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Review of Rodent Models of Attention Deficit Hyperactivity Disorder

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a polygenic neurodevelopmental disorder that affects 8–12% of children and >4% of adults. Environmental factors are believed to interact with genetic predispositions to increase susceptibility to ADHD. No existing rodent model captures all aspects of ADHD, but several show promise. The main genetic models are the spontaneous hypertensive rat, dopamine transporter knock-out (KO) mice, dopamine receptor subtype KO mice, *Snap-25* KO mice, *guanylyl cyclase-c* KO mice, and *latrophilin-3* KO mice and rats. Environmental factors thought to contribute to ADHD include ethanol, nicotine, PCBs, lead (Pb), ionizing irradiation, 6-hydroxydopamine, neonatal hypoxia, some pesticides, and organic pollutants. Model validation criteria are outlined, and current genetic models evaluated against these criteria. Future research should explore induced multiple gene KOs given that ADHD is polygenic and epigenetic contributions. Furthermore, genetic models should be combined with environmental agents to test for interactions.

Keywords

Attention deficit hyperactivity disorder; ADHD; neurodevelopment; rodent models; polygenic disorders; environmental influences

Introduction

Attention deficit hyperactivity disorder (ADHD) is diagnosed based on symptoms of inattention, hyperactivity-impulsivity, or both. Studies on ADHD have grown exponentially since it was first described in 1775 (Barkley and Peters, 2012). ADHD is the most common neuropsychiatric disorder with 8–12% of children diagnosed (Danielson et al., 2018).

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Meta-analyses indicate that the prevalence of ADHD does not differ significantly between Europe, Asia, Africa, Australia, and the Americas (Polanczyk et al., 2014). There is no reliable evidence of an increase in prevalence over the last three decades (Polanczyk et al., 2014). Concerns about over- or under-diagnosis of ADHD are not supported by relevant data (Sciutto and Eisenberg, 2007). A new international consensus report was published on ADHD and the major findings are summarized in Table 1. Most of the conclusions are based on meta-analyses of large clinical studies. While the report does not contain new information, it provides the strongest data available on the phenotype, genetics, and associated risk factors in ADHD (Faraone et al., 2021).

ADHD continues into adulthood in up to 50% of those diagnosed as children with variable symptoms (Faraone et al., 2006) that sometimes include functional impairments (Biederman et al., 2000) (Simon et al., 2009). A meta-analysis of longitudinal follow-up studies indicated that ~15% of patients with ADHD continue to meet the full diagnostic criteria for ADHD up to age 25. After that, ~50% exhibit partial remission, with persistence of milder, but often problematic, symptoms (Faraone et al., 2006). However, patients diagnosed by strict DSM-IV criteria as combined type show up to 80% affected as adults (Cheung et al., 2015; van Lieshout et al., 2016; Franke et al., 2018). Discrepancies in ADHD prevalence may be due to how diagnostic criteria are applied, including age of onset, methods used to capture symptoms, and the application of impairment criteria (Willcutt, 2012).

There are three subtypes of ADHD characterized by the DSM: (1) Inattentive, (2) Hyperactive-impulsive, and (3) Combined (American Psychiatric Association, 1980). Inattentive subtype patients present as dreamy and disengaged and have less accurate information processing and trouble focusing. They also have difficulty sustaining attention, are more distractible, lack persistence, and are less organized. Hyperactive/impulsive subtype patients are more distractible, have reduced persistence (Garralda, 1992), exhibit excessive movement, and lack impulse control. The combined type exhibits all three symptoms. There are sex differences in the rates of ADHD. In child and adolescent clinics, up to 80% of ADHD patients are male (Kooij et al., 2010). There are also sex differences within the subtypes. Hyperactive-impulsive subtype patients are more commonly boys whereas the inattentive subtype is more commonly girls. Interestingly, by late adolescence, while sex differences in inattention remain, the level of hyperactivity-impulsivity in boys declines to the level of girls (Larsson et al., 2011), suggesting that the expression of core ADHD symptoms is more similar across the sexes in adults.

ADHD is heterogeneous with symptom variations resulting, in part, from gene variations that evidence suggests interacts with environmental factors, but what these environmental influences are remains elusive (Ficks and Waldman, 2009; Rutter et al., 2015; Palladino et al., 2019). However, ADHD is considered a gene × environment disorder, i.e., the product of genetic, epigenetic, and environmental factors acting in concert. There are often co-morbid contributions from other disorders such as tuberous sclerosis, autism spectrum disorder (ASD) and exposure to environmental agents/drugs, such as lead (Pb), tobacco, alcohol, and other drugs, or rare neurodevelopmental disorders such as creatine transporter deficiency that show increased rates of ADHD (van de Kamp et al., 2013).

Treatment of ADHD is directed at symptoms or for disorders such as tuberous sclerosis-related ADHD, at tumor suppression such as targeted therapies with mTOR inhibitors, e.g., everolimus. This is the case for other comorbid disorders as well (Nigg et al., 2010). Children with ADHD may also have other idiopathic conditions, such as intellectual impairment or a specific learning disability, sleep disorder (Biederman et al., 1991), mood disorder (Cortese et al., 2009), disruptive behavior, anxiety, ASD (Biederman et al., 1991; Antshel et al., 2013), substance abuse disorder (Biederman et al., 1991; Wilens et al., 2011; Bernardi et al., 2012), executive function deficits (Nigg et al., 2005), or other cognitive impairments of memory, temporal processing, or motivation (Sonuga-Barke et al., 2010; Sjöwall et al., 2013; Coghill et al., 2014).

The complexity of ADHD makes developing preclinical models challenging. Nevertheless, animal models can help isolate characteristic symptoms of ADHD and trace these at a cellular/molecular level, the problem has been and continues to be developing accurate models. When successful however, animal models contribute to an understanding of the neurochemical, neuropathological, genetic, and environmental factors that contribute to ADHD. Model systems permit hypothesis testing, can control genetic and environmental influences, and permit invasive methods not possible in humans. By being simpler, animal models focus on specific characteristics one or two factors at a time.

A useful model should be valid and predictive, and ideally useful for testing new therapeutic targets. Many species can be used including non-human primates. However, primate models are a limited resource, costly, and raise ethical issues. Rodents have the advantage of being genetically mutable, less costly, and less time-consuming than non-human primates. Furthermore, rodent studies can be powered to detect effects of interest, such as behavioral outcomes associated with clinical symptoms and are well-suited for hypothesis testing. While other mammalian and non-mammalian species can provide relevant information, especially regarding the genetic basis of the disorder, this review focuses on rodent models and draws attention to gaps in the development of gene × environment interaction models that could provide new perspectives on ADHD. The reader is referred to other reviews on ADHD as well (Russell et al., 2005; van der Kooij and Glennon, 2007; Faraone et al., 2021). A glaring gap in the current literature is that research focusing on genetic factors and those modeling environmental factors have proceeded in parallel with little to no crossover. If the oft acknowledged hypothesis is correct that ADHD is the product of gene × environment interactions, then what is missing are models that integrate the two with the goal of creating more realistic models. Here we review models on both sides of this divide and conclude with some suggestions about convergent models.

Genetics

ADHD is a complex gene × gene and gene × environment disorder that is significantly heritable. Twin and adoption studies estimate ~76% heritability and yet there are no large effect gene variants that are predominant in idiopathic ADHD. Rather the genetic contributions arise from multiple small effect genes (Acosta et al., 2004). Polymorphisms of monoaminergic genes are implicated, including variants of dopamine D1, D4, and D5 receptors (DRD1, DRD4, DRD5), alpha-adrenoreceptors, and transporters for dopamine,

norepinephrine, and serotonin (5-HT) (DAT, NET, SERT), synaptic proteins such as SNAP-25 (required for neurotransmitter release and trafficking of glutamate N-methyl-D-aspartate). Combinations of these and other variants co-occur as risk factors, predisposing to ADHD, except in syndromes with known genetic mutations such as tuberous sclerosis. Idiopathic ADHD is thought to be triggered by environmental perturbations such as childhood infection, exposure to a developmental neurotoxic substance, or from a maternal exposure to viruses or other neurotoxic agents during pregnancy. From a modeling perspective, creating polygenic models has proven to be difficult. Rather than engineer multiple mutations into a rodent, selective breeding has been used with some success.

Gene × Environment Interactions

As noted, ADHD has genetic contributions, but these rarely replicate. One reason may be that the expression of the risk genes depends on epigenetic programming. Epigenetic markers are influenced by both the genome and environment of the individual, although environmental factors appear to be less influential than those that are heritable (Faraone et al., 2005; Nikolas and Burt, 2010). It is likely that heritability estimates for ADHD based on twin studies are affected by gene × environment, which may account in part for inconsistencies. There are studies suggesting that polygenic combinations interact with environmental factors in specific ways that make tracing origins difficult, such as between *DRD4* variants and prenatal smoking (Pluess et al., 2009), between *SLC6A3/DAT1* and prenatal alcohol (Brookes et al., 2006), between *SLC6A4/SERT* and maternal stress (Müller et al., 2008), between monoamine oxidase A (*MAO-A*) variants and adverse parenting (Li and Lee, 2012), and between latrophilin 3 (*LPHN3*) variants and prenatal stress (Choudhry et al., 2012).

Structural and functional abnormalities

Studies report reduced brain volume in patients with ADHD, particularly of the cerebellum, corpus callosum, prefrontal cortex, and basal ganglia of the right hemisphere (Castellanos et al., 1996; Filipek et al., 1997; Castellanos et al., 2002; Hill et al., 2003). In addition, patients with lesions of the right frontal cortex often display ADHD-like behavior (Clark et al., 2007).

