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Review article

The translational genetics of ADHD and related phenotypes in model organisms

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder resulting from the interaction between genetic and environmental risk factors. It is well known that ADHD co-occurs frequently with other psychiatric disorders due, in part, to shared genetics factors. Although many studies have contributed to delineate the genetic landscape of psychiatric disorders, their specific molecular underpinnings are still not fully understood. The use of animal models can help us to understand the role of specific genes and environmental stimuli-induced epigenetic modifications in the pathogenesis of ADHD and its comorbidities. The aim of this review is to provide an overview on the functional work performed in rodents, zebrafish and fruit fly and highlight the generated insights into the biology of ADHD, with a special focus on genetics and epigenetics. We also describe the behavioral tests that are available to study ADHD-relevant phenotypes and comorbid traits in these models. Furthermore, we have searched for new models to study ADHD and its comorbidities, which can be useful to test potential pharmacological treatments.

1. Genetic models

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5% of children and adolescents and 2.5% of adults worldwide. ADHD is markedly impairing, as it can significantly increase the risk for substance abuse and for other psychiatric disorders (about 89% of ADHD individuals have a comorbid psychiatric disorder (Sobanski, 2006)), and contribute to educational and occupational failure, accidents, and criminality. ADHD results from the interaction of genetic and environmental risk factors that alter the structure and function of brain networks involved in behavior and cognition. Twin studies have estimated a heritability around 70–80% (Franke et al., 2012), and genome-wide association studies (GWAS) estimated a SNP heritability that ranges from 0.10 to

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0.28 (Anttila et al., 2018; Demontis et al., 2019b; Lee et al., 2013b), supporting the contribution of common variants to the etiology of ADHD. The largest GWAS of ADHD to date (20 K ADHD patients and 35 K controls) identified 12 independent risk loci, adding important new information about the underlying biology of ADHD (Demontis et al., 2019b). Furthermore, several studies have demonstrated a significant genetic overlap between ADHD and other psychiatric disorders, such as autism spectrum disorder (ASD), major depression (MD) and schizophrenia (Anttila et al., 2018; Lee et al., 2019), many of which co-occur frequently with ADHD. Although much progress has been made during the last five years in defining the genetic landscape of ADHD, there is still a long way to go to fully understand the molecular underpinnings of the disorder and related comorbidities. The use of animal models can help us to undeterstand the role of specific genes related, not only to ADHD, but also to its comorbid traits. Here, we review the genes that have been related to ADHD and other comorbid psychiatric traits in rodents, zebrafish and fruit fly (Fig. 1), as well as the different tests used to study these phenotypes and different pharmacological approaches applied (Table 1).

1.1. Rodents

Rodents have been extensively used in psychiatric research because of their sophisticated behavioral repertoire and their (relative) genetic similarity to humans. Moreover, while human brains are clearly larger and more developed, core anatomical features are shared between rodents and humans, including the structures and networks that govern particular behaviors. For example, in both humans and rodents, the fear and reward circuits are well-conserved (Gururajan et al., 2019). Historically, rats were the preferred species in behavioral research due to their ability to quickly learn and perform complex cognitive tasks without much experimenter manipulation. However, from the 1980 s until recently, the advance of genetic tools to manipulate the mouse genome led to an explosion in their use in preclinical settings and the conversion of rat tasks to those more suited to mice. The recent development of CRISPR-Cas9, TALEN and RNAi technologies has seen an increase in the use of genetically-manipulated rats (Meek et al., 2017). While complex behaviors, such as attention and impulsivity cannot be assessed until after weaning, this period of the rodent's development correlates well with adolescence in humans. Therefore, rodents can be used to look across most of the lifespan at behaviors related to ADHD and possible influences of genetic and drug treatments on these. Moreover, rodents can easily be used to determine the effects of a variety of environmental insults or enrichments concomitant with drug and genetic studies. In keeping with the general direction in psychiatric research, i.e., the RDOC approach (Insel et al., 2010), the complexity of ADHD cannot be fully replicated in preclinical models but specific traits or endophenotypes can be. Thus, investigation of such behaviors will ultimately provide greater understanding of the neurobiological bases of these traits and, by extension, the disorder as a whole.

1.1.1. Testing ADHD-related behaviors in rodents

A wide range of behavioral tests and tasks can be used in mice and rats to assess phenotypes that resemble symptoms observed in ADHD patients. The main tests that are currently employed in preclinical research are listed in Table 1 and Supplementary Table S1; although this is not a comprehensive list since there are a number of tasks, such as the probabilistic reversal learning task (Ineichen et al., 2012) and the affective bias test (Stuart et al., 2017), which have not yet been widely used in ADHD-related research. Below, we provide only a short overview of the three main phenotypic domains (hyperactivity, impulsivity and inattention) that clinically characterize ADHD and can be assessed in rodents (Supplementary Table S1). Both mice and rats are suitable for determining the underlying neurobiology and drug/genetic components that can bidirectionally affect these domains.

Hyperactivity is the easiest domain to quantify and can be monitored via automated tracking systems and software or even simply via counting line crossings. Moreover, different forms of activity can be recorded, such as home-cage locomotion, which can reveal changes across different phases of the circadian cycle, or novelty-induced locomotor activity in a novel environment (i.e. an open field chamber).

Impulsivity and inattention can be looked at using operant tasks, which can be performed in traditional Skinner boxes or more sophisticated touchscreen chambers. Regardless of equipment, the tasks

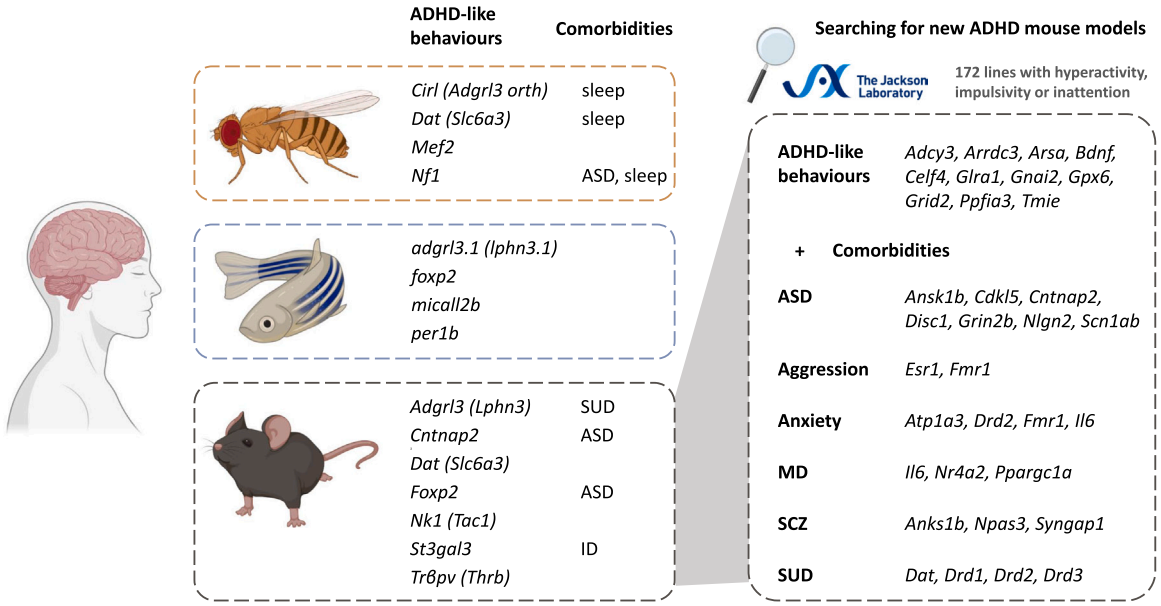

Fig. 1. Animal models of ADHD-related genes. Left panel: Genes involved in ADHD-related behaviors, hyperactivity, impulsivity or inattention, in fruit fly (*Drosophila melanogaster*), zebrafish (*Danio rerio*) and mouse (*Mus musculus*), and observed behavioral alterations related to ADHD comorbidities, including autism spectrum disorder (ASD), substance use disorders (SUD) sleep alterations, and intellectual disability (ID). Right panel: search for new models of ADHD in the Jackson database. Behavioral alterations in at least one of the three main ADHD-related phenotypes had to be present: hyperactivity, impulsivity or inattention. A total of 172 genetically modified mouse lines with ADHD-related behaviors were identified, 62 presenting also other behavioral alterations related to ADHD comorbidities. All the genes in the panel have also been related to ADHD in humans, and those with other behavioral alterations were also related to the comorbidity in humans.

Table 1
Summary of tests performed to study ADHD-related phenotypes and comorbid disorders in rodents, zebrafish and fruit flies.

		Tests used		
Disorder	Traits	Rodents	Zebrafish	Fruit fly
ADHD-related phenotypes	Hyperactivity	Open-field test	Locomotive assays	Activity monitoring, capillary feeder (CAFE) assay, open-field assay
	Impulsivity	5-choice serial reaction time task, Go/NoGo, continuous performance test, delay discounting, variable delay to signal	Locomotion (swimming) monitoring, 5-choice serial reaction time task	Courtship disinhibition assay
	Inattention	5-choice serial reaction time task, continuous performance test, Go/NoGo, variable delay to signal	5-choice serial reaction time task, object recognition task, social attention paradigm	Tethered flight paradigms, Buridan's paradigms, optomotor maze
Autism spectrum disorder	Impaired social behavior and communication, stereotypic behavior, cognitive rigidity	Three-chambered social approach, partition test, nesting behavior, ultrasonic vocalizations, open-field test, Morris water maze, T/Y maze	Shoaling assays, Y maze, interaction with conspecifics, visually-mediated social preference test	Habituation learning assay, grooming, social behavior assay, courtship song assay, Y-maze
Aggressive behavior	Aggression, social dominance	Resident intruder test, Dyadic social interaction test, social dominance test	Dyadic fight test, interaction with mirror image assay	Dyadic fight test
Anxiety	Anxiety-related behaviors, thigmotaxis	Open field, elevated plus maze, elevated zero maze, light dark box, stress-induced hyperthermia, vogel test, defensive burying, four plate test	Active avoidance conditioning	Open-field assay
Major depression	Anhedonia, despair	Sucrose preference test, Porsolt forced swim test, Tail-suspension test, progressive ratio, female urine sniffing test		Learned helplessness paradigm
Schizophrenia	Impaired sensorimotor gating	Prepulse inhibition test	Prepulse inhibition test	Larval prepulse inhibition test
Substance use disorders	Reward	Drug-induced locomotor activity or conditioned place preference	Place preference paradigm	Appetitive taste memory test, associative learning assay

evaluated in the lever-pressing/nose-poke apparatus and in the touchscreen are similar. In some cases, the touchscreen version can include more complex visual *stimuli* and allow for more fine-tuned and subtle parameters to be manipulated. However, whether this mechanism alters the behavior of the rodent has not been extensively looked at. Also, various paradigms are available in rodents to determine the individual's ability to perform set-shifting task (Heisler et al., 2015), whereby the reward can be identified either via the substrate (i.e. sawdust vs bedding) or the scent (i.e. ginger vs mint). Similarly, both intra- and inter-dimensional set-shifting can be evaluated. 5-choice serial reaction time task (5-CSRTT) can be performed in rats and mice, with some differences in training between the species, and allow researchers to determine a variety of behavioral components such as impulsivity, (in)attention, perseverance and motivation (Robbins, 2002). The continuous performance test (Kim et al., 2015; Sullivan et al., 2021) has recently been back-translated into a versatile test for assessing sustained attention, behavioral inhibition and motivation in rodents. Another test that has recently been developed for use in rodents is delay discounting, which is mainly used to evaluate impulsive choice, as well as to determine motivation and attention (Mar and Robbins, 2007; Mitchell, 2014). As with the clinical version of the test, the rodent has to choose between a small immediate reward and a larger delayed reward.

In Supplementary Table S1, we have also described tests that can be performed in rodents to assess endophenotypes related to ADHD comorbidities. Since these tests are not directly associated to ADHD and have been extensively reviewed previously, we refer the reader to the table and recent reviews (Freudenberg et al., 2018; Gururajan et al., 2019; Slattery and Cryan, 2017, 2012).

1.1.2. Strains and genetically modified rodent lines used as ADHD models

To date, several strains and genetically modified rodent lines have been used as genetic models of ADHD, the main ones have been recently reviewed by de la Peña et al. (2018) and Regan et al. (2022). In rodents, some spontaneous mutations lead to a hyperactive phenotype. This is the case for Coloboma (Cm) mice (Hess et al., 1992) and the Spontaneous Hyperactive Rat (SHR) (Sagvolden et al., 1992). Cm is a mouse strain developed by neutron irradiation that caused a mutation on chromosome 2 which disrupts about 20 genes. This mutation includes *Snap25,* pointed as the putative causal gene of the phenotype since polymorphisms in this gene have been associated with ADHD in humans (Antonucci et al., 2016; Corradini et al., 2009) and the rescue of its expression in Cm mice reduces hyperactivity. SNAP25 dysfunction in Cm mice produces alterations in the monoaminergic system, such as reduced dopamine release in the dorsal striatum (Raber et al., 1997) and increased norepinephrine concentration in the striatum, locus coeruleus, and nucleus accumbens (Jones et al., 2001), that support the construct validity of this animal model. In addition, Cm mice display the three main features of ADHD: inattention, impulsivity and hyperactivity, giving them face validity as a model for ADHD. However, the predictive validity of Cm mice is limited since hyperactivity seems to be attenuated with amphetamine but not with methylphenidate (Hess et al., 1992). On the other hand, the SHR strain was developed by inbreeding of rats of the Wistar-Kyoto (WKY) strain. These rats also show the core symptoms of ADHD (hyperactivity, impulsivity and inattention) compared to WKY rats (Sagvolden, 2000; Yamada, 2011). However, these results are controversial (van den Bergh et al., 2006), especially because WKY is a particularly inactive strain (Alsop, 2007). Besides, the most classical neurodevelopmental model of ADHD created by lesion in brain systems was obtained by neonatal 6-hydroxydopamine (6-OHDA) injection. These mice displayed good face validity, as they exhibit the major ADHD-like symptoms (hyperactivity, attention deficit and impulsivity) together with comorbid behaviors that usually appear in ADHD patients, such as anxiety-like and antisocial behaviors and decreased cognitive functioning (Bouchatta et al., 2018). Moreover, they also show predictive validity, as methylphenidate can effectively attenuate these ADHD-related traits (Bouchatta et al., 2018).

Several knockout and transgenic mice have been proposed as ADHD models (Fig. 1), mostly based on targeting genes involved in dopamine transmission, a key neurotransmitter in ADHD. One of the best described ADHD mouse models is the dopamine transporter (*Dat* or *Slc6a3*) knockout (KO) mouse (Efimova et al., 2016). DAT-KO mice show spontaneous hyperactivity, impulsive-like behavior and impaired attention and/or learning and memory deficits, giving them face validity as an animal model of ADHD. Importantly, these ADHD-related behaviors can be attenuated by treatment with methylphenidate, amphetamine, and/or atomoxetine, conferring them predictive validity (de la Peña et al., 2018). DAT plays a critical role in regulating extracellular dopamine concentration and strong evidence supports that abnormal DAT function may be involved in ADHD. Genetic studies have reported associations between gene variants and ADHD (Spencer et al., 2013); however, both increased and decreased *DAT* expression have been reported in human ADHD patients (Madras et al., 2005; Sakrikar et al., 2012; Volkow et al., 2007), hindering the establishment of its role in ADHD etiology, and thus, the construct validity of the DAT-KO mouse remains partial. In addition, the *DAT* knockdown mouse (*Dat*-KD) (Zhuang et al., 2001) or the *DAT* cocaine-insensitive mouse (*Dat*-CI) (Chen et al., 2006; Napolitano et al., 2010) are other *Dat* mutant mice presenting ADHD-related features. Finally, genetically modified mouse models not targeting dopaminergic genes also exist, such as the tachykinin-1 receptor (*Nk1r*) KO mouse (NK1R-KO) (Yan et al., 2010, 2009) and the Trβpv knock-in (KI) mouse (Siesser et al., 2006, 2005). These mutants present altered monoaminergic transmission and ADHD core behavioral features, some of which can be ameliorated with pharmacological treatment (methylphenidate, amphetamine or atomoxetine), giving them good face, predictive and construct validity as ADHD animal models (Fig. 1; reviewed (de la Peña et al., 2018)).

