers measurably in ADHD with comorbid externalising or internalising conditions (Cuffe et al., 2015). Suboptimal decision making, impaired delay discounting and excessive risk-taking behaviour track to adulthood (Schoenfelder and Kollins, 2016; Pollak et al., 2018), and eventually shorter life expectancy is found in the

ADHD patients due to death by suicide and accidents (Dalsgaard et al., 2015). It can well be thought that the common co-morbidities of ADHD such as depression, addiction, and obesity develop secondarily to the primary disease owing to lifestyle differences. Yet there are reasons to argue that the roots of co-morbidities trace back to much earlier, to the genetic predisposition and early development (Biederman et al., 1998; Gnanavel et al., 2019).

1.2 ADHD as a genetic disorder and relevance of life events to its development

ADHD is a highly heritable disorder, with a heritability estimate of 0.76 (Faraone et al., 2005). However, the genetics of ADHD is not Mendelian, but polygenic and only a few risk genes have been identified in genome-wide association studies (GWAS) (Demontis et al., 2019). As for all common mental disorders, most of the genetic risk variants identified so far do not seem to be in protein coding but rather regulatory regions (Frydas et al., 2022; Quinn et al., 2018; Xiao et al., 2017). This opens up the possibility that genetic risk interacts with environmental factors.

While in case of ADHD research the role of genetics has overshadowed environment, quantitative heritability estimates are imprecise owing to the multiple potential impacts of familial aggregation, and gene-environment correlation must also be taken into account. Many factors in physical and social environment are statistically related to the development of ADHD. ADHD is associated with premature birth and low birth weight (Faraone et al., 2015; Momany et al., 2018) that have both intrinsic and environmental components. Maternal stress, as well as tobacco smoking or alcohol intake during pregnancy,

are risk factors of ADHD, and other toxic compounds in the environment, poor nutrition, and adverse life conditions during childhood have also been found to contribute to overall ADHD risk (Sciberras et al., 2017; Zhu et al., 2014). While all these factors are far from being specific to ADHD, it is noteworthy that ADHD risk ratios increase the lower is the Apgar score, indicative of the perinatal factor severity (Halmøy et al., 2012). It should however be borne in mind that environmental effects are not free of genetic influence (see Section 5.1).

1.3 ADHD co-morbidity has genetic origins

Major co-morbidities of ADHD also have significant genetic components. In twin studies, the heritability of depression has been assessed just below 40% whereas it is thought that subtypes of this disorder exist with higher heritability rate (Flint and Kendler, 2014). Heritability is even more notable within the variety of substance use disorders (Prom-Wormley et al., 2017) and obesity (Singh et al., 2017), with heritability estimates between 40-70% (Kendler et al., 2012; Herrera and Lindgren, 2010).

GWAS have also agreed on the existence of common aspects in the genetic background of ADHD and its comorbidities, including depression, substance abuse and obesity (Demontis et al., 2019; Anttila et al., 2018). The polygenic risk score of ADHD can predict several other conditions, with the largest power of explanation for body mass index (BMI; r^2=0.45), tobacco smoking (r^2=0.33), lower cognitive abilities (r^2=0.38), alcohol abuse (r^2=0.20) and some facets of the personality dimension neuroticism (Du Rietz et al., 2018), the latter being a major risk factor for depression (Kendler et al., 2006). Genetic correlation (r_g)

between ADHD symptoms and problem drinking has been estimated up to 50% (Derks et al., 2014). ADHD clustered together with major depression in the SNP based meta-analysis of eight psychiatric disorders by the Psychiatric Genetics Consortium, and r_g was 0.44 (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

2. ADHD and dopamine

As the genetic studies reveal a contribution of multiple genes to ADHD, the underlying pathogenesis of the disorder remains unknown. One of the most plausible hypotheses implies that genes with impact on the central dopamine system are implicated in the etiopathology of ADHD, and that might interact with environmental conditions. This gains support from multiple, converging lines of evidence. Drugs used to treat ADHD act on catecholaminergic neurotransmission, and both cortical and subcortical dopamine systems are disturbed in ADHD (Faraone, 2018). Alteration in dopamine transporter function is the most consistently observed neurochemical peculiarity in ADHD (Krause, 2008) and treatment response to methylphenidate closely correlates with increase in dopamine release as estimated by positron emission tomography (Volkow et al., 2012). Dopaminergic activity is necessary for maintenance of a normal hedonic tone, that is, one's characteristic ability to feel pleasure. Low hedonic tone has been suggested as a common endophenotype of ADHD, depression and substance abuse (Sternat and Katzman, 2016).

2.1 The dopaminergic system

Midbrain dopamine producing neurons can be found in the substantia nigra (SN), the ventral tegmental area (VTA) and the retrorubral field. These nerve cells give rise to projections to many cortical and subcortical areas that are traditionally described as the dopaminergic mesotelencephalic pathway and often divided into nigrostriatal, mesolimbic and mesocortical components. These emerge from the A8, A9, and A10 cell groups: A8 and A9 cells contribute to all these components while A10 cells mostly innervate ventral and partially dorsal striatum (Björklund and Dunnett, 2007). The development of midbrain dopamine neurons is a complex process governed by multiple signalling pathways and specific morphogens, guided by the genetic programme but likely to be affected by environmental factors with impact on epigenetic fine-tuning (Perrone-Capano and Di Porcio, 2010; Wang et al., 2020). The mesocortical dopamine pathway is organized along a mediolateral axis: the evolutionarily older system from the VTA innervates the anterior cingulate cortex and medial frontal areas while in primates, who have a more expanded cortical dopamine innervation, the lateral dopamine perikarya in the dorsolateral and lateral SN project to dorsal and lateral areas of the prefrontal cortex (Williams and Goldman-Rakic, 1998).

Dopamine is synthetized from tyrosine with one intermediate step and stored in synaptic vesicles in dopaminergic nerve terminals. Activity of the enzyme tyrosine hydroxylase (TH) is the rate-limiting factor in dopamine synthesis. Once released, dopamine can act on five subtypes of dopamine receptors, all belonging to the G-protein coupled receptors superfamily. Dopamine D_1 and D_5 subtypes are coupled to G_s and other receptors to G_i proteins; D_1 and D_5 share many

functional characteristics as do D_2 and D_3. Released dopamine can be transported back to the presynaptic terminals by high affinity uptake by the dopamine transporter (DAT), and metabolized by a number of enzymes, of which the most important are the monoamine oxidases (MAO) and catecholamine-O-methyl transferase (COMT). Levels of the main stable metabolites of dopamine, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), increase with higher neurotransmitter release. The number of dopamine neurons in human brain has been estimated at about half a million in humans, but their axonal arborization is extended and branching extensive, innervation including en passant synapses (Volpicelli et al., 2020). In recent years, it has been recognized that dopamine neurons are heterogenous and can be divided into subtypes based on their gene expression profiles (Anderegg et al., 2015; Poulin et al., 2020). Consistent evidence is available for seven dopamine neuronal subtypes, with distinct localization and expression of landmark genes, but more are likely to be defined. Their divergence by function remains to be examined in more detail. Recent studies have also clarified the process of dopamine release as occurring at synaptic hotspots containing active zone proteins that mediate vesicle priming and release (Banerjee et al., 2022).

2.2 Dopamine, physiology and behaviour relevant to ADHD and co-morbidities

Dopamine is a catecholamine neurotransmitter implicated in a large variety of physiological functions (Klein et al., 2019), especially in the experience of pleasure, reward-seeking behaviours and delay discounting, drug addiction and, most generally, motivated behaviour. Dopamine is the major player for exploitation and foraging behaviour in the whole animal kingdom from

Drosophila to *Homo sapiens* (Beeler and Mourra, 2018). In humans, dopaminergic neurotransmission plays a major role in reward regulation, decision making, executive functioning and action selection of planned movements (Mobbs et al., 2018) and, via these domains, is crucially involved in a number of neuropsychiatric disorders such as ADHD, substance use and mood disorders, schizophrenia, as well as conditions such as Parkinson's disease and obesity. Subcortically, dopamine maintains response to salient environmental stimuli and helps to initiate either approach or avoidance (Ikemoto and Panksepp, 1999). For behavioural fine-tuning, dopamine enables successful cognitive control in prefrontal cortex where the mesocortical projections support stimulus gating, maintaining and relaying functions that comprise executive control, helping to integrate sensory information with knowledge on context in order to prepare appropriate responses and ensure that behaviour is flexible as necessary (Ott and Nieder, 2019).

Research in animals, including primates has shown that dopamine release is modulated in either a phasic or a tonic way, and spiking of dopamine neurons is basically a prediction algorithm for future rewards, their timing and relative size (Schultz, 2015). In striatum, the dopamine-mediated reward signals are integrated to respond properly to sensory cues (Valjent et al., 2019), and furthermore integrated with input on aversive stimuli (Tidey and Miczek, 1996; Luo et al., 2018). While animal models and neurophysiological single cell clamps have provided good insight into how temporal prediction of reward works, characterization of long-range connectivity in humans is still incomplete despite the availability of some smaller fMRI studies. Recent animal studies with viral

vector-based technologies have revealed that individual groups of dopamine neurons make unique contributions to the processing of reward and aversion (Verharen et al., 2020).

This level of resolution can not yet be applied to humans. However, it is known that in various neuropsychiatric diseases the ability to delay or self-limit rewards like social cues, food or illicit drugs and alcohol is limited (Grimm et al., 2017; Dalley et al., 2008; Castrellon et al., 2019). These diseases range from ADHD and addictive disorders to obesity, and one common feature of these diseases is an impairment of the dopaminergic reward system. Behavioural studies in patients with ADHD have shown association of symptoms of hyperactivity/impulsivity with steeper temporal discounting in a condition where the rewards and delays have been real (Scheres et al., 2008). Recent brain imaging studies have supported the role of the striatum as a central node in reward processing and prediction, and revealed that blunted response during reward anticipation in ventral striatum can been observed in various neuropsychiatric diseases from ADHD to depression to obesity (Whitton et al., 2015; Faraone, 2018; Volkow et al., 2017).

2.3 Dopamine, early life stress and the development of psychopathology

The dopamine system is also suggested to mediate the impact of early adversities on vulnerability to psychopathology (Gatzke-Kopp, 2011) as alterations in dopaminergic signalling at early age can elicit enduring changes in brain function at molecular and cellular levels (Areal and Blakely, 2020). Besides its role as a neurotransmitter, dopamine acts as a growth differentiating factor

during development, being especially significant for differentiation and migration of the inhibitory gamma-aminobutyric acid interneurons of the cerebral cortex. Dopamine also impacts neuronal differentiation in adult age (Ohira, 2020). Some evidence connects developmental trajectories to the modulatory effect of a variety of neuropeptides on dopaminergic systems (Bisagno and Cadet, 2014; Phua et al., 2020; Romanov et al., 2020).