The most consistent anatomical findings are deficits in neural activity in frontal-striatal and frontal-parietal circuits (Dickstein et al., 2006). Neuroimaging studies show functional abnormalities in dorsal and inferior cortex, anterior cingulate cortex, basal ganglia, thalamus, and cerebellum (Tannock, 1998; Moll et al., 2000; Kim et al., 2002; Bush, 2010). Functional magnetic resonance imaging (fMRI) has revealed reduced striatal activation in adolescents with ADHD during a reward anticipation task, suggesting impaired reinforcement-related frontal-striatal pathways (Scheres et al., 2007). Increases in striatal DAT of up to 70% were reported in one study of children and adults with ADHD, suggesting that *DAT1* gene expression in the striatum of these patients resulted in reduced synaptic dopamine (Cheon et al., 2003). However, other studies have not found this effect.

Model Criteria

Face, construct, and predictive validity are important in developing animal models. (1) Face validity requires that the behavioral characteristics of ADHD be exhibited, including impulsiveness, hyperactivity, especially in familiar environments, and attention deficits. Many rodent models are hyperactive in novel environments but few are hyperactive in familiar environments, even though hyperactivity in familiar environments is characteristic of ADHD (Russell et al., 2005). (2) Construct validity has not been attained for ADHD because the etiology of the disorder is unknown. However, partial construct validity has been achieved by showing the role of several gene variants found in children with ADHD. Another avenue to partial construct validity is developing models that possess the core symptoms of ADHD across multiple functional domains rather than in only one domain, e.g., impulsivity, attention deficits, reduced working memory, and hyperactivity. There are many rodent models that exhibit hyperactivity, but few possess the other symptoms. Inattention and impulsivity can be modeled using several methods, including altered DRL (differential reinforcement of low rates of responding to contingent reinforcement) operant performance, impaired extinction of learned behaviors, premature responses on delayed matching to sample tasks, and related schedule-controlled methods, but these have not been consistently used to provide convergent evidence for the different models. (3) Predictive validity is when a model exhibits corrective changes to the characteristic behaviors that have comparable effects in ADHD patients. Since ADHD is a developmental disorder, a good model should have a developmental onset (Willner, 1986).

Face validity

Impulsivity is a prominent ADHD symptom (Taylor, 1998; Johansen et al., 2002) that is seen on tasks requiring timed responses, usually delayed responses. Rodents with this characteristic perform poorly on schedules of reinforcement because the impulsivity interferes with waiting before a rewarded response becomes available. In children with ADHD, impulsiveness usually develops gradually and interferes with academic performance especially as materials become more difficult with each advancing grade in school (Sagvolden and Sergeant, 1998).

Sustained attention deficits are seen when stimuli are spaced or the task is repetitive and requires vigilance (Taylor, 1998). Children with ADHD may have normal task attention at the beginning, but performance deteriorates more rapidly in children with ADHD compared with controls. In addition, children with ADHD often resume responding after a short delay despite the absence of reinforcement whereas comparison children do not (Sagvolden and Sergeant, 1998).

Hyperactivity, like impulsiveness, may or may not be seen in children with ADHD in novel environments, such as during test sessions but emerge in static environments that offer little for them to do (Sleator and Ullmann, 1981; Cook et al., 1995). Children with ADHD tested on fixed reinforcement schedules become hyperactive with extended testing (Sagvolden and Sergeant, 1998) and some rodent models recapitulate this pattern.

Construct Validity

As noted, ADHD has heritable components, but there are no large effect gene variants that by themselves confer ADHD. Rather the genetic contributions arise from multiple small effect genes (Acosta et al., 2004). Polymorphisms of monoaminergic genes are implicated, such as variants of *DRD1*, *DRD4*, *DRD5*, alpha-adrenoreceptor, *DAT*, *NET*, and *SERT*. However, creating a model even with CRISPR/Cas9 methods of all of these would be challenging, even if theoretically possible. Combinations of these variants and perhaps yet to be identified variants likely predispose children to ADHD, except in syndromes with known genetic mutations such as tuberous sclerosis or developmental disorders such as ASD. ADHD not arising from specific syndromes, may occur spontaneously or be triggered by an unknown environmental perturbation. These events may be from chronic exposure to a developmental neurotoxic substance or from a prenatal maternal exposure. From a modeling perspective, creating both neurotoxin-induced and polygenic models have not yet been attempted.

A rodent model should possess the structural, neuropathological, neurochemical, and behavioral changes associated with ADHD, i.e., reduced frontal lobe EEG activity, caudate abnormalities, and brain volume reductions (Lou et al., 1989; Paule et al., 2000; Castellanos et al., 2002). Several neurotransmitters are implicated in ADHD. Most of the evidence points to the involvement of norepinephrine and dopamine but some evidence implicates changes to 5-HT, acetylcholine, opioids, and glutamate (Cortese, 2012). Much of the evidence implicating catecholamines is the use of psychostimulants to treat ADHD. Psychostimulants (methylphenidate and amphetamine) inhibit DAT and NET, and amphetamine also increases neurotransmitter release, inhibits metabolism by inhibiting MAO-A, and interferes with VMAT-2-mediated vesicular reuptake. In children, methylphenidate improves spatial working memory, attentional set-shifting, and inhibits responses to irrelevant stimuli. Models with these characteristics have the potential to provide insights into the role of neurotransmitters in hyperactivity and impulsivity and are mentioned further below.

Predictive Validity

Animal models should predict behavioral responses to existing treatments known to work in affected children and demonstrate benefits from new therapeutic entities prior to first human use.

Genetic Models

Spontaneously Hypertensive Rat

Spontaneously hypertensive rats (SHR) were developed by selective breeding of Wistar-Kyoto (WKY) rats that exhibited high cytosolic blood pressure. The affected rats were reselected at each generation until a consistent line of hypertensive rats was developed across many generations (Okamoto and Aoki, 1963). It is worth noting that although dopamine affects cortical blood flow (Krimer et al., 1998), hypertension is not seen in ADHD patients which limits the validity of this model. To separate the hyperactivity from hypertension, the Wister Kyoto-derived hyperactive (WKHA) rat was later developed (Okamoto and Aoki, 1963) but it has not seen widespread use. The connection between SHR

and ADHD arose accidently when it was found that SHR were more active compared with the normotensive WKY rats.

SHR possess face validity in that they are hyperactive, impulsive, and inattentive compared with WKY controls. SHR are more active than WKY rats on multiple tests. Although SHR are hyperactive compared with WKY rats in tests such as the residential figure-eight maze, they are less active than Sprague Dawley rats in open field tests and less active than WKY rats in running wheels (Ferguson and Cada, 2003). This suggests that the hyperactivity depends on which control group is used. This needs further investigation because if the WKY rat is not the proper control it casts doubt on the generality of the hyperactivity seen in SHR (van den Bergh et al., 2006; Alsop, 2007). For instance, when compared with Sprague Dawley and Wistar rats, SHR show decreased activity in both an open field and home-cage test (Sagvolden et al., 1993). On the other hand, like children with ADHD, SHR show symptom variability. They also show deficient response engagement and make more errors on schedule controlled operant tasks testing impulsiveness (Sagvolden, 2000; Sagvolden et al., 2005; Wiersema et al., 2005). SHR are also overactive compared with WKY rats during operant discrimination testing. And, male SHR over-respond compared with WKY rats, possibly reflecting impulsiveness as seen in hyperactive boys while female SHR show perseveration, perhaps reflecting inattention as seen in ADHD girls. Overall, SHR show some face validity, but questions remain because some of the predicted behavioral changes appear on some tasks and not others where they would be expected.

When it comes to predictive validity, methylphenidate attenuates the ADHD-like behaviors described above in SHR (Wultz et al., 1990; Sagvolden et al., 1992a; Sagvolden et al., 1992b; Aspide et al., 2000; Ueno et al., 2002b; De Bruin et al., 2003; Adriani and Laviola, 2004; Jentsch, 2005). But in some studies, methylphenidate and amphetamine do not decrease SHR hyperactivity compared with controls, but increase it, as it does in most strains. In addition, psychostimulants and guanfacine, an alpha2-adrenoreceptor agonist, has been shown to ameliorate hyperactivity, impulsivity, and inattention in SHR in some cases, thereby providing some predictive validity evidence for this model (Myers et al., 1982; Sagvolden, 2006).

SHR also have neuropathological changes similar to those observed in patients with ADHD. SHR brain volumes, particularly the prefrontal cortex and hippocampus are smaller than in WKY rats (Bendel and Eilam, 1992; Sabbatini et al., 2000). MRI data show increased ventricular volume in SHR compared with WKY rats at 3 months of age (Bendel and Eilam, 1992). There are also fewer neurons in SHR brains compared with WKY rats (Sabbatini et al., 2000; Tomassoni et al., 2004).

Genetically, SHR have a 160 base-pair insertion in the non-coding region upstream of exon 3 for *Dat* (Mill et al., 2005). In association with ADHD, human studies report repeats in the 3'-untranslated region of *DAT* (Cook et al., 1995; Dougherty et al., 1999; Bobb et al., 2005). Expression of *Dat* is transiently reduced in SHR midbrain during the first month of postnatal development which later normalizes (Mill et al., 2005). This change reduces dopamine uptake and contributes to dopamine-mediated activity. Differences in dopamine metabolism are also reported in SHR, which is consistent with the developmental changes

in *DAT* expression and dopamine reuptake in patients (Cook et al., 1995; Bobb et al., 2005). Changes in DAT show construct validity in that children and adults with ADHD are reported to have changes in DAT (Madras et al., 2005).