1.1.3. Searching for new mouse models to study ADHD and its comorbidities in the Jackson database

Since not much information is available on mouse models to study ADHD-related phenotypes together with other comorbidities, we explored available information on different mouse lines to identify novel models that could be used for ADHD, either with or without other psychiatric comorbid phenotypes. To systematically browse all the existing mouse lines and strains that present ADHD-related behaviors we used the Jackson Laboratory mouse strains database (https://www.jax.org/mouse-search). We performed a search of mouse strains that present any of the three main ADHD-related phenotypes: "hyperactivity", "impulsivity" or "inattention". We found 172 strains with specific genetic modifications in single genes (Fig. 1 and Supplementary Table S2). We then reported their behavioral alterations and found that, interestingly, 111 of these strains present only ADHD-related behaviors and 62 others present also behaviors related to other psychiatric disorders (Tables 2–3 and Supplementary Table S2). To further understand the functions of these genes we performed a KEGG pathway and Gene Ontology (GO) Biological Process over-representation analysis (http://webgestalt.org; Tables 2–3).

1.1.3.1. ADHD-related phenotypes without other known behavioral alterations. In the Jackson database we found 111 genetically modified mouse strains (with a total of 103 genes mutated) that present exclusively one or more of the ADHD-related phenotypes (hyperactivity, impulsivity or inattention), and not any additional behavior related to other psychiatric disorders (Table 2 and Supplementary Table S2). From these 111 strains, 104 present only hyperactivity, one presents only impulsivity (*Comt*) and three strains present only inattention (*Psen1*, *Snap25* and *Tardbp*) (see Supplementary Table S2). The identification of these strains is likely biased to hyperactivity probably because this behavior can be easily evaluated in a simple open-field test, frequently used as a routine test, whereas attention and impulsivity have to be tested with a specific test such as 5-CSRTT (Table 1 and Supplementary Table S1) (Higgins and Breysse, 2008), or can also be evaluated with other visual detection tasks requiring attentional engagement. In addition, not all complex tests might have been performed for some of these strains, so these results could be incomplete or biased, and these animals could present other behavioral phenotypes not tested yet.

From the 111 strains that present exclusively ADHD-related behaviors, we identified 103 known causal genes, 11 of them significantly associated with ADHD (Table 2) by analyzing, at gene level, the summary statistics from the last ADHD GWAS meta-analysis (Demontis et al., 2019b) on MAGMA (v1.06) (de Leeuw et al., 2015). Among them, we found genes with relevant brain functions which deficiency is associated with behavioral alterations present in ADHD patients, such as the *Bdnf* gene, associated with hyperactivity, obesity and hyperphagic behavior in mice (Kernie et al., 2000), and the *Arsa* gene, related with declined school performance, behavioral problems and neurological symptoms in humans (Ługowska et al., 2014). In addition, we found that this gene set of 103 altered mouse genes presenting exclusively ADHD-related behaviors is enriched for genes involved in regulation of trans-synaptic signaling and forebrain development, as well as for dopaminergic synapse genes, among other categories (Table 2). There is ample evidence at genetic, pharmacological, neuroimaging and neuropsychological levels that dysregulation of synaptic transmission and dopaminergic pathways contribute to the pathophysiology of ADHD (Arnsten, 2006; Del Campo et al., 2011; Mota et al., 2020a; Prince, 2008). Thus, it is expected that animal models with altered dopaminergic genes present ADHD-related behaviors, as has been reported in *DAT* KO mice. This evidence supports the use of the Jackson database to identify new candidate genes for ADHD and related psychiatric traits, however, further studies are needed to explore these animal models in detail and determine their contribution to the etiology of ADHD.

1.1.3.2. ADHD-related phenotypes with other behavioral alterations. A striking feature of ADHD clinical manifestation is the frequent co-occurrence with other neuropsychiatric conditions (Katzman et al., 2017). Up to 89% of individuals with ADHD also receive a diagnosis of one or more additional psychiatric disorders (Sobanski, 2006). We subsequently explored rodent models that present ADHD features together with other behavioral abnormalities related to typical ADHD comorbid major psychiatric conditions (Fig. 1).

1.1.3.2.1. ADHD and autism spectrum disorder (ASD). Both ADHD and ASD are two early-onset neurodevelopmental disorders with a high comorbidity. Indeed, 20–50% of children with ADHD also meet the criteria for ASD, and genetic studies have demonstrated shared heritability and genetic overlap between these disorders (Lee et al., 2019; Rommelse et al., 2011, 2010). In mice, behavioral tests are used to evaluate traits resembling ASD features: impairment of social interaction and communication, repetitive behaviors and behavioral inflexibility (Table 1 and Supplementary Table S1)(Ey et al., 2011; Kazdoba et al., 2016; Silverman et al., 2010). In the Jackson database, we have found 27 genetically modified mouse lines that present both hyperactivity and ASD-related symptoms (Table 3, Supplementary Table S2). From them, 23 present impaired sociability, determined by using the three-chambered social approach or the partition test, and 16 also show increased stereotypic behavior, that can be evaluated in an open-field test identifying repetitive motor movements and increased self-grooming, or in a marble-burying test (Tables 1–3 and Supplementary Tables S1–2).

Added to the impaired sociability and repetitive behaviors, some mice present other traits that can be considered as ASD-related such as altered nest building, a form of homecage activity often linked to social behavior (Silverman et al., 2010), appears in nine genetically modified mice (*Cdkl5 cKO, Cdkl5-/y, Cntnap2-/-, Crebbp-/-, Gabrb3-/-, Magi2 Tg, Shank2-/-, Shank3-/-, Uba6 NKO)*. Another ASD trait present in some mice is cognitive rigidity and perseveration, that can be evaluated in a

Table 2
Genes related to ADHD phenotypes identified in genetically modified mouse lines (Jackson database).

	Traits	Test used	Genes	KEGG pathways*	GO Biological Process*	Genes associated with ADHD[1]
ADHD-related symptoms (with and without comorbidities)	Hyperactivity	Open-field test, water maze	*Abca2; Abcg1; Actl6b; Adcy3; Adcyap1; Adipor2; Ankfn1; Anks1b; Ap3b2; Ap3d1; Apaf1; App; Arrdc3; Arsa; Atf2; Atp1a3; Atrn; Bdnf; Cacna2d3; Cacna2d4; Cacng2; Cadm1; Calm1; Camk2a; Cdh23; Cdk17; Cdk5r1; Cdkl5; Celf4; Chd3; Chd7; Chrd; Chrm1; Chrm4; Cic; Ckap5; Clic5; Cntnap2; Comt; Crebbp; Dgat1; Dgkb; Disc1; Dnajb5; Drd1; Drd2; Drd3; Dtnbp1; Dusp18; Eef1b2; Elmod3; En2; Eps15l1; Espn; Esr1; Fmr1; Fos; Foxi1; Fxr2; Gabra1; Gabra3; Gabrb3; Git1; Glra1; Gnai2; Gnao1; Gpr135; Gpr88; Gpx6; Gria1; Grid2; Grin2b; Hmox1; Htr2c; Htt; Igsf9b; Il6; Ints3; Kcna4; Kcne1; Ldlr; Lepr; Lmx1a; Lrrk2; Magi2; Maob; Mapk3; Mapt; Mcoln3; Myo6; Myo7a; Ncor1; Nlgn2; Nlgn3; Nox3; Npas3; Npc1; Nr4a2; Nr4a3; Nup153; Oprd1; Otc; Otog; Per1; Pitx3; Pkd2l2; Pnpla6; Pou4f3; Ppargc1a; Ppfia3; Ppm1f; Psap; Psen1; Ptchd1; Ptprk; Rab5b; Rgs4; Rnf214; Scn1a; Shank2; Shank3; Sirt1; Slc12a6; Slc1a2; Slc26a10; Slc5a7; Slc6a3; Slc6a8; Slc9a6; Snai2; Snap25; Snca; Sobp; Syngap1; Syt4; Tardbp; Tbc1d8; Tbx10; Tecpr2; tip; Tmie; Uba6; Ush1c; Ush1g; Vim; Vldlr; Wdr41; Whrn; Zbtb20; Zeb1; Zpld1*	Dopaminergic synapse; Amphetamine addiction; cAMP signaling pathway; Circadian entrainment; Adrenergic signaling in cardiomyocytes; Neuroactive ligand-receptor interaction; Glutamatergic synapse; Aldosterone synthesis and secretion; Alzheimer disease; Lysosome	Regulation of trans-synaptic signaling; Regulation of membrane potential; Cognition; Locomotory behavior; Synapse organization; Neuron death; Neurotransmitter transport; Ear development; Divalent inorganic cation transport; Response to radiation	*ADCY3, ARRDC3, ARSA, ATP1A3, BDNF, CELF4, GLRA1, GNAI2, GPX6, GRIA1, GRID2, MAPT, MYO7A, NPAS3, OPRD1, PPFIA3, RGS4, TMIE*
	Impulsivity	5-choice serial reaction time task	*Cadm1; Comt; Per1; Shank3*			
	Inattention	5-choice serial reaction time task, visual detection task, virtual object recognition task	*Comt; Psen1; Ptchd1; Snap25; Tardbp*			
Exclusively ADHD-related symptoms (without comorbidities)	Hyperactivity	Open-field test, water maze	*Abca2; Abcg1; Actl6b; Adcy3; Adcyap1; Adipor2; Ankfn1; Ap3b2; Ap3d1; Apaf1; APP695; Arrdc3; Arsa; Atf2; Atrn; Bdnf; Cacna2d4; Cacng2; Calm1; Cdh23; Cdk17; Cdk5r1; Celf4; Chd3; Chd7; Chrd; Chrm4; Ckap5; Clic5; Dgat1; Dgkb; Dnajb5; Dusp18; Eef1b2; Elmod3; Eps15l1; Espn; Fos; Foxi1; Gabra1; Git1; Glra1; Gnai2; Gpr135; Gpx6; Grid2; Htr2c; Snca; Ints3; Kcna4; Kcne1; Ldlr; Lepr; Lmx1a; Lrrk2; Maob; Mapk3; Mcoln3; Myo6; Ncor1; Nox3; Nr4a3; Nup153; Otc; Otog; Per1; Pitx3; Pkd2l2; Pnpla6; Pou4f3; Ppfia3; Ppm1f; Psap; Ptchd1; Ptprk; Rab5b; Rtl10; Rxylt1; Sirt1; Slc12a6; Slc1a2; Slc26a10; Slc6a8; Slc9a6; Snai2; Snca; Sobp; Tbc1d8; Tbx10; Tecpr2; tip; Tmie; Ush1c; Ush1g; Vldlr; Wdr41; Whrn; Zeb1; Zpld1*	Adrenergic signaling in cardiomyocytes; Cocaine addiction; Circadian entrainment; Amphetamine addiction; Alzheimer disease; Dopaminergic synapse; Cushing syndrome; Cholinergic synapse; Lysosome; Insulin secretion	Ear development; Locomotory behavior; Regulation of trans-synaptic signaling; Neuron death; Response to ammonium ion; Divalent inorganic cation transport; Forebrain development; Response to antibiotic; Response to oxidative stress; Organic hydroxy compound metabolic process	*ADCY3, ARRDC3, ARSA, BDNF, CELF4, GLRA1, GNAI2, GPX6, GRID2, PPFIA3, TMIE*
	Impulsivity	5-choice serial reaction time task	*Comt; Per1*			
	Inattention	5-choice serial reaction time task, visual detection task, virtual object recognition task	*Comt; Psen1; Ptchd1; Snap25; Tardbp*			

* Identified using WebGestalt software. Pathways and GO terms sorted by significance of enrichment, FDR< 0.05. Weighted set cover was applied to reduce redundancy.

[1] Genes presenting a nominal association (p-value<0.05) in the gene-based analyisis using summary statistics from Demontis et al., 2019.

classic reversal task using the Morris water maze or the spontaneous alternation T maze test, as found in *Cntnap2-/-* mice, as well as in a marble burying task, like in *Fmr1*^{I304N} mice (Table 1 and Supplementary Table S1) (Crawley, 2007; Peñagarikano et al., 2011; Silverman et al., 2010; Zang et al., 2009). Finally, a decrease in the number of ultrasonic vocalizations (USVs), normally emitted by mice in social situations, has been related to communication deficits, relevant to ASD (Table 1 and Supplementary Table S1). *Cntnap2-/-* pups and *Shank3 Tg* (a conditional KI that results in overexpressed *Shank3* in dendritic spines in the cortex, hippocampus and striatum) pups emitted significantly lower number of ultrasonic calls than wild-type littermates (Han et al., 2013; Peñagarikano et al., 2011). Also, when allowed to interact with a novel wild-type female mouse, *Shank2-/-* male mice emitted ultrasonic vocalizations less frequently than did wild-type animals, and took longer to make the first call (Won et al., 2012). In a pup retrieval assay, *Shank2-/-* female mice retrieved the pups less efficiently than did wild-type mice (Won et al., 2012).

This group of 27 genes that are altered in mouse lines showing hyperactivity and ASD-related symptoms is enriched in genes that participate in cognition, regulation of synapse structure and activity, and locomotor behavior, important functions related to ASD and ADHD (Table 3). The majority of the genes altered in these genetically modified mouse lines are listed in the SFARI database (https://gene.sfari.org/) as genes implicated in the susceptibility to autism, and some of them have also been related to ADHD in patients (Table 3 and Supplementary Table S3). These genes are highly expressed in brain, where they play a role in synaptic transmission, cell adhesion or neurogenesis. Among them, the knock-out of the *Cntnap2* gene, one of the best studied genes in ASD, recapitulates most of the features found in ASD patients (i.e. social deficits, repetitive behaviors and reduced vocal communication) and also presents hyperactivity, one of the major ADHD-related traits, making it a good candidate to study the biological bases underling these comorbid disorders (Vecchia et al., 2019b).

1.1.3.2.2. ADHD and aggressive behavior. Aggressive behavior is highly comorbid with ADHD and can be assessed as a trait or as part of diagnostic categories such as conduct disorder, oppositional defiant disorder or callous unemotional. About 47% of children with ADHD have oppositional defiant disorder and around 30–50% of them have comorbid conduct disorder (Eskander, 2020). Conversely, ADHD prevalence is also high in young and adult offenders, estimated around 30% (Sebastian et al., 2019; Young and Thome, 2011). Moreover, a recent GWAS meta-analysis identified three genome-wide significant loci for ADHD and disruptive behavior disorders, suggesting a shared genetic architecture between these two conditions (Demontis et al., 2019a).

In animal models, the most widely used test to assess aggression is the resident-intruder, since aggression often occurs in mice to establish and defend a territory (Table 1 and Supplementary Table S1) (Freudenberg et al., 2016). Social dominance can be assessed using the tube test. In general, aggressive behavior is only tested in males and, when assessed in females, usually maternal aggression is tested (Takahashi and Miczek, 2015). In the Jackson database we found 10 genetically modified mouse lines presenting hyperactivity and altered aggressive behavior, which showed either increased aggression (*Cacna2d3-/-*, *Cadm1 Tg*, *Camk2a+/-*, *Disc1 Tg*), decreased aggression (*Crebbp Tg*, *Esr1-/-*, *En2-/-*, *Gria1-/-*) or decreased social dominance (*Fmr1-/-* and *Rgs4-/-)* (Table 3, Supplementary Table S2).

Some of these genes are involved in long term potentiation, two of them have been related to aggressive behavior in humans (*CAMK2A* and *EN2*) and four have been related to ADHD too (*DISC1*, *ESR1*, *FMR1* and *RGS4*; Table 3 and Supplementary Table S3). Polymorphisms in the *ESR1* gene, coding for the estrogen receptor 1, have been associated with anger, neuroticism, indirect aggression and antisocial behavior (Fernàndez-Castillo and Cormand, 2016), and with ADHD (Pinsonneault et al., 2017). Mutations in the *DISC1* gene have been related with a broad range of psychiatric disorders, including ADHD and conduct disorder, but also schizophrenia, bipolar disorder and depression (Thomson et al., 2013). In the same line, mouse models of the *Disc1* gene show typical behaviors associated to psychiatric disorders like alterations in locomotor activity (hyperactivity in males and hypoactivity in females), deficits in prepulse inhibition and increased despair behavior (Gómez-Sintes et al., 2014), making them good models to study comorbidity among psychiatric disorders.

