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Zebrafish models for attention deficit hyperactivity disorder (ADHD)

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Highlights

- ADHD is a neurodevelopmental disorder that affects an increasing number of people worldwide.
- Zebrafish is a prominent model to assess the underlying mechanisms of ADHD and it comorbidities.
- Advantages and disadvantages of using zebrafish to model ADHD were discussed.
- Current zebrafish ADHD models and future directions are highlighted.

Abstract

Attention deficit hyperactivity disorder (ADHD) is a common, debilitating neurodevelopmental disorder associated with inattentiveness, pathological hyperactivity and impulsivity. Despite the mounting human and animal evidence, the neurological pathways underlying ADHD remain poorly understood. Novel translational model organisms, such as the zebrafish (*Danio rerio*), are becoming important tools to investigate genetic and pathophysiological mechanisms of various neuropsychiatric disorders. Here, we discuss ADHD etiology, existing rodent models and their limitations, and emphasize the advantages of using zebrafish to model ADHD. Overall, the growing utility of zebrafish models may improve our understanding of ADHD and facilitate drug discovery to prevent or treat this disorder.

Keywords: ADHD; zebrafish; behavior; genetics; dopamine; noradrenaline; serotonin.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common debilitating neurodevelopmental disorder **that affects approximately 8% - 12% of children worldwide**, with most symptoms persisting into adulthood **(Faraone et al., 2003; Polanczyk et al., 2015)**. Clinically,

ADHD is characterized by increased levels of hyperactivity, impulsivity and inattention (Halperin et al., 1992; Spencer et al., 2007; Wolraich et al., 1996), often seen with distractibility, fidgeting and excessive talking (Wilens et al., 2010). Although currently recognized major subtypes of this disorder include hyperactive, inattentive and mixed-type (Riccio et al., 2006; Sagvolden et al., 2005a), ADHD is likely to be caused, and mediated, by a number of different genes and neurophenotypes (Faraone, 2018; **Gillis et al., 1992; Goodman, 1989; Schmitz et al., 1995; Stevenson, 1992)**. **There are several behaviors associated with ADHD that are transdiagnostic for comorbid and related disorders, suggesting common mechanisms (Carey et al., 2016; Farb and Ratner, 2014; Sharp et al., 2014; Sternat and Katzman, 2016). For example, adult ADHD is often comorbid with affective and substance abuse disorders, and has been linked to increased risk of traffic accidents, criminal offenses and other psychosocial problems** (Anastopoulos et al., 2018; Kessler et al., 2006; Marraccini et al., 2017). The developmental cognitive dysfunctions in ADHD severely impair **individual's ability to function** in academic, occupational and social settings (DuPaul et al., 2006; Wehmeier et al., 2010). Overall, ADHD is **unlikely to be** linked to one specific mechanism but to many different combinations of aberrant changes in dopaminergic, noradrenergic and serotonergic systems (Cortese, 2012; Potter et al., 2014; Purper-Ouakil et al., 2011). Thus, the etiology of ADHD almost certainly involves the interaction of genetic and environmental factors (e.g., premature birth, maternal smoking or alcohol consumption during pregnancy) (Bidwell et al., 2018).

The pharmacological treatments of ADHD includes psychostimulants (e.g., methylphenidate and **d-**amphetamine derivatives) and non-psychostimulant medication (e.g., atomoxetine, clonidine and guanfacine) (Cortese and Angriman, 2017; **Jensen et al., 1999; Michelson et al., 2001; Safer et al., 1996; Stein et al., 1996**). Other treatments for ADHD include cognitive behavioral therapy (CBT), especially efficient when combined with pharmacotherapy (**Adesman, 1992;** Goode et al., 2018; Mongia and Hechtman, 2012; **Safren et al., 2005**). Although pharmacotherapies do alleviate ADHD symptoms, they have limited efficacy, numerous adverse

effects, **and often fail to treat or prevent the manifestation of the full-blown disorder** (Chu et al., 2017). To improve our understanding of ADHD pathobiology, several rodent models of this disorder have been developed (Kostrzewa et al., 2008; Sagvolden et al., 2005a; van der Kooij and Glennon, 2007). However, none of them fulfil all validity criteria, such as the expression of combinate ADHD-related behaviors and shared neurological pathways (Sontag et al., 2010). Therefore, it is critical to develop, innovate and validate alternative complementary models to further explore ADHD-related mechanisms.