A recent meta-analysis of rodent studies suggests that only a few indicators of dopaminergic function are reliably affected by early life stress, but that some striatal measures are robustly altered (Bonapersona et al., 2018): tyrosine hydroxylase activity has been found reduced and levels of the principal metabolite DOPAC elevated by stress. Such findings suggest that tonic dopaminergic activity is altered in animals with early experience of adversities, and this, in turn, can reduce phasic responses to salient stimuli, resulting in lower flexibility in reward-driven behaviour.

Given all these premises, one could expect that gene by environment (G × E) interactions between the key genes for shaping dopaminergic activity and adverse life events abound, and are shared to a significant degree between ADHD, affective disorders, substance abuse and obesity. However, no study has explicitly addressed any of the possible parallelisms of dopamine-related G × E in these conditions. Owing to this knowledge gap we therefore review the existing literature on dopamine-related G × E for ADHD and each major co-morbid condition.

3. Dopamine gene variants and G × E with particular reference to ADHD

The general theme of G × E in ADHD will receive limited treatment here as it is extensive on its own and has been recently reviewed elsewhere (Franke and Buitelaar, 2018; Nigg et al., 2010). The reports on candidate gene variants and environmental factors moderating each other in the development of ADHD represent a large variety of genotypes and environmental factors, and herewith the focus will be on the dopamine system. Indeed, dopamine-related genes have been examined most often, and *DRD4*, *DAT1*, and *MAOA* polymorphisms have been found to interact with factors ranging from maternal tobacco smoking during pregnancy to inferior parenting behaviour (Franke and Buitelaar, 2018; Nigg et al., 2010). Among dopamine related candidate genes, studies on the *DRD4* gene polymorphisms are the most compelling and suggest a modest association with ADHD (Faraone et el., 2001; Faraone and Mick, 2010; Faraone et al., 2005; Gizer et al., 2009; Hawi et al., 2015; Li et al., 2006; Li et al., 2014).

3.1 *DRD4*

Dopamine-D_4-receptors are located in the frontal cortex at high levels, and also in some subcortical regions such as the amygdala, while striatal levels are low (Oak et al., 2000). The most studied polymorphism in the *DRD4* gene, initially associated with the personality trait *Novelty Seeking* (Malhotra et al., 1996) is a variable number of (imperfect) tandem repeats in exon 3 (2-11 repeats of a 48 bp region), most commonly 2, 4 and 7 repeats (>90% of the observed population allelic diversity), coding a proline-rich sequence of 16 amino acids in the third intracellular loop of the receptor (Lichter et al., 1993). In most studies

individuals have been described as short or long allele carriers (6 and less vs. 7 and more) (Ding et al., 2002; Van Tol et al., 1992). Early in vitro experiments suggested that the 7R variant has a blunted response to dopamine in comparison with that of the 4R or the 2R variant (Van Tol et al., 1992). This has not been well replicated, and more recent in vitro electrophysiological studies and in vivo optogenetics have suggested greater functional efficiency in 7R compared to 4R variants, possibly due to heteromerization with dopamine-D_2-receptors (Zhong et al., 2016; Bonaventura et al., 2017) which has been underscored by a functional bioluminence resonance energy transfer study (Sánchez-Soto et al., 2018). Interestingly, presence of the *DRD4* polymorphism interacts with a *DRD2* polymorphism in association with alcohol dependence (Mota et al., 2013b) and this interaction was also related to the risk of conduct disorder in ADHD patients (Mota et al., 2013a; see section 5.2).

DRD4 exon 3 polymorphism meta-analyses show a modest but significant association with ADHD (OR 1.16-1.9), especially with symptoms of inattention rather than impulsivity/hyperactivity (Faraone et al., 2001; Faraone et al., 2005; Li et al., 2006). Paradoxically, *DRD4* 7R carriers may have better attention performance in neuropsychological tests under certain conditions (Faraone and Mick, 2010). In one study, the 4R homozygotes were found to make more omission and commission errors, and to have higher response time variability in the continuous performance test (Kim et al., 2017), but only if they also carried a variant of another ADHD risk gene, *GIT1* (G protein-coupled receptor kinases (GRK) interacting proteine gene). Otherwise, the better attention performance of longer *DRD4* allele carriers has been observed in the context of emotional stimuli

(Wells et al., 2012) as well as smoking-related cues (Munafó et al., 2008). In learning and memory tasks the 7R carriers demonstrated higher attention to high-priority items relative to low-priority items, whereas their attention to minor items was impaired, a finding that may be interpreted as a plasticity gene effect (Gorlick et al., 2015). Given that these experimental studies have had a limited number of participants, such a speculation may be premature, but the concept of plasticity alleles (Belsky and Pluess, 2009), as applied to the *DRD4* 7R (Wells et al., 2012; Gorlick et al., 2015), would be consistent with a better performance of carriers of a "risk allele" under demanding conditions and for brief periods. "Plasticity genes" or plasticity alleles refer to the issue of common occurrence of gene variants that appear as generating increased susceptibility to either negative or positive environmental influences (Belsky et al., 2009). If the predominant environmental impacts are fitting with the predisposition brought about by a plasticity allele, then it may even be under positive selection while under other circumstances its effects, including on procreative potential, are negative. Indeed, 7R is a result of a recent mutation that has been under heavy positive selection after emerging in Upper-Paleolithic about 50 000 years ago (Wang et al., 2004), but whether this selection has any relationship to ADHD traits as has been suggested (Ding et al., 2002) is far from certain (Thagaard et al., 2016). It would nevertheless be expected that in certain conditions the healthy 7R subjects also perform poorly, and indeed the 7R carriers with the diagnosis of ADHD are more prone to make mistakes in tests such as matching figures, and be prone to give wrong answers more quickly (Langley et al., 2004).

In the vast literature on the variable number of tandem repeat (VNTR) *DRD4* genotype, a common theme is the higher environmental sensitivity of the 7R carriers. This includes externalizing behaviour (Bakermans-Kranenburg and van IJzendoorn, 2006) that could be observed at very early age (Windhorst et al., 2014; King et al., 2016). Association of the *DRD4* 7R genotype with ADHD is more clear in boys, and it is often observed in early age (El-Faddagh et al., 2004). It is not immediately apparent whether this is owing to sex-related biological differences or rather to the gender role aspects and thus a G × E issue. In a similar vein, the impact of both nature and nurture can be significant in the geographic variation of the association between *DRD4* 7R and ADHD, which seems to be more obvious in South American populations, moderate in European-Caucasians, rather contradictory in Asian populations and the weakest in Middle–Eastern populations (Nikolaidis and Gray, 2010). The *DRD4* 7R has however a very low prevalence in Asians, and both 2R and 7R alleles (*vs.* 4R) have been associated with ADHD in Chinese populations (Leung et al., 2017; Leung et al., 2004). An identified environmental factor leading to higher odds of ADHD in DRD4 7R carriers is *in utero* exposure to tobacco smoking (Neuman et al., 2007).

A few other *DRD4* polymorphisms have been studied for potential association with ADHD. No significance in meta-analysis of 6 studies (Gizer et al., 2009) was found for the 120 vs 240 bp duplication 1.2 kB upstream of transcription start site but the haplotype of 240 bp and exon 3 7R allele may go along with higher levels of inattention (Faraone et al., 2005). A single nucleotide polymorphism (SNP) 521 bp upstream of the transcription start site (−521 C/T; rs1800955) has

been reported to be functional in vitro, with the T allele showing 40% lower expression; this allele has an association with ADHD (OR 1.21; Gizer et al., 2009). No G × E interaction has however been reported for these gene polymorphisms.

3.2 *DRD2*

The gene for dopamine-D_2-receptor, much studied in connection to addiction (see below), has not been consistently associated with ADHD (Gizer et al., 2009). Regarding the G × E aspect, lead exposure and a polymorphism affecting DRD2 function (rs1800497, also known as TaqIA) were interactively associated with the thinning of cortex in certain brain areas in children with ADHD, which was not observed in healthy controls (Kim et al., 2018). It should be noted that the TaqIA polymorphism that has a small but consistent association with alcohol use disorder (Smith et al., 2008) was mistakenly attributed to the *DRD2* region and is instead located within the coding region of a gene that lies 10 kB downstream, *ANKK1* (ankyrin repeat and kinase domain containing 1; Neville et al., 2004). Some (Pohjalainen et al., 1998; Jönsson et al., 1999) but not all (Laruelle et al., 1998) studies have found lower striatal dopamine D_2 receptor availability in the A1 allele carriers, and the A1 allele may by associated with higher expression of dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa (DARPP-32, Kunii et al., 2014). Because DARPP-32 is a key regulator of the downstream dopaminergic (and glutamatergic pathways), and by convention of dealing with the Taq1 polymorphism as dopamine D_2 receptor related, it will be included in the corresponding section. Further work with *in vitro* and *in vivo* models has recently suggested that *ANKK1* expression could be indicative of a

net effect of activity in competing pathways of different dopamine receptors (Koeneke et al., 2020).

3.3 DRD5 and *DRD1*

Dopamine-D_5-receptors have a distinct role in striatal synaptic plasticity that is instrumental to normal spontaneous motor activity (Centonze et al., 2003). *DRD5* has a dinucleotide repeat approximately 18.5 kb from the 5′ end (Hawi et al., 2003), and according to meta-analyses and a joint analysis of data from 14 published and unpublished studies, the 148 bp repeat is associated with ADHD (OR 1.24-1.34), whereas the 136-bp repeat may be weakly protective (Li et al., 2006; Lowe et al., 2004; Gizer et al., 2009; Wu et al., 2012). A single study has however reported a significant association for the 148 bp repeat with protective effect (Mill et al., 2004). A number of less studied genotypes and haplotypes of *DRD5* have also been associated with ADHD (Faraone and Mick, 2010). However, this applies to childhood ADHD as no association has been found in adults (Klein et al., 2016). Some evidence exists that *DRD1* variants similarly have an effect on childhood but not adulthood ADHD (Ribasés et al., 2012).