In SHR, tyrosine hydroxylase (TH) expression is reduced in the neostriatum and nucleus accumbens, although striatal dopamine content and dopamine metabolites do not differ between SHR and control rats (Fuller et al., 1983). SHR have increased extracellular tonic dopamine release in the nucleus accumbens shell (Carboni et al., 2003). Heal et al. (2008), using microdialysis showed increased striatal dopamine overflow in SHR. Carboni et al. (2003), stimulated dopamine release with methylphenidate and amphetamine in the nucleus accumbens shell and found a larger dopamine increase in the SHR compared with WKY rats. This differential increase was reversed by increasing KCl stimulation in the nucleus accumbens shell which caused WKY rats to have larger increases of extracellular dopamine release compared with that seen in the SHR. These data suggest that from higher dopamine tone in the nucleus accumbens shell of SHR in combination with lowered intracellular dopamine reserves contributed to SHR increased activity compared with WKY rats. While some studies find no differences in extracellular dopamine concentrations in SHR compared with control rats (Kirouac and Ganguly, 1995; Ferguson et al., 2003), studies find decreased basal extracellular dopamine concentration in the caudate nucleus and nucleus accumbens compared with controls at 8–9 weeks of age (Linthorst et al., 1991; de Jong et al., 1995; Fujita et al., 2003). Studies using slice preparations and *in vivo* studies using microdialysis find increased DRD2 mediated inhibition of dopamine release in SHR compared with control rats (Linthorst et al., 1991; van den Buuse et al., 1991; Russell, 2000). Overall, these studies suggest hypodopaminergic function in the SHR model.

While some studies find no differences in DRD1, DRD2, and DRD3 expression (Fuller et al., 1983; Van den Buuse et al., 1992; Linthorst et al., 1993), others show an upregulation of DRD1 and DRD2 expression in nucleus accumbens, striatum, and frontal cortex (Chiu et al., 1982; Le Fur et al., 1983; Chiu et al., 1984; Lim et al., 1989; Sadile, 2000; Papa et al., 2002) but no change in DRD3. Higher DRD1 and DRD2 expression are consistent with decreased dopamine release causing upregulation of receptors. Surprisingly, nomifensine, a DAT and NET inhibitor, increases dopamine release to the same extent in SHR and WKY rats in the nucleus accumbens and caudate-putamen. This is difficult to reconcile with increased dopamine tone, but perhaps increased DAT in the nucleus accumbens shell is compensatory for low DAT activity in striatum. However, this does not explain why stimulated dopamine release is the same in SHR and WKY rats and so far, no satisfactory account for this has been reported. Moreover, the results in SHR for dopamine release and DAT activity are not consistent with the reported increased DAT in the striatum of patients with ADHD (Jucaite et al., 2005).

The DRD2 activity reported in some studies could be a compensatory mechanism for low DAT function during early development in SHR. The net effect of such changes has been suggested to cause elevated extracellular dopamine during the preweaning period in SHR (Russell, 2000) that later becomes dopamine hypofunction. In agreement with later decreased stimulus-evoked dopamine, postsynaptic DRD1 levels are increased in caudate-putamen and nucleus accumbens in SHR consistent with a role of dopamine in ADHD

(Kirouac and Ganguly, 1993; Watanabe et al., 1997; Carey et al., 1998). SHR also have spatial working memory deficits, similar to children with ADHD who have working memory impairments (Ueno et al., 2002a; De Bruin et al., 2003; Hernandez et al., 2003; Kantak et al., 2008).

Concern about SHR hypertension remains a potential problem. Hypertension is a risk factor for adverse cognitive outcomes (Swan et al., 1998; Gottesman et al., 2014; Iadecola and Gottesman, 2019). Four- to five-week-old SHR do not show hypertension (de Jong et al., 1995), but many studies are done past this age in SHR and the ADHD-related symptoms remain as hypertension emerges. It is not clear whether late-onset hypertension is a problem in this model or not.

In sum, the SHR model has been extensively investigated and shows several ADHD-relevant characteristics (hyperactivity, working memory deficits, impulsivity, and in some tests reduced attention). However, the issue of whether WKY rats are appropriate controls persists (Alsop, 2007). The SHR is the most widely used model of ADHD because it shows face, partial construct, and predictive validity. SHR are the product of selective breeding for hypertension that for unknown reasons was discovered to be hyperactive and then was found to possess other characteristics of ADHD. Because SHR are the result of selective breeding for an unrelated trait, which genes or combination of genes are critical in producing SHR-related ADHD-like phenotype remains unknown.

Genetic Models*: SNAP-25* KO Coloboma Mouse

Because of the difficulty of modeling multiple small effect gene variants, and the limitations of selective breeding, there is a place for single-gene mutant models for understanding how specific pathways influence ADHD symptoms. A case in point is the *Snap-25* mutant coloboma (*Cm*/+) mouse, because *SNAP-25* polymorphisms are associated with ADHD (Mill et al., 2004; Feng et al., 2005). SNAP-25 regulates membrane trafficking and is involved in the release of neurotransmitters as well as regulating translocation of proteins (e.g., NMDA receptor subunits) to the cell membrane (Oyler et al., 1989). Altered expression of *SNAP-25* has multiple effects on neuronal function and the mutant mouse displays distinct neurodevelopmental abnormalities. Homozygosity of *Snap-25* knock-out (KO) in mice is perinatally lethal, but heterozygous mice have delays in tests of motor skills such as righting reflex and bar-holding, and dysmorphology of the eye through delayed attachment of the lens vesicle and microphthalmia (Theiler and Varnum, 1981; Heyser et al., 1995). Many attention and impulsive tasks rely on visual processing, and thus, the results obtained from such tasks should be interpreted carefully with this mouse.

The heterozygous mouse displays spontaneous hyperactivity and thigmotaxis, but it lacks attention deficits (Hess et al., 1992; Hess et al., 1996). In conjunction with the hyperactivity it displays head bobbing (also called circling) that persists into adulthood (Heyser et al., 1995). Thigmotaxis is at odds with human ADHD. A study by Bruno et al. (2007), showed in a delayed reinforcement procedure that *Snap-25* mice had impaired latent inhibition, suggesting impulsivity. The hyperactivity of *Snap-25* mice was ameliorated by high doses of amphetamine but not by methylphenidate. The difference in response to psychostimulants is puzzling and requires further investigation. A genetic rescue of *Snap-25* was created by

crossing *Snap-25* KO mice with transgenic mice overexpressing the gene (Hess et al., 1996). The rescue normalized activity and dopaminergic transmission (Steffensen et al., 1999).

Neurochemically, *Snap-25* mice have an increase in DRD2 expression in the ventral tegmental area (VTA) and substantia nigra, implicating inhibition of dopamine-driven neuronal firing. Dopamine release and dopamine metabolites [3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] are decreased in the striatum of *Snap-25* mice, consistent with dopaminergic hypofunction. Striatal DRD1 and DRD2 expression are unaltered. TH expression is unaltered in VTA and substantia nigra of these mice, whereas TH and alpha 2A adrenoreceptor expression are increased in the locus coeruleus (Bruno and Hess, 2006). There are also changes in norepinephrine. HPLC data show an increase in norepinephrine concentrations in the striatum and nucleus accumbens (Jones et al., 2001). Depletion of norepinephrine by DSP-4 reduces hyperactivity in *Snap-25* heterozygous mice, but the effect is incomplete in that activity is not fully normalized to control levels (Jones and Hess, 2003). Taken together, these data indicate that the hyperactivity is likely related to upregulated noradrenergic activity. The phenotype of the *Snap-25* heterozygous mouse appears to be the result of noradrenergic hyperfunction and dopamine hypofunction, similar to that proposed for the SHR model. This model has two of the four cardinal behavioral characteristics of a relevant model, hyperactivity and some evidence of impulsivity, but not of attention deficit or impaired working memory.

Genetic Models: Dopamine transporter (DAT) Knockout Mouse

Dat KO mice lack the gene that encodes DAT and represents another model with characteristics of ADHD. DAT recycles dopamine and is also the main clearance mechanism of released dopamine (Cook et al., 1995; Giros et al., 1996). DAT is a major target for amphetamine and methylphenidate and *DAT*-gene alterations have been associated with ADHD (Cook et al., 1995; Swanson et al., 1998). However, the *Dat*-KO mouse is an extreme model of reduced DAT reuptake, and it is not consistent with reported increased DAT in the striatum of patients with ADHD (Jucaite et al., 2005). The extremes are exemplified by *Dat*-KO mice that show impaired growth and increased rates of premature death (Giros et al., 1996; Gainetdinov et al., 1998). The *Dat*-KO mouse has provided information concerning the neurobiological consequences of impaired DAT function.

Dat KO mice are hyperactive in novel environments, exhibit impaired extinction in operant tasks (Giros et al., 1996), have spatial learning and memory deficits (Gainetdinov and Caron, 2001; Trinh et al., 2003), and show sleep dysregulation. Administration of amphetamine or methylphenidate attenuates the hyperactivity (Gainetdinov et al., 1998; Jones et al., 1998a; Gainetdinov and Caron, 2001) which is difficult to explain if these mice have no DAT and the drug's principal mode of action is via inhibiting DAT-mediated reuptake. One possibility is that there is residual DAT function due to incomplete *Dat* deletion. It is also possible that the attenuation of hyperactivity by psychostimulants in *Dat*-KO mice indicates another mechanism of action such as through other amine transporters such as NET and/or SERT (Morón et al., 2002).