The zebrafish (*Danio rerio*) is an increasingly popular animal model in neuroscience and biological psychiatry (Meshalkina et al., 2017; Orger and de Polavieja, 2017). Their robust behavioral repertoire (Kalueff et al., 2013), the availability of well-established behavioral tests (Parker et al., 2013; Parker et al., 2012), and the power of automated behavioral testing soft- and hardware (Carreno Gutierrez et al., 2018; Parker et al., 2013), make zebrafish a useful animal model of human brain disorders. Here, we discuss the advantages and limitations of zebrafish ADHD models, and their utility for probing molecular and genetic mechanisms of this disorder. We also outline the importance of further validation of ADHD models using zebrafish, and critically evaluate their value for searching novel treatments for this disorder.

2. Neurological and genetic bases of ADHD

Although ADHD is strongly linked to environmental factors, various genetic, biochemical and neural bases of this disorder have been identified (Bonvicini et al., 2016; Comings et al., 2000; Hawi et al., 2015; Paclt et al., 2005). **Table 1** summarizes genes consistently implicated in clinical ADHD. Multiple human genes that co-segregate with ADHD include those regulating central dopaminergic, serotonergic and noradrenergic systems (Lesch et al., 2008; Zhang et al., 2012) (**Fig. 1**). These genetic and neurobiological associations are further supported by the clinical efficacy of stimulant medications that interacts with monoaminergic signaling in animal models (Gainetdinov et al., 1999; Giros et al., 1996; Russell, 2011). Importantly, although ADHD-linked genes

independently confer a small risk for ADHD, they offer the framework for genetic mapping of likely candidates to probe their role in this disorder (Field et al., 2013; Gold et al., 2014). Both common and rare genetic variants confer ADHD risk (Lo et al., 2003; Martin et al., 2015), and may be important for developing novel individualized treatments (Gold et al., 2014). Concerning ADHD hereditability, twin studies have demonstrated that genetic additive and dominant effects are strong components (around 75%) of child and adolescent ADHD (Faraone et al., 2005). Furthermore, inhibitory control deficits act as a cognitive marker of genetic risk, and are shared with non-affected first degree relatives (Goos et al., 2009); however, ADHD patterns of inheritance are certainly not Mendelian, and are far from being fully elucidated (Freitag et al., 2010).

In humans, there are several approaches to study ADHD which combine performance-related measures with intermediate measures of behavior and neurobiology, such as neural imaging and psychophysiological analysis (Luman et al., 2010). For example, magnetic resonance imaging (MRI) has demonstrated that dopaminergic release is correlated with BOLD responses in the ventral striatum (Knutson and Gibbs, 2007). Such neural imaging studies are very encouraging and provide the basis for future research; however, the number of these studies is relatively scarce (Plichta et al., 2009; Rubia et al., 2009; Scheres et al., 2006; van Meel et al., 2005). Pharmacological interventions are widely used to research ADHD in humans, including in particular the clinical efficacy of catecholaminergic agonists and re-uptake inhibitors (McCarthy, 2014; Weyandt et al., 2014). Although human research offers the opportunity to observe the disorder *in situ*, there are several limitations when working with humans in terms of elucidating mechanisms, including ethical constraints, but also population variations and individual variation in, and lack of specificity of, responses to treatment (Hall and Myers, 2016). Here, we discuss the role of different animal models of ADHD, their clinical and translational relevance, the existing limitations and future studies in this field.

3. Traditional animal models of ADHD

Developing animal models should have sufficient face and construct validity (Willner, 1986). For ADHD, a model should mimic fundamental behavioral characteristics -- impulsiveness, sustained inattention and hyperactivity -- that develop over time (Russell et al., 2005; Sagvolden et al., 2005b). Currently, rodent models are most commonly used to study ADHD (Davids et al., 2003; Fan et al., 2012; Tripp and Wickens, 2012), as both rats and mice exhibit overt hyperactivity, impulsivity and attention deficits, thereby providing adequate face validity as ADHD models (Russell, 2007, 2011; Russell et al., 2005). For example, the dopamine transporter (DAT) knockout mice display ADHD-like hyperactivity and learning deficits (Gainetdinov et al., 1999), but unlike adults and children with ADHD show lower expression of DAT (Cheon et al., 2003; Dougherty et al., 1999; Krause et al., 2000). Other models of ADHD-related neurotransmitter deficits include mutants with aberrant serotonin (Bouwknecht et al., 2001; Brunner et al., 1999; Smoller et al., 2006; Zhuang et al., 1999) and glutamate systems (Callaway et al., 1992; Rempel et al., 1993). Although showing reasonable face, construct and predictive validity, some expected ADHD-like phenotypes (e.g., hyperactivity or inattention) are not expressed simultaneously by these mutants.