3.4 TH

Because the enzyme tyrosine hydroxylase is rate-limiting to the synthesis of both dopamine and noradrenaline, *TH* genotype is of obvious interest. Reports on the association between *TH* genotypes and ADHD are however scarce. The intronic tetranucleotide five-repeat polymorphism is not associated with ADHD, neither

in case-control nor familial design studies (Barr et al., 2000; Comings et al., 1995; Payton et al., 2001). *In vitro* studies have indicated that the SNP polymorphism rs2070762 is functional as an intronic enhancer site (Wang et al., 2008) and it has shown nominal associations with both childhood and adulthood ADHD diagnosis (Ribasés et al., 2012). Rs2070762 also moderates the efficacy of methylphenidate treatment in ADHD children, the C-allele carriers showing less effect of treatment in subjects whose mother had been smoking tobacco during pregnancy (Pagerols et al., 2017).

3.5 DAT1

While multiple receptor proteins mediate the effect of dopamine to intracellular signal transduction, the dopamine transporter (DAT) is responsible for all the re-uptake of dopamine. Due to the efficacy of DAT-targeting psychostimulant treatment in ADHD, the potential association of *DAT1* and ADHD has been studied thoroughly. Most attention has been paid to the functional 3′UTR VNTR and indeed, meta-analyses show a small but significant association between the 480-bp/10R risk allele and ADHD in childhood (Faraone et al., 2005; Gizer et al., 2009; Hawi et al., 2015). Significant, but weak to modest in size, associations were also reported for several other *DAT1* polymorphisms (Gizer et al., 2009). *DAT1* has been the most investigated gene in imaging genetics of ADHD, but the variable results obtained remain patchy (Klein et al., 2017). Several variants of *DAT1* have been found to moderate the association between being small for gestational age and ADHD (Waldie et al., 2017). Some variability in results of individual studies on the *DAT1* 3′UTR VNTR genotype may be related to the association of the *DAT1* genotype mainly with the hyperactive-impulsive subtype

of ADHD, or the role of environmental variables (Gizer et al., 2009). For example, young children homozygous for *DAT1* 10R allele have higher hyperactive/impulsive symptom scores if exposed prenatally to tobacco smoke as compared to 10/9 and 9/9 genotypes and with no exposure, a similar pattern also holds for oppositional behaviour (Kahn et al., 2003). In contrast, the *DAT1* 440 bp (9R) allele and exposure to tobacco smoke were found to be associated with the combined subtype of ADHD (OR of 2.9) as compared to unexposed subjects without the 9R allele (Neuman et al., 2007). The two aforementioned studies had however rather different samples, illustrating the challenges to the G × E perspective: In the report by Neuman et al. (2007) the subjects were twins mainly of European descent (84%), with a mean age of 13 years; in the population-based study by Khan et al. (2003), 60% of the participants were of African-American and 12% of Hispanic background, with a mean age of 5 years. Association of *DRD4* and *DAT1* genotypes with ADHD also depend on how the phenotype has been defined with regard to subtyping and severity (Todd et al., 2005).

In comparison of childhood and adult ADHD, different alleles of *DAT1* are associated across the life span, the 9R being the risk allele in adults (Franke et al., 2010). Why this is so is not clear yet, but hypothetically the ADHD in 9R carriers is more persistent and more frequently carried into adulthood; also, individuals that need medical treatment may be different in childhood and adulthood. Such a discrepancy indirectly suggests requirements on the dopaminergic system change during life (Franke et al., 2010) and the *DAT1* genotype may have a particularly significant interaction with the environmental demands that change

with age. For example, adults have more freedom to determine their activity levels in the short run while they have more long-term commitments. In terms of real-life behaviours, adult *DAT1* 9R carriers caused traffic accidents more often (Tokko et al., 2019) and pose a higher general risk in traffic (Luht et al., 2019). In contrast, the 10R/10R appeared to correspond to a plasticity genotype in the latter study, as it was sensitive in terms of traffic behaviour to an intervention aiming at impulsivity reduction. Somewhat speculatively, the DAT1 9R allele may be not related to the pathogenetic basis of ADHD but instead *independently aggravate* its behavioural consequences: The presence of this allele among young ADHD patients is associated with lower inhibitory control-related activation in the left striatum, right dorsal premotor cortex, and bilaterally in the temporoparietal cortical junction (Bédard et al., 2010) and the 9R allele was predictive of high traffic risk only in subjects with high level of ADHD symptoms (Tokko et al., 2022).

So far, evidence for G × E has come from studies examining prenatal impacts: Tobacco exposure during fetal stage interacts with *DAT1* 9R allele causing an OR of 2.9 as compared to unexposed subjects without the risk allele (Neuman et al., 2007), and maternal prenatal alcohol consumption interacted with the *DAT1* 10R/intron 8 3R haplotype to yield an OR of 3.5 for ADHD (Brookes et al., 2006).

3.6 MAOA

Monoamine neurotransmitters, including dopamine, can be catabolized by the two monoamine oxidase isoenzymes, of which MAO-A is more relevant for neuropsychiatric disorders. During infancy the expression levels of MAO-A and

MAO-B are highly correlated, but this correlation begins to decline already during childhood (Tong et al., 2013). In the brain, MAO-A is most extensively expressed in dopaminergic neurons (Westlund, 1994). By far the most studied variant of the *MAOA* gene is the upstream VNTR (uVNTR) polymorphism in the promoter region (Sabol et al., 1998). This polymorphism comprises 2-5 repeats and based on in vitro findings, the can be didvided into more highly expressing 3,5R and 4R alleles (*MAOA*-H) and more lowly expressing 2R, 3R or 5R alleles (*MAOA*-L) (Sabol et al., 1998). *MAOA*-L genotypes are associated with lower brain volume in the limbic regions, and in subjects with *MAOA*-L the responses of prefrontal cortex and amygdala to angry and fearful faces were diminished or increased, respectively (Meyer-Lindenberg et al., 2006). *MAOA-L* variants are associated with higher levels of aggression, more specifically to reactive, impulsivity related aggression, possibly precipitated by early exposure to adverse environment. The whole G × E field got a major boost when it was shown in the Dunedin birth cohort that childhood maltreatment leads to more antisocial behaviour in adolescence/adulthood at a significantly higher rate in males carrying the *MAOA*-L allele (Caspi et al., 2002), and consistent findings have been produced in many subsequent studies (Nilsson et al., 2006; Godar et al., 2016). Mostly *MAOA*-L subjects express higher aggressiveness upon provocation (McDermott et al., 2009), and the association between *MAOA*-L and violent and antisocial behaviour is mostly present in males (Reif et al., 2007; Ficks and Waldman, 2014). Besides the *MAOA* uVNTR, another functional polymorphism of the *MAO*A gene (rs6323, G941T; G allele leading to elevated MAO-A activity) has been studied in relation to aggression (Hotamisligil and Breakefield, 1991). A composite score of self-reported state and trait aggression

was associated with the polymorphism, with the T allele more common in less aggressive subjects (Sarwar et al., 2021). Teacher-rated aggression in adolescents was higher in T allele carriers, but this behaviour appears only in subjects experiencing interpersonal problems (Wang et al., 2018). T allele carriers reported a higher tendency to express anger in a very specific group males with a history suicide attempts, no such association was reported for the control group (Antypa et al., 2013). Thus the risk allele of rs6323 for aggression cannot be confirmed yet, also it seems to differ from the risk allele for ADHD (e.g. Karmakar et al., 2014).

Much attention has been devoted to this target, but evidence for implicating *MAOA* in ADHD is inconsistent. Studies on the association of ADHD and the *MAOA* uVNTR have yielded mixed results (Gizer et al., 2009), the *MAO*A-L (3R, 5R) alleles has been shown to be more prevalent or preferably transmitted in ADHD children (Das et al., 2006; Manor et al., 2002), but so has the *MAOA*-H (4R) allele (Manor et al., 2002). Another polymorphism of the *MAOA* gene that has been more frequently studied and successfully associated with ADHD is rs6323. Rs6323, a number of other SNPs, and uVNTR have been associated with ADHD in haplotype analyses, with the *MAOA*-L alleles and rs6323 G-allele contributing to the risk (Domschke et al., 2005; Hwang et al., 2018; Xu et al., 2007; Faraone and Mick, 2010; Kwon et al., 2014; Rommelse et al., 2008). For example, in an Indian population, the risk alleles of several SNPs in the *MAOA* gene, including the G allele of the rs6323 polymorphism, and uVNTR *MAOA*-L allele in haplotype with rs6323, were preferentially transmitted from mothers to ADHD probands, this was detected only in male probands, and was suggested by the author as one of the possible reasons for higher ADHD prevalence in males. The G-allele of rs6323

was also associated with ADHD symptom scores, mainly with hyperactivity (Karmakar et al., 2017). Also, the rs6323 G-allele, and uVNTR *MAOA*-L allele (in several haplotypic combinations) are more common in ADHD with oppositional-defiant and conduct disorder, increasing the odds ratio for the disorders up to approximately 2 (Karmakar et al., 2014). Although rs6323 was more prominently associated with hyperactivity (Karmakar et al., 2017), twelve *MAOA* SNP-s, and their haplotype, were associated with ADHD and ADHD-inattentive subtype, with ORs of 1.7 to 2.0 (Guan et al., 2008). The simple association of *MAOA* uVNTR with ADHD remains elusive - although metadata show no association at all, there is considerable heterogeneity between studies (Gizer et al., 2009). This heterogeneity, and previous reports concerning the sensitivity of *MAOA* uVNTR to life events, suggests that environmental factor should be considered when searching for associations between *MAOA* uVNTR and ADHD. Similarly to aggressive behaviour, there is evidence for G × E in ADHD. *MAOA* uVNTR genotype may interact with different aspects of adverse environment in leading to hyperactive behaviour: *MAOA*-L was associated with increased hyperactivity in children who experienced stressful events, whereas this genotype did not interact with family adversity (Enoch et al., 2010). In contrast, in boys who received negative parenting (inconsistent discipline, poor monitoring and physical punishment) the *MAOA*-H genotype was associated with ADHD symptoms (Li and Lee, 2012). The persistence of attention problems throughout adolescence was more stable in carriers of the *MAOA*-L and related to environmental adversities in an age-dependent manner (Zohsel et al., 2015). The rs6323 variation was associated with effortful control in Chinese schoolboys only if parenting behaviour, acceptance and involvement, was taken into account

(Zhao et al., 2020). The uVNTR *MAOA*-L genotype may be associated with a subtype of ADHD with more pronounced conduct problems, and boys with high activity *MAOA* genotype have been shown to react more favourably to methylphenidate regarding conduct problems (Guimarães et al., 2009; Lawson et al., 2003). *MAOA* genotype has also been proposed as associated to specific, emotional dysfunction/psychopathic traits in ADHD (Fowler et al., 2009).