In *Dat*-KO mice, dopamine release is cleared slowly leading to a 5-fold increase in extracellular dopamine (i.e., a hyperdopaminergic state) in the striatum compared with

wildtype mice (Gainetdinov et al., 1999). Fast scan cyclic voltammetry of extracellular striatal dopamine levels shows impaired dopamine clearance in *Dat* KO mice by 300-fold compared with controls (Jones et al., 1998b). Stimulated dopamine release by microdialysis is decreased which presumably reflects phasic release and suggests dopamine hypofunction. *Drd2* mRNA was decreased by 50% in the substantia nigra and VTA of *Dat*-KO mice (Giros et al., 1996). A further analysis showed decreased DRD2 function compared with controls using patch-clamp electrophysiology, fast scan cyclic voltammetry, and pharmacological agonists and antagonists (Jones et al., 1999). These changes may affect long-term potentiation (LTP) resulting in reduced synaptic strength and impaired associative learning in the *Dat*-KO mice (Gainetdinov et al., 1999).

Inhibitors of NET and DAT do not affect *Dat*-KO mouse hyperactivity, whereas inhibitors of SERT and drugs that activate 5-HT, such as 5-HT receptor agonists and precursors reduce hyperactivity in *Dat*-KO mice (Gainetdinov and Caron, 2001). *Dat*-KO mice demonstrate that hyperactivity induced by high extracellular dopamine can be regulated by enhancing serotonergic tone (Barr et al., 2004). Antagonists of the 5-HT_{2A} receptor reverse the behavioral effects seen in *Dat*-KO mice (Barr et al., 2004).

Dat knockdown (KD) mice were created as a less extreme model of DAT loss. The *Dat*-KD mouse was developed by breeding *Dat* heterozygous mutants on a 129 Sv/J genetic background (Zhuang et al., 2001). The *Dat*-KD mouse does not have growth reduction and is not associated with premature death as seen in the *Dat*-KO model (Zhuang et al., 2001). *Dat*-KD mice resemble *Dat*-KO mice in that they are hyperactive and have impaired response inhibition (Zhuang et al., 2001; Ralph-Williams et al., 2003; Thakker et al., 2004). A study using natural rewards showed that the *Dat*-KD mice were less distractible than controls measured by latency to reach a food source in a runway (Peciña et al., 2003). This could be interpreted as an indication that the *Dat*-KD mice do not have impaired attention, but this effect needs further investigation. *Dat*-KD mice have attenuated hyperactivity after administration of the DRD1/2 agonist apomorphine or the DRD2 agonist quinpirole (Zhuang et al., 2001). These data are consistent with a hyperdopaminergic role in this model of ADHD.

In addition, DAT KO mice were tested in three procedures, delayed spatial alternation, delayed non-spatial alternation, and reversal of delayed non-spatial alternation. DAT KO mice were impaired in delayed spatial alternation and delayed non-spatial alternation but not in reversal non-spatial alternation (Del'Guidice et al., 2014). Moreover, DAT heterozygous mice have deficits in attention and response inhibition in the 5-choice serial reaction test (5-CSRTT) (Mereu et al., 2017). An interesting genetic variant model based on several ADHD cases that carry an Ala559Val substitution in the *Dat* gene in mice (Davis et al., 2018). This mouse has reduced DAT function and hence excess synaptic dopamine. The mouse is hyperactive and has impulsivity and response inhibition deficits in the 5-CSRTT and reduced presynaptic dopamine vesicular release, in essence, another type of dopamine hypofunction.

Overall, DAT KO, hets, KD and one variant model collectively have the four behaviors characteristic of an ADHD phenotype, hyperactivity, attention deficits, working memory deficits, and impulsivity.

Genetic Models: Dopamine receptor KO mice

Mice lacking DRD1, DRD2, DRD3, DRD4, and DRD5 have all been generated, but most do not have an ADHD-like phenotype. The most studied of these is the *Drd4* KO mouse. Some alleles for the human *DRD4* gene are associated with ADHD (Rowe et al., 1998; Grady et al., 2003), however the *Drd4* KO mouse is hypoactive and does not exhibit impulsivity or inattention (Rubinstein et al., 1997; Helms et al., 2008). *Drd4* KO mice, however, have increased sensitivity to alcohol, cocaine, and methamphetamine (Rubinstein et al., 1997). Similar to *Snap-25* heterozygous mice, dopamine release is decreased in the dorsal striatum of *Drd4* KO mice, whereas in contrast to *Snap-25* heterozygous mice, dopamine synthesis and its metabolite DOPAC are elevated (Thomas et al., 2007). Overall, the *Drd4* KO mouse model does not have the key characteristics of ADHD.

Genetic Models: Guanylyl Cyclase-C KO mice

Guanylyl cyclase-C (GC-C) colocalizes in the VTA and substantia nigra pars compacta with TH and may modulate dopamine signaling. When the ligands for GC-C, such as guanylin or uroguanylin, are administered they bind to GC-C and generate 3’,5’-monophosphate (cGMP) which acts upon metabotropic glutamate receptors that impinge on dopaminergic cells. *Gc-c* KO mice are reported to be hyperactive in familiar and novel environments, exhibit extended novel odor investigation, and reduced hyperactivity in response to amphetamine or 8-Br-cGMP (Gong et al., 2011). We tried to reproduce the hyperactivity in these mice. We obtained the mice from the same colony as Gong et al. (2011) but found no evidence of hyperactivity. Using a battery of tests, we found few phenotypic changes in *Gc-c* KO mice except a modest novel object recognition deficit and reduced tactile startle but no change in acoustic startle (Mann et al., 2019). This model does not fit most of the criteria as a model of ADHD.

Genetic Models: *Latrophilin-3* knockout mice and rats

LPHN-3 is a member of the LPHN sub-family of adhesion G protein-coupled receptors (aGPCRs) whose role in attention, learning, and memory is largely unknown. LPHNs bind to neurexins (Silva et al., 2011; O’Sullivan et al., 2012), tenuerins (Boucard et al., 2012), and fibronectin leucine rich transmembrane proteins (O’Sullivan et al., 2012) that regulate synaptic activity via trans-synaptic coupling (Sando et al., 2019). *LPHN-3* gene variants are associated with familial ADHD and in ADHD population studies, particularly in those having the combined type of ADHD (Arcos-Burgos et al., 2010; Domene et al., 2011; Gomez-Sanchez et al., 2016; Huang et al., 2019). Based on these findings several animal models of *Lphn-3* disruption were created. There are four such models: *Drosophila*, zebrafish, mouse, and rat. Here we will discuss the mouse and rat models. However, both the *Drosophila* and zebrafish models are consistent with the rodent models in showing hyperactivity, impulsivity, and for zebrafish corrective effects of methylphenidate and atomoxetine on faster swimming in KD fish (Lange et al., 2012; van der Voet et al., 2016; Lange et al., 2018).

Lphn3 constitutive KO rats are hyperactive (Regan et al., 2019). The hyperactivity is present at postnatal day (P)35 and remains at P50. In a novel open-field, *Lphn3* KO rats are hyperactive and remain hyperactive after treatment with amphetamine, however, relative to their pre-drug baseline, *Lphn3* KO rats' activity declines whereas activity in wildtype rats increases after amphetamine challenge. *Lphn3* KO rats are also hyperactive in a familiar, home-cage, environment which many other models do not show. The *Lphn3* KO rats also exhibit increased reactivity to an acoustic startle stimulus, another behavior consistent with ADHD. These rats also have attention and inhibitory control deficits (Sable et al., 2021).

Biochemically, no differences in tissue concentrations of dopamine, norepinephrine, 5-HT, or their major metabolites by HPLC were found in brain regions where LPHN3 is most abundantly expressed (striatum, hippocampus, and PFC) (Regan et al., 2019). However, western blots revealed that striatal dopamine markers were altered. TH was increased, suggesting greater dopamine and/or norepinephrine synthesis, and DAT was increased suggesting increased dopamine reuptake. Concomitantly, *Lphn3* KO rats had decreased DRD1 levels. If increased TH causes increased dopamine overflow, it may have resulted in compensatory downregulation of DRD1. Consistent with this, DARPP-32 was also reduced. Since DARPP-32 is a downstream effector of postsynaptic transduction, this may be a response to the DRD1 reduction. *Lphn3* KO rats also have increased synaptic dopamine concentrations, release, and reuptake in the striatum in slice preparations measured by fast-scan cyclic voltammetry (Regan et al., 2020). These results suggest that there is an increase in synthesis and release of dopamine causing synaptic overflow that may explain the hyperactivity observed in the *Lphn3* KO rats.

Lphn3 KO rats exhibit cognitive deficits in tests of egocentric learning and memory in the Cincinnati water maze, a test that depends on striatal dopamine (Braun et al., 2015; Braun et al., 2016; Vorhees and Williams, 2016) and on allocentric learning and memory in the Morris water maze, a test of spatial learning and memory that depends on glutamatergic function (Regan et al., 2021). These results are consistent with the decreased DRD1 and DARPP-32 levels and increased DAT and TH levels in the neostriatum noted above (Regan et al., 2019; Regan et al., 2021). *Lphn3* KO rats also display deficits in cognitive flexibility and inhibitory control (Regan et al., 2021) as shown by impaired reversal and shift learning in the Morris water maze (Vorhees and Williams, 2006), effects seen in some ADHD patients. New data on this rat, show that *Lphn3* (Sable et al., 2021) KO rats have deficits in DRL suggesting deficits in impulsivity and on DSL (delayed spatial alternation) suggesting deficits in working memory

Lphn3 KO mice have also been created. In a novel open field, *Lphn3* KO mice travelled greater distances in the center and periphery compared with wildtype littermates (Wallis et al., 2012; Mortimer et al., 2019). *Lphn3* KO and wildtype mice both had increased activity after cocaine, but at the highest dose, the drug induced hyperactivity was attenuated in KO compared with wildtype mice (Wallis et al., 2012). *Lphn3* KO mice also have exaggerated reward seeking on a fixed ratio schedule, but performed similarly to wildtype mice for working memory (Orsini et al., 2016). *Lphn3* KO mice have increased mRNA expression of *Slc6a4, 5-ht2a*, *Dat1*, *Drd4*, neural cell adhesion molecule (*Ncam*), nuclear receptor related 1 (*Nurr1*), and *Th* (Wallis et al., 2012). In dorsal striatum *Lphn3* KO mice have increased

dopamine and 5-HT levels by HPLC compared with wildtype littermates (Wallis et al., 2012).