While rodent or non-human primate models are critical for dissecting behavioral and neural mechanisms of ADHD, they are expensive and generally time-consuming (Sontag et al., 2010). Therefore, alternative models with the potential for high-throughput screening to identify genetic alterations and new pharmacological treatments have an important role in uncovering the mechanisms of ADHD and it comorbidities (Amsterdam and Hopkins, 2006; Kalueff et al., 2014b; Mezzomo et al., 2018; Parng et al., 2002). **As will be discussed further, the zebrafish is an important complementary model that has high face, construct and predictive validity, and has the potential to assist in the challenge of understanding ADHD.**

4. Zebrafish as an alternative model for ADHD

The zebrafish continues to emerge as a novel model organism to study shared, evolutionarily conserved ‘core’ mechanisms of complex psychiatric disorders (Howe et al., 2013; Kalueff et al., 2014b; Postlethwait et al., 2000; Stewart et al., 2015). Zebrafish are easy to breed (Nasiadka and

Clark, 2012), their embryos develop externally and the transparency of the eggs facilitates developmental studies, and manipulation of neural circuits *in vivo*, **Fig. 2.** (Fetcho and Liu, 1998; Kyun Ko et al., 2011; Meng et al., 2008; Norton, 2013).

The utility of both larval and adult zebrafish in neuroscience has considerably grown recently due to their high genetic and physiological similarity to other vertebrates, including humans, relative ease of genetic manipulation, and homologous CNS functions and anatomy (Gerlai, 2010a, b, 2011). Despite topographical differences between fish and mammalian brain structures, the neuronal pathways involved in zebrafish brain physiology are generally highly conserved, including all major neurotransmitter systems (Higashijima et al., 2004; McLean and Fetcho, 2004; Panula et al., 2010; Thakkar, 2011; Tropepe and Sive, 2003). The zebrafish genome has been fully sequenced, where approximately 70% of human genes have at least one obvious zebrafish orthologue (Howe et al., 2013). **Furthermore, a large number of genes have been targeted to develop zebrafish mutant lines using genome editing technology for forward and reverse genetic studies (i.e., using CRISPR** (Clustered regularly interspaced short palindromic repeats) (Hruscha et al., 2013), TALENs (Transcription activator-like effector nucleases) (Clark et al., 2011), gene-breaking transposon-based approaches (Heintze et al., 2013), TILLING (Targeting Induced Local Lesions in Genomes method) (Moens et al., 2008), viral vector-mediated insertional mutagenesis (Amsterdam and Hopkins, 2006), morpholino antisense oligonucleotides (Bill et al., 2008), optogenetics (Nagel et al., 2003; Zhang et al., 2007)), **and these screens have recently been combined with *in vivo* visualizing of neural activity and electrophysiological recording** (Higashijima et al., 2003; Stewart et al., 2015).

Behavioral phenotypes of zebrafish provide important insights into neural mechanisms of normal and pathological brain function (Champagne et al., 2010; Kalueff et al., 2013; Spence et al., 2008). The well-characterized behavioral repertoire of zebrafish spans the domains of locomotor activity, aggression, anxiety, sociability and cognition, often associated with neuropsychological disorders (Buske and Gerlai, 2011; Jones and Norton, 2015; Levin et al., 2007; Maximino et al., 2015; Stewart et al., 2011; Stewart et al., 2014). Although the functions of genes involved in

psychiatric disorders are still relatively understudied in zebrafish, this species may also provide novel genetic information related to neuropsychiatric disorders (Norton, 2013).