3.7 COMT

The role of the other enzyme, catechol-O-methyltransferase (COMT) in dopamine metabolism became well acknowledged after introduction of COMT inhibitors to the treatment of Parkinson's disease (Lee et al., 2017). A common functional polymorphism in the *COMT* gene at codon 158 (Val108/158Met; rs4680) leads to 3-4-fold higher enzyme activity in Val homozygotes as compared to the Met homozygotes (Lotta et al., 1995). This polymorphism is thought to have a particular significance to dopamine function in the prefrontal cortex with reduced prefrontal cortical signal/noise ratio if dopamine levels are low (Egan et al., 2001; Mier et al., 2010). All meta-analyses have refuted a simple association of this *COMT* polymorphism and ADHD (Gizer et al., 2009; Faraone and Mick, 2010; Sun et al., 2014). Because of different distributions of the *COMT* risk allele in ethnic populations (Palmatier et al., 1999; Sun et al., 2014) meta-analytic methods combining data from different ethnic groups may not be best suited to reveal the association of COMT and ADHD, and more homogenous samples are required for further investigation. As to gene-gene interactions, the combination of *COMT* and *DAT1* risk alleles may increase the risk for ADHD in boys

(Akutagava-Martins et al., 2016). One study found evidence for G × E in the form that the *COMT* Val/Val genotype was associated with more inattention/hyperactivity symptoms in conditions of inferior socio-economic status (Nobile et al., 2010). In another, the *COMT* Val/Met genotype, family caregiving and socioeconomic risk during early childhood in a high-poverty risk rural environment had an interactive effect on ADHD symptom levels during kindergarten- and schoolyears, with Met-allele carriers more susceptible than Val/Val individuals to adverse environment (Abraham et al., 2020).

Conclusively, functional polymorphisms in the dopamine-related genes *DRD4*, *DAT1*, *MAOA,* and *COMT* have been shown to present environment-sensitive associations with both full-blown ADHD and its specific symptoms, with the risk/plasticity genotype. Also *DRD5* gene variants have been associated with ADHD, while the association of *DRD1*, *DRD2* and *TH* variants with ADHD symptomatology remains inconclusive at the moment.

4. Dopamine gene variants and G × E in domains often presenting as co-morbid with ADHD

4.1 Co-morbidity of ADHD with depression and negative emotionality, addiction and substance use disorders (SUD), and obesity and eating disorders

In community samples the rate of major depressive disorder in youths with ADHD is 5.5 times higher than in youths without ADHD; rates in different studies have been in the range of 12.5 to 50% (Angold et al., 1999). In clinical samples the comorbidity rate is even higher (Daviss, 2008). The prevalence of clinical depression is more than nine times higher in adults with ADHD (Chen et al.,

2018). Depression, similarly to ADHD, is a dimensional state, and persistent negative emotionality, including neuroticism, is the strongest predictor of depression and also genetically closely related (Smith et al., 2016). Co-morbid ADHD is a risk factor of low treatment response in depression, in particular with the selective serotonin reuptake inhibitor treatment (Katzman et al., 2017). In children the underlying genetic basis of ADHD and depression may be largely shared, with estimated 67-77% genetic correlation (Cole et al., 2009). In line with this, the first successful ADHD GWAS provided robust evidence for a shared genetic basis of depression (and related phenotypes) and ADHD (Demontis et al., 2019). The genetic correlation of ADHD with major depressive disorder was r_g=0.42, p= 7.38*10-38, and that of ADHD with depressive symptoms r_g=0.45, p= 7.00*10-19. While ADHD and depression are well known to co-occur in adulthood, little is known about the trajectory of the co-morbidity (Franke et al., 2018). Previously hypotheses have focused on environmental impacts along the lines that depression might be a psychological consequence of negative sequelae of ADHD, such as rejection, experiencing bullying, suffering from low self-esteem and else. Genetic studies have started to delineate the biological connections with a major heritability component to co-morbidity which is in line with longitudinal studies (Biederman et al., 1998). That co-morbidity develops on the basis of neurochemical development is supported by the fact that methylphenidate treatment reduces the probability of depression (Chang et al., 2016). Research on the neurobiology of depression has largely focused on serotonergic and noradrenergic systems, but a substantial body of evidence also suggests a role for dopaminergic dysfunction (Nutt, 2008). Dopamine-related genes have indeed been implicated in depression and suicidal behaviour through

candidate gene studies, with the strongest evidence for *TH*, *MAOA, COMT*, and *DRD2* (Mandelli and Serretti, 2013).

The association between ADHD and SUD may involve partly interdependent and partly independent contributions of common genetic vulnerability, other comorbid conditions, aspects of personality such as novelty-seeking and impulsivity, and self-medication attempts (Martinez-Raga et al., 2013b). GWAS strongly argue for genetic correlation of ADHD and many kinds of addictive behaviours (Demontis et al., 2019). The relative risk of co-morbidity of ADHD and SUD is higher in females than in males (Ottosen et al., 2019). Comorbid ADHD and substance use severely impact health and quality of life, with higher likelihood of suicide attempts, more hospitalizations, more probable occurrence of poly-substance abuse, lower rate of treatment adherence, and less likely abstinence (Arias et al., 2008; Kooij et al., 2013). Several polymorphisms in the genes of the main components of the dopaminergic system may be associated with addiction (Levran et al., 2015).

Obesity is a major co-morbidity of ADHD in both children and adults, and is more prominent in adults (Altfas, 2002; Cortese and Vincenzi, 2012; Cortese et al., 2016; Nigg et al., 2016; Chen et al., 2018). This co-morbidity has genetic origins (Demontis et al., 2019) that may be related to polygenic co-variance of body mass index and impulsivity (Barker et al., 2021). Most of relevant research has been focused on reduced physical activity and abnormal eating patterns as possible causes of weight gain in ADHD patients, with little attention to physiological mechanisms such as executive functions as well as appetite control

and hormonal and metabolic regulation (Hanć and Cortese, 2016). Involvement of sleep pattern alterations and inflammatory mechanisms has alternatively been proposed, but the cause-effect paths have remained unclear; involvement of both genetic and environmental aspects however appears undisputable (Cortese, 2019). ADHD has also been associated with eating disorders such as bulimia nervosa, binge eating and several measures of overeating (Kaisari et al., 2017). While hyperactivity appears to be associated to restrictive eating behaviour in males, ADHD-related impulsivity is rather associated with overeating and bulimia (Kaisari et al., 2017). The relationship between ADHD and eating disorders might however be mediated by other mental health related factors (mood, anxiety, stress-related disorders and substance use), as using these as covariates attenuated the association between ADHD and eating disorders (Ziobrowski et al. 2018).

4.2 DRD4

4.2.1 Depression and negative emotionality

The *DRD4* exon 3 VNTR 7R/longer variants have been associated with ADHD as well as autism and substance abuse, but also environmental stress reactivity and lower cognitive performance; however, not all studies agree (Mandelli and Serretti, 2013; Pappa et al., 2015; Ptácek et al., 2011; Xia and Yao, 2015). While *DRD4* does not appear as major depression-related gene, the association of this gene with the co-morbidity of substance abuse and depression has led to a suggestion of its role in conditions where internalizing and externalizing issues co-occur (Bobadilla et al., 2013). A few G × E interaction studies are compatible with the notion that the 7R allele functions as a plasticity allele. Thus, depressed

7R allele carriers were found to be particularly accurate in decoding subtle negative facial cues (Zahavi et al., 2016) and among adult adoptees, the 7R allele and history of parental problems together increased the level of attachment issues, while more positive family history made the 7R carriers the best in attachment regulation (Bakermans-Kranenburg et al., 2011). Another study, not conducted among adoptees but on a population-based sample, found the 7R allele carriers more resilient to childhood adversities (Das et al., 2011a).

Further G × E interaction studies add detail but not robustness to these findings. Childhood problems were found to cause more stress in adulthood only in *DRD4* 7R carriers compared to people with less childhood adversities (Bakermans-Kranenburg et al., 2011). Subjects with the *DRD4* long allele (7-8R) were more likely to develop PTSD symptomatology after a natural disaster (Dragan and Oniszczenko, 2009). ADHD children who were *DRD4* 7R carriers had higher expression of autistic/social incompetence symptoms (Reiersen et al., 2008) or were more aggressive during their preschool years (Farbiash et al., 2014). This might again be owing to G × E interaction because another study found that the *DRD4* 7R may lead to oppositional and aggressive behaviour in young (3 years) children only if maternal insensitivity during infancy had been observed (Bakermans-Kranenburg and van IJzendoorn, 2006). As to physiology, *DRD4* 7R carriers have lower HPA-axis reactivity to acute (social) stress in the Trier Social Stress Test) (Armbruster et al., 2009).

4.2.2 Addiction and SUD

Simple association between SUD and the *DRD4* VNTR genotype appears unlikely, but subjects with substance use related problems who carry the *DRD4* 7R show increased reactivity to substance related cues in brain imaging, more craving, and higher rates of consumption; this has been conceptualized as an increased "urge for addictive substances" (McGeary, 2009). *DRD4* 7R has also been found to increase the chance of opioid dependence (Chen et al., 2011), higher tobacco and cannabis use, and binge-drinking (Olsson et al., 2013). One study reported that the long allele carriers display more "hard" drug use and self-medication than short allele homozygotes (McGeary et al., 2007). Adult non-treatment seeking and heavily drinking *DRD4* 7R carriers had a significantly higher urge to drink following alcohol consumption (Ray et al., 2010). The *DRD4* genotype effect may also depend on the level of intoxication, interacting with indirectly estimated blood alcohol content: the increase in the urge to drink increased less with elevated blood alcohol levels in *DRD4* 7R (Ray et al, 2010). Nevertheless, among smokers the *DRD4* 7R carriers consumed more cigarettes than 4R (Das et al., 2011b), and *DRD4* 7R males reported to drink larger amounts of alcohol per session (Laucht et al., 2007).

There is preliminary evidence for G × E interactions in alcohol use disorder, e.g., *DRD4* 7R carriers had more severe alcohol dependence symptoms in case of childhood adversities (Park et al., 2011). In a real-life simulating environment (fake pub) young adult *DRD4* 7R carriers were more susceptible to social environment as they consumed substantially more alcohol in the presence of a heavy-drinking individual (Larsen et al., 2010). In contrast, a longitudinal prospective study of adolescent's alcohol consumption did not find that best

friend's drinking pattern interacted with the genotype (van der Zwaluw et al., 2012). Results from another longitudinal study have however offered a possible explanation to the apparent controversy; namely, although alcohol consumption of friends is a major contributor to alcohol intake throughout adolescence and young adulthood, it is moderated by the *DRD4* 7R genotype only in adulthood (Mrug et al., 2014). *DRD4* 7R carriers furthermore had more persistent alcohol dependence symptoms if they had been in college/sorority (Park et al., 2011). Another prospective large-scale gene-environment study on young adults did not corroborate the environment and *DRD4* gene interaction on alcohol consumption (Carlson et al., 2015). In *DRD4* 7R carriers the risk for potential addiction may arise from favourable outcomes during alcohol consumption: Only in 7R carriers did alcohol increase the subjective assessment of levels of positive social bonding compared to control and, to a lesser degree, to placebo (Creswell et al., 2012).