Another study using the *Lphn3* KO mouse (Mortimer et al., 2019), found that the KO mice are hyperactive, impulsive, and have motoric disturbances. The mice were impaired in spatial learning and memory in a Barnes maze (a test of reference memory) and had decreased aggression in a resident-intruder test. Using RNA-sequencing, the number of genes found to exhibit differential expression was small, implying a discrete effect that has yet to be further defined. The largest expression difference was in *Dat* in the prefrontal cortex.

Overall, the two KO models of *Lphn3* in rats and mice show all four of the behavioral phenotypes associated with ADHD: hyperactivity, impulsivity, attention deficits, and working memory impairment.

Environmental Chemicals: Mixtures

Rodent models of environmental effects test one agent at a time, but in human epidemiological studies, associations between developmental environmental exposures and ADHD are found with multiple chemicals in the same study population making rodent models difficult to compare to human data. Moreover, human environmental exposures are seldom easily defined as exposed versus unexposed, but rather consist of a range of exposures or of criteria created groups of those most exposed versus those least exposed. Such exposure scenarios have not been used in rodent models. There are a number of human epidemiological review studies or meta-analyses testing the effects of environmental agents associated with ADHD.

Kern et al. (2017) reviewed studies from the perspective of differences in effects of developmental environmental exposures as a function of sex. They reviewed human and animal studies for developmental neurotoxicity for which males showed greater effects than females. There were associations between prenatal and childhood lead (Pb) exposure with males more affected than females in most outcomes including for ADHD symptoms in males, an effect for which they found partial support in animal studies. Developmental exposure to methylmercury (MeHg), on the other hand, while showing developmental neurotoxicity, had only weak male greater than female effects and no association with ADHD-like behaviors.

Rats exposed to PCBs during development were hyperactive and impulsive, and these effects were more pronounced in male offspring. Organochlorine pesticides (dieldrin, endosulfan, heptachlor, DDT, DDE) also induce developmental neurotoxicity in rodents but no evidence of sex differences or ADHD-like behaviors were reported. Polycyclic aromatic hydrocarbons (PAHs) also are developmental neurotoxins in rodents with males more affected than females but no association with ADHD-like effects. A similar pattern was found for organophosphate (OP) pesticides (chlorpyrifos, diazinon, malathion, and parathion).

Endocrine disruptors such as bisphenol A (BPA) and phthalates used in plastics are developmental neurotoxins in rodents and BPA is associated with ADHD in children

exposed to higher levels with boys more affected than girls. Developmental phthalate exposure effects were also associated with boys more than girls and boys had more inattention and rule-breaking behaviors but were not diagnosed with ADHD. Air pollution and proximity to diesel and car exhaust particles are associated with impulsivity and impaired working memory with significantly higher prevalence in boys than in girls but not at a level sufficient for an ADHD diagnosis.

Developmental exposure to flame retardants such as polybrominated diphenyl ethers (PBDE) are also found to negatively affect children's IQs, psychomotor development, and attention with no sex differences. Some rodent studies also find that manganese (Mn) exposure in rodents during development results in a hyperactive phenotype in the offspring (Kern et al., 2010) but see below.

Lenters et al. (2019) examined data from a Norwegian birth cohort of 2606 mother-child pairs for associations between exposure to environmental contaminants and ADHD. Perfluorooctate sulfonate (PFOS) was associated with ADHD with an odds ratio of 1.77, β-hexachlorocylohexane (HCH) was associated with an odds ratio of 1.75 with more boys affected than girls (Lenters et al., 2019). But they found no increase in ADHD from exposure to DDT or hexachlorobenzene (HCB).

Maitre et al. (2021) interrogated a database that included six longitudinal birth cohort studies in Europe. Among these 1287 children they looked for associations with a range of behavioral outcomes, including ADHD. Air pollution and maternal smoking produced the strongest associations with ADHD. Other neurobehavioral effects were associated with Pb, copper, indoor air pollution, and poor diet but not with ADHD (Maitre et al., 2021)

Nilsen and Tulve (2020) conducted a meta-analysis between chemical exposures, stressors, and ADHD, including associations with MAO-A. After their literature search they ended up with 47 studies. They found that developmental exposure to Pb, phthalates, organic pollutants, and cigarette smoke were significantly associated with an ADHD diagnosis. Developmental Pb exposure had the largest odds ratio of the associations examined in relation to ADHD of 3.39 and with a formal ADHD diagnosis with an odds ratio of 4.06. Next were associations with childhood exposure to MeHg or Mn. The odds ratio for MeHg and ADHD was 2.68 and for Mn and ADHD it was 2.63. For phthalates, the odds ratio was 3.31 with a higher ratio of 3.54 for boys than 3.12 for girls. Organic contaminants were pooled and included OP pesticides, PCBs, pyrethroid insecticides, and trichlorophenol (TCP). For this group, the associated odds ratio for ADHD was no effect (0.99), whereas for cigarette smoke the ratio was significant at 2.7.

There were several other associations, but they did not have sufficient data to determine an odds ratio. These included perfluorinated and nonylphenol compounds and arsenic. Limited associations were found between perfluorinated chemicals and arsenic and ADHD but not for nonylphenol compounds. They also found associations between genetic variants in MAO-A and ADHD. Nilsen and Tulve (2020) identified studies that looked for associations between low expressing MAO-A variants, childhood trauma, and ADHD and found higher prevalence of ADHD when both childhood trauma and low MAO-A expression co-occurred.

Xi and Wu also reviewed chemical exposures and ADHD. As in the above reviews they found associations between Pb, MeHg, and PCBs and ADHD with some association with PAHs and air pollution for particle sizes of PM2.5 and PM10 (Xi and Wu, 2021).

Other environmental factors that increase the diagnosis rates of ADHD have only been recently investigated and have limited data. For example, fluoride. While considered safe at levels of 0.7 mg/L in drinking water, increased odds ratio for an ADHD diagnosis to 6.1 is found when there was a 1 mg/L higher level of fluoride in drinking water above regulatory acceptable levels (Riddell et al., 2019). Similarly, a study in Mexico linked increased fetal exposure to fluoride with an increase in ADHD prevalence. What is missing are data regarding the potential genetic susceptibility factors that may co-occur when children are exposed to elevated levels of these environmental agents (Bashash et al., 2018).

Environmental Chemicals: Lead (Pb)

Developmental Pb exposure is one of the most often reported associations with increased prevalence of ADHD in children (Silbergeld, 1997; Aguiar et al., 2010). For Pb there are also non-human primate and rodent studies that find associations between Pb exposure and ADHD-like behavior (Cory-Slechta, 2003). Early Pb exposure in mice results in ataxia and hyperactivity that is reduced by d-amphetamine. Pb impairs performance on delayed spatial alternation in monkeys, a test of working memory (Levin and Bowman, 1986; Levin et al., 1987; Rice and Karpinski, 1988; Rice and Gilbert, 1990). Rodent studies of developmental Pb exposure are not as consistent in finding hyperactivity as are the human and non-human primate studies (Cory-Slechta et al., 1991). For example, high dose Pb exposure (10 mg Pb/kg/day) given developmentally to rats produced working memory deficits but not hyperactivity, whereas lower, human-relevant doses do not consistently affect working memory or activity in rats (Cory-Slechta et al., 1991; Sprowles et al., 2018). Performance on vigilance tasks is impaired in rats developmentally exposed to Pb and these data imply attention deficits (Brockel and Cory-Slechta, 1999; Stangle et al., 2007). Neurochemically, Pb-exposed animals have reduced dopamine signaling (Levin et al., 1987; Cory-Slechta, 1997). However, other studies are not concordant in finding any dopamine changes. In fact, Pb increases dopaminergic signaling in mesolimbic pathways (Zuch et al., 1998), whereas no differences were noted in Pb-exposed rats administered methamphetamine (Sprowles et al., 2018). Changes in dopamine signaling may play a role in the Pb-induced deficits on fixed interval and delayed spatial alternation tests, but not on repeated acquisition tasks (Levin et al., 1987; Cory-Slechta, 1997). The increased prevalence of ADHD in epidemiological studies in children chronically exposed to Pb are sufficiently consistent to conclude that Pb is a likely environmental factor in ADHD in children with greater exposure than is currently occurring. Animal models support this association but with wide variation in findings depending on dose, exposure age, outcome measures, species, and strain. As noted above, in studies of multiple chemical exposures in children, the association between Pb and ADHD is the most consistent of the environmental agents studied (Kern et al., 2017; Nilsen and Tulve, 2020; Maitre et al., 2021; Xi and Wu, 2021) but in animals there is much less consistency.

Environmental Chemicals: PCBs

PCBs are a group of industrial compounds consisting of 209 congeners once used as lubricants and coolants in electrical equipment as well as in building materials before being banned in many countries (Mariussen and Fonnum, 2006). PCBs are chemically stable and resistant to degradation, and worldwide many areas continue to be contaminated (Fonnum and Mariussen, 2009). Adolescents and adults are exposed through consumption of contaminated food, of which seafood from contaminated rivers and lakes is the most prevalent source (Safe, 1990; Mariussen and Fonnum, 2006; Fonnum and Mariussen, 2009). Low-level exposure to PCBs during development has adverse effects on neurobiological, cognitive, and behavioral function (Schantz, 1996; Bushnell et al., 2002). Exposure to PCBs during childhood is associated with impulsivity, reduced attention and concentration, poorer working memory, and lower IQ (Jacobson and Jacobson, 1996b, a; Grandjean et al., 2001; Stewart et al., 2003; Stewart et al., 2005; Sagiv et al., 2010); symptoms consistent with ADHD (Eubig et al., 2010). These data led to the suggestion that developmental PCB exposure may be an environmental risk factor in children with ADHD, especially in areas where contamination is widespread.