1.1.3.2.3. ADHD and anxiety. Around 25% of children with ADHD have comorbid anxiety disorders (Levy, 2004; Schatz and Rostain, 2006). The tests used in anxiety include elevated plus maze, elevated zero maze, light-dark box or open-field test (Table 1 and Supplementary Table S1) (Himanshu et al., 2020). Hyperactivity and differences in anxiety are present in 27 genetically modified mouse lines in the Jackson database, the vast majority assessing anxiety in the elevated plus maze (Table 3, Supplementary Table S2). From these lines, 11 show increased anxiety-related behaviors (*Cic-/-*, *Il6-/-*, *Magi2 Tg*, *Myo7a sp*, *Nlgn2 Tg*, *Oprd1-/-*, *Shank2-/-*, *Shank3-/-*, *Slc5a7 Tg*, *Uba6-/-*, *Vim-/-*), and 16 lines show decreased anxiety-related behaviors (*Atp1a3 Tg*, *Cadm1 Tg*, *Camk2a+/-*, *Cdkl5-/y*, *Crebbp Tg*, *Drd3-/-*, *Fmr1 Tg*, *Gria1-/-*, *Igsf9b-/-*, *Mapt Tg*, *Npc1 Tg*, *Rnf214-/-*, *Syngap1+/-*, *Syngap Tg*, *Syt4-/-*, *Zbtb20 Tg)*. Remarkably, sex differences were identified for one of them: *Magi2* transgenic mice show increased anxiety in males but not in females (Zhang et al., 2015). It should be considered that anxiety in *Camk2+/-* and *Uba6-/-* lines was only assessed using the open-field test, in which the animals showed increased thigmotaxis, but no other specific tests for anxiety were used (Chen et al., 1994; P. C. W. Lee et al., 2013a; Yamasaki et al., 2008). In addition to hyperactivity, *Cadm1 Tg* and *Shank3-/-* mouse lines showed also impulsive behavior (Drapeau et al., 2018; Sandau et al., 2012).

These genes seem to be involved in synapse organization, regulation of neurotransmitter levels, cognition and adult behavior (Table 3). Eleven of them have previously been related to ADHD in patients, and *ATP1A3, DRD3, FMR1, IL6, NLGN2* with anxiety (Table 3 and Supplementary Table S3). Interestingly, interleukin-6, encoded by *IL6* gene, is involved in inflammatory response, and higher IL6 serum levels are found in patients with ADHD (Chang et al., 2020; Darwish et al., 2019; Elhady et al., 2020) and anxiety (Key et al., 2022; Renna et al., 2018), as well as in patients with depression (Ting et al., 2020). In addition, higher levels of pro-inflammatory cytokines and chemokines, including IL-6, have been found in juvenile SHRs (animal model of ADHD described above) compared to Wistar Kyoto rats, suggesting a cooperation of the neurological and immune systems in the pathogenesis of ADHD (Kozłowska et al., 2019).

1.1.3.2.4. ADHD and major depression. ADHD and major depression are two psychiatric conditions that co-occur frequently, with ADHD being 7.5 times more prevalent in chronic depression than in the general population (Bron et al., 2016). Importantly, genetic studies have demonstrated the existence of shared genetic risk factors between them using different bioinformatic approaches (Du Rietz et al., 2018; Lee et al., 2019).

In the Jackson database we found seven genetically modified mouse strains that present both hyperactivity and alterations in depressive-like behavior (Table 3 and Supplementary Table S2). One of the core symptoms of depression is anhedonia, the reduced ability to experience pleasure, which can be tested in rodents with the sucrose preference test (Table 1 and Supplementary Table S1). We found anhedonia in two genetically modified strains: *Ppargc1a-/-* mice (Agudelo et al., 2014; Lin et al., 2004), and a knock-in for *Magi2* (gene expressed under the control of *Camk2a* in the excitatory neurons of the forebrain) (Zhang et al., 2015), and enhanced hedonic behavior in *Il6-/-* mice (Butterweck et al., 2003; Zhang et al., 2015). Despair is another depression-like behavior that can be tested in mice using the Porsolt forced swim test or the tail-suspension test (Table 1 and Supplementary Table S1) (Yankelevitch-Yahav et al., 2015). In the Porsolt forced swim test, *Nr4a2+/-* mice showed a depression-like profile compared to wild-type animals (Rojas et al., 2007). Conversely, reduced despair and depression-like behavior was found in *Camk2a-/-* (Yamasaki et al., 2008), *Syt4-/-* (Ferguson et al.,

Table 3
Genes related to ADHD phenotypes and comorbid disorders identified in genetically modified mouse lines (Jackson database).

Comorbidity	Traits	Test used	Genes	KEGG pathways*	GO Biological Process*	Genes previously related to patients	
						ADHD	Comorbid disorder
Autism spectrum disorders	Impaired social behavior and communication, stereotypic behavior, cognitive rigidity	Three-chambered social approach, partition test, nesting behavior, ultrasonic vocalizations, open-field test, Morris water maze, T maze	*Anks1b, Cdkl5, Cntnap2, Crebbp, Disc1, En2, Fmr1, Gabrb3, Gnao1, Gria1, Grin2b, Htt, Magi2, Mapt, Nlgn2, Nlgn3, Npas3, Rgs4, Scn1a, Shank2, Shank3, Syngap1, Uba6*	Nicotine addiction, Long-term potentiation, Glutamatergic synapse, Dopaminergic synapse	Regulation of synapse structure or activity, Localization within membrane, Cognition, Locomotor behavior, Regulation of membrane potential, Neuron death	*Anks1b, Cdkl5, Cntnap2, Disc1, Fmr1, Grin2b, Nlgn2, Npas3, Rgs4, Syngap1, Uba6*	*Anks1b, Cdkl5, Cntnap2, Crebbp, Disc1, En2, Fmr1, Gabrb3, Gria1, Grin2b, Htt, Mapt, Nlgn2, Nlgn3, Scn1a, Shank2, Shank3, Syngap1*
Aggressive behavior	Aggression, social dominance	Resident intruder test, Dyadic social interaction test, social dominance test	*Gria1, Cacna2d3, Cadm1, Camk2a, Crebbp, Disc1, En2, Esr1, Fmr1, Rgs4*	Long-term potentiation	–	*Camk2, Esr1, Fmr1, Rgs4*	*Disc1,Esr1, Fmr1, Rgs4*
Anxiety	Anxiety-related behaviors, thigmotaxis	Open field, elevated plus maze, elevated zero maze, light dark box	*Atp1a3, Cadm1, Camk2a, Cdkl5, Cic, Crebbp, Drd3, Fmr1, Gria1, Igsf9b, Il6, Magi2, Mapt, Myo7a, Nlgn2, Npc1, Oprd1, Rnf214, Shank2, Shank3, Slc5a7, Syngap1, Syt4, Uba6, Vim, Zbtb20*	–	Adult behavior, Cognition, Neuromuscular process, Synapse organization, Regulation of cell morphogenesis, Regulation of neurotransmitter levels	*Atp1a3, Cdkl5, Cic, Drd3, Fmr1, Il6, Shank3, Slc5a7, Syngap1, Uba6, Zbtb20*	*Atp1a3, Drd3, Fmr1, Il6, Nlgn2*
Major depression	Anhedonia, despair	Sucrose preference test, Porsolt forced swim test, Tail-suspension test	*Camk2a, Il6, Magi2, Nr4a2, Ppargc1a, Shank3, Syt4,*	–	Glutamate receptor signaling pathway, Response to xenobiotic stimulus, Positive regulation of neuron differentiation	*Il6, Nr4a2, Ppargc1a,*	*Il6, Nr4a2, Ppargc1a,*
Schizophrenia	Impaired sensorimotor gating	Prepulse inhibition test	*Anks1b, Fxr2, Gabra3, Hmox1, Npas3, Shank3, Syngap1*	–	Localization within membrane	*Anks1b, Npas3, Syngap1*	*Anks1b, Fxr2, Hmox1, Npas3, Shank3, Syngap1*
Substance use disorders	Reward	Drug-induced locomotor activity or conditionated place preference	*Atp1a3, Cadm1, Cic, Chrm1, Drd2, Drd1, Drd3, Dtnbp1, Gpr88, Gria1, Nr4a2, Shank3, Slc6a3*	Dopaminergic synapse, cAMP signaling pathway	Locomotory behavior, Cognition, Synapse organization	*Drd1, Drd2, Drd3, Nr4a2, Slc6a3*	*Drd1, Drd2, Drd3, Dtnbp1, Slc6a3*

* Identified using WebGestalt software. Pathways and GO terms sort by significance of enrichment, FDR< 0.05. Weighted set cover was applied to reduce redundancy.

2000) and *Il6-/-* mice (Chourbaji et al., 2006). In the case of *Il6-/-* mice, these results are supported by the ones obtained in the sucrose preference test (Butterweck et al., 2003). *Shank3 Tg* mice showed a reduction in the duration of immobility in the tail-suspension test compared to wild-type, suggesting a reduction in despair in the transgenic animals (Han et al., 2013).

These genes seem to participate in the glutamate receptor signaling pathway, response to xenobiotic stimulus and neuron differentiation (Table 3). Interestingly, some of those genes have previously been associated both with ADHD and depression, such as *PPARGC1A*, *NR4A2* and *IL-6* (Table 3 and Supplementary Table S3).

1.1.3.2.5. ADHD and schizophrenia. Recent genetic studies have demonstrated a significant genetic correlation between ADHD and schizophrenia (Anttila et al., 2018; Lee et al., 2019). Moreover, both disorders share symptoms such as impaired attention and deficits in inhibition and working memory (Donev et al., 2011). In mice, impaired prepulse inhibition (PPI) is widely accepted as the most significant endophenotype of schizophrenia and it is considered indicative of disrupted sensorimotor gating, which clinically correlates in patients with symptoms such as thought disorder and distractibility (Table 1 and Supplementary Table S1) (Amann et al., 2010; Powell et al., 2012; Van Den Buuse, 2010). In the Jackson database we have found eight genetically modified mouse lines that present both hyperactivity and decreased PPI and involve seven different genes (*Anks1b*, *Fxr2*, *Gabra3*, *Hmox1*, *Npas3*, *Shank3*, *Syngap1*) (Supplementary Table S1–2). Two other genetically modified mouse strains (involving *Fmr1* and *Mapt* genes) presented increased PPI, but this altered behavior is not related to schizophrenia. Individuals with schizophrenia suffer also from various cognitive deficits, including impaired working memory, that can be tested in mouse models using different paradigms such as novel object recognition, contextual and cued fear conditioning, or mazes (Table 1 and Supplementary Table S1) (Amann et al., 2010). In the Jackson database, three mouse lines (*Shank3 Tg, Syngap1+/-, Fxr2-/-)* present also working memory impairments added to decreased PPI, and five mouse lines (*Anks1b-/-, Npas-/-, Shank3 Tg, Shank3-/-, Syngap1+/-*) present impaired social behavior, another endophenotype of schizophrenia (Amann et al., 2010), added to a decreased PPI.

All these genes, except for *GABRA3*, have already been related to

schizophrenia in patients (Supplementary Table S2–3). Moreover, microdeletions in *ANKS1B*, *de novo* mutations in *SYNGAP1* and common variants in *NPAS3* were found in ADHD patients (Berryer et al., 2013; Carbonell et al., 2019; Weber et al., 2011). *SYNGAP1* loss-of-function variants are causally associated with several neurodevelopmental disorders (e.g. intellectual disability, severe epilepsy, ASD and schizophrenia) and ADHD is a common comorbid diagnosis with SYNGAP1-related disorders (Kilinc et al., 2018). In the same line, there are clear evidences that *Syngap1*+/- mice present several schizophrenia-related phenotypes (e.g. reduced prepulse inhibition and social isolation), however, ADHD-traits like hyperactivity are more controverted across studies (Kilinc et al., 2018).

1.1.3.2.6. ADHD and substance use disorders (SUD). Apart from the core ADHD symptoms, this psychiatric disorder is associated with an increased risk of harmful outcomes like substance abuse, and about 40% of ADHD patients present lifetime SUD (Piñeiro-Dieguez et al., 2016). This high co-occurrence is explained both by environmental (Green et al., 2010; Konstenius et al., 2017) and genetic risk factors (Du Rietz et al., 2018; Treur et al., 2021).

We have found 12 genetically modified mouse strains in the Jackson database that present hyperactivity and alterations in substance use phenotypes (Table 3 and Supplementary Table S2). The effects of drugs of abuse in mice can be studied using both unconditioned and conditioned behaviors (Martelle and Nader, 2013). Regarding the first ones, the most studied is the drug-induced locomotor activity (Table 1 and Supplementary Table S1), apparently produced by increased dopamine release. Compared with wild-type animals, *Chrm1-/-* (Gerber et al., 2001) and *autoDrd2-/-* mice (lacking D2 autoreceptors specifically) (Bello et al., 2011) display supersensitivity to the locomotor effects of cocaine. Similarly, other mouse strains exhibit locomotor supersensitivity to drugs: *Gria1-/-* mice after morphine injection (Vekovischeva et al., 2004, 2001), and *Nr4a2*+/-, *Atp1a3(Myk/+)*, *Chrm1-/-, Gpr88-/-* and *Shank3 Tg* mice after amphetamine administration (Gerber et al., 2001; Han et al., 2013; Kirshenbaum et al., 2011; Quintana et al., 2012; Rojas et al., 2007). Conversely, a low dose of amphetamine in the conditional *Cic-/-* mice (deletion of *Cic* in the developing forebrain) and in *Cadm1 Tg* mice (GFAP-DNSynCAM1, dominant-negative form of SynCAM1 specifically targeted to astrocytes) exerted a paradoxical calming effect, previously described in patients and some ADHD mice models (Lu et al., 2017). Interestingly, *Dat*-CI mice showed increased locomotion induced by amphetamine and morphine, but not by cocaine (Lu et al., 2017), and *Drd1-/-* mice showed a cocaine dose-dependent decrease in locomotion (Xu et al., 1994).

On the other hand, the rewarding effects of drugs can also be studied using conditioned behaviors like conditioned place preference (CPP) or drug self-administration (Table 1 and Supplementary Table S1). We found two genetically modified mice that showed hyperactivity and alterations in CPP. *Drd3-/-* mice showed increased morphine-induced CPP at lower doses compared to wild-type, but this effect was attenuated at the highest dose (Acilli et al., 1996; Francès et al., 2004). *Dat-CI* mice were unable to develop CPP induced by cocaine, but not by amphetamine (Chen et al., 2006), suggesting that the lack of response was produced only by the inability of cocaine to block DAT. Finally, *Dys-/-* mice showed hyperactivity combined with alterations in the operant learning paradigm (self-administration) with reward pellets, that may be due to an increased impulsive and compulsive behavior during early sessions (Carr et al., 2013; Cox et al., 2009).

These genes are involved in dopaminergic synapse, cognition and synapse organization (Table 3). Some of the genes highlighted here are key genes in the dopaminergic (*Drd1, Drd2, Drd3* and *Slc6a2*) or glutamatergic (*Gria1* and *Dtnbp1*) neurotransmission systems, essential elements of the reward system and widely studied both in ADHD and drug addiction (Table 3 and Supplementary Table S3). Interestingly, *Drd1*, *Drd2* and *Slc6a3* genes have previously been related to ADHD and SUD in patients (Supplementary Table S3). Although genes encoding the dopamine receptors are classic candidates for ADHD, experimental evidence from KO mice for these genes affecting ADHD-relevant endophenotypes is weak (Leo and Gainetdinov, 2013). Contrarily, knocking-out DAT in mouse (encoded by the *Slc6a3* gene) leads to profound changes in the dopamine release resulting in locomotor hyperactivity (Giros et al., 1996), that can be reduced with the administration of psychostimulant drugs (Gainetdinov et al., 1999), mimicking the therapeutic effects that stimulants provide to many individuals with ADHD.

1.1.3.3. Strains with genetic alterations involving several genes. In the Jackson database we found four genetically modified and six spontaneous or radiation-induced mouse strains with genetic alterations that affect more than one gene that display hyperactivity among other behavioral and neurological phenotypes (Supplementary Table S4). Apart from the Cm mice, described above, the most interesting ones are the mouse strains that bear a deletion that mimics a copy number variation (CNV) on human 16p11.2. This CNV encompasses 26 genes that are highly conserved on mouse chromosome 7F3, it has been reported in ADHD patients and it is among the most common genetic variations found in ASD (Gudmundsson et al., 2019). There are two mouse strains with an heterozygous deletion of this region: 16p11 + /- mice exhibit normal social behavior but show hyperactivity (Portmann et al., 2014), and 16p11.2df mice show both hyperactivity and stereotypic behaviors (Horev et al., 2011). On the other hand, we found mice with a duplication of about 3 Mb (about 19 genes) in chromosome 11 (Dp(11)17) that spans the genomic interval commonly deleted in Smith-Magenis syndrome patients, who present a behavioral phenotype that closely resembles ADHD (Gnanavel, 2014). These mice show hyperactivity together with abnormal social interaction and increased anxiety (Walz et al., 2004).

1.1.4. Rodent models used to test pharmacological treatments

As stated above, rodents are ideal to investigate genetic and environmental factors underlying ADHD-related phenotypes and the effect of ADHD medications on them. Indeed, in the last few decades, numerous studies have investigated how the deficiency of specific candidate genes affects the behavioral traits related to the core and comorbid symptoms of ADHD, being *SLC6A3*, encoding the dopamine transporter (DAT), the most extensively studied one in this context in mouse. Given the fact that psychostimulants act predominantly via this transporter, DAT represents the gold standard for pharmacological treatment. The consensus from these studies is that DAT deficiency causes novelty-induced hyperactivity, increased impulsivity, inattention, and cognitive impairments. These deficits can be reversed by both amphetamine and methylphenidate (reviewed in Homberg et al., 2016). These findings have been corroborated in the recently generated DAT-KO rats (Adinolfi et al., 2019), thus supporting the involvement of DAT in ADHD-related phenotypes.