The advantages and limitations of zebrafish as a model in translational neuroscience research have been extensively discussed elsewhere (Fontana et al., 2018; Kalueff et al., 2014a; Kalueff et al., 2014b; Lieschke and Currie, 2007; Nguyen et al., 2013; Stewart et al., 2014; Stewart et al., 2015), and will not be addressed here in depth. However, in addition to many important advantages, the use of zebrafish models in neuropsychiatric disorders presents some limitations (Stewart et al., 2014), including species differences in brain development (Ito and Yamamoto, 2009) and anatomy vs. mammals (Aizawa, 2013), as well as genome duplication in teleost fishes (Lu et al., 2012). Because of this, many zebrafish genes have two copies, where mammals have only one copy (Lu et al., 2012). The resulting genetic difference can complicate the analysis of specific genes associated with diseases, particularly if the effect of a mutated gene is masked by unaltered paralogous gene (Stewart et al., 2015). Finally, while psychiatric illnesses remain among the most poorly treated diseases (Kokel and Peterson, 2008), the large-scale drug screens in mammals are inefficient and impractical (Kokel and Peterson, 2008). Thus, the zebrafish becomes an important model for medium-and high-throughput behavior-based drug discovery (Rihel et al., 2010; Rihel and Schier, 2012). Combining *in vivo* relevance of behavior-based phenotyping with the automation of modern drug-screening technologies, zebrafish provide a powerful approach to improve our understanding of ADHD neurobiology and accelerate psychiatric drug discovery (Kokel and Peterson, 2008). Finally, zebrafish screens help examine various brain genes implicated in ADHD (Huang et al., 2015; Lange et al., 2018; Lange et al., 2012; Martinez et al., 2016), collectively becoming a promising organism in this field (Stewart et al., 2015).

4.1. Behavioral tests to study ADHD in zebrafish

All three ADHD-related phenotypes - inattention, impulsiveness and hyperactivity (Winstanley et al., 2006) have already been described in zebrafish using automated video-analyses

(Cahill, 2007; Creton, 2009; Gerlai et al., 2000; Kalueff et al., 2013; Parker et al., 2013). For example, the five-choice serial reaction time task (5-CSRTT) assesses impulsiveness and attention, two important ADHD-related behaviors, by measuring the ability of adult zebrafish to respond to one of five perceptually identical stimuli (presented in one of five distinct spatial locations) which appear randomly after a variable inter-trial interval (ITI) (Parker et al., 2014; Parker et al., 2013). Zebrafish perform well on the 5CSRTT, revealing noradrenergic control of zebrafish impulsivity, as it is reduced by acute atomoxetine (Parker et al., 2014). These data parallel those in mammals, and show face, construct and predictive validity of this experimental model to assess ADHD-related symptoms in zebrafish. However, impulse control is difficult to assess in larval animals, presenting a disadvantage for early-onset ADHD models in zebrafish. Despite some attempts to measure impulsivity of larval zebrafish, their findings have been largely correlational and open to interpretation (Lange et al., 2012; Parker et al., 2015). Thus, without a careful evaluation of neural circuits recruited in larvae during putative impulsivity, any suggestion of the potential to manipulate or measure impulsivity in larvae behaviorally should be taken with caution. Moreover, the role of attention in the zebrafish 5CSRTT is yet to be established. Interestingly, ‘correct' responses in the 5CSRTT increased following exposure to nicotine, a cholinergic agonist known to increase attention in zebrafish (Parker et al., 2014). However, as attention was not directly manipulated (i.e., by increasing task demand), it remains unclear if the task tested attention and whether sustained attention in zebrafish is under cholinergic control.

Common in clinical ADHD, hyperactivity can be assessed in various behavioral tests in zebrafish. For example, it can be assessed in larval zebrafish (Lange et al., 2013) by placing animals in well-plates and recording for 5-10 min (Ingebretson and Masino, 2013; Lange et al., 2012; MacPhail et al., 2009; Ulhaq et al., 2013), assessing the swim episode frequency (Hz) and duration (ms), swim speed (mm/s), active swim time (s) and total distance swum (cm) (Ingebretson and Masino, 2013). The hyperactivity profile of adult zebrafish can utilize the novel tank or the open field tests. The novel tank test is the most commonly used test to assess locomotion and anxiety-

like phenotypes (Blaser and Rosemberg, 2012; Stewart et al., 2011). This test consists of placing individual fish in a novel environment, where they usually swim in the bottom section and gradually increase the activity in the upper sections of a tank, assessing total distance travelled (m), average speed (m/s), absolute turn angle (º) and immobility (s) (Egan et al., 2009). Alterations in these parameters can be used for hyperactivity profiling, making this test an important tool to investigate ADHD-related symptoms in adult zebrafish. Similar to the novel tank, the open field assesses zebrafish behavior in a novel environment, typically - a plastic/glass cylinder or box virtually divided into center and periphery, to assess time spent (s), distance travelled (m) and number of visits to these pre-defined zones, thus reflecting zebrafish locomotor and exploratory behaviors and thigmotaxis (preference for the tank edges) (Grossman et al., 2010). Both tests may be important tools to assess hyperactivity in ADHD models, and together can enable a fuller characterization of zebrafish phenotypes.