Male rats administered PCBs prenatally and/or postnatally are impulsive and hyperactive (Sable et al., 2009). PCBs have no effects on sustained attention (Bushnell et al., 2002). Amphetamine disrupts DRL performance less in PCB-exposed rats than in controls (Sable et al., 2009). Neurochemically PCB-exposed rats have reduced dopamine in the prefrontal cortex and striatum (Seegal et al., 1991; Seegal et al., 1997). PCBs also decrease expression of DAT and VMAT2 in dopaminergic neurons *in vitro* (Caudle et al., 2006; Fonnum et al., 2006). This suggests dysregulation of dopamine signaling. Mice with alterations to the aryl hydrocarbon receptor were dosed during early development with a mixture of planar and coplanar PCBs and examined in a battery of tests. In wildtype mice, there was an increase in novel environment activity, an effect not observed in the transgenic mice. However, startle responses and LTP decreased in wildtype PCB exposed mice (Curran et al., 2011).

Environmental Chemicals: Organophosphate Pesticides

Pesticides are a large and diverse group of chemicals that are broadly classified as organochlorines, OPs, carbamates, and pyrethroids. Within these categories there are numerous chemical entities. In a review of epidemiological studies of childhood exposure to pesticides, Roberts et al. (2019) identified 12 studies testing associations between different types of insecticides and ADHD. Ten of the 12 studies found pesticide-ADHD associations and two did not. Sagiv et al. (2021) conducted a prospective study enrolling women during pregnancy and obtained urine samples at 13 and 26 weeks of gestation and quantified a metabolite of OP pesticides. 351 children were evaluated between 7–12 years of age and higher maternal metabolite levels were associated with more behavioral problems and lower working memory scores, a common finding in ADHD children, than in those with lower metabolite levels.

Chang et al. (2018) compared the exposure history of 93 children (average age 8) with ADHD and 112 children without ADHD for exposure to OP pesticides and found that the ADHD children had higher urinary metabolites than comparison children. They also tested

the groups for differences in *DRD4* genotypes and found no significant relationship with outcome.

Banhela et al. (2020) reviewed the literature on associations between pesticides and a range of neurobehavioral outcomes, including ADHD and polymorphisms for paraoxonase-1 (*PON-1*) since OP pesticides are metabolized by paraoxonases and arylesterases. After extracting 79 studies and evaluating them for relevance, they ended up with 6 that met inclusion criteria. Although evidence was found of associations between OP exposure and sensory, behavioral, and cognitive outcomes, only 2 of the 6 studies found evidence of associations between OPs and hyperactivity.

(Berg et al., 2020) evaluated the effect of the OP chlorpyrifos (CPF) in rats exposed to different doses (0.1, 0.3, or 1 mg/kg) given daily from P1–4 and tested as adults. They found effects from CPF exposure on ultrasonic emissions, but no effects related to an ADHD-like phenotype (i.e., no effects on locomotor activity or conditioned contextual or cued fear).

Gomez-Gimenez et al. (2018) tested the developmental effects of one prototypical pesticide from different classes for effects on locomotor activity and coordination as indices of ADHD-like behaviors. From the OPs they chose CPF, from the carbamates they chose carbaryl, from the organochlorines they chose endosulfan, and from the pyrethroids they chose cypermethrin. Each compound was administered to gravid rats from embryonic day (E)7 to P21. Rotorod performance and 60-min open-field locomotor activity were assessed when the offspring were P60-P90. There were no effects on rotorod in males but in females the cypermethrin, endosulfan, and CPF (0.3 mg/kg) groups were impaired. In the open field, the CPF 0.1 mg/kg males and females had significantly increased activity. Also, the CPF 0.3 mg/kg males and cypermethrin and endosulfan females had increased cerebellar GABA.

Environmental Chemicals: Pyrethroid Pesticides

Deltamethrin is a Type 2 pyrethroid pesticide widely used in agricultural, medical, and household applications. As other types of pesticides have had restrictions placed on their use, the use of pyrethroids has increased, including around children. There are a few studies reporting an association between childhood pyrethroid exposure and neurodevelopmental disorders, including ADHD, ASD, and developmental delay (Oulhote and Bouchard, 2013; Shelton et al., 2014; Wagner-Schuman et al., 2015). Not only is deltamethrin associated with ADHD in children it is reported to induce an ADHD-like phenotype in mice (Richardson et al., 2015).

In an open-field, male mice exposed to deltamethrin developmentally were hyperactive, however rats given similar exposures were not, and in fact the treated rats were hypoactive compared with controls (Lazarini et al., 2001; Johri et al., 2006; Pitzer et al., 2019). The increased activity in deltamethrin-treated male mice was normalized by treatment with methylphenidate (Richardson et al., 2015), whereas deltamethrin-exposed rats responded similarly to amphetamine challenge compared with controls (Pitzer et al., 2019). Using a fixed ratio wait operant paradigm, prenatal and postnatal deltamethrin-exposed male mice were impulsive suggesting attention deficits. Mice exposed to developmental deltamethrin also had deficits in working memory when tested for spontaneous alternation in a Y-maze

(Richardson et al., 2015). Rats, on the other hand, exposed to deltamethrin neonatally had cognitive flexibility deficits in the Morris water maze and changes in monoamine markers but no evidence of a working memory deficit (Pitzer et al., 2019). Deltamethrin-exposed male rats and mice both had decreased amphetamine-stimulated extracellular dopamine release in the nucleus accumbens by microdialysis (Richardson et al., 2015; Pitzer et al., 2019). There were no changes in dopamine levels or metabolites assessed by HPLC in rats or mice exposed to deltamethrin. In neostriatum, male rats developmentally exposed to deltamethrin, had decreased *Drd1* mRNA compared with controls with no changes to protein levels of DAT, DRD1, or DRD2 in striatum (Pitzer et al., 2021). While the evidence implicating pyrethroids in ADHD is limited, pesticides have been widely suggested as environmental risk factors for ADHD and cognitive impairment. A challenge in testing for such associations is that there are many pesticides, and they are used in different settings resulting in widely varied exposures. The highest exposures occur in agricultural workers and in dense inner-city housing for pest control. In addition, pesticide exposures are difficult to measure because some have short half-lives and common metabolites. This combined with the fact that they are often applied as mixtures makes epidemiological studies of the effects of these chemicals more difficult. However, as analytical techniques improve, the capacity to measure complex metabolites is improving and this will help identify those that are developmentally neurotoxic. In the meantime, rodent models where dose and age of exposure are varied systematically, will provide the best approach currently available to test hypotheses about the neurodevelopmental effect of these compounds.

Environmental Chemicals: Pesticides

Abreu-Villaca and Levin (2017) reviewed all classes of pesticides: organochlorines, OPs, carbamates, pyrethroids, and the newer neonicotinoids for human and animal neurotoxicity. The review's primary focus was on developmental neurotoxicity. The authors' identified multiple studies implicating organochlorines, OPs, and pyrethroids as being significantly associated with increased prevalence of ADHD in children, whereas no such associations were found for carbamates or neonicotinoids. However, data on neonicotinoids are very limited making evaluation of evidence inconclusive.

Other Models: Prenatal nicotine/smoking

Children exposed *in utero* to tobacco smoke have increased diagnoses of ADHD (Kwan et al., 2020). In a cross-sectional study of Vietnamese first-graders (6–7 y.o.), using parent and teacher ratings using the Vanderbilt questionnaire, of the 525 students evaluated 4.6% were identified as having ADHD. The adjusted odds ratio of having ADHD if they had a first-degree relative with ADHD was 85.2, indicating a significant genetic contribution. Other significant contributions were maternal cigarette smoking during pregnancy (odds ratio 4.78) and prenatal alcohol exposure (odds ratio 8.87) (Hoang et al., 2021). From a dataset from six European longitudinal studies, smoking had the strongest association with ADHD with an adjusted odds ratio of 1.31 (Maitre et al., 2021). Nilsen and Tulve (2020) conducted a meta-analysis for ADHD associations with Pb, phthalates, organic pollutants, and cigarette smoke and included associations with MAO-A. The odds ratio for children having ADHD if exposed to cigarette smoke was 2.7 which is less than for Pb (odds ratio 3.08) and phthalates (odds ratio 3.36) but greater than for the other chemicals examined.

Another human study used a Finnish cohort of 1079 women and measured cotinine levels during pregnancy. They found an adjusted odds ratio for ADHD of 2.21 (Sourander et al., 2019). Associations with maternal smoking were also found by Xi and Wu (2021).