Candidate-gene association studies and GWAS have identified a number of novel ADHD risk genes and, as mentioned above, several genetically modified mouse models have been generated to investigate their potential role in ADHD pathogenesis. One of them is *ADGRL3 (LPHN3)*, and knockout mice for this gene are hyperactive, impulsive, and display increased social behavior and decreased aggression. While the effects of methylphenidate and amphetamine have not yet been published, *Adgrl3* deficiency was shown to dysregulate cortical DAT expression (Mortimer et al., 2019). These findings were replicated in a rat model, as the *Adgrl3-KO* rats were shown to have a blunted response to amphetamine (Regan et al., 2019). Another candidate gene, *CNTNAP2*, has been associated with ADHD and ASD and its deletion in mice results in hyperactivity and social impairments (Jurgensen and Castillo, 2015; Peñagarikano et al., 2011). Interestingly, risperidone attenuates the hyperactivity but does not rescue the social deficits. For more details on these studies we refer the interested reader to our recent review paper which describes cross-species (*Drosophila*, zebrafish,

mouse, and human cell lines) findings on these genes (Vecchia et al., 2019b).

1.1.5. Genes identified in GWAS of ADHD and behavioral alterations in mice

The first twelve genome-wide significant risk loci for ADHD were recently described (Demontis et al., 2019b). Some of these genes have previously been linked to behavioral alterations (Fig. 1). It is the case of *FOXP2*, encoding a transcription factor of the forkhead box family, which has been in the limelight of research ever since rare mutations were found to cause a severe speech disorder (Lai et al., 2001), sometimes accompanied with mild cognitive impairment (Reuter et al., 2017). *FOXP2* has previously been associated with other complex psychiatric disorders like schizophrenia (Oswald et al., 2017; Sanjuán et al., 2021; Tolosa et al., 2010). *Foxp2* knockout mice present major deficits in reversal learning together with a downregulation of D1R expression (Co et al., 2020), and abnormal social behavior (Medvedeva et al., 2019). Another genome-wide significant hit in Demontis et al., 2019b lies in the *TMEM161B-AS1* locus, encoding a lncRNA. A risk variant in *Tmem161b* (rs10514299) has been shown to predict striatal activation during reward processing in alcohol dependence (Muench et al., 2018), which is further evidence that this target is worth pursuing in a mouse model.

The identification of *ST3GAL3*, a gene encoding the beta-galactosidase-alpha-2,3- sialyltransferase-III, as a risk gene for ADHD was unexpected, as loss-of-function mutations were previously implicated in pervasive intellectual disability (Edvardson et al., 2013; Hu et al., 2011). While *St3gal3-/-* mice display severe developmental delay and neurological deficits, partial inactivation of this gene (*St3gal3*+/-) produce cognitive deficits in males, while females showed increased locomotor activity and increased cognitive control (Rivero et al., 2021). Moreover, subtle alterations in the brain region and/or sex-specific expression of several markers implicated in oligodendrogenesis, myelin formation, and protein sialylation as well as cell adhesion/synaptic target glycoproteins of ST3GAL3 were reported.

Finally, while no behavioral findings have been reported in *Dusp6-/-* (dual-specificity phosphatase 6) mice, this gene has been related to obesity, which is a frequent comorbidity of ADHD (Kittel-Schneider et al., 2022; Ruan et al., 2016). Even though the majority of these risk genes have not been previously linked to ADHD-related behavioral changes, they represent attractive targets for further exploration.

1.1.6. Concluding remarks - rodents

To our knowledge, no models have been proposed to date for the study of ADHD with comorbid conditions. Our systematic searches in the Jackson database have now provided new insights on different mouse lines that show primarily hyperactivity with or without alterations in other behaviors related to psychiatric comorbid conditions. As mentioned before, the selection of these mouse lines is biased to hyperactivity since this behavior is easily tested in routine tests, such as the open-field test. Moreover, although less commonly assessed, it is also possible to study whether this observed hyperactivity is due to novelty and/or lack of habituation (i.e. open-field) compared with basal (home-cage) activity. Although numerous tests for measuring inattention and impulsivity traits are available, they have only been tested and described in a few mouse lines in the database due, in part, to the requirement of specialized equipment and active, as opposed to passive, measurement. Thus, it would be interesting to perform specific tests assessing inattention and impulsivity in these mouse lines (Table 1 and Supplementary Table S1) to investigate the presence of these ADHD-related traits apart from hyperactivity. The same should be mentioned regarding other specific behavioral alterations, since tests like PPI, CPP or the resident-intruder test might not have been performed on many mouse lines.

Additionally, it is important to mention that hyperactivity can be a potential confounder in the interpretation of findings from other tests, since the majority rely on locomotor activity. In certain tests, such as the 5-CSRTT or CPT, this can be less problematic but baseline locomotor alterations should always be taken into consideration when assessing attention and impulsivity.

Most of the mouse lines that were identified in our review feature alterations in only one gene. As for other mental disorders, it seems highly unlikely that any single-gene approach can capture the full breath of complex-genetic human disorders, especially when considering the further layer of gene × environment interaction complexity. Nevertheless, many of the genetically modified lines identified in the Jackson database involve specific genes that have been previously related to ADHD and comorbidities in patients (Tables 2–3 and Supplementary Table S3), which make them good models to use in future studies delineating prototypic mechanisms (rather than disorders). These mechanisms may then be more important for comorbidity – in terms of cross-disorder abnormalities – rather than (artificially defined) "pure" disorders. Moreover, as described above (Demontis et al., 2019b), the recently reported 12 genome-wide hits for ADHD represent strong targets for assessment in genetically-modified mice.

1.2. Zebrafish

The zebrafish has been used as a model for developmental biology for decades because of their rapid development and transparency at embryonic stages. Zebrafish develop outside of the mother making it easy to collect and manipulate embryos. Tools to manipulate genes, ablate cells and both visualize and manipulate neural activity using light have also been established (Albadri et al., 2017; Curado et al., 2007; Förster et al., 2018). In parallel, robust behavioral tests have been set up, enabling zebrafish to be used in translational studies of human diseases including psychiatric disorders (Norton, 2013). Although the formation, position, and function of neurotransmitter signaling pathways sometimes differ between zebrafish and other vertebrates, comparative studies are beginning to precisely map these differences, allowing the transfer of information between species (Panula et al., 2010). The ease of generating large numbers of zebrafish make them ideal for high-throughput analyses and imaging studies. As a model for translational studies, the zebrafish is particularly useful for optogenetic dissection of behavior, and time-lapse analysis of neural development. The ability to apply chemical compounds to fish by immersion rather than injection into the stomach or brain makes zebrafish an excellent animal for screens to identify psychoactive drugs, an approach that has already been used for aggression, sleep and feeding (Jordi et al., 2018; Norton, 2012; Rihel et al., 2010). Despite the impossibility of fully modelling a complex disorder such as ADHD, zebrafish have already been used to study different aspects of this disease. In the next sections we will describe recent research into the neurobiology of ADHD in this species.

1.2.1. Testing ADHD-related behaviors in zebrafish

1.2.1.1. Hyperactivity. Hyperactivity is the easiest of the three core symptoms of ADHD to measure in zebrafish. Zebrafish larvae move around consistently from about 5 days onwards, displaying beat and glide swimming that is driven by pectoral fin movements (Budick and O'Malley, 2000). At around one month, the adult pattern of locomotion emerges. Activity can be quantified by placing a single fish in a tank and using videotracking to extract parameters such as distance swum, speed of swimming, number of movement bouts and acceleration within bouts (Table 1) (Norton, 2012). Previous reports of zebrafish ADHD-like models have described both an increase in the distance swum (Huang et al., 2015; Lange et al., 2012; Yang et al., 2018) and heightened acceleration during swim bouts, termed motor impulsivity (Lange et al., 2012; Spulber et al., 2014). However, changes to locomotion are a fairly non-specific read-out of fish behavior – and more evidence is required to relate this phenotype to ADHD.

1.2.1.2. Impulsivity. Two types of impulsivity have been described in zebrafish, motor and cognitive impulsivity. Motor impulsivity, as described above, represents sharp bouts of acceleration followed by periods of inactivity in contrast to the smooth locomotion curve usually displayed by larval zebrafish (Lange et al., 2012; Spulber et al., 2014). However, whether these periods of acceleration really represent impulsivity has been questioned (Parker et al., 2012) and further research is required to understand this phenotype. Cognitive impulsivity can be measured using the 5-CSRTT, a sophisticated test that has been adapted from a similar rodent paradigm (Table 1 and Supplementary Table S1). A single adult fish is placed into an arena that contains five light emitting diodes (LEDs). The fish first selects an illuminated LED by nose poking to collect a food reward. Once this has been learned, a variable inter-trial interval is added in which animals have to wait several sections before nose poking the LED. Selection of an incorrect (non-illuminated) LED can be scored as reduced attention (an error of omission), whereas inability to wait for the duration of the inter-trial interval is scored as impulsivity (Parker et al., 2014, 2012). Pre-treatment of zebrafish with atomoxetine or amphetamine decreases impulsivity in this task, whereas methylphenidate has the opposite effect, making fish more impulsive (Parker et al., 2014). This suggests that noradrenaline signaling may influence performance of this task in fish. Therefore, the 5-CSRTT may be a useful test for ADHD models, even though it can only be used at adult stages.

1.2.1.3. Inattention. Changes in attention are a core symptom of ADHD that are likely to involve a number of physiological and psychological processes. To date, there have been few studies that have measured attention in zebrafish, and it is not clear whether zebrafish can maintain an attention set in a similar manner to other vertebrates (Echevarria et al., 2011). Major categories of attention include: orienting, expectancy, stimulus differentiation, sustained attention, and parallel processing (Bushnell and Bushnell, 1998). Orienting has been measured in a social attention paradigm in which male zebrafish were permitted to eavesdrop upon different stimuli: two male zebrafish fighting each other; two non-interacting males separated by a barrier; or an empty tank (Abril-De-Abreu et al., 2015) (Table 1). The focal fish's orientation and proximity to the stimulus was used as a read-out of attention. Sustained attention has been measured using a novel object recognition test (Braida et al., 2014) (Table 1). The amount of time spent interacting with an object presented on a video screen was recorded. Wild-type zebrafish could differentiate between a familiar and novel object up to 24 h later. 5-CSRTT has also been used to quantify sustained attention (Table 1) (Fizet et al., 2016). Zebrafish have to select one of five same color LEDs to get a food reward, ignoring the non-illuminated stimuli. Although they are capable of performing this task, zebrafish have a lower accuracy rate and response time on this test compared to rodents. This means that it is not clear whether attention measured in the 5-CSRTT can really be compared between zebrafish and other vertebrates.

1.2.2. Characterizing ADHD-related genes in zebrafish

Despite the difficulty of modelling all aspects of ADHD, zebrafish still represent an ideal model to investigate the expression and function of ADHD-linked genes in the brain. Knock-down or mutagenesis techniques can be used to investigate the function of candidate genes during neural development and the signaling pathways that they influence. Several ADHD candidate genes have been characterized in zebrafish, including *adhesion G protein-coupled receptor L3.1* (*lphn3.1/adgrl3.1*) and *period1b* (Fig. 1).

One of the first ADHD-linked genes to be studied in zebrafish was *adgrl3.1 (lphn3.1),* one of two zebrafish homologues of human *Adhesion G-protein Coupled Receptor 3*. Many of the polymorphisms in *ADGRL3* associated with ADHD are located in introns rather than the coding region, suggesting that enhancers for other genes may be affected rather than *ADGRL3.1* itself (Martinez et al., 2016). Arguing against this, an enhancer called ECR47 is expressed in the ventral forebrain, midbrain and hindbrain of zebrafish in a manner that recapitulates some of the expression pattern of *adgrl3.1* (Lange et al., 2012; Martinez et al., 2016). Transient knock-down of *adgrl3.1* makes zebrafish larvae hyperactive during both the day and night (Lange et al., 2012; Reuter et al., 2016). These animals also alter their swimming trajectory, displaying sharp bouts of acceleration that have been called motor impulsivity (Lange et al., 2012). Both of these phenotypes can be rescued by applying the prototypical ADHD treatment drugs methylphenidate and atomoxetine (Lange et al., 2012), a form of construct validity that suggests hyperactivity could be used as an endophenotype in this model. Reduction of *adgrl3.1* function also leads to a reduction and displacement of dopaminergic neurons in the posterior tuberculum, a part of the ventral diencephalon that is important for locomotion (Tay et al., 2011). Although *adgrl3.1* morphants display similar levels of dopamine in the brain as wild-type siblings, they are insensitive to drugs that interact with D1 and D2-like dopamine receptors (Lange et al., 2018). This suggests that morphants have a saturating increase in dopamine signaling that may increase locomotion by activating post-synaptic receptors. The link between *adgrl3.1* function and ADHD-like changes in behavior has been confirmed in mouse and rat (Mortimer et al., 2019; Regan et al., 2020, 2019; Wallis et al., 2012), providing strong evidence for the link between this gene and disrupted dopaminergic signalling. The ability to apply drugs to larval zebrafish by immersion means that zebrafish lacking *adgrl3.1* function represent an ideal model to screen for novel ADHD treatments. This would require a stable mutant line to be created, and ideally, further behavioral phenotyping (including impulsivity and attention) to be carried out at adult stages.

The *period1b* (*per1b*) gene is part of the circadian clock that maintains diurnal rhythms. Circadian dysfunctions are thought to contribute to the etiology of many psychiatric disorders, including ADHD (Das et al., 2016; Hodgkins et al., 2013a). Adult zebrafish *per1b* mutants display hyperactivity, inattention in a two choice serial reaction time task (similar to the 5-CSRTT described above, see Table 1) and impulsivity (Huang et al., 2015), although this was measured in a mirror test that is frequently used to study aggression (Gerlai et al., 2000) (Table 1). They also have a disruption in their circadian changes in locomotion. The hyperactivity phenotype can be rescued with methylphenidate and deprenyl, adding weight to *per1b* mutants as a model for ADHD (Huang et al., 2015). *Per1b* mutants display a reduction and disorganization of posterior tuberculum dopamine neurons (similar to the *adgrl3.1* phenotype) as well as changes in the expression of genes related to dopamine signalling: *monoamine oxidase* (*mao*) and *dopamine beta hydroxylase* (*dbh)* expression is increased, whereas *orthopedia homeobox (otp) a*, *otpb*, *mesencephalic astrocyte-derived neurotrophic factor* (*manf*), *wingless and integrated* (*wnt*) *1*, *wnt3a*, *wnt5a1* and *adgrl3.1* expression is decreased (Huang et al., 2015). Excitingly, this suggests that both *per1b* and *adgrl3.1* act in a similar pathway to control ADHD-like behaviors via dopamine neurotransmission. Treatment of *per1b-/-* mutants with auriculasin, a prenylated isoflavone extracted from the root of *Flemingia philippinensis,* decreases hyperactivity and normalizes the expression of dopamine-pathway genes (Wang et al., 2018). This shows that auriculasin may represent a novel treatment option for some aspects of ADHD, and demonstrates the power of fish models to identify novel drug targets. The *per1b* mutant is the most extensively characterized zebrafish ADHD model to date, mainly because it is a stable mutant line meaning that impulsivity and inattention can be measured in adult fish. However, the interpretation of the impulsivity phenotype may need investigating in more detail since altered interaction with a mirror could indicate decreased aggression in these mutants rather than inattention.

The *foxp2* gene encodes a transcription factor (previously described in the rodents Section 1.1.5), and changes in *foxp2* expression revealed alterations in GABAergic signaling in the brain associated with increased locomotor activity in zebrafish (Lüffe et al., 2021). Genetic and/or pharmacological disruption of either the GABA synthesizing enzyme

Gad1 or the GABA-A receptor induced hyperlocomotion similar to *foxp2* mutants, whereas the GABA-A receptor agonist muscimol rescued the foxp2 deficiency-induced hyperactive phenotype.

The Mical family is a conserved group of cytosolic multidomain proteins that are important for synaptogenesis, axon guidance and myofilament organization. Polymorphisms in *MICALL2* were identified by GWAS and eQTL sequencing of Han Chinese patients that display impaired executive inhibition, one of the core symptoms of ADHD (Yang et al., 2018). *micall2b* (*microtubule associated monooxygenase, calponin and LIM domain containing like protein 2b*), one of the zebrafish homologues of *MICALL2,* is expressed in the nervous system, whereas *micall2a* is not (Yang et al., 2018). Morpholino knock-down of *micall2b* triggers hyperactivity in larval zebrafish, a phenotype that can be rescued with atomoxetine (Yang et al., 2018). However, neither attention nor impulsivity has been measured in these animals, and the response of morphants to methylphenidate has not been measured (Yang et al., 2018). This suggests that *micall2b* needs to be investigated in more detail, in particular to understand the role of this gene in nervous system development and synaptogenesis.