5. Current ADHD-related studies with zebrafish

Although zebrafish models of ADHD and other neurodevelopmental disorders are relatively new, their importance continues to grow (Kalueff et al., 2014a; Kalueff et al., 2014b; Norton and Bally-Cuif, 2010; Norton, 2013). Similar to rodents, mutant zebrafish with ablated circadian gene period1b (*per1b*) show changes in dopamine levels by disruption circadian cycle which leads to hyperactivity and attention deficits (Huang et al., 2015). Moreover, even the alterations of circadian cycle are not described as a core symptom of ADHD, this study supports the high construct validity of zebrafish as an ADHD model. Capitalizing on zebrafish genetic tractability, other mutant zebrafish show high face, construct and predictive validity as ADHD models (Fetcho and Liu, 1998; Fontana et al., 2018; Kalueff et al., 2014b; Norton and Bally-Cuif, 2010; Norton, 2013; Stewart et al., 2015). For example, knocking down the zebrafish homolog gene *micall2b* evokes a hyperactive/impulsive-like fish behaviors reversed by atomoxetine, a clinically approved anti-ADHD (Yang et al., 2018). Related to ADHD in children, this gene codes a cytosolic multidomain

protein that have a role in axon guidance, myofilament organization and synaptogenesis (Beuchle et al., 2007; Terman et al., 2002).

Another interesting line of research stems from the *LATROPHIN3* (*LPHN3*) gene strongly linked to ADHD susceptibility clinically (Franke et al., 2012; Lange et al., 2012). Morpholino oligonucleotides (MOs) targeting of the *lphn3.1* gene evoke several ADHD-like behaviors in zebrafish larvae, including hyperactivity and increased motor impulsivity (Lange et al., 2012). In addition, the *lphn3.1* MO animals display fewer dopaminergic neurons in brain areas responsible for locomotion, thus strongly implicating *lphn3.1* in the development of the dopaminergic system in zebrafish (Lange et al., 2012), similar to rodents (Wallis et al., 2012), and ADHD. Additionally, the behavioral alterations of *lphn3.1* MOs were reversed by both methylphenidate and atomoxetine, increasing the construct validity of the model (Lange et al., 2012). Zebrafish morphants *lphn3.1* have also hyposensitivity to dopamine agonists and antagonists, suggesting hyperactivation and saturation of dopamine signaling (Lange et al., 2018). Further studies can combine pharmacological agents with zebrafish lacking *lphn3.1* function to help understand the functional interactions between LPHN3 and dopamine that lead to ADHD in humans (Lange et al., 2018). Although the loss of *lphn3.1* function is related to ADHD-symptoms in larvae, future studies are also needed to better characterize the behavioral phenotypes in this model in adult zebrafish.

ADHD is a neurodevelopmental disorder (Poelmans et al., 2011), and targeting its 'developmental' aspect in zebrafish becomes important. Although chemical models are difficult to compare with human pathological conditions, chemically induced zebrafish models of ADHD have gained attention in developmental neuroscience research, including methylphenidate to chemically induce attention deficits and hyperactivity (Levin et al., 2011). Used to treat ADHD in humans, this drug presents developmental risk to the unborn fetus during gestation (Gray et al., 2007; Soileau, 2008; Zhu et al., 2010). Interestingly, the zebrafish embryo exposed to methylphenidate 0-5 days past fertilization display long-term behavioral deficits as adults (reduced choice accuracy and

diving response in three-chamber spatial learning task) but unaltered monoamine levels 30 days past fertilization (Levin et al., 2011).

6. Future directions

Although pharmacological (Gonzalez et al., 2016; Levin et al., 2011; Spulber et al., 2014; Zhang et al., 2011) and genetic manipulations (Huang et al., 2015; Lange et al., 2018; Lange et al., 2012; Martinez et al., 2016; Yang et al., 2018) provide consistent ADHD-like responses in zebrafish, many questions remain open (Table 2). For example, while larvae can present ADHD-like phenotypes (Lange et al., 2018; Lange et al., 2012; Levin et al., 2011), it is unclear whether and how these behavioral changes persist in adults. Because ADHD is a neurodevelopmental disorder, studying behavioral and neurochemical changes across the lifespan is critical. Furthermore, ADHD is a complex, multifaceted and heterogeneous disorder that involves multiple neurotransmitter pathways beyond monoamines (Sergeant et al., 2003), and further studies using mutants directly targeting these pathways may improve the face, construct and predictive validity of zebrafish ADHD models. Finally, ADHD endophenotypes are not manifested by the disruption of one neuronal pathway, but from an interaction of shared circuits, making the discovery of new alternative treatments challenging (Mueller et al., 2017). A recent large-scale screen analyzed the behavioral effects of >10,000 drugs in larval zebrafish (Jordi et al., 2018) may foster pre-clinical development of new ADHD treatments and improve our understanding of how ADHD-related genes modulate a wide range of neural circuits.