In rodents prenatal nicotine exposure causes hyperactivity in the offspring (Vaglenova et al., 2004; Santiago and Huffman, 2014), although there are studies that do not find this effect (Shacka et al., 1997; Tizabi et al., 2000; Romero and Chen, 2004; Franke et al., 2008) or find the opposite, reduced activity (Ajarem and Ahmad, 1998; Roy et al., 2002). In rats, prenatal nicotine exposure is associated with reductions in the number of correct choices in a radial-arm maze of working memory and impaired performance and increased impulsivity in the 5-CSRT as adolescents with no effect when tested as adults (Levin et al., 1993). Others find no prenatal nicotine changes on these tests (Cutler et al., 1996; Levin et al., 1996). Some studies show that ADHD medications, such as methylphenidate, ameliorate nicotine-induced hyperactivity in rodents (Zhu et al., 2017). Mice exposed to cigarette smoke from E0 to P21 spent increased time in the open in the elevated zero maze with males having more open arm entries than females. However, locomotor activity was only increased in the center area of an open-field test for the first 5 min whereas at other intervals the cigarette smoke-exposed mice had reduced activity. No deficits in learning and memory were observed for these mice and in some cases the cigarette smoke-exposed mice performed better than controls (Amos-Kroohs et al., 2013). The variation in behavioral findings from these studies is likely due to different doses, routes of administration, age of exposure, and species (Polli et al., 2020). Nevertheless, the human and animal studies of prenatal tobacco/nicotine exposures demonstrate effects in the offspring that sometimes causes hyperactivity and impulsivity and/or an increased prevalence of ADHD.

Other Models: Neonatal 6-Hydroxydopamine Lesions

Neonatal 6-hydroxydopamine (6-OHDA) lesions in rats do not cause impulsivity but do cause hyperactivity, attention changes, and impaired spatial discrimination learning, which improves after methylphenidate or d-amphetamine treatment (Shaywitz et al., 1978; Davids et al., 2002). Rats lesioned on P1 display hyperactivity in adulthood after an initial hypoactivity phase in a novel environment and persistent hyperactivity after repeated testing (Luthman et al., 1989). The hyperactivity was accompanied by decreased dopamine levels, increased DRD4, and increased SERT binding in the striatum but not in the cerebral cortex (Luthman et al., 1989; Zhang et al., 2001; Zhang et al., 2002a). Hyperactivity was not altered by DAT inhibitors but was reduced by DRD4 antagonists as well as SERT and NET inhibitors (Zhang et al., 2001; Zhang et al., 2002a, b). These data indicate that psychostimulants reduce hyperactivity in 6-OHDA lesioned rats by inhibiting NET and SERT, but not by inhibiting DAT.

6-OHDA lesions in mice was found to reduce striatal dopamine and TH-positive midbrain neurons in both wildtype and *Drd4*-KO mice, however the KO mice did not develop hyperactivity or behavioral inhibition deficits (Avale et al., 2004). Furthermore, a DRD4 antagonist prevented hyperactivity in wildtype mice following 6-OHDA lesions. These results are relevant in that they suggest that DRD4 is essential for the expression of hyperactivity and impaired behavioral inhibition after 6-OHDA lesions, which lends support

to the postulated role of DRD4 in ADHD, in contrast to the data from the *Drd4* KO mice which are inconsistent with the 6-OHDA lesion data.

Other Models: Neonatal Anoxia

Neonatal anoxia increases the risk of ADHD (Lou, 1996). It also results in neurochemical abnormalities in monoamines, hyperactivity, and spatial memory deficits in rats that persists into adulthood (Dell'Anna et al., 1991; Miguel et al., 2015). Acute anoxia also causes changes in cerebellar norepinephrine with an initial decrease followed but an increase a week later. These rats also had a decrease in 5-HT and increase in 5-hydroxyindoleacetic acid (5-HIAA) (Dell'Anna et al., 1993). Striatal dopamine was decreased while dopamine metabolites were increased (Dell'Anna et al., 1993). There are also data suggesting that dopamine turnover is increased after anoxia (Dell'Anna et al., 1993). Perinatal asphyxia increases *Th* mRNA levels in the VTA and substantia nigra and *Drd1* and *Drd2* mRNA in the striatum (Gross et al., 2000). These data show a complex temporal sequence of changes that occur in norepinephrine signaling following perinatal anoxia and in children result in increased prevalence of ADHD-related behaviors.

Other Models: Fetal alcohol

One consequence of maternal drinking during pregnancy is Fetal Alcohol Spectrum Disorder (FASD) characterized by intellectual deficits, abnormal facial features, smaller head circumference, and reduced growth (Murawski et al., 2015). Although ADHD and FASD are separate disorders, a significant number of FASD children exhibit ADHD-typical behaviors implicating alcohol as an exogenous factor linked with ADHD (Knopik et al., 2005; Bhatara et al., 2006; Kodituwakku, 2007). As noted, several epidemiological studies in children find increased odds ratios for ADHD after intrauterine alcohol whether it be in Vietnamese (Hoang et al., 2021) or North American children (O'Neill et al., 2021).

Rats exposed prenatally to ethanol have symptoms consistent with ADHD, such as hyperactivity in an open-field (Gilbertson and Barron, 2005) and deficits in attention in the 5-CSRTT (Nio et al., 1991). Prenatal exposure to ethanol also leads to visuospatial deficits, including impairments in the Morris water maze (Kim et al., 1997; Girard et al., 2000). Prenatal ethanol-exposed rodents have working memory deficits in the radial-arm maze (Reyes et al., 1989) and in spontaneous alternation in a T-maze (Nagahara and Handa, 1997), both characteristic of ADHD. Both mice and rats exposed prenatally to ethanol have changes in dopamine (Boggan et al., 1996; Diaz et al., 2014; Naseer et al., 2014). Prenatal alcohol exposure increases locomotor activity responses to amphetamine, methylphenidate, and the DRD2 agonist apomorphine compared with controls, the opposite response to the hyperactivity dampening effect reported in other models of ADHD-like activity (Means et al., 1984; Blanchard et al., 1987; Hannigan et al., 1990; Gentry et al., 1995). Prenatal alcohol exposure at early postnatal ages alters dopamine levels (Detering et al., 1980b; Detering et al., 1980a; Cooper and Rudeen, 1988), increases TH (Detering et al., 1980a), and decreases DRD1 and/or DRD2 receptor binding in striatum (Lucchi et al., 1984; Druse et al., 1990; Nio et al., 1991) and cortex (Druse et al., 1990) which are also not ADHD-like changes. The association between FASD and increased rates of ADHD in children indicates that prenatal alcohol is an environmental risk factor for ADHD, but the animal model data

are very mixed in relation to ADHD-like behaviors. However, like other risk factors, no mechanism or susceptible genes have been identified for how transplacental alcohol changes the developing brain that leads to ADHD.

Validity

Establishing the validity of genetic and environmentally induced rodent models of ADHD remains challenging because the pathogenesis of ADHD remains ill-defined. The major source of validation lies in efforts to model the symptoms and the efficacy of psychostimulants to reduce symptoms. Because ADHD is polygenic no single rodent model of ADHD is likely to ever recapitulate the human condition. Each model has strengths and weaknesses, but each contributes a piece to the puzzle for understanding aspects of ADHD.

The etiology of ADHD stems from multiple small effect gene variants acting together, and these combinations appear to vary across the ADHD spectrum and many, if not all, may have environmental triggers. Fitting the gene × environment together in a unified model may not be possible, it may be better viewed as a collection of disorders requiring a collection of models. One overarching way of conceptualizing developmental disorders is that they represent a type of decanalization, i.e., a partial loss of the optimal trajectory program that controls brain development, an idea taken from ethology and suggested in the etiology of schizophrenia (McGrath et al., 2011) that may also apply to ADHD. According to this concept, the heterogeneity found in ADHD is the result of the spread or reduced coherence of genetic pathways that may occur at different stages of brain ontogeny.

Despite the growing evidence that there are gene × environment interactions involved in the etiology of ADHD, rodent models testing for such effects are nearly absent. Nor have studies tackled how different gene variants lead to different ADHD symptoms. On the environmental factors side, no one has dissected which factors pose the greatest risk for leading to ADHD or if combinations of environmental factors have an even greater contribution to the etiology of the disorder. Since ADHD occurs in only a fraction of those exposed to exogenous agents, more attention is needed to map which genetic variants, epigenetic markers, and environmental factors occur in those exposed and are affected versus those who are not affected.

All the models reviewed display some form of hyperactivity or hyper-reactivity. Although these are the easiest outcomes to assess in rodents, they are not sufficient to establish an adequate model of ADHD. Behaviorally, all models should show hyperactivity, impulsivity, attention deficits, and working memory impairments. On this basis, the face validity of the neonatal hypoxia and *Snap-25* models are less persuasive than others. The SHR has the behavioral phenotype of an appropriate ADHD model, but also carries abnormal genes for hypertension and there remain concerns about whether SHR to WKY comparisons are sufficient to validate the model. The *Snap-25* heterozygous mice have eye abnormalities not relevant to ADHD and may explain some of the deficits in these mice. The next steps might be (1) use CRISPR/Cas9 to create two dual gene KO, conditional KO or KD models, (2) use one of the better KO models in combination with different doses of an environmental agent with the largest association to ADHD (e.g., Pb, nicotine, alcohol, or insecticides). These are

demanding experiments and are high risk, but if a better model is the result then it would be worth the effort. Predictive validity will be an important consideration in any model and should be a priority primarily by using current therapeutic drugs to help corroborate the model's potential translational value. Of the animal models described, the neonatal 6-OHDA and *Dat* KO models show the predicted response to psychostimulants by decreasing activity. Moreover, an improved model should show that when treated the key behavioral abnormalities are corrected or improved. Newer models, such as the *Lphn3* KO rat shows promise as it has the four key behavioral changes but has yet to show stimulant-induced improvements in each of the behavioral characteristics relevant to ADHD. This model is strengthened, however, by the existence of parallel models with similar behavioral changes in *Drosophila*, zebrafish, and mice.