The RAB6A GEF Complex Partner 1 (RIC1) protein is important for collagen trafficking from the Golgi apparatus through the cell. Human patients with polymorphisms in *RIC1* display CATIFA syndrome that includes cleft lip, cataract, tooth abnormalities, intellectual disability, facial dysmorphism and ADHD (Unlu et al., 2020). *ric1-/-* mutant zebrafish exhibit reduced locomotion, a reduced forebrain and cerebellum, as well as a craniofacial phenotype and changes to the musculature (Unlu et al., 2020). Some of these phenotypes – such as the reduced forebrain and cerebellum size – may represent endophenotypes for ADHD. However, the reduction of locomotion, and lack of information regarding attention and impulsivity means that the link between this mutant line and ADHD is not very clear.

Several other ADHD-linked genes have been studied in zebrafish without considering their behavioral function. For example, a SNP in the last intron of *GFOD1 (Glucose-Fructose Oxidoreductase Domain Containing 1)* has been associated with inattention in a study of ADHD families (Lasky-Su et al., 2008). In zebrafish, *gfod1* is widely expressed in the nervous system, with prominent expression in GABAergic neurons (Lechermeier et al., 2020). In a similar approach, *SIRBP1* (*Signal Regulatory Protein B1*) has been identified by CNV analysis of patients with a high level of impulsive-disinhibition behavior (Laplana et al., 2014). Expression analyses in zebrafish show that the fish *SIRPB1* homologue is expressed in the midbrain and muscle tissue. Further work would be required to understand if and how this contributes to impulsivity and ADHD (Laplana et al., 2014).

1.2.3. Using zebrafish to investigate comorbid symptoms of ADHD

As mentioned above, human ADHD patients display a range of comorbidities with other psychiatric symptoms, including ASD and SUD. Zebrafish have been used to investigate behaviors linked to all of these disorders.

Similar to ADHD, ASD cannot be fully modelled in zebrafish. Although some ASD-linked symptoms such as social interaction can be studied, other symptoms such as language impairment can not (Table 1) (Meshalkina et al., 2018). Several studies have characterized the expression of genes linked to ASD in the brain, and examined their behavioral function (Hoffman, 2016; Liu et al., 2018; Vecchia et al., 2019a).

Zebrafish have also been used to measure reward behavior, a component of drug addiction that could help understand SUD (Table 1). For example, a conditioned place preference (CPP) paradigm has been used to identify changes in gene expression caused by exposure to amphetamine (Webb et al., 2009). In a similar approach, a screen for mutant fish lines that display altered CPP behavior has been used to identify *SLIT3* as an important gene mediating nicotine preference in both zebrafish and humans (García-González et al., 2020).

1.2.4. The effect of ADHD treatment drugs on neural development and behavior

Current treatment options for ADHD include methylphenidate and atomoxetine, psychostimulants that interact with dopamine and noradrenaline neurotransmission. However, the effect of long-term stimulus medication on the developing brain has not been explored in detail. The effect of both acute and chronic methylphenidate treatment has been examined in wild-type zebrafish (Brenner et al., 2020; Levin et al., 2011). Acute immersion in 50 mg/L methylphenidate for the first five days of development increased the level of dopamine, noradrenaline and serotonin (5-HT) in the brain during larval stages (Levin et al., 2011). However, this phenotype recovered by one month, with drug-treated animals showing similar levels of these neurotransmitters as untreated control siblings. Furthermore, methylphenidate exposed larvae spent more time at the bottom of a novel tank (an anxiety phenotype) and exhibited decreased choice accuracy in a spatial learning test at adult stages, despite being drug-free for most of their lives (Levin et al., 2011). In a follow up study, Brenner and colleagues applied methylphenidate sub-chronically from 14, 21 or 28 days post fertilization until 12 weeks before measuring anxiety, predator avoidance and social interaction. Methylphenidate tended to decrease the fish's response to environmental stimuli, and the drug had a stronger effect on behavior when applied at later stages (Brenner et al., 2020).

1.2.5. Investigation of toxins and drugs that may trigger ADHD in humans

The symptoms of ADHD are caused by a combination of genetic susceptibility and environmental factors. Several studies have used zebrafish to examine how exposure to drugs or toxins during development can alter behavior, with potential implications for this disease. Zebrafish have been immersed in either polychlorinated biphenyls (PCBs) or perfluorooctane sulphonate (Lovato et al., 2016; Spulber et al., 2014). Both types of pollutant have been linked to an increased incidence of ADHD in humans (Rochester et al., 2018a). Embryonic exposure to the PCB mixture Aroclor (A) 1254 enhanced thigmotaxis (the preference for the side of arena, used as a read-out of anxiety) and decreased the response to a visual startle stimulus that could be a measure of attention (Lovato et al., 2016). Treatment with perfluorooctane caused persistent hyperactivity and disorganized spontaneous locomotion including fewer bouts of swimming (suggestive of motor impulsivity). This phenotype could be rescued with dexamphetamine, indicating that PCB exposure could trigger ADHD in human patients (Spulber et al., 2014). Zebrafish have also been used to investigate whether pain medication can lead to ADHD-like symptoms. Acetaminophen (also known as N-acetyl-p-aminophenol (APAP) or paracetamol) is a commonly used over-the-counter pain medication. There is evidence that prolonged acetaminophen use during pregnancy may increase the likelihood of a child displaying ADHD (Reuter et al., 2016). However, application of a low dose of acetaminophen during embryogenesis does not alter the locomotion of either wild-type of *adgrl3.1* morphants at 6 days (Saad et al., 2016). Similar results were found in a study performed in wild-type mice (Huang et al., 2015; Lange et al., 2012). This suggests that acetaminophen usage during gestation may not trigger ADHD, but further studies are needed to investigate this in more detail.

1.2.6. Concluding remarks – Zebrafish

Zebrafish have already been used as a model to investigate some aspects of ADHD, including the expression of candidate genes in the brain and the neurotransmitter signalling pathways they influence. Two interesting observations have arisen from these studies. Firstly, although the ADHD candidate genes *adgrl3.1* and *per1b* are widely expressed throughout the brain, loss of function appears to only affect a select group of dopamine neurons in the diencephalon (Huang et al., 2015; Lange et al., 2012). It would be fascinating to understand why these neurons are more susceptible to loss of gene function compared to other groups. Secondly, both *adgrl3.1* and *per1b* are expressed inposterior

tuberculum neurons, which are very important for the control of locomotion. A more detailed characterization of this brain area is needed to understand how it relates to groups of dopamine neurons in other vertebrate species.

Despite progress in establishing zebrafish as a model for this disease, there are some areas of research that could be improved. The current measurements of hyperactivity and (cognitive) impulsivity are convincing, but attention is still understudied in this species. The only zebrafish ADHD model that has been examined for all three core symptoms of ADHD – hyperactivity, impulsivity and inattention – is *per1b* (Huang et al., 2015). Other well-characterized candidate genes, such as *adgrl3.1* (Lange et al., 2018, 2012; Reuter et al., 2017), need further investigation.

The zebrafish has already contributed to understanding of several human psychiatric disorders, including anxiety and schizophrenia (Norton, 2013). Coupled to the increasing number of tools available in this species, it seems likely that zebrafish are poised to increase our understanding of ADHD, including searching for novel drug treatments for this disease.

1.3. Fruit fly

The fruit fly, *Drosophila melanogaster,* is a popular model in neurogenetics and it has been used to establish the link between genes and behaviors for half a century (Bellen et al., 2010; Benzer, 1967). *Drosophila* is cost-efficient and has a short generation time (~10 days). Approximately 75% of human genes have equivalents in *Drosophila* (Bier, 2005). The *Drosophila* genome is less redundant than the human one, and consequently mutations in a gene that represents the sole orthologue of a vertebrate gene family may cause more prominent phenotypes. The nervous system of *Drosophila*, with 15,000 neurons at larval stage and 250,000 in adulthood (Burne et al., 2011), is a relatively simple yet sufficiently complex model to study nervous system development, function, and behavior. Importantly, while there is little similarity between human and *Drosophila* brain anatomy, the principal building blocks and many neuronal processes and mechanisms are conserved (Coll-Tane et al., 2019; Hirth and Reichert, 1999; van der Voet et al., 2014).

Drosophila is well suited to study neurodevelopmental and neuropsychiatric disorders, as it provides a multitude of approaches to investigate their underlying mechanisms and associated pathologies, from a molecular, subcellular, and circuit level to disease-relevant behavior and cognitive processes. Such approaches include genetic or pharmacological induction of disease models, the former in a tightly spatiotemporally controlled manner if desired (Brand and Perrimon, 1993; Duffy, 2002). The generated models can be first phenotyped and/or molecularly characterized, and then, phenotypes of interest can be further subjected to modification attempts, e.g. in genetic interaction and/or drug rescue experiments. The pool of publicly available stocks that can be readily utilized to manipulate any gene of interest in *Drosophila* is enormous and steadily increasing (Bellen et al., 2011; Bischof et al., 2012; Dietzl et al., 2007; Jenett et al., 2012; Matthews et al., 2005; Perkins et al., 2015). Here, we will summarize the main phenotyping assays that can and have been applied in *Drosophila* models of ADHD (Table 1). Furthermore, we will highlight the insights that the characterization of ADHD risk genes in *Drosophila* has already provided. Lastly, we will briefly discuss the potential and perspectives of using *Drosophila* as a disease model in this field.

1.3.1. Drosophila behavioral assays relevant for ADHD

ADHD is a phenotypically complex disorder, which in its complexity cannot be recapitulated in *Drosophila* or other animal models. Nonetheless, there are many behavioral traits sharing biological mechanisms with ADHD that lend themselves to modelling in animals, and numerous approaches to study them in *Drosophila* exist (Coll-Tane et al., 2019; Van Alphen and Van Swinderen, 2013; van der Voet et al., 2014). This also applies to behavioral assays that are relevant to the core symptom domains of ADHD: (in)attention, (hyper)activity, and impulsivity.

1.3.1.1. Hyperactivity. Among the behavioral analyses, those quantifying locomotor activity and sleep appear highly relevant to characterize ADHD genes. Locomotor activity in the fly can model the hyperactivity component of the clinical diagnosis of ADHD. Human ADHD genes were found to be enriched among *Drosophila* genes, and mutations in these genes were unbiasedly linked to ADHD face-valid behaviors including locomotor hyperactivity (Van Der Voet et al., 2016). Locomotor activity is classically monitored in *Drosophila* using the Trikinetics' well-established *Drosophila* Activity Monitoring (DAM) system, which registers the number of infrared beam crossings of individual flies at one or multiple positions in a test tube (Table 1). Recently, video tracking-based methods have increasingly gained interest due to their higher resolution and ability to assess different locomotor components. Video-based tracking also allows assessment of additional states and behaviors such as arousal, sleep pressure, and feeding [eg. *Drosophila* Arousal Tracking (DART) system (Faville et al., 2015), ethoscope (Geissmann et al., 2017), Activity Recording Capillary (ARC) Feeder or CAFE system (Murphy et al., 2017)]. Furthermore, the development of open source software such as Ctrax (Branson et al., 2009) and JAABA (Kabra et al., 2013), which can be customized to detect various *Drosophila* behaviors, allows video-tracking based methods to be developed to assess additional behaviors including attention (Frighetto et al., 2019) and grooming (Qiao et al., 2018).

1.3.1.2. Inattention. Attention deficit is one of the core features of ADHD, however, attentional processes are also widely affected in other neurodevelopmental and neuropsychiatric disorders, such as intellectual disability, ASD, schizophrenia, and depression (Luck and Gold, 2008; McClain et al., 2017). In *Drosophila,* attention-like processes have predominantly been studied using vision-based behavioral paradigms (comprehensively reviewed previously (De Bivort and Van Swinderen, 2016; Van Swinderen, 2011)). Attention-like processes are classically measured in tethered flight paradigms arena or in Buridan's paradigms (Table 1) (Götz, 1980). In tethered flight paradigms, a single fly is secured to a torque meter which records changes in flight dynamics in response to visual stimuli presentation (Van Swinderen, 2011). A variation of this paradigm measures walking dynamics of a tethered fly on an air-supported ball (Paulk et al., 2015). Evidence shows that dopamine levels influence performance in tethered flight paradigms (Koenig et al., 2016a; Van Swinderen and Andretic, 2011). Buridan's paradigms assess fixation strength on visual objects, which is measured by the angle of deviation between the fly's trajectory and either of two inaccessible visual landmarks (Colomb et al., 2012). Transient activation of dopamine signaling during development impairs fixation strength in adult (Ferguson et al., 2017). An adapted version of Buridan's paradigm has been used to assess selective attention by measuring behavioral responses of flies to distracting secondary stimuli (Table 1) (Frighetto et al., 2019; Kirszenblat et al., 2018). Classical visual paradigms have been combined with live brain activity recordings through electrophysiology or calcium imaging (Seelig et al., 2010; Tang and Juusola, 2010; Van Swinderen and Brembs, 2010). Such combinatorial approaches allow for more comprehensive insights into attention-like processes in *Drosophila*. Deficits in attention-like processes have been shown in *radish* mutants, a *Drosophila* model of memory consolidation deficits, and were rescued by methylphenidate (Koenig et al., 2016b, 2016a; Van Swinderen and Brembs, 2010). To date, attention-like behaviors have not been reported in *Drosophila* models of neuropsychiatric disorders.

1.3.1.3. Impulsivity. In other organisms, impulsivity is mostly measured with delay discounting or response inhibition (Dalley et al., 2011). To date, only few studies have investigated impulsivity in *Drosophila*,

mostly assessing impulsivity in form of courtship disinhibition (Table 1). Exposure to psychoactive substances, including ethanol, causes male courtship disinhibition towards both females and other males (Lee et al., 2008). Such behaviors were identified to be modulated by dopamine receptors (Aranda et al., 2017).

1.3.2. Established Drosophila models of ADHD-related genes

Because of its highly efficient genetics, disease modelling in *Drosophila* so far has mostly focused on characterizing the function of single candidate genes. In recent years, several ADHD risk genes have been linked to ADHD-related phenotypes in *Drosophila*, particularly increased locomotor activity.

SLC6A3 (or *DAT*) was one of the earliest identified ADHD-associated genes (Cook et al., 1995). As mentioned above, it encodes the dopamine transporter (DAT). The length of a variable-number tandem repeat (VNTR) in the 3' untranslated region (UTR) of *SLC6A3* correlates with the level of DAT protein in humans (Van Dyck et al., 2005). *DAT* mutant flies, originally termed *fumin*, exhibit increased dopamine levels and hyperactivity (Hamilton et al., 2013; Kume et al., 2005). Administering the mood stabilizer valproic acid has been shown to ameliorate hyperactivity (Landgraf et al., 2016). In addition, *fumin* flies display deficits in grooming, sleep, and circadian behaviors (Kayser et al., 2014; King et al., 2016; Kume et al., 2005). Van der Voet et al. showed that downregulating *Drosophila DAT*, *Cirl* (the orthologue of *ADGRL3* (*LPHN3*)), and *Nf1* specifically in neurons, increased activity and reduced sleep, and administering methylphenidate rescued the phenotypes (Van Der Voet et al., 2016). Neurofibromatosis type 1 (NF1) is a monogenic neurocutaneous syndrome characterized by benign nerve sheath tumors, caused by loss-of-function of the *NF1* gene (Barker et al., 1987). Patients with NF1 also suffer from cognitive impairment ranging from learning disabilities to intellectual disability, and have a high incidence of ADHD features (Mautner et al., 2002; Payne et al., 2021; Pride et al., 2012). The *Drosophila* model of *Nf1* loss-of-function also displays excessive spontaneous grooming (King et al., 2016). *ADGRL3* was identified as an ADHD candidate gene from a linkage study based on large multigenerational families in a population isolate (Arcos-Burgos et al., 2010). Similar findings have also been reported in zebrafish (Lange et al., 2018, 2012) and rodent *ADGRL3* models (Orsini et al., 2016; Wallis et al., 2012), suggesting that the role of *ADGRL3* in ADHD-like behaviors is evolutionary conserved. Another classic ADHD candidate gene is *SLC9A9*, encoding a sodium/proton transporter protein of the solute carrier family. Knockout of *Nhe3*, the *Drosophila SLC9A9* orthologue, caused altered electrophysiology upon visual stimuli, similar to findings in individuals with ASD (Vilidaite et al., 2018). The link between *Nhe3* and ADHD-like behaviors in *Drosophila* has yet to be established.