Drug use in young adult rural African-American youngsters occurred more often in subjects with *DRD4* 7R genotype who experienced high levels of life stress during late adolescence (Brody et al., 2012). Although the *DRD4* polymorphism had no independent impact on cannabis use, Dutch adolescents with the 7R alleles used more cannabis when less monitored by their parents, whereas subjects with the same genotype used cannabis the least if monitored more (Otten et al., 2012).

4.2.3 Obesity and eating disorders

The *DRD4* VNTR risk/plasticity allele 7R has been associated with higher BMI in several studies (Fontana et al., 2015; González-Giraldo et al., 2018; Hanć et al.,

2018), and with eating more of palatable food. In some studies the presence of BMI effects of the *DRD4* polymorphism strongly depends on ethnic background (Guo et al., 2006; Guo et al., 2007). The mechanism has been searched for in the realm of cognitive processing and in obese subjects carrying the *DRD4* 7R allele information processing was slower in neuropsychological tests (Ariza et al., 2012). However, testing of executive function with multiple tests in a sample of boys with ADHD did not reveal any difference by overweight, while overweight was more common in the 7R allele carriers in this study (Hanć et al., 2018).

A wide variety of G × E interactions have been described for the *DRD4* VNTR genotype regarding diet and body composition. The 7R allele was found associated with dietary fat intake as measured with a food questionnaire in 4-year-old girls so that, under adverse socioeconomic conditions (low income) fat intake was higher with 7R whereas in favourable conditions fat intake was lower (Silveira et al., 2016). In another study, the *DRD4* 7R allele was associated with obesity in interaction with home environment in young children: the 7R allele carriers who had experienced less maternal sensitivity at 6-14 months of age had higher BMI (Levitan et al., 2017). In a group of female seasonal affective disorder patients, the highest lifetime BMI was associated with the interaction between DRD4 7R allele carrier status and springtime birth season (Levitan et al., 2006). The authors hypothesized that the combination of seasonal low affect and energy conservation/weight gain could be caused by lower level of nutrients and light exposure in autumn/winter/spring pregnancies, causing a “thrifty” phenotype, that may have been beneficial in the distant past but not adaptive any longer in modern environment. The highest BMI was reported in bulimic 7R allele carriers

born in fall (Levitan et al., 2010). Some data has emerged that *DRD4* genotype may be implicated in food consumption and food related environment - children carrying the 7R allele, and especially those living in areas with proportionally less healthy food retailers, had more energy-dense diets e.g. high-fat, high-sugar food (Paquet et al., 2021). A path model of the role of dopamine genes including *DRD4* in the ADHD and obesity link was recently tested (Patte et al., 2020) and will be discussed below (4.3.3).

In summary, for the DRD4 studies of all major co-morbidities have focused on the exon 3 VNTR, and suggest the carriers of the 7R variant are more responsive to either beneficial or aversive environments.

4.3 DRD2

4.3.1 Depression and negative emotionality

The *DRD2* gene is associated with adolescent depression (Xia and Yao, 2015), but the sex/gender factor may be of importance: For example, in a genetically isolated population in Northern Finland depressive symptoms were associated with the *DRD2* rs4274224 genotype only in males (Nyman et al., 2011). For this gene, again most of the findings concern the TaqIA (rs1800497) polymorphism associated with alcoholism (Blum et al., 1990) that later was demonstrated to be located in the neighbouring *ANKK1* gene (Gluskin and Mickey, 2016) but affects *DRD2* expression. In the longitudinal Cardiovascular Risk in Young Finns study stressful life events did increase depressive symptoms in A2 homozygotes, whereas A1 carriers, usually considered to have heightened risk for alcoholism, were unaffected (Elovainio et al., 2007). Positive parenting did not interact with

this polymorphism in a longitudinal study in Chinese children to predict depressive symptoms (Cao et al., 2018). This study nevertheless reported that a different *DRD2* polymorphism, A241G, interacted with maternal parenting during adolescence in a complex manner (Cao et al., 2018). While A1 homozygotes had higher levels of depression symptoms in a study on small children, interaction with parental intrusiveness increased these symptoms in A2 homozygotes while the A1 carriers became less depressed (Hayden et al., 2010). On the other hand, other reports suggest that in specific population groups, or in case of specific stressors, it may be the A1 allele carriers who respond with higher depression levels to life adversity (Vaske et al., 2009a, 2009b; Zhang et al., 2015).

4.3.2 Addiction and SUD

The *DRD2/ANKK1* TaqI polymorphism has a well established association with alcoholism, as alcoholism occurs more often in subjects carrying the A1 allele (Munafò et al., 2007). A meta-analysis of 44 studies suggested the odds ratio to be 1.26 (Smith et al., 2008). Importantly, a longitudinal follow-up of alcohol dependent patients treated for acute alcohol intoxication revealed that the A1 carriers had shorter survival (Balldin et al., 2017). In meta-analysis, the *DRD2/ANKK1* TaqI is also associated also with smoking initiation (Munafò et al., 2004) but not with several other measures of tobacco smoking (Munafò et al., 2009). As to the G × E interactions, these come from rather mixed environments and have used quite different measures, either not finding interactions of *DRD2/ANKK1* Taq1A and childhood adversity (Schellekens et al., 2013), or demonstrating that alcohol consumption levels were higher only in case of more

occupational/home/monetary stress in male *DRD2*/*ANKK1* A1 allele carriers of Mayan descent (Madrid et al, 2001). Another finding was that interaction with past home environment smoking and self-reported craving in adolescent smokers was more pronounced in *DRD2*/*ANKK1* TaqI A2 homozygotes with high exposure to tobacco smoke (Kleinjan et al., 2015).

Concomitant presence of the risk alleles of *DRD4* and *DRD2* polymorphisms was found protective of alcohol dependence (Mota et al., 2013b), and the risk allele of *DRD2* was associated with conduct disorder in ADHD patients only if the *DRD4* risk allele was not present (Mota et al., 2013a; see section 3.1). Mechanistic speculations on the necessary level of alteration of receptor dimerization can be constructed; however, it would be necessary to test how subjects with these risk variant combinations behaviourally cope with environmental demands.

4.3.3 Obesity and eating disorders

DRD2 has been one of the most studied genes in relation to nutrition/obesity owing to expression in circuits responsible for cognitive and appetitive functions, and the sensitivity to environmental cues, manifesting in G × E (Sun et al., 2017). The *DRD2*/*ANKK1* TaqI polymorphism has again received most attention. Children with two *DRD2*/*ANKK1* TaqI risk alleles recalled markedly higher energy intake, including sugar intake, and had higher adiposity measures compared to children with one or no risk alleles (Cardel et al., 2019). Obese Chilean girls carrying the *DRD2*/*ANKK1* TaqI A1 allele scored higher in Satiety Responsiveness and Emotional Undereating scales, while obese boys with the A1 allele scored higher in Enjoyment of Food scale (Obregón et al., 2017). Thus,

while this genotype does not consistently predict obesity or adiposity, the *DRD2*/*ANKK1* TaqI A1 allele is associated with lower food related self-control and in some studies preference for fast food (Yeh et al., 2016; Lek et al., 2018). The *DRD2*/*ANKK1* TaqI genotype has been found to interact with the obesity-related gene *FTO*: The *FTO* rs8050136 genotype had an impact only on body fat amount, waist circumference and fasting insulin levels only in *DRD2* TaqI allele A1 carriers in an adult sample of subjects with increased risk for diabetes (Heni et al., 2016). The *DRD2*/*ANKK1* TaqI genotype may also affect the ability to achieve and maintain healthy weight (Winkler et al., 2012; Roth et al., 2013). The incentive value of food is dependent on the obesity level, and in obese people the A1 allele has been associated with excessive reinforcing value of food, leading to higher caloric intake, at least in laboratory conditions (Epstein et al., 2007). Brain imaging study measuring food-related striatal activation showed that blunted striatal response to food–related cues is a risk factor for both current high BMI and prospective increase in BMI, especially in subjects carrying the A1 allele (Stice et al., 2008). The *DRD2* Taq1a genotype may play a role in healthy eating habits and food related environmental cues: In a middle-aged Canadian sample, healthy eating was associated with the genotype so that the A1-allele carriers were more susceptible to increased promotional exposure (Nielsen et al., 2020). Other interactive effects reported for the *DRD2*/*ANKK1* TaqI include more emotional eating in adolescent A1 allele carriers if their mothers or fathers were excessively controlling (van Strien et al., 2010), and overall significantly poorer results of A1 allele carriers in neuropsychological tests of executive function if being obese (Ariza et al., 2012).

Patte and colleagues (2020) postulated a model in which the *DRD4* VNTR polymorphism contributed to occurrence of ADHD symptoms leading to overeating that would be further moderated by *DRD2* variants to produce an increase in BMI. In their adult sample (n=421) of mostly females of European origin and a broad range of BMI (average 32.5), *DRD4* genotype was not significantly associated with ADHD symptoms, the symptoms however contributed to overeating and by this route (but not directly) to higher BMI. Overeating was also moderated by the *DRD2* multilocus genetic profile score (including four polymorphisms), but this association was entirely accounted for by the *DRD2/ANKK1* TaqI polymorphism.

In summary, the *DRD2/ANKK1* TaqI polymorphism may be related with lower self-control in aversive circumstances, facilitating the development of ADHD co-morbidities, but this may depend on other dopamine-related genotypes, e.g., *DRD4* and *FTO*.

4.4 DRD5 and *DRD1*

4.4.1 Depression and negative emotionality

DRD5 has not received much attention in studies on clinical depression, but evidence for its involvement in the neurobiology of depression has been found in animal models (Kang et al., 2020). In one published study no robust G × E interaction effect was found for *DRD5* in the development of depression (Nyman et al., 2011). Similarly have clinical studies produced relatively little evidence for the implication of *DRD1*, but a recent animal experiment demonstrated a rapid antidepressant-like effect of optogenetic stimulation of D_1-expressing pyramidal

neurons in prefrontal cortex; activity of these neurons was also critical for the antidepressant-like effect of ketamine (Hare et al., 2019).