The most promising models may turn out to be those with the same genetic variants as seen in patients by creating point mutations. The challenge with this approach is determining which mutation(s) to create. For example, in the case of *LPHN3* there are 21 mutations associated with ADHD. Creating 21 genetic models is not feasible, therefore, human studies that help identify which variants confer the greatest risk would help zero-in on the best targets. This approach will contribute to better construct validity and may be one of the best ways to advance the field (Acosta et al., 2004; Arcos-Burgos et al., 2010; Huang et al., 2019; Puentes-Rozo et al., 2019; Bruxel et al., 2020; McNeill et al., 2020). This would apply to *SNAP-25*, *DAT*, *DRD4*, *LPHN3*, and other genetic changes associated with ADHD in humans, such as *ANKK1, LRP5, LRP6, BAIAP2* that have not been sufficiently characterized in animal models with respect to the cardinal ADHD-like behaviors noted herein.

Conclusion

Useful models of ADHD should possess construct, face, and predictive validity. A challenge with ADHD is the absence of a known pathophysiology combined with the fact that the disorder is polygenic with no large effect genes driving symptoms. The absence of etiology for idiopathic ADHD continues to hamper progress. Under these circumstances, the best models will recapitulate the phenotype of ADHD (hyperactivity, impulsivity, attention deficit, and working memory deficit), along with the efficacy of ADHD medications to normalize behavior and connect these to genetic and environmental changes. Studies testing gene × environment remain an unexplored area that may provide additional insights. In this regard, the most frequently reported environmental agents leading to ADHD-like symptoms are Pb, insecticides, such as pyrethroids), Mn, PCBs, and nicotine. Many labs have well developed models of developmental exposure to these agents, they need only combine their models with one of the better genetic models to test for interactions. Such combinations should provide new perspectives on ADHD.

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Highlights

- ADHD is polygenic, the sum of multiple small effect gene variants
- Evidence suggests environmental factors contribute to ADHD
- Existing genetic models are evaluated in relation to validation criteria
- Epigenetic contributions have not yet been investigated
- No two or three combination knockout/knockdown models have been described
- No gene × environment models have been described

Table 1

World Federation of ADHD International Consensus (Faraone et al., 2021)

Category	Consensus Finding
Phenotype	Hyperactive/impulsive
	Inattentive
	Combined
Cognitive	No association with IQ
Psychiatric	Increased depression, bipolar, ASD, anxiety, & substance use disorders
Prevalence	5.9% prevalence
	2.5% prevalence in adults declines to <1% by age 50
	14% prevalence in Black children
Genetics	Polygenic: multiple small-effect genes
	Single gene syndromic causes
	Risk genes, *ANKK1, DAT1, LRP5, LRP6, SNAP25, ADGRL3/LPHN3, DRD4, BAIAP2*
	Shared familial risks with autoimmune disorders, hypospadias, and intellectual disability
Environmental	High Pb increases risk 2–4 times
	Prenatal smoking >50% risk but not after adjustment for family history of ADHD
	Second-hand smoke >60% risk but confounders not fully tested
	Limited data on 794 children show small increased association with artificial food dyes by parental rating, not by teacher rating
	Data from 10,000 births and 113,000 children show 33% risk from prenatal acetaminophen
	Danish registry of 913,000 children finds >50% risk from prenatal valproic acid
	Norwegian registry of 24,000 children high phthalate exposure increases risk 3X
	Study of 1139 U.S. children finds 2X risk from organophosphate pesticides
	Air pollution no increased risk except one S. Korean study finds risk from NO_2, SO_2, & particulates
	4826 mother-child pairs study found no risk from breast milk and perfluoroalkyl substances
	25,000 children M-A * finds no association with sugar
Environment	Small correlations With low ferritin, high omega-3 PUFAs, and/or low Vit. D
	Sig. correlations with very low birth weight, maternal hypertension, preeclampsia, obesity, hyperthyroidism, prior miscarriage
Other associations	Enterovirus, child abuse, low SES, paternal criminality, maternal mental disorders, marital discord, parental education, parental unemployment, death in family
Executive function	Moderately lower IQ and reading, effects on spelling and math, and problem solving, working, memory, focused attention, sustained attention, verbal memory, cognitive rule violations
	Prone to immediate over delayed reward
	Slightly greater risk-taking
	Slightly greater delaying gratification
Neuroimaging	Small to very small reductions in frontal, cingulate, and temporal regions
	Reduced hippocampal volume
	Reduced splenium size
	Reduced fMRI activation of right inferior frontal cortex

Category	Consensus Finding
Co-morbidities	Obesity 45% more likely to have ADHD,
	Asthma 50% more likely to have ADHD
	Type I diabetes 40% more likely to have ADHD
	If ADHD 30–50% more likely to have psoriasis
	If epilepsy 50–60% more likely to have ADHD
	If autoimmune disease 24% more likely to have ADHD
	If ADHD more likely to have eye disorders
	If ADHD more likely to have, metabolic disorders (9X; viral pneumonia (5X), kidney failure (4X), high blood pressure (4X),Type 2 diabetes (2 X), migraine (2X)
Education	In treated ADHD children, more likely to have low academic achievement (3X), drop out of school (2X), need special education (8X), 50% more likely to be injured, 40% more likely to be unemployed
Substance use disorders	If ADHD 50% more likely to have drug or alcohol use disorder
Medications	Many studies show ADHD medications effective and improve school performance, and reduces injuries, criminality, suicidality, substance abuse, and unplanned pregnancies
	Side-effects: Generally acceptable

* M-A = Meta-analysis

Table 2

Genetic Models of ADHD

Model	Face validity	Construct Validity	Predictive validity	Limitations	Citations
SHR (rat)	Hyperactive, Impulsive, inattentive, responsive to some stimulants, brain changes	Selective breeding for core symptoms	Not responsive to nomifensine and some stimulants	Hypertensive 160 base-pair deletion not fully characterized	(1)
SNAP-25 KO Mouse	Hyperactive, impaired latent inhibition, reduced motor coordination	SNAP-25 variants associated with ADHD in children, SNAP-25 is a synaptic protein	SNAP-25 variants are found in ADHD	Eye defects	(2)
DAT KO Mouse	Hyperactive, impaired extinction, sleep disturbance, reduced reference memory, changes in DA, active reduced by apomorphine or quinpirole	DAT is altered in by PET in ADHD	DAT changes found in children with ADHD	DAT is not absence in ADHD, but reduced	(3)
DRD4-KO Mouse	Increased sensitive to alcohol, cocaine, and methamphetamine, Not hyperactive	DRD4 variants found in ADHD	Consistent with some human findings	DRD4 KO mice are hypoactive not hyperactive	(4)
Guanylyl Cyclase-C KO Mouse	Hyperactive in novel & familiar environments	Not established	Reduced activity to amphetamine and 8 Br-cGMP	No evidence of similar change in ADHD & mouse hyperactivity not reproducible	(5)
Lphn3 KO Mouse & Rat	Hyperactive in familiar and novel environments, Impulsive, reference and egocentric learning and memory deficits	Variants found in ADHD	Decreased relative activity to amphetamine	New model, needs more data	(6)

(1)(Okamoto and Aoki, 1963; Myers et al., 1982; Fuller et al., 1983; Le Fur et al., 1983; Chiu et al., 1984; Lim et al., 1989; Wultz et al., 1990; Linthorst et al., 1991; van den Buuse et al., 1991; Bendel and Eilam, 1992; Sagvolden et al., 1992a; Sagvolden et al., 1992b; Van den Buuse et al., 1992; Linthorst et al., 1993; Sagvolden et al., 1993; Cook et al., 1995; de Jong et al., 1995; Kirouac and Ganguly, 1995; Watanabe et al., 1997; Carey et al., 1998; Krimer et al., 1998; Sagvolden and Sergeant, 1998; Dougherty et al., 1999; Aspide et al., 2000; Russell, 2000; Sabbatini et al., 2000; Sadile, 2000; Sagvolden, 2000; Papa et al., 2002; Ueno et al., 2002b; Carboni et al., 2003; De Bruin et al., 2003; Ferguson and Cada, 2003; Fujita et al., 2003; Adriani and Laviola, 2004; Tomassoni et al., 2004; Bobb et al., 2005; Jentsch, 2005; Madras et al., 2005; Mill et al., 2005; Sagvolden et al., 2005; Wiersema et al., 2005; Sagvolden, 2006; van den Bergh et al., 2006; Alsop, 2007; Heal et al., 2008; Kantak et al., 2008)

(2)(Theiler and Varnum, 1981; Oyler et al., 1989; Heyser et al., 1995; Hess et al., 1996; Steffensen et al., 1999; Jones et al., 2001; Jones and Hess, 2003; Mill et al., 2004; Feng et al., 2005; Bruno and Hess, 2006; Bruno et al., 2007)

(3)(Cook et al., 1995; Giros et al., 1996; Gainetdinov et al., 1998; Jones et al., 1998b; Gainetdinov et al., 1999; Jones et al., 1999; Gainetdinov et al., 2001; Zhuang et al., 2001; Morón et al., 2002; Peciña et al., 2003; Ralph-Williams et al., 2003; Trinh et al., 2003; Barr et al., 2004; Thakker et al., 2004)

(4)(Rubinstein et al., 1997; Rowe et al., 1998; Swanson et al., 1998; Grady et al., 2003; Thomas et al., 2007; Helms et al., 2008)

(5)(Gong et al., 2011; Mann et al., 2019)

(6)(Lange et al., 2012; O'Sullivan et al., 2012; Wallis et al., 2012; Boucard et al., 2014; O'Sullivan et al., 2014; Orsini et al., 2016; van der Voet et al., 2016; Lange et al., 2018; Mortimer et al., 2019; Regan, 2019; Sando et al., 2019; Regan, 2020; Regan et al., 2020; Regan et al., 2021; Sable et al., 2021; Sando and Sudhof, 2021)