Massive efforts in the past decades have identified a multitude of ADHD candidate genes. As most genes are emerging through GWASs, their biological relevance for the etiology of the disorder remains to be demonstrated. Using established genetic tools and behavioral assays in *Drosophila*, it is possible to systematically investigate candidate genes in a high-throughput manner (Rohde et al., 2016). Among genes linked to the 12 loci associated with ADHD in the latest GWAS meta-analysis (Demontis et al., 2019b), *FOXP2*, a transcription factor previously described in the *Rodents 1.1.5 section*, has evoked particular interest. The *Drosophila FoxP* is highly expressed in the nervous system and is required for synaptic development and dendritic morphogenesis (Castells-Nobau et al., 2019). It plays a role in behaviors such as learning, perceptual decision making, social interaction, and locomotor function (Castells-Nobau et al., 2019; DasGupta et al., 2014; Lawton et al., 2014; Mendoza et al., 2014). Many rodent studies have addressed the role of *FoxP2* in neurogenesis and behaviors, as described elsewhere, suggesting an evolutionary conserved function of *FOXP2*. However, the role of *Drosophila FoxP* in attention or (hyper)activity remains to be addressed. Another high confidence risk gene identified in the same GWAS is the transcription factor *MEF2C*. *Foxp2* was found to repress *Mef2c* transcription through DNA binding and repressing *Mef2* rescued vocalization and spinogenesis defects of *Foxp2* knockout mice (Y. C. Chen et al., 2016b). In *Drosophila*, *Mef2* has been shown to play a role in ADHD-related behaviors. *Mef2* is required for maintaining normal circadian behavior (Blanchard et al., 2010; Sivachenko et al., 2013) and neuronal knockdown of *Mef2* causes increased locomotor activity and sleep loss (Klein et al., 2020). In the same study, Klein et al. showed that *TRAPPC9* is associated with ADHD, and the knockdown of the *TRAPPC9 Drosophila* orthologue *brun* in circadian neurons caused increased locomotor activity and decreased total sleep time. Recently, Harich et al. (2020) reported a Dutch family with ADHD and cooccurring disorders to segregate with a microduplication in 8p23.3, comprising the *FBXO25* gene. They then continued to functionally validate the newly discovered candidate gene by demonstrating that overexpression of *Drosophila FBOX25* caused ADHD-like behaviors.

1.3.3. Using Drosophila to investigate comorbid symptoms of ADHD

A striking feature of ADHD clinical manifestation is the frequent co-occurrence with other neuropsychiatric conditions (Katzman et al., 2017). This makes further behavioral traits that can be studied in *Drosophila* relevant to ADHD research and modelling. These include habituation learning, repetitive behavior, working memory, addiction, sleep and circadian rhythm, as well as neuromorphological anomalies reported in ADHD and other disorders.

1.3.3.1. Habituation deficits. With ASD being the most commonly comorbid condition of ADHD, it is relevant to measure habituation learning. Habituation is defined as a decrease in response to a repeated or prolonged, harmless stimulus that is not caused by sensory or motor fatigue (Rankin et al., 2009). It is a simple, evolutionary conserved form of non-associative learning, that provides an essential building block of higher cognitive functions (Rankin et al., 2009). Habituation provides a filter mechanism that allows us and all other animals to distinguish novel from known information. Habituation is thus relevant to ADHD, particularly to inattention, which is considered to arise from a failure to filter out irrelevant environmental stimuli (Biederman, 2005; Faraone et al., 2000). Indeed, evidence suggests that slower habituation to visual stimuli in children and adults with ADHD is correlated with inattention symptoms (Jansiewicz et al., 2004; Massa and O'Desky, 2012). Habituation was long considered to mainly result from synaptic depression of excitatory neurons. However, emerging evidence, most importantly from *Drosophila*, demonstrated that habituation can result from potentiation of GABAergic inhibition, a finding that can readily explain a considerable amount of historic literature (Ramaswami, 2014). Psychiatric disorders, especially ASD and schizophrenia, are hypothesized to be an outcome of imbalance in excitatory/inhibitory activity (Lisman, 2012; Rubenstein and Merzenich, 2003).

Habituation can be measured in *Drosophila*, among other assays (Acevedo et al., 2007; Asztalos et al., 2007; Das et al., 2011; Paranjpe et al., 2012), in the light-off jump habituation paradigm (Table 1). This behavior fulfils all habituation criteria (Engel and Wu, 1996; Rankin et al., 2009). A semi-automated version of the paradigm allows habituation assessment in a high-throughput manner (Fenckova et al., 2019). Using this paradigm, *Drosophila* models of more than a hundred monogenic neurodevelopmental disorders have been shown to display habituation deficits (Fenckova et al., 2019; Mullin et al., 2015; Stessman et al., 2017; Wolf et al., 2007). These include the fly models of the disorders caused by mutations in *NF1* and numerous other genes operating in the Ras-MAPK pathway, as well as genes with synaptic function such as *NRXN1*, *DLG2/3* and *SHANK2/3*, most of which are established to present with ADHD-like symptoms in patients. Interestingly, habituation deficits were enriched among those *Drosophila* models of monogenic syndromes characterized by co-occurrence of ASD (Fenckova et al., 2019). A similar evaluation for ADHD is hampered by unavailability of clinical reference lists.

1.3.3.2. Repetitive behavior: grooming. Grooming is an evolutionary conserved innate animal behavior that consists of stereotypical sequences of actions. Grooming is a repetitive behavior, thus it may be relevant to neurodevelopmental disorders such as obsessive-compulsive disorder and ASD (Bubeníková-Valešová et al., 2008; Whitehouse and Lewis, 2015). Fruit flies clean their body parts of dusts and microbes using their legs in a fixed repertoire of cleaning movements (Seeds et al., 2014). Assessment of fly grooming behavior can be done by scoring grooming events (King et al., 2016; Qiao et al., 2018) or efficiency, by quantifying the amount of dust removed during grooming (Barradale et al., 2017; Phillis et al., 1993; Seeds et al., 2014) (Table 1). Several genes have been reported to play a role in grooming behavior in *Drosophila*, including the D1-like dopamine receptor 1 dDA1 (Pitmon et al., 2016). In addition, abnormal grooming behavior is observed in *Drosophila* model of Fragile X syndrome (Tauber et al., 2011) and Neurofibromatosis type 1 (King et al., 2016), both characterized by high frequency of ADHD and ASD.

1.3.3.3. Working memory defects. Working memory has barely been studied so far in *Drosophila* disease models but it is of obvious interest given its implication in ADHD and other neuropsychiatric disorders including schizophrenia and ASD (Schwarz et al., 2016). Meta-analysis studies have shown that individuals with ADHD exhibit verbal and visuo-spatial working memory deficits (Martinussen et al., 2005; Matt Alderson et al., 2013). *Drosophila* has been shown to form visuospatial working memory for objects similar to vertebrates. In 2008, the Strauss lab described a detour setup, in which they showed that flies can remember the position of an object in an arena for several seconds after it has been removed from their environment (Neuser et al., 2008) (Table 1). Strikingly, the very first mutant they identified to display deficits in this paradigm was *ignorant*, the ortholog of the *RPS6KA3* alias *RSK2* gene implicated in Coffin-Lowry syndrome, a severe intellectual disability syndrome. This visual and spatial working memory is an attractive paradigm, even more so since its neuronal substrates have been mapped (Kuntz et al., 2012) and nitric oxide signaling, a risk pathway for psychiatric disorders (Freudenberg et al., 2015), has also been implicated in this form of working memory (Kuntz et al., 2017). A recent study started to investigate free-movement patterns in a Y-maze as a measure for spatial working memory and executive function in humans, mice, zebrafish, and fruit flies (Table 1) (Cleal et al., 2021). They found that flies, like vertebrates, systematically explored the maze, apparently remembering their past positions or choices. Translational efforts across species are of major importance for future perspectives of modelling neurodevelopmental and psychiatric disorders.

1.3.3.4. Substance use disorder. As mentioned above, ADHD increases the risk of developing SUD. Reward and addiction-like behaviors have extensively been studied in *Drosophila*. Assays to test these behaviors, the underlying neuronal circuits and molecular pathways as well as their parallels to human behavior have recently been comprehensively reviewed elsewhere (Lowenstein and Velazquez-Ulloa, 2018) (Table 1). Interestingly, several genes that regulate circadian rhythm have been implicated in ethanol and/or cocaine sensitivity, including *period*, *clock*, *cycle*, and *discs overgrown*. The classic learning and memory genes *rutabaga* and *dunce* have been shown to regulate appetitive memory and ethanol preference (Lowenstein and Velazquez-Ulloa, 2018).

1.3.3.5. Sleep disturbances. Sleep disturbances are another prominent feature in ADHD. Approximately 25%− 50% of children with ADHD report sleep problems (Corkum et al., 1998; Hodgkins et al., 2013b). A recent study of Norwegian children revealed that shorter sleep duration was able to predict later psychiatric symptoms (Ranum et al., 2019). Improving sleep behavior in children with different neurodevelopmental disorders, including ADHD, has been shown to improve cognition, mood, and behaviors (Phillips et al., 2020).

Drosophila is a suitable model to elucidate the role of ADHD genes in sleep. *Drosophila* displays a sleep-like state which possesses key features characterizing sleep: a species-specific posture and/or resting place, modulation by a circadian clock, increased arousal threshold, and a homeostatic response to sleep deprivation (Hendricks et al., 2000; Tononi, 2000). Furthermore, similar neurobiological processes are involved in sleep regulation in mammals and in *Drosophila* (reviewed in (Ly et al., 2018)). Sleep in *Drosophila* can be measured by assessing locomotor activity, as described above. It can be deduced from 5 min of inactivity, as the arousal threshold significantly increases after 5 min of inactivity (Huber et al., 2004). Both locomotor activity and sleep have been used to characterize *Drosophila* models of ADHD (Van Der Voet et al., 2016). Neuronal knockdown of *DAT*, *Cirl*, and *Nf1* have been shown to cause sleep loss, as mentioned above. Also, sleep disturbances have been previously reported in *Nrx-1* mutants (*Drosophila* ortholog of *NRXN1*) (Larkin et al., 2015; Tong et al., 2016) and upon *DISC1* overexpression in a *Drosophila* model of schizophrenia (Sawamura et al., 2008).

1.3.3.6. Circadian rhythm alterations. Defects in circadian rhythm have been extensively connected to many neurodevelopmental and psychiatric disorders including ASD and schizophrenia, and they are increasingly recognized to contribute to the etiology of the disorders rather than only representing a consequence (Jagannath et al., 2013; Menet and Rosbash, 2011). ADHD-associated genes such as *DAT*, *Mef2*, and *period* have been shown to play a role in *Drosophila* circadian rhythm (Bargiello and Young, 1984; Blanchard et al., 2010; Kume et al., 2005; Sivachenko et al., 2013; Top and Young, 2018). Circadian rhythm is generated by a highly conserved molecular clock, which oscillates in about ~24 h following the earth rotation period and synchronize behaviors to the time of the day (Jagannath et al., 2013; Menet and Rosbash, 2011). This molecular clock can be synchronized by environmental cues such as light and temperature. *Drosophila* has been instrumental in understanding these processes at the genetic, biochemical and circuit level, as reviewed in detail elsewhere (Dubowy and Sehgal, 2017). Circadian rhythm in *Drosophila* is assessed by monitoring locomotor activity (Dubruille and Emery, 2008), as already described above.

1.3.4. Application of Drosophila to investigate pharmacological treatments and drug response in ADHD

Drosophila is an ideal model to discover novel treatment approaches through unbiased large-scale screening. Many large-scale drug screen studies in *Drosophila* have successfully identified new therapeutic compounds (Gladstone and Su, 2011; Pandey and Nichols, 2011). In contrast to classical *in vitro* drug screens, screening in *Drosophila* allows using ADHD-relevant behaviors as readouts, which may increase the chances to discover compounds that are conceptually novel.

Methylphenidate is one of the most prescribed drugs for treating ADHD symptoms (Posner et al., 2020). In flies, methylphenidate has also been shown to ameliorate deficits in attention-like processes in a *Drosophila* memory consolidation mutant (Van Swinderen and Brembs, 2010) and hyperactivity-like behavior in *Drosophila* models of ADHD (Van Der Voet et al., 2016), as already mentioned. Recently, Rohde et al. (2019) analysed the genetics underlying the behavioral response to methylphenidate using the Drosophila Genetic Reference Panel (DGRP), a collection of fully sequenced inbred lines derived from a natural population facilitating genotype-phenotype mapping (MacKay et al., 2012). They identified several genes contributing to variability in the drug response and found that the most active wild-type genotypes became less active upon acute methylphenidate supplementation. These findings argue that the inverted-U shape dose response of methylphenidate is evolutionarily conserved.

It has been proposed that environmental exposure to toxins such as bisphenol A (BPA) contribute to ADHD, particularly in boys (Rochester

et al., 2018b). BPA exposure has also been linked to various health issues in humans and animals, including fruit flies (Crain et al., 2007; Kaur et al., 2015; Richter et al., 2007; Rochester, 2013). Early BPA exposure is associated with increased neuropsychiatric disorders symptoms in children (Adesman et al., 2017; Braun et al., 2011; Hong et al., 2013; Perera et al., 2012; Yolton et al., 2011). In flies, Kaur et al. (2015) reported that exposure of wild-type flies to BPA caused abnormal social interaction, reduced locomotion, and increased grooming episodes. Together, these findings illustrate the potential of *Drosophila* to study the effect of exposure to risk-conferring environmental toxin to behaviors.

Additionally, *Drosophila* has recently been shown to be of use to study non-pharmacological therapies. In an innovative study, Belfer and colleagues reported that a behavioral regime, resembling sleep opportunity restriction therapy (SRT), increases total sleep in short-sleeping *Drosophila* mutants, including DAT-deficient flies (Belfer et al., 2021). Sleep restriction therapy (SRT) is widely used as a part of cognitive behavior therapy for insomnia (CBT-I) and performing SRT alone is sufficient to confer most CBT-I benefits (Miller et al., 2014). It is yet to be reported whether SRT may alleviate ADHD-like behavioral alterations. A recent translational study demonstrated that SRT successfully reversed sleep fragmentation in *Drosophila* mutants for *kismet*, the sole orthologue of the high-confidence autism risk gene *CHD8*, and for *CHD7,* mutations in which cause CHARGE syndrome (Coll-Tané et al., 2021). Remarkably, the study also demonstrated that *kismet*'s sleep defects are of developmental origin, suggesting that SRT may be able to override sleep fragmentation in a multitude of neurodevelopmental disorders. These two studies are strongly encouraging the use of *Drosophila* as a model to further exploit behavioral therapies to disease-relevant phenotypes.

1.3.5. Concluding remarks - Drosophila

Drosophila is a leading model organism that has already provided major breakthroughs in monogenic neurodevelopmental disorders, including the first drug reversal in Fragile X Syndrome (McBride et al., 2005), the first large-scale approaches to intellectual disability /ASD disorders (Fenckova et al., 2019; Kochinke et al., 2016; Oortveld et al., 2013), and countless mechanistic insights into specific genetic disorders. Regardless, the study of ADHD in *Drosophila* is still in its infancy. So far, mostly face-valid behaviors, above all locomotor activity, have been used to investigate specific aspects of ADHD. Here we have summarized the already considerable contribution to our understanding of genetics and neurobiology of the disorder. These achievements, with time, are increasing the confidence in the relevance of the applied behaviors and paradigms. Beyond the discussed, there may be further phenotypical readouts that are relevant to ADHD. Arousal thresholds, for example, is a recurring theme in neurodevelopmental disorders, including ADHD (Bellato et al., 2020; Garcia-Rill, 2019).

Recently, somatic comorbidities, such as obesity or susceptibility to infection, are moving into the limelight and are straight forward to be investigated in *Drosophila* models of ADHD (Cortese et al., 2016; Fliers et al., 2013; Miyazaki et al., 2017; Mota et al., 2020b; Nielsen et al., 2017; Nigg et al., 2016; Tylee et al., 2018). Supported by exceptional toolboxes and resources, it is possible to efficiently address the function of candidate genes (Caygill and Brand, 2016; McGuire et al., 2004; Mohr et al., 2014; Schlegel et al., 2017), dissect the underlying circuits and mechanisms, and critical time frames during development, with important implications for potential reversibility of the observed defects. In particular, the cost- and time-efficiency of *Drosophila*, together with the high-throughput manner in which some of the above assays can be conducted makes the fly an organism of choice for approaches that are highly needed in the ADHD field. These include investigating the large amount of emerging candidate genes and variants that require biological support (Chao et al., 2017; Şentürk and Bellen, 2018; Takano-Shimizu-Kouno and Ohsako, 2018), such as the top 50 or 100 findings of the recent GWAS (Demontis et al., 2019b). Testing larger collections of drugs using behavioral assays of confirmed relevance may also generate new breakthroughs (Narayanan and Rothenfluh, 2016; Pandey and Nichols, 2011). Many assays, however, do need significant set-ups and expertise, which at present may still limit their widespread application.