4.4.2 Addiction and SUD

Nominal association of the *DRD5* SNP-s with addiction has been reported (Wei et al., 2012; Levran et al., 2015), but the ADHD-related upstream VNTR was not specifically associated with co-morbidity of ADHD and SUD (Carpentier et al., 2013). No evidence has been provided as to the interaction with environment.

Several SNPs in the related *DRD1* gene may influence the development of drug abuse (Zhu et al., 2013; Levran et al., 2015) although multiple measures taken make further rigorous studies necessary. *DRD1* does not seem to have been examined in the context of interaction with the environment.

4.4.3 Obesity and eating disorders

The *DRD5* gene variants have not been found to associate with obesity, but methylation of this gene has shown an association with BMI (Ramos-Lopez et al., 2018). Neither has *DRD1* been associated with obesity, but animal studies suggest the role of the dopamine D_1 receptor in exercise motivation (Roberts et al., 2012) and in the timing of feeding and diet induced overconsumption and obesity (Grippo et al., 2020), suggesting a possible contribution to ADHD-related obesity.

In summary, the role of genes encoding the dopamine D_1 and D_5 receptor subtypes largely is postulated on the basis of evidence from animal models, and

hypothesis-based human study with a proper design would be valuable either to confirm or reject their substantial implication.

4.5 TH

4.5.1 Depression and negative emotionality

As in case with ADHD, genetic association of *TH* with depression is surprisingly weak while there are a few leads implicating the *TH* Pst1 polymorphism (Furlong et al., 1999) or a functional tetranucleotide repeat variation in the first intron (HUMTH01 microsatellite; D'Souza and Craig, 2008; Jönsson et al., 1996; Meloni et al., 1998) in mood disorders or suicide attempts (Serretti et al., 1998; Souery et al 1996; Persson et al., 1997). The potential for the *TH* involvement G × E interaction is suggested by a report that occupational stress leading to depressive symptoms was associated with methylation of the gene (Miyaki et al., 2015).

4.5.2 Addiction and SUD

There is limited evidence suggesting associations of *TH* gene variants with several manifestations of addiction. The functional *TH* gene SNP polymorphism rs2070762 increases the risk for opioid addiction (Randesi et al., 2017). The tetranucleotide repeat polymorphism in intron 1 of the *TH* gene is associated with severe tobacco smoking; the 4-repeat allele was found to be protective from tobacco dependence (Anney et al., 2004; Olsson et al., 2004). In a population of hospital patients undergoing alcohol rehabilitation, the *TH* gene polymorphism Val81Met (rs6356) Val/Val genotype was overrepresented, the OR for alcoholism with this genotype being 1.98 (Celorrio et al., 2012). Such distinction

in allelic distribution is noticeable only in subjects with early onset alcoholism but not in late onset alcoholics (Dahmen et al., 2005). The rs10770141 (C−824T) polymorphism, with the T-allele leading to more active enzyme and higher levels of urinary monoamine metabolites (Fukuda et al., 2013; Rao et al., 2010; Rao et al., 2007) has been associated with opioid dependence (Liu et al., 2020). In a population-based sample none of the 8 genotyped *TH* SNPs (not including rs6356) were associated with excessive alcohol intake (Celorrio et al., 2016). G × E interactions have however not been studied yet.

4.5.3 Obesity and eating disorders

The *TH* gene has been associated with obesity in the *IGF2-INS-TH* (insulin-like growth factor 2/proinsulin/tyrosine hydroxylase) haplotype analyses (Rodríguez et al., 2006). Chronic high-fat diet-induced obesity is associated with upregulation of tyrosine hydroxylase gene expression in mice (A.K. Lee et al., 2010), together with D_2 and D_4 receptor gene expression (Huang et al., 2005). In male rats tyrosine hydroxylase (and DAT1) gene expression was also increased by feeding high fat diet to their mothers, in association with increased body fat and related metabolic alterations (Barrand et al., 2017). Apart from diet, relevant studies to the impact of environmental factors in obesity appear missing.

Summarizing the finding with the tyrosine hydroxylase gene a relatively larger number of variants have been suggested to play a role, but with very limited replication. To reject *TH* gene as a candidate a well-powered and, in terms of environment, well-controlled investigation would however be needed.

4.6 DAT1

4.6.1 Depression and negative emotionality

The dopamine transporter gene *DAT1* has received much attention in depression studies but it does not appear as an independent contributor to depression. On its own the *DAT1* 3' UTR VNTR genotype was weakly associated with suicide attempts, but not in interaction with abuse in adults (Murphy et al., 2011). A few studies have suggested more specific effects that may have relevance to co-morbidities. Depressed *DAT1* 9R carriers were more accurate while decoding subtle positive facial cues, and depressed 10R homozygotes were more efficient in detecting negative cues (Zahavi et al., 2016). If differences in this experimental paradigm are relevant to depression, it should follow that the *DAT1* genotype, while not important for the overall risk of depression in population, could differentially contribute to specific pathogenetic pathways of depression in subgroups of patients (Harro and Oreland, 2001). In one stratum of people, characterized by obesity, 9R homozygotes have been found with higher levels of depressiveness if not with clinical depression (Bieliński et al., 2017). Another *DAT1* (rs1042098) polymorphism was related to depressive symptoms in 11 years old children, especially in interaction with birth weight: T homozygotes with low birth weight had more depression symptoms than C allele carriers with low birth weight and average birth weight children irrespective of genotype (D'Souza et al., 2016). Yet another *DAT1* polymorphism (rs40184) interacted with early developmental environment in increasing risk to depression: the TT (vs CC and CT) genotype was associated with depression diagnosis and suicidal ideation, but not anxiety, only in interaction with perceived maternal rejection

(Haeffel et al., 2008) in a highly specific study group (incarcerated young male adolescents and young adults).

One study examined a sample comprising children aged 5-10 years with or without ADHD, used birth weight as a global measure of prenatal environment, and modelled the development of negative emotionality and externalizing behaviour (Tung et al., 2017). The authors found that putative dopaminergic genetic plasticity (*DRD4* 7R allele + *DAT1* 10R/10R) interacted with prenatal environment (higher birth weight) to predict less negative emotionality in childhood, and by this means contributed to lower externalizing behaviour in childhood and adolescence.

4.6.2 Addiction and SUD

DAT1 polymorphisms have been found to moderate the effects of pharmacotherapy of substance use disorders (Patriquin et al., 2015), and be associated with addiction (Bhaskar et al., 2012; Stolf et al., 2017). The VNTR polymorphism was reported to moderate the relationship between acute response to alcohol and symptoms of alcohol use in future, so that within 6 years of follow-up, the acute effect was predictive of the development of symptoms in the 9R-allele carriers (Schacht et al., 2019). The 9R-allele carriers were more sensitive to drug cues in states of intense craving (Moeller et al., 2013). Nevertheless, G × E interactions have not been studied.

4.6.3 Obesity and eating disorders

DAT1 10/10 genotype has been associated with a higher BMI in healthy young adults (González-Giraldo et al., 2018) and with higher consumption of palatable foods as well as to larger waist circumference in young children (Fontana et al., 2015). In contrast, in a study on obese subjects the *DAT1* 9R homozygotes had not only higher levels of depression symptoms but also higher BMI (Bieliński et al., 2017). Yet another *DAT1* variant, TT genotype of the rs1048953 polymorphism, was associated with higher daily caloric intake (Fontana et al., 2015). Explicit testing of G × E interactions of the *DAT1* genotypes with obesity remains to be carried out.

Thus, studies have mostly focused on the *DAT1* 3' UTR VNTR genotype that appears to be a variation associated with the plasticity in the dopamine system and deserves further investigation.

4.7 MAOA

4.7.1 Depression and negative emotionality

Genes encoding the two major dopamine catabolizing enzymes have both been reported to interact with the environment in relation to depression. In pooled analysis of all reported childhood psychiatric problems, the *MAOA*-L variants were more susceptible to early-life adversity (Kim-Cohen et al., 2006). In several studies not considering the environmental factors, however, *MAOA*-H genotypes are associated with depression (Kim-Cohen et al., 2006; Lung et al., 2011). A number of studies have reported the *MAOA* uVNTR effect on depression interactively with gender; e.g., the functionally more active *MAOA* promoter

variants lead to higher levels of recurrent depression only in females (Schulze et al., 2000), probably after experience of stressful life events (Plieger et al., 2019).

It has been proposed that *MAOA* genotype effect on behaviour is likely to be traced back to fetal development (Harro and Oreland, 2016). Indeed, *MAOA* G × E interactions may be detectable as early as 5 weeks after birth: Maternal life events and socioeconomic status (deprived neighbourhood) at 32th week of pregnancy in combination with child's *MAOA*-L genotype led to expression of negative emotionality (crying and fussing over minor routine hassles) in 5 week old children (Hill et al., 2013). Maternal sensitive parenting (observed during play behaviour) towards toddlers (29 weeks) however interacted with the child's *MAOA*-L genotype in leading to angrier reactions in response to mild everyday frustration producing situations in children at 14 months of age (Pickles et al., 2013). Newborn *MAOA*-L carriers displayed higher levels of negative emotionality temperament and had a more prolonged cortisol response to acute stress (Bajgarova and Bajgar, 2020). In preschool children *MAOA* uVNTR genotype was associated with depression and anxiety symptoms interactively with caretaker depression and perceived family conflict: Boys with the *MAOA*-L variants were more reactive to adverse settings. In case of low levels of caretaker depression, children with *MAOA*-L genotypes had the least depression symptoms (Lavigne et al., 2013).

A possible framework incorporating *MAOA* genotype, environment and psychopathology was proposed by Beach et al. (2010) in a retrospective study of childhood maltreatment and lifetime psychopathology in adult adoptees: The G ×

E interaction of *MAOA* and adverse childhood events can lead to depressive symptoms either directly (as a function of high activity *MAOA* variants) and via antisocial behaviour (as a function of low activity gene variants). It may also be that the *MAOA* genotype and environment interaction becomes evident only in more severe cases of maltreatment: More depressive symptoms were found only among adolescents with severe forms of maltreatment and with the low activity *MAOA* genotype, while adolescents with high activity *MAOA* genotype and history of severe maltreatment were using more efficient self-coping strategies in preventing depression (Cicchetti et al., 2007).

In conclusion, *MAOA* displays modest association with depression, both independently and interactively with environment, possibly also interactively with sex and ethnic background. There is some support that higher activity genotypes may be a risk factor independently or in low adversity situations only, whereas the low activity variant is more reactive to adverse environments in producing psychopathology.