2. Environmental impact and epigenetics

The risk for ADHD and related comorbidities, especially depression and SUD, is influenced by genetic variation in interaction with environmental factors, i.e. gene-by-environment (GxE) interaction. In experimental animal models, GxE interaction was confirmed, for example, mice deficient for the serotonin transporter exposed to prenatal, early-life or social defeat stress (Bartolomucci et al., 2010; Carola et al., 2008; Schraut et al., 2014) and in non-human primates with allelic variation of genes influencing serotonergic transmission (Canli and Lesch, 2007).

Environmental adversity and subsequent epigenetic programming of brain development comprises maternal substance use (e.g. nicotine, alcohol, psychostimulants, opioids) and medication, environmental toxicants (e.g. organophosphates, polychlorinated biphenyls, lead) and infection/immune activation during the prenatal period as well as stressful experiences and unfavorable psychosocial conditions (diet/nutritional factors, maternal neglect and hostility, physical abuse, trauma) throughout infancy and childhood. The dramatic cultural and environmental changes in modern societies have pushed human physiology away from robust physiological mechanisms that would prevent disease, and the risk for common diseases have risen in the last century, explained by the decanalization hypothesis (Gibson, 2009), which may have a high impact in psychiatric disorders such as schizophrenia (Burrows and Hannan, 2013; McGrath et al., 2011).

In the investigation of epigenetic regulation, such as DNA methylation, histone modifications and microRNA (miRNA) expression, animal models have provided critical insights. Preclinical studies offer controllable experimental conditions in which the neurobiological consequences of GxE are explored at the levels of the epigenetic molecular machinery. This section summarizes our knowledge of intrinsic and environmental stimuli-induced epigenetic modifications and their consequential effects on gene expression and behavior.

Numerous studies in models have established links between severe or chronic early-life adversity and the risk for neurodevelopmental disorders and stress-related diseases later in life, such as depression, anxiety disorders and SUD. However, moderate and limited exposure to stress may enable adaptive processes, which result in enhanced stress coping and resilience. Epigenetic variation is categorized into heritable and context-dependent modifications (Crews, 2008), which either occur in the germline and are transmitted across generations, or occur in somatic cells and dynamically persist only across the lifespan. While findings suggest transgenerational epigenetic inheritance of stress or nutrition and a role of ancestral experience before conception in the health of future generation(s), the mechanisms involving DNA methylation and miRNAs are controversial (for review: (Babenko et al., 2015; Jawaid et al., 2018; Kovalchuk, 2012)).

2.1. Molecular substrates of epigenetic modification

Remarkable evidence points to a central role of epigenetic modification of chromatin structure in controlling gene expression and behavior, although the mechanisms of this control are not yet fully understood (Schuebel et al., 2016) The nucleosome is the fundamental subunit of chromatin structure and comprises a short stretch of DNA wrapped around two copies of core histones H2A, H2B, H3, and H4. Post-translational modifications to histone proteins, predominantly acetylation and phosphorylation, as well as DNA methylation, regulate chromatin architecture, affecting transcription factor binding to specific DNA sequences and ultimately gene expression (Fig. 2). Histone acetylation and phosphorylation may facilitate the deposition or removal of

more stable histone tail modifications, such as methylation, and therefore have the potential to moderate long-term gene expression (Barth and Imhof, 2010). Both marks are generally associated with active transcription (Clayton and Mahadevan, 2003; Crosio et al., 2003). Depending on the residues modified, lysine methylation of histones is associated with gene activation (H3K4, H3K36, and H3K79) or repression (H3K9, H3K27, and H4K20). Histone tails can also be modified by methylation of arginine residues (Yang and Bedford, 2013), also associated with both activation and repression of gene transcription.

DNA methylation, i.e., the covalent attachment of a methyl group to

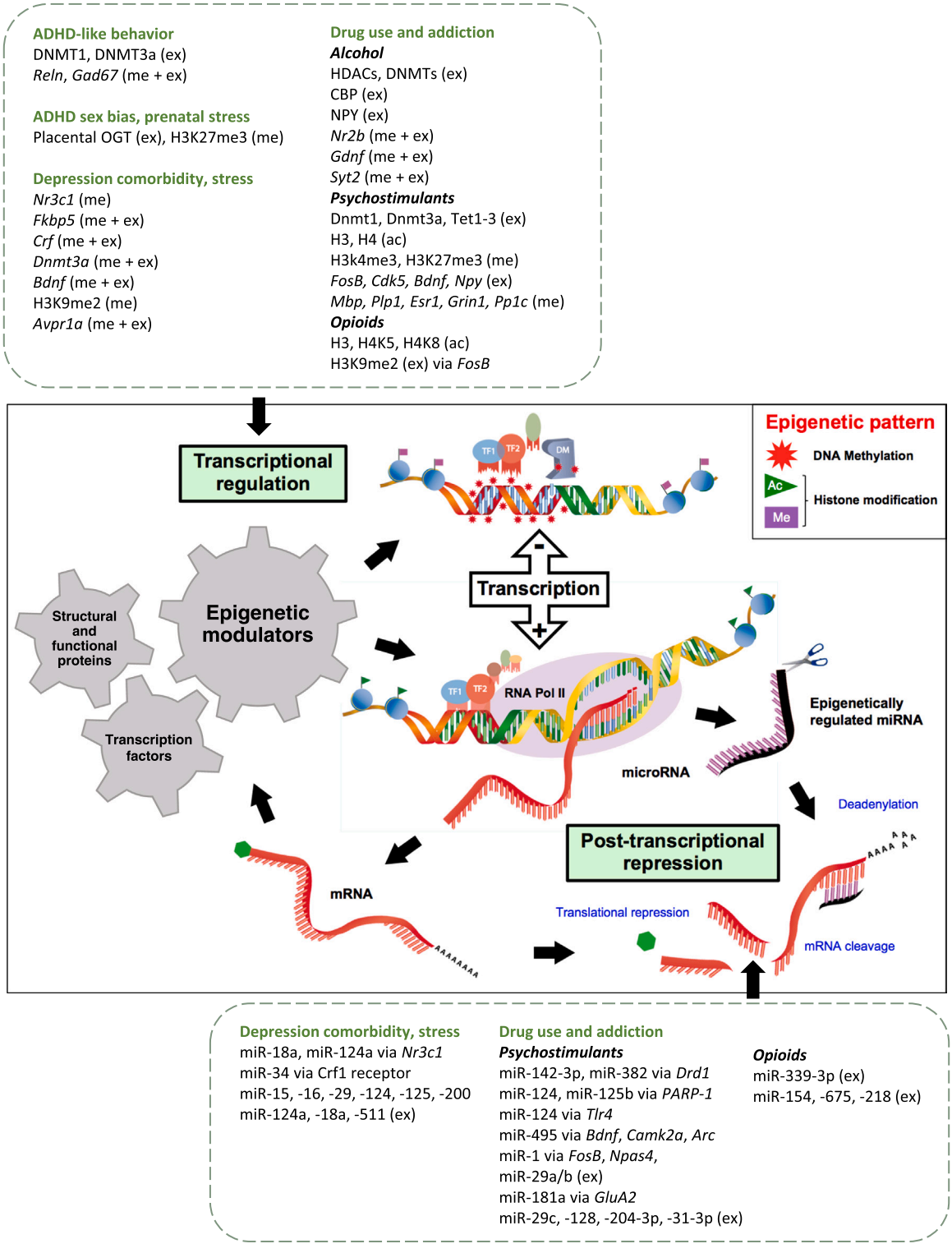

Fig. 2. Regulatory circuits of epigenetic programming and gene expression. Epigenetic mechanisms including DNA methylation and histone modifications as well as miRNAs regulate gene expression patterns at both the transcriptional and post-transcriptional level. At the same time, epigenetics and miRNAs control each other to form regulatory circuits and to maintain physiological functions. Epigenetic regulators and a selection of target genes of ADHD-like traits and comorbidities are boxed for both transcriptional regulation and post-transcriptional repression (me, methylation; ex, expression; ac, acetylation). For further details on genes and epigenetic mechanisms see Section 2.

the 5′ position of a cytosine found at cytosine-phosphodiester-guanine (CpG) dinucleotides, is generally associated with transcriptional silencing when occurring in promoter regions (Fig. 2). DNA methyltransferases DNMT1, DNMT3A, and DNMT3B are responsible for DNA methylation. The gene silencing effects of DNA methylation are partly mediated by methyl-CpG-binding domain (MBD) proteins (Roloff et al., 2003). MBD proteins also provide a platform for the cross-talk between histone modifications and DNA methylation by forming chromatin remodeling complexes comprising histone proteins, histone methyltransferases, histone deacetylases, and ATPase chromatin remodeling complexes (Mazzio and Soliman, 2012). In summary, epigenetic modulation of gene expression occurs through activation or repression of specific gene programmes by a combination of chromatin remodelling, activation and enzymatic modification of DNA and histones as well as nucleosomal subunit exchange.

Finally, these mechanisms are complemented by postranscriptional repression expedited by miRNAs that bind to the 3′-UTRs of the target mRNAs to regulate their expression by either repressing translation or inducing degradation of mRNA (Huntzinger and Izaurralde, 2011) (Fig. 2). A single miRNA is able to fine-tune the expression of multiple genes and may influence groups of target proteins more rapidly compared to transcriptional repressors.

2.2. Stressful experience in ADHD and comorbid depression

While ADHD etiopathogenesis is driven by genetic variation, the disorder and its comorbidities, such as depression, are also influenced by environmental adversity, i.e. the interaction of specific genetic predisposition to disease with maladaptation to stressful experience (Burns et al., 2018). The timeline of these context-dependent modifications commences during fetal adaptation to the intrauterine and maternal environments that shape brain development, ultimately leading to permanent structural and functional alterations in adulthood.

Epidemiological evidence suggests that the genetic risk for ADHD is influenced by prenatal environmental adversity, such as stress, toxicants and substance use (Markham and Koenig, 2011; Rodriguez and Bohlin, 2005; Ronald et al., 2011; Van den Bergh et al., 2020). While prenatal stressors impact the risk for cognitive and behavioral abnormalities associated with ADHD, evidence indicates the involvement of alterations in myelination and GABAergic transmission. In mice, offspring born from mothers exposed to prenatal restraint stress during pregnancy showed locomotor hyperactivity and deficits in attention, information processing, learning and memory as well as social interaction (Matrisciano et al., 2013). In addition, prenatally stressed mice displayed increased concentrations of DNA methyltransferases DNMT1 and DNMT3a, preferentially expressed in GABAergic neurons of frontal cortex and hippocampus, at birth and in adulthood. The increase in DNMTs was associated with enhanced methylation and hydroxymethylation of CpG-rich transcriptional control regions and decreased expression of the genes encoding Reelin (*Reln*) and Glutamic acid decarboxylase 67 (*Gad67*). Similar effects of prenatal stress were also reported for the GABAergic system in the basolateral amygdala in association with increased anxiety-like behavior (Zhu et al., 2018). Some of these findings correspond to changes observed in the post-mortem brains of patients with neurodevelopmental and psychiatric disorders (Deussing and Jakovcevski, 2017).

While sex biases in ADHD symptom presentation are well documented, the mechanisms mediating vulnerability or resilience to ADHD are unknown. *In utero* environmental adversity is more likely to confer a higher ADHD risk in males versus females. Nugent and coworkers (2018) recently reported that sex differences in placental O-linked N-acetylglucosamine transferase (*OGT*) expression associated with trimethylation of histone H3 at lysine K27 (H3K27me3) mediates the effects of prenatal insults on neurodevelopmental programming, with high levels of H3K27me3 establishing resilience in females (Burns et al., 2018; Dick and Provencal, 2018; Dirven et al., 2017; Pishva et al., 2017).

Several stress-related diseases, such as depression and anxiety disorders, are frequently associated with persistent ADHD. In particular, stress associated with educational and occupational failure as well as social adversity can increase susceptibility to affective disorders throughout the lifespan. Stressors activate the hypothalamic-pituitary-adrenal (HPA) axis to allow the organism to cope. Numerous studies on epigenetic modification of regulators of HPA function provide evidence that the epigenome is both stably and dynamically regulated in response to environmental stimuli not only during critical developmental periods but also in adulthood.

Although the molecular mechanisms of stress-induced fetal programming of brain development and plasticity remain incompletely understood (Schraut et al., 2014), deficits in maternal care during the postnatal period may cause DNA methylation changes in the promoter region of the Glucocorticoid receptor (GR) gene (*Nr3c1*) in the brain. Early studies in rats demonstrated that the negative feedback via glucocorticoid-induced activation of GR in corticolimbic networks is compromised as a consequence of maternal neglect, which triggers decreases in transcription of *Nr3c1* encoding GR associated with decreased methylation of a single CpG in the Nerve growth factor-inducible protein A (*NGFI-A*) response element in the *Nr3c1* transcriptional control region (TCR) in hippocampus (Weaver et al., 2004). Post-transcriptional repression mediated by repeated restraint stress-induced miR-18a or miR-124a binding to the 3'UTR of *Nr3c1* was also identified as a potential mechanism of regulating GR expression in the adult rat brain (Xu et al., 2019).

Stress exposure may induce alterations in the epigenetic modification of FK506 binding protein 5 (FKBP5), a GR co-chaperone protein and regulator of GR sensitivity (Klengel et al., 2013). Chronic stress and glucocorticoid administration during adulthood was shown to increase anxiety-like behavior as well as hippocampal cortical *FKBP5* expression by decreasing DNA methylation at the *Fkbp5* locus (Lee et al., 2010). Epigenetic regulation of genes encoding Corticotrophin Releasing Factor (*CRF*) and its receptors were studied in various models of early life and adult stress exposure (Chen et al., 2012). For instance, stress during murine pregnancy was reported to result in enhanced HPA axis associated with decreased methylation of two CpGs in the *Crf* transcriptional control region (TCR) and increased *Crf* mRNA expression in the central nucleus of the amygdala in male offspring (Mueller and Bale, 2008). A concomitant methylation in the TCR of *Nr3c1*, encoding the GR in hippocampus, indicates a coordinate adaptive response of multiple HPA axis-related genes. A similar modification in the *Crf* gene methylation and increased *Crf* expression were demonstrated following chronic social defeat stress, alterations that were reversed by antidepressant treatment (Elliott et al., 2010). Moreover, social defeat in adult mice increased anxiety-like behavior and decreased *Dnmt3a* mRNA levels as well as genome-wide DNA methylation in prefrontal cortex (PFC), which were rescued by overexpression of *Dnmt3a* (Elliott et al., 2016). Finally, stress-induced CRF signalling alterations may be moderated by the miR-34 family via the Crf1 receptor in neurons in the hypothalamus and amygdala (Haramati et al., 2011). These findings collectively suggest that epigenetic mechanisms at the DNA and RNA level lead to a disrupted negative glucocorticoid feedback characterized by elevated hippocampal and PFC GR levels.

Some studies have focused on social adversity as a profound stressor in the risk for depression. Social defeat stress during early adolescence, a prototypical rodent model of depression (Bartolomucci et al., 2010), induced down-regulation of *Bdnf* gene expression and a depressive phenotype, including increased social avoidance and cognitive inflexibility, in adult mice (Xu et al., 2018). Specially, reduced levels of total *Bdnf* isoform IV transcripts were associated with increased dimethylation of histone H3 at lysine K9 (H3K9me2) immediately downstream of the *Bdnf* IV promoter in the medial prefrontal cortex (mPFC), whereas no alterations were found in DNA methylation of the *Bdnf* IV promoter. Chronic antidepressant treatment reverse epigenetic changes related to *Bdnf* transcription, but only rescue the depressive phenotype partially.

Unlike *Bdnf* histone modification, varying social experiences across the life cycle was reported to modulate expression and methylation of the vasopressin receptor 1a (*Avpr1a*) gene in mice (Bodden et al., 2017). These findings suggest that epigenetic regulation of gene expression may recruit distinct modification pathways in a gene-specific manner.

In *Drosophila,* chronic unpredicted mild stress (CUMS) protocols using starvation, cold, heat, vibration, aversive cues, or a combination of different stressors have been applied to induce learned helplessness as a model for depression. Upon exposure to the adverse stimuli, *Drosophila* learned helplessness models exhibit depressive-like behaviors, such as increased aggression and reduced lifespan, locomotor activity, climbing, and mating behaviors (Yang et al., 2013, Ries et al., 2017, Kim et al., 2020), some of which have been shown to correlate with reduced levels of serotonin (Ries et al., 2017). Increasing serotonin levels by feeding the serotonin precursor 5-hydroxy-L-tryptophan or sucrose, as well as treatment regimes with lithium chloride or creatine/taurine mixtures have been found to alleviate these behavioral alterations (Ries et al., 2017, Kim et al., 2020).

The emerging role of miRNAs in stress-related disorders, such as depression, and its therapeutic implication, has recently been reviewed comprehensively (Dwivedi 2014; Ortega et al., 2021). In brief, miRNAs, including miR-15, -16, -29, -124, -125 and - 200, may participate in the adaptive cellular responses to early-life or chronic stress exposure (Allen and Dwivedi, 2020). In rats, upregulation of miR-124a and miR-18a in the PFC and hippocampus and downregulation of miR-511 in the PFC were demonstrated as relevant to depressive-like behavior (Xu et al., 2019). Differential expression of these and numerous other miRNAs are likely involved in the pathophysiology of depressive disorders; they may also represent potential biomarkers with diagnostic, prognostic and predictive value as well as therapeutic targets.

2.3. Drug use and addiction

SUD are among the most common comorbidities in ADHD. The impact of drugs of abuse, including nicotine, alcohol, psychostimulants and opioids, on the modification of epigenetic regulators was previously reviewed in detail (Browne et al., 2020; Ponomarev et al., 2017). Drug-seeking behavior and dependence in ADHD may either be a consequence of reduced cognitive control or self-medication as a failed attempt to alleviate distress, such as restlessness, uncomfortable emotional states or loneliness following social exclusion. Elucidating the epigenetic mechanisms of drug use and addiction is likely to contribute to the understanding of ADHD-related pathophysiologic as well as therapeutic molecular, cellular and system pathways. Exposure to drugs alters gene expression and initiates long-term adaptation of brain regions and neural circuitry involved in reward processing and motivation, such as the mesocorticolimbic system-projecting dopaminergic neurons of the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Nestler, 2001; Shaham and Hope, 2005). Moreover, adaptive plasticity and structural consolidation leading to addiction and relapse is partially mediated by epigenetic modification of gene expression (Wong et al., 2011).

Molecular mechanisms controlling drug-induced transcriptional, synaptic and behavioral activity involve chromatin remodeling of neuronal gene programs and subsequent addictive behavior. Repeated exposure to drugs of abuse might promote changes in levels of histone acetylation, phosphorylation and methylation, together with alterations in DNA methylation (5mC) and hydroxymethylation (5hmC) levels in neurons of the NAc, the brain's reward center. The impact of three major drugs of abuse, i.e. alcohol, psychostimulants and opioids, will be highlighted in an exemplary manner in this section.

Although there is emerging data on the effects of alcohol on epigenetic mediators, few studies have systematically and comprehensively examined changes in the expression of genes encoding for chromatin modifying proteins after chronic alcohol exposure, withdrawal, and abstinence. A general role of histone deacetylases (HDAC) and DNA methyltransferases (DNMTs) was reported in different alcohol use-related behaviors, including consumption, dependence and withdrawal (Barbier et al., 2015; Pandey et al., 2008; Ponomarev et al., 2017; Warnault et al., 2013). Also, altered methylation and expression of individual genes including, the *NMDA* receptor *Nr2b* in murine cortical neurons (Marutha Ravindran and Ticku, 2004) and glial-cell-derived neurotrophic factor (*Gdnf*) promoter, was revealed in NAc and VTA following alcohol consumption in rats (Pandey et al., 2008). Pandey and coworkers (2008) also demonstrated enhanced levels of histone H3 and H4 acetylation in the CREB-binding protein (CBP) and Neuropeptide Y (NPY), as well as decreased levels of HDAC activity, in rat amygdala, to be involved in the anxiolytic effects of acute ethanol. Conversely, the development of anxiety in alcohol withdrawal was associated with decreased histone acetylation and increased HDAC activity in the amygdala (Pandey et al., 2008). In a rescue approach, the HDAC inhibitor trichostatin A prevented the development of alcohol withdrawal-related anxiety by reversing the diminished levels of histone acetylation and inhibiting the enhanced HDAC activity. Barbier and associates (2015) showed that a global increase of DNA methylation as well as decreased expression of genes encoding synaptic proteins involved in neurotransmitter release in the mPFC influence alcohol-induced behavior and molecular plasticity (Barbier et al., 2015). Both alcohol consumption as well as dependence-induced hypermethylation and decreased expression of the gene encoding Synaptotagmin 2 (*Syt2*) were prevented by a DNA methyltransferase inhibitor. Finally, Warnault and collegues (2013) demonstrated that excessive alcohol consumption increases DNMT1 levels and reduces histone H4 acetylation in the NAc of rodents, while inhibition of DNMT and the augmentation of histone acetylation with several HDAC inhibitors prevents harmful alcohol abuse (Warnault et al., 2013).

Psychostimulants, such as cocaine and amphetamines, are typically (ab)used in ADHD and thus represent either a highly effective therapeutic strategy (i.e. methylphenidate, D-amphetamine) or a potentially harmful approach of self-medication (cocaine, methamphetamine). The latter impact neuronal structure and function in specific brain regions in a therapeutically uncontrolled mode, resulting in frequently adverse persistent changes at the molecular, cellular, neural system and behavioral levels (Koob and Simon, 2009; Nestler, 2013). In rodents, acute cocaine treatment is generally correlated with increased H4 acetylation at activated transcriptional control regions of specific genes, whereas H3 acetylation appears to predominate at chronically induced promoters, with reductions being evident at global levels of both the H3k4me3 and H3K27me3 after exposure to cocaine (Biliński et al., 2012). Using a mouse behavioral sensitization model, Anier and associates (2018) reported that acute cocaine treatment decreased *Dnmt1, Dnmt3a,* as well as the Ten-eleven translocation enzyme gene *Tet1, and Tet2* mRNA levels in the NAc, whereas *Dnmt* mRNAs and enzyme activities were increased (Anier et al., 2018). In contrast, cocaine withdrawal was associated with increased expression and activity of Dnmts and decreased expression and activity of Tet1 and Tet3 in the NAc. All these changes were associated with enhanced global DNA and selected candidate gene modifications.

Long-term cocaine as well as (meth)amphetamine intake activates or represses many genes, e.g. immediate early gene *FosB*, Cyclin-dependent kinase 5 (*Cdk5*), Brain-derived neurotrophic factor (*Bdnf*) and Neuropeptide Y (*Npy*) (Kumar et al., 2005; Renthal et al., 2008). Moreover, numerous reports have demonstrated that genome-wide alterations in DNA (hydroxy)methylation contribute to psychostimulant-induced modulation of gene expression (for review: (Godino et al., 2015; Vaillancourt et al., 2017). For example, differential (hydroxy)methylation occurs in genes encoding Myelin basic protein (*Mbp*), Proteolipid protein-1 (*Plp1*), Estrogen receptor-1 (*Esr1*), Glutamate receptor subunit zeta-1 (*Grin1*), Serine/threonine-protein phosphatase gamma catalytic subunit (*Pp1c*) and several potassium channels in frontostriatal circuitries Anier et al., 2013; Bodetto et al., 2013; Cadet et al., 2017; Laplant et al., 2010; Massart et al., 2015).

Considerable work has focused on the impact of cocaine and amphetamines on miRNA expression in rodent's brain, specifically in frontostriatal networks and of marker proteins implicated in psychostimulant-induced adaptative plasticity, such as dendritic spine remodeling (Cahill et al., 2018; Nielsen et al., 2012). Several miRNAs have been implicated in cocaine-induced behavior and molecular mechanisms. For example, cocaine-induced hyperlocomotor activity and D1 receptor expression in the caudate-putamen is regulated by miR-142–3p and miR-382 (Tobón et al., 2015). Cocaine-induction of poly (ADP-ribose) polymerase-1 (*PARP-1*) is regulated by miR-124 and miR-125b (Dash et al., 2020, 2017). MiR-124 was also shown to moderate cocaine-mediated activation of microglia and upregulation of pro-inflammatory cytokines by targeting Toll-like receptors 4 (TLR4) (Chivero et al., 2020; Periyasamy et al., 2018). MiR-495 targets several addiction-related genes in the NAc, such as *Bdnf*, *Camk2a* and *Arc* (Bastle et al., 2018), while miR-1 and its target genes, *FosB* and *Npas4*, are implicated in cocaine-induced behavior in a medium spiny neuron (MSNs)- and circuit-specific modulatory manner (Forget et al., 2021). Both chronic cocaine and amphetamine treatment influences miR-29a/b expression resulting in a reduction of mushroom-shaped dendritic spines on hippocampal neurons (Lippi et al., 2011) and identifies miR-181a as a key regulator of GluA2 subunit of AMPA-type glutamate receptors in mice (Saba et al., 2012). Methamphetamine impacts regulatory pathways that modulate dendritic spines, axon guidance and synaptic transmission via miR-29c, miR-128, miR-204–3p regulating expression of numerous targets in the NAc (Li et al., 2021; Ni et al., 2019; Su et al., 2019), whereas the miR-31–3p/RhoA pathway in murine hippocampus is involved in methamphetamine-conditioned place preference (Qian et al., 2021).

While studies examining how epigenetic modifications contribute to SUD have focused on alcohol and psychostimulants, research on opioid-induced changes to the epigenetic landscape is also evolving. In rodents, repeated administration of opioids increased global H3 acetylation and hyperacetylation at H4K5 and H4K8 in the mesolimbic dopamine system (Chen et al., 2016a; Sheng et al., 2011), thus promoting an accessible chromatin state and an enhanced transcriptional activity of numerous genes. Also, chronic morphine treatment was found to reduce H3K9me2 in NAc, VTA and Locus coeruleus, thus repressing *FosB* expression, and to induce changes in methylation at genes related to glutamatergic signaling (Mashayekhi et al., 2012; Sun et al., 2012). However, neither chronic opioid administration with stable or escalating doses, nor self-administration, altered genome-wide DNA methylation in the mesocorticolimbic dopamine system of rodents (Chao et al., 2014; Imperio et al., 2018). Only a single study identified several changes in global or promoter-specific 5mC and 5hmC levels across multiple brain regions following chronic morphine exposure in rats (Barrow et al., 2017). These results contrast with evidence that cocaine alters global DNA methylation in the PFC and NAc (Massart et al., 2015). Finally, brain region-specific increases have been observed for miR-339–3p (Wu et al., 2013), whereas decreases have been observed for miR-154, miR-675, and miR-218 following long-term opioid exposure (Tapocik et al., 2013).

Taken together, all these findings provide converging evidence that drugs of abuse promote a higher degree of permissive histone acetylation and lower levels of repressive histone methylation as well as alterations to DNA modification patterns and noncoding RNA expression throughout the brain's reward circuitry. Following drug exposure, the persistence of epigenetic modifications in affecting neuronal function is still an object of study.

2.4. Concluding remarks - Epigenetics

Even though the impact of environmental factors on ADHD and related comorbidities still presents itself as a map with many white patches, some underlying epigenetic mechanisms contributing to brain development, plasticity and disease have been revealed by experimental animal models. Here, we provided a selective overview of animal models assessing environmental stressors contributing to the elucidation of epigenetic mechanisms of ADHD and related comorbidities. We also discussed how individual factors, such as genetics, sex, and age, as well as the type, and timing of early-life adversity, may create differential susceptibility and moderate outcomes. Several lines of evidence indicate that epigenetic modifications shape interactions between the constitutive genetic vulnerability for ADHD and environmental insults in early life, resulting in persistent changes in gene expression and behavior across the life cycle. While the reviewed rodent studies provide valuable insights into short-term epigenetic response to adult life stress, an in-depth assessment of persistent epigenetic changes over prolonged periods of time is needed to understand the enduring nature of environmental adversity and associated ADHD symptomatology.

Studies into mechanisms investigating adversity-induced epigenetic marks, and G*xE studies (G* representing one or multiple risk genes) in rodent models carrying ADHD-associated gene variants are largely lacking (Weidner et al., 2019). In the future, studies would need to include advanced chromatin analysis and next-generation sequencing approaches combined with bioinformatics to identify gene networks regulated by specific epigenetic modifications.

Although challenges remain in elucidating the complexity of how the early adversity interacts with individual factors to determine epigenetic patterns, and in translating these mechanistic findings into ADHD patient populations, we shed some light on the potential for identifying effective interventions in vulnerable individuals. Studies manipulating epigenetic mechanisms in specific brain regions have emerged as potential therapeutics for addiction. These studies involve inhibitors of enzymes that modify DNA and histones, such as DNMT and HDAC inhibitors, commonly referred to as epigenetic editors, which have the potential to modify gene expression and downstream behavior via regulation of chromatin structure (Ponomarev, 2012; Spanagel, 2009; Walker et al., 2018). Finally, pharmacological interventions, such as antidepressant treatment was shown to revert early life stress-induced histone modifications. Similar to the window of increased plasticity for epigenetic programming during early life, the consequences of stress during adulthood are likely analogous and may thus be targeted by therapeutic strategies.

3. Concluding remarks

Decades of research into ADHD have provided evidence that ADHD is a highly multifactorial disorder, mostly caused by genetic factors with variable effect size, that often presents with other comorbid traits. For a better understanding of the genetic underpinnings, cell biology and neuropathophysiology of ADHD and its co-occurring disorders, valid experimental animal models are needed. Thus, the scope of this review is to provide an overview of the existing and potential rodent, zebrafish and fruit fly models for ADHD and its comorbidities, with a special focus on genetic and epigenetic models.

In this review we discussed various preclinical models in multiple model organisms that have already been applied, to a varying degree, for studying the role of ADHD candidate genes, and have advanced our understanding of gene functions and mechanisms that underlie phenotypes relevant to ADHD and comorbid disorders. The nervous systems of rodents, zebrafish, and fruit flies are simpler than the human one, yet sufficiently complex to study nervous system development, function, and also behavior. While the brain anatomical structures of these organisms significantly differ from the human brain, their organization in functional centres and circuits, their main cellular building blocks, their anatomy, principles and mediators of neurotransmission are conserved to a striking degree. Studying the role of genes relevant to ADHD and other comorbid traits in animal models is therefore possible and necessary. However, using single animal models - most of which feature alterations in only one gene - does not capture the complexity of multifactorial ADHD and its comorbidities. Large amounts of data are

required to unbiasedly identify the most common phenotypes in monogenic models of ADHD, evaluate how far they match or outperform face-valid phenotypes, and determine to what extent mechanisms and pathophysiology identified would also apply to human multifactorial ADHD. An intensive investment into functional studies in animal models is therefore required to move on beyond face validity and reach a satisfying degree of construct and predictive validity. It thus remains a challenge to provide preclinical models that mirror the complexity of ADHD with the currently available approaches. After decades of investment into GWAS and exome/genome sequencing studies to identify candidate genes that contribute to ADHD, investment into preclinical follow-up research is timely.

Indeed, a potential direction that might propel the ADHD field forward is to work towards an integration of the insights that come from studying multifactorial and monogenic neurodevelopmental disorders. Single disruptive mutations in hundreds of genes have been proved to cause Intellectual Disability and/or Autism (see SysNDD database (https://sysndd.dbmr.unibe.ch/) and SFARI (https://gene.sfari.org/)), and a significant number of these syndromes (though to be comprehensively annotated) show a high incidence of ADHD. Although e.g. individuals with Fragile X syndrome, Neurofibromatosis or other recognizable neurodevelopmental disorders with ADHD are unlikely to be included in ADHD cohorts, modelling the underlying genes can provide important insights into the neurobiology of ADHD, e.g. by mapping the face-valid phenotypes to specific neuronal substrates or critical developmental periods.

A complementary application of animal models in ADHD research, paralleling the human approaches, is to identify animal strains that exhibit face-valid behaviors and (endo)phenotypes related to ADHD and/or comorbid traits, and conduct GWAS or transcriptomic analyses in these models to identify candidate genes that contribute to the face-valid behaviors or (endo)phenotypes related to ADHD or other comorbid traits. As already discussed above, few of the genes identified in such studies have already been associated with ADHD and related disorders (Gonzales et al., 2018; Harbison et al., 2013), and many others are yet to be further explored for their ADHD association. Integrative analyses using data from rodents (from transcriptomic studies and KO models) and humans (GWAS and Mendelian disorders) have also succeeded in unraveling genes relevant for aggression (Zhang-James et al., 2019). Thus, this approach combining genetic data from animal models and humans might be useful to identify robust genes consistently involved in ADHD-related behaviors.

Finally, one of the strengths of the small animal model is the ability to screen, even unbiasedly, novel therapeutic compounds while allowing face-valid ADHD-relevant behaviors as readouts. It is conceivable that such approaches will identify hits that are different and more effective than those targeted by drugs identified in cellular or *ex vivo* systems that can recapitulate ADHD characteristics only to a highly limited extend. Additionally, model organisms have been used to study the effects of non-pharmacological interventions for neuropsychiatric disorders such as behavioral therapy. Such encouraging findings open a myriad of opportunities for animal research into ADHD, its behavioral traits and clinically and genetically overlapping neuropsychiatric and -developmental disorders.

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Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104949.

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