4.7.2 Addiction and SUD

MAOA uVNTR genotype has been associated with alcohol and illicit drug dependence (Gade et al., 1998). As is common to this genotype, psychopathology has mostly been associated with *MAOA*-L genotype in interaction with adversities in childhood: the low activity *MAOA* genotypes was associated with alcoholism only among sexually abused women (Ducci et al., 2008). In a study on alcohol consumption at age 17-18, the interaction was sex dependent: Similarly to antisocial behaviour, the *MAOA*-L uVNTR genotype together with psychosocial

risk factors was increasing alcohol use in boys, but in girls the risk was with *MAOA*-H genotype (Nilsson et al, 2011). This pattern of association has been corroborated in a study measuring cigarette, alcohol and cannabis use: Male college students with *MAOA*-L uVNTR genotype and with a history of childhood emotional abuse had the highest number of substances used (range 0-3). In female students, though, the greatest number of substances were used by subjects with a history of abuse and *MAOA*-H genotype (Fite et al., 2019; Fite et al., 2020). Interestingly, the *MAOA* genotype affects the relationship between the aldehyde dehydrogenase 2 (*ALDH2)* genotype and anxious/depressive alcoholism, with the protective properties of the less efficient *ALDH2* variant (leading to higher blood acetaldehyde levels) even further increased by *MAOA*-H alleles (S.-J. Lee et al., 2010).

4.7.3 Obesity and eating disorders

MAOA uVNTR has extensively been studied in male delinquent groups, and a study on alcohol dependent incarcerated subjects also associated the *MAOA*-L genotype with higher BMI (Ducci et al., 2006). In females, again G × E interactions are observed in the *MAOA*-H carrier group. *MAOA*-H females had a more prominent gestational weight gain (Goldfield et al., 2013), and while the *MAOA*-H genotype was associated with lower BMI levels in Chinese adolescent girls, this association was prevented by life adversities (Xie et al., 2014).

Altogether these findings suggest the *MAOA* gene expression to be an important sensor of adverse environments, while its biological effect may be in shaping

brain development at early stages and thus the associations with co-morbidities may result from different coping strategies under environmental pressures.

4.8 COMT

4.8.1 Depression and negative emotionality

The *COMT* Val108/158Met (rs4680) polymorphism is associated with differences in prefrontal brain activity during both cognitive (more activation in Met allele carriers) and affective processing (more activity in Val allele carriers) (Mier et al., 2010). The Val allele may lead to lower cognitive function but may also increase stress tolerance (Smolka et al., 2005). *COMT* 158Met allele carriers had higher levels of activation in hippocampal and prefrontal regions in response to negative affective stimulation; and 158Met homozygotes had a more pronounced connectivity between limbic and prefrontal cortical regions in a fMRI study (Drabant et al., 2006). Higher limbic and prefrontal activity in response to negative stimulation in 158Met allele carriers may render these subjects to be at elevated risk for negative affect (Smolka et al., 2005). Adult 158Met allele carriers with genetic depression load have an exaggerated stress hormone response (Jabbi et al., 2007a). *COMT* Val/Val genotype and *DAT1* 9/9R genotypes interactively associated with lower Sadness levels in a self-reported affective personality scale; this was attributed to the simultaneous lower frontal dopamine levels associated with the former and higher striatal levels with the latter genotype (Felten et al., 2011).

G × E interactions with *COMT* are inconclusive. In children, early stressful life events diminish cortisol in the Trier Social Stress Test and *COMT* 158Met allele

carrier status increased this stress response, but the two factors did not interact (Armbruster et al., 2012). Adverse early life events were associated with a blunted acute cortisol response in *COMT* rs4680 Met-allele homozygotes and carriers, and in contrast with increased response in Val-homozygotes (Lovallo et al., 2019). Genotypic differences in stress-response and temperament could be detected already in early infancy, as *COMT* rs4680 Met-allele was associated with positive emotionality in temperament and a more efficient downregulation of cortisol levels (Bajgarova and Bajgar, 2020). The *COMT* Val/Met polymorphism was reported to interact with maternity-related stressors in increasing the risk to postpartum depression, though the association only held for an early period (6 weeks) after giving birth (Comasco et al., 2011). A longitudinal birth cohort study found that a *COMT* haplotype (rs5993883–rs2239393–rs4680; risk haplotype CGG) interacted with high level of adversities during early developmental years to lead to depression in adulthood; this was more pronounced in males (Nyman et al., 2011). In a sample of severely depressed patients, more *COMT* 158Met allele carriers than Val/Val homozygotes had any adverse life events (Life-Events and Difficulty Schedule) prior to the occurrence of depression. Indeed presence of stressful events was most marked in *COMT* 158Met allele carriers who also had the short serotonin transporter promoter allele (Mandelli et al., 2007). There was also a gene-gene interaction present, *COMT* Met-allele in combination with the T-allele of *MAOA* T941G functional polymorphism was especially protective of childhood abuse. The stress-reaction modulation by *COMT* genotype may also interact with the *MAOA* gene; the 158Met-allele carriers, especially homozygotes, display higher acute endocrine

stress reactions if carrying the low expressing *MAOA* genotype (Jabbi et al., 2007b).

4.8.2 Addiction and SUD

Data on the involvement of *COMT* genotypes on SUD are many but contradictory (Kauhanen et al., 2000; Hallikainen et al., 2000; Tiihonen et al., 1999; Enoch et al., 2006). Perhaps the most clearly replicated result is the involvement of the Val allele of the Val108/158Met polymorphism in smoking (Tammimäki and Männistö, 2010). Some variance in alcoholism study outcomes has been attributed to different drinking environments, contrasting regular social (risk for 158Met) to heavy episodic (risk for 158Val) drinking (Enoch, 2006a). A few studies do suggest that *COMT* G × E interactions occur in the development of addiction. One study reported that males with a history of childhood adversities who carried the low-activity 158Met allele developed alcohol dependence more readily than the Val homozygotes (Schellekens et al., 2013). Adverse early life events were associated with earlier age of the first alcoholic drink and the number of different illicit drugs ever tried, and this association was more pronounced in Met allele carriers (Lovallo et al., 2019). A possible mechanism for explaining the effect of G × E by the *COMT* genotype and environment in addiction related behaviour involves reward sensitivity: The 158Met homozygotes with a history of childhood adversities, compared to heterozygotes and Val homozygotes, display a greater activation of ventral striatum and anterior cingulate cortex as a response to a reward in a neuropsychological game (Boecker-Schlier et al., 2016). Among Chinese inpatients with SUD, subjects with the *COMT* rs737866 TT genotype together with childhood adversities was

associated with earlier onset of heroin use, in part mediated through impulsivity (Li et al., 2012).

4.8.3 Obesity and eating disorders

COMT Val158Met genotype has been reported as not associated with BMI (Wallace et al., 2015) but the Val-allele was associated with preference for unhealthy food. Two other polymorphisms (rs933271 and rs4646310) in the *COMT* gene predicted BMI change during adolescent years (Zhao et al., 2017). Once more, explicit testing of G × E interactions with *COMT* genotypes with obesity is missing in literature.

In population-representative samples, the functional *COMT* variants are associated in a gender-dependent manner with such major adaptive resources as education and career choice (Kurrikoff et al., 2018), so further investigations should include salient life course modifiers.

5. Caveats and perspectives

In summary, the role of dopamine neurons and genes encoding the pivotal proteins for dopaminergic neurotransmission in ADHD, depression, substance use disorders and obesity is beyond doubt, and that they are involved in the frequently occurring co-morbidity of ADHD with these other conditions is highly likely. Nonetheless, direct evidence for this mostly remains to be produced. A large number of factors that has placed limitations to relevant studies exist and these have to be addressed in further investigation. In the following comments a few of these factors, as derived from the neurobiological background and the

overview of the literature above, have been highlighted for consideration in the design of future studies.

5.1 The challenge to measure environment, and separate its effect from that of genes

Many studies report a highly specific association between a gene variant and a phenotypic measure without any consideration of environmental variables. On the other hand, studies that include environmental variables may have these defined in a highly specific manner that makes the possibility of true replication questionable. Quite a number of such reports may describe false positive findings. Most studies include age, sex, social factors etc. as confounding factors but standard statistical approaches may be inadequate; in stringent analysis gene × covariate + environment × covariate interaction terms should be included (Keller, 2014).

Environments contain many factors that have been shaped by genetics of the subjects and their parents. Animal studies have suggested that maternal care is dopamine-dependent (Li, 2020), and thus likely to vary by parental dopamine gene makeup, providing an early source of differential stimulation of the offspring that will feed interaction with their own genotype. Furthermore, choices that people make are to a large extent derived from their genetic predisposition (Scarr and McCartney, 1983), so several, probably all "environments" that are measured have major heritable components that can have modest to moderate impact (Kendler and Baker, 2007). For example, what children and adolescents eat is to a large degree determined by the choice of

their parents with whom they also share gene variants. Further, these heritable components vary by environment and over life course. After leaving the home of parents, in young adults the food choice will become individualized while affected by acquired habits.

Thus, simple lumping small studies together into a meta-analysis does not do justice to the data, because the categorization of environment may be qualitatively different and, by definition, G × E interactions are bound to vary qualitatively in distinct environments. Analytical models usually have the disadvantage of assumption of linear relationships, and this may be far from reality. G × E interactions are not multiplications of equal, independent partners. Each individual is surrounded by several "environments". In our example on diet, the family has eating traditions that are shaped by but not entirely representative of cultural preferences and geographical constraints, and more generally world-wide, the socio-economic conditions make a strong impact on diet. This constellation of environments may change profoundly in the life course, especially with the individual heading to independent life.

Environment is often operationalized in terms of adverse life events. The selection of these events has not been well standardized and such standardization may raise further issues if comparing studies performed at different stages of life curve or in distinct cultural contexts. Adverse stimuli often co-occur and cumulate, making quantification problematic and necessitating new analytic strategies (Nilsson et al., 2018). Furthermore, we should probably take into account the positive life events as protective factors. Most models of

differential susceptibility follow the diathesis-stress model that emphasizes the higher risk of developing negative consequences when exposed to adverse environmental influence; in contrast, the vantage sensitivity model would consider the higher genetic sensitivity being associated with an increased response to positive influence where less sensitive individuals benefit less (Assary et al., 2018).

It is expected that as the public databases are increasing in size, modern machine learning methods will come to aid. What is required is improvement in quality of defining environments, together with conceptual development regarding what in the environment matters most.

5.2 Dimensionality and dynamics of ADHD symptomatology, with possible relevance to co-morbidity

It need be noted that symptoms of ADHD are not categorical and exclusively present in patients, but are all dimensional and can be rated as continuous measures within any population (Mulligan et al., 2009). Patients with diagnosed ADHD therefore can be conceived as being at the end of a normal distribution of symptom severity that however interferes with their social functioning leading to significant impairment (Faraone et al., 2006; Faraone and Larsson, 2019). Twin studies have consistently shown that the extreme and sub-threshold ADHD symptoms are genetically strongly linked (Levy et al., 1997; Larsson et al., 2012). The dimensional aspect of ADHD does also have a role in co-morbidity: The probability of an occurrence of co-morbidity rises with the number of ADHD symptoms present. For example, in an adult general population of the NEMESIS

study, the proportion of subjects with any mental disorder co-morbidity was continuously increasing within a 3-year period with increased number of ADHD symptoms: It was 11% in symptom-free participants and 75% among those with 4 or more ADHD symptoms of the ASRS screen (that is, essentially corresponding to the ADHD diagnosis), but 26% if 1-2 symptoms were present and 57% among subjects with three symptoms (Vogel et al., 2018). Total ASRS scores have been associated with co-morbidity in a dose-dependent manner in other samples (Estévez et al., 2012). The sub-syndromal inattention symptoms have been particularly significant in predicting symptoms of depression and anxiety (Das et al., 2012). Both genetic and environmental factors could contribute to the qualitatively similar relationship of clinical and sub-syndromal ADHD with co-morbid conditions. Clinically diagnosed ADHD and ADHD scores in general population have a strong genetic overlap (Demontis et al., 2019), and subjects with sub-syndromal ADHD symptoms have reported less healthy lifestyle (Weissenberger et al., 2018) similarly to full-blown ADHD. Symptoms of ADHD in general population are statistically associated with personality traits similarly to ADHD patients, with positive association with neuroticism and psychoticism, and negative correlation with extraversion scores (Li et al., 2019).

ADHD is a dynamic entity (Francx et al., 2015). Twin studies show that new sets of genetic risk factors appear during adolescence and early adulthood (Chang et al., 2013). Subjects who are categorized as having the condition undergo changes of the symptom profile during development. Hyperactivity symptoms wane during development while inattention remains stable thus becoming more prevalent, and emotional lability also increases with age (Franke et al., 2018).

The dimensional continuum and the changeability of the symptomatology through development may be related to the relationship of typical early and adult onset ADHD, the latter possibly based on subthreshold childhood ADHD (Faraone and Biederman, 2016). Diagnosis itself may be delayed owing to the innate high compensatory capacity of the individual (Katzman et al., 2017). Thus, large-scale analyses should go beyond case-control design by inclusion of dimensionally measured ADHD symptoms, and correct for age and sociodemographic measures such as education or profession.

5.3 Samples and targets

All samples are biased one way or another, and examining a selection of candidate genes brings about the well-acknowledged statistical issues. Hypothesis-free testing of the whole genome in large samples compensates for a few of the shortcomings of candidate-based research, but it may appear that GWAS has denied the role of dopamine: In genome-wide association analyses, genes directly relevant to catecholaminergic neurotransmission have not popped up for ADHD. Indeed this is true for other major neurotransmission systems, but it is likely that as the number of analyzed cases is increased, many candidate genes will appear in GWAS as well. Inclusion of 36,989 patients and 113,075 control cases helped to demonstrate that *DRD2* is associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) that is a highly heritable disorder and exclusively treated with drugs that bind to dopamine D_2 receptor. In pathogenesis, many hidden G × G interactions are likely to occur (e.g., Fageera et al., 2020), and each gene variation has a potential to be included in several pathogenetic pathways at the individual level. Altogether this

means that dopamine-related genes may have each a small effect in general but a large effect together, shaping the overall activity of the dopaminergic system.

Only a few studies have addressed the impact of dopamine G × E by means of composite risk scores. The score of five dopamine-related genotypes interacted in children with fetal growth/weight at birth such that higher number of risk alleles (*DRD2* rs1800497/Taq1A and rs1799732/−141delC; *COMT* Val158Met/rs4680; *DAT1* and *DRD4* VNTRs) was associated with increased sugar intake during a laboratory test but only in children with intrauterine growth restriction (Silveira et al., 2018). In another study, adolescents with higher levels of community adversity (poverty, single parent households, low-income jobs and unemployment in the community) expectedly had higher BMI levels and higher weight gain, but BMI and its increase were more pronounced in subjects with a composite risk score of sensitivity alleles of mostly DA-related genes (*DAT1* 3'UTR VNTR; *DRD4* exon 3 VNTR; 5-HTTLPR; *MAOA* VNTR) (Wickrama et al., 2013). Using a set of dopamine related genes (n=264) previously associated with ADHD and BMI, Mota and colleagues (2020) could detect that the *Dopamine-DARPP32 Feedback in cAMP Signaling pathway* was enriched in both ADHD/BMI and ADHD/obesity analysis, the former of the overlappings being associated with lower volume of the putamen.

The genome-wide analyses permit a more sophisticated polygenic score based analyses but will require a large number of participants with well-characterized phenotype and rigorous environmental data. Studies using environmental risk data together with polygenic risk scores derived from mega-analyses have

already addressed major depression (Mullins et al., 2016) and dimensional, sub-syndromal expression of depression (Jermy et al. 2022), substance use disorders (Barr et al., 2020) and obesity (Khera et al., 2019), and co-morbidity between depression and metabolic traits (Hagenaars et al., 2020). This approach will also shed light on the role of genes (and environment) more specifically at the endophenotype level. For example, the common polygenic risk of ADHD and depression was expressed in executive functioning deficit and specified to inhibitory control (Chang et al., 2020).

5.4 What constitutes a dopamine-related gene?

By tradition, neuropsychopharmacology considers genes directly encoding proteins responsible for dopamine synthesis, signal reception, re-uptake and catabolism as "dopamine genes". Nevertheless, dopaminergic neurons, synapses and signal transduction critically depend on a variety of other proteins, with higher or smaller selectivity to the dopamine system. The role of such proteins and their encoding genes will need to be included in the dopamine G × E perspective of ADHD co-morbidities.

The mesotelencephalic dopamine projection has a very complex regulatory network, and several of these regulatory mechanisms involve genes implicated in ADHD. For example, polymorphisms in genes associated with inflammatory pathways are found in ADHD, and these have the potential to regulate both pre- and postsynaptic components of dopaminergic neurotransmission (Dunn et al., 2019); in turn, dopamine receptors are involved in regulation of neuroinflammation by controlling the activation status of microglia and

astrocytes (Xia et al., 2019), and the adaptiveness of stress response appears to depend on the dopamine-mediated alterations in inflammation-related signals (Furuyashiki and Kitaoka, 2019). It has been pointed out that many factors involved in the specification of dopamine neurons and in the development of immune system are shared (Mesman and Smidt, 2020). For another example, *LPHN3/ADGRL3*, encoding an adhesion G protein coupled receptor, has been associated with ADHD (Franke et al., 2012) as well as with substance abuse disorders (Arcos-Burgos et al., 2019); *Lphn3* knockout mice are hyperactive as have dopamine transporter dysregulation (Mortimer et al., 2019), and *Lphn3* knockout rats display hyperactivity reducible by amphetamine treatment as well as changes in striatal tyrosine hydroxylase, DAT and DRD1 expression levels (Regan et al., 2019).

Dopamine release is under inhibitory control by serotonin via 5-HT_{2C} receptors and this may be clinically significant in a number of conditions (Trivedi et al., 2008); a meta-analysis found the *HTR2C* gene variants significantly associated with ADHD (Hou et al., 2018). In addition to other classic neurotransmitter systems, several neuromodulators are also critically important in dopamine function. A prominent candidate is neuropeptide Y (NPY), a particularly strong orexigenic signal, also a candidate for mediating resilience to stress, that can alter the activity of dopaminergic neurons in the ventral tegmental area (West and Roseberry, 2017). Dopamine effects on locomotion are offset by blockade of NPY Y_1 receptors (Kask and Harro, 2000), and dopamine can inhibit the feeding response to NPY (Gillard et al., 1993). Chromosomal regional duplication involving the NPY gene was associated with ADHD, a trend for higher BMI, and

lower brain response to reward expectation (Lesch et al., 2011), making this neuropeptide one of the most appealing candidates for dopamine G × E studies addressing ADHD co-morbidities.

Detailed studies of the dopamine D_2 receptor interactome have highlighted the close coupling of activity with several other neurotransmitter and neuromodulator receptors and ion channels, some of which may contribute to the expression of ADHD symptomatology (Chen et al., 2020). Further candidates include genes encoding intracellular proteins that are necessary for maintenance of dopaminergic synaptic function. For example, cyclin-dependent kinase-like 5 (CDKL5), a serine-threonine kinase is responsible for phosphorylation of dopamine transporter, and its absence in DAT-expressing neurons causes methylphenidate-sensitive hyperlocomotion in an animal model (Jhang et al., 2020). Given the likely dysfunction of dopamine release in ADHD, genes encoding the active zone proteins necessary for maintenance of axon terminal structure or vesicle priming such as Munc3, RIM and liprins (Banerjee et al., 2022), make further attractive targets. Neurobiologically informed hypothesis-based analyses that focus on such pathways enable hypothesis based testing in smaller samples with more rigorous definition of key environmental measures.

5.5 Conclusion

A host of findings have led to the notion that multiple G × E interactions in the dopamine system can be causally related to ADHD co-morbidities throughout the life course with early beginning. Based on large number of candidate gene studies on ADHD, medical conditions frequently comorbid with ADHD, and gene-

environment interactions, cautious suggestions about the role of *DRD4*, *DAT1* and *MAOA* may be drawn, information regarding other polymorphisms remains contradictory. Some evidence suggest that the *DRD4* exon 3 VNTR and *MAOA*-uVNTR may mediate interactions with environment in ADHD generally, and comorbid conditions specifically. Although one by one many pertinent reports could be thought of as likely false positives, all this converging evidence may also reflect the complexities of environments and the multiple adaptive response pattern of the developing brain to the dynamic and interfering challenges. Two distinct and complementary strategies could be envisioned for the future: High-throughput studies on very large samples using composite scores to permit pathway analysis and subsequent candidate gene/interaction studies on (inevitably) smaller, environment representative and well phenotyped samples, preferentially followed up longitudinally to facilitate life-course analyses.

Acknowledgments

This research was supported by the Estonian Research Council (PRG1213) and the European Commission Horizon 2020 Programme Projects CoCA (No 667302) and Eat2beNICE (No 728018).

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