ADHD is frequently comorbid with other brain disorders, including (in the order of co-occurrence) depression, substance abuse, obsessive–compulsive, conduct, borderline personality and anxiety-related disorders (Cumyn et al., 2009). Such high comorbidity may reflect not only co-existing, independent pathologies, but can be part of shared, common transdiagnostic pathogenetic pathways between these conditions (Katzman et al., 2017). Cutting across different disorders, such comorbidities may reflect a true nature of ADHD pathobiology, thereby meriting further scrutiny in

both clinical studies and animal modeling. The overall ADHD genetic architecture remains poorly understood due to its complex multifactorial etiology and likely heterogeneity (Doyle, 2015). Consistent with recent research domain criteria (RDoCs) approach, this calls for novel zebrafish models of ADHD that would mimic its clinical comorbidities beyond ADHD-related domains. The RDoCs strategy defines psychopathologies as phenomena of multilevel neurobiological nature and assumes that underlying biological mechanisms are similar across species and individuals (Cuthbert, 2014). There are 5 behavioral domains outlined in the RDoCs approach: general regulation and arousal behavior, positive valence, negative valence, and social interactions (Anderzhanova et al., 2017). Thus, due zebrafish brain and behavioral similarities (Gerlai, 2011; Higashijima et al., 2004; Kalueff et al., 2014b; Stewart et al., 2014), the analysis of the RDoC system appear as a novel approach for ADHD model validation allowing the discovery of the true nature of this disorder.

Human ADHD shows overt sex differences in terms of incidence rates, clinical features and neurobiological mechanisms. In general, women present less severe hyperactivity, inattention, impulsivity and externalizing problems (e.g. aggression and antisocial personality disorder) than male ADHD patients, but display higher intellectual impairments and more internalizing problems (e.g., anxiety, depression and eating disorders) (Arnett et al., 2015; Gershon, 2002). Various animal models also present sex differences in ADHD, including both behavioral and neurobiological responses (Gray, 1971; Jonasson, 2005; Volgin et al., 2018). In zebrafish, sex differences affect different behavioral domains, including the activity levels, an important factor when studying ADHD (Tran and Gerlai, 2013; Volgin et al., 2018). For example, female zebrafish from the high activity sub-group prefer the top portion of tank compared with the low-activity females, whereas males do not show this preference (Tran and Gerlai, 2013). Although female and male zebrafish exhibit different activity profile, the sex differences in attention deficits tasks (e.g., 5CSRTT) has not yet been examined.

Individual differences or “personality” traits also contribute to ADHD clinically, and are present in various animal models, including zebrafish (Dall et al., 2004; Tran and Gerlai, 2013;

Volgin et al., 2018). In humans, for example, low conscientiousness and agreeableness are associated to inattention and hyperactivity, respectively (Nigg et al., 2002). Conduct problems in ADHD children (Sonuga-Barke et al., 2002) also represent an important personality trait correlating with ADHD severity. In zebrafish, individual differences are observed in several behavioral domains including locomotion, anxiety (Tran and Gerlai, 2013) and cognition (Toms and Echevarria, 2014). For example, high-, medium- and low- anxiety (Stewart et al., 2014) and activity levels (Tran and Gerlai, 2013) are typically observed in zebrafish novel tank task. As observed for sex differences, the individual attention-related phenotypes have not been examined in depth, but may represent an important factor in zebrafish ADHD models to consider.

In conclusion, zebrafish is rapidly becoming a critical novel model organism for ADHD research. Multiple zebrafish behavioral tests discussed here demonstrate similar behavioral aspects of this disorder, unraveling its genetic and neurochemical mechanisms. Together, larval and adult models show consistent results through repeated manifestation of ADHD-related behaviors, providing important insights into the etiology of this disorder and offering a unique opportunity to study ADHD across the lifespan. Finally, combining behavior-based phenotyping with automated drug screening technologies, zebrafish emerge as a powerful animal model to discover novel drugs to treat ADHD.

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Figure Captions

Figure 1. Major ADHD-related proteins and their association with the monoaminergic systems (**A.** the dopaminergic system, **B.** the noradrenergic system, **C.** the serotoninergic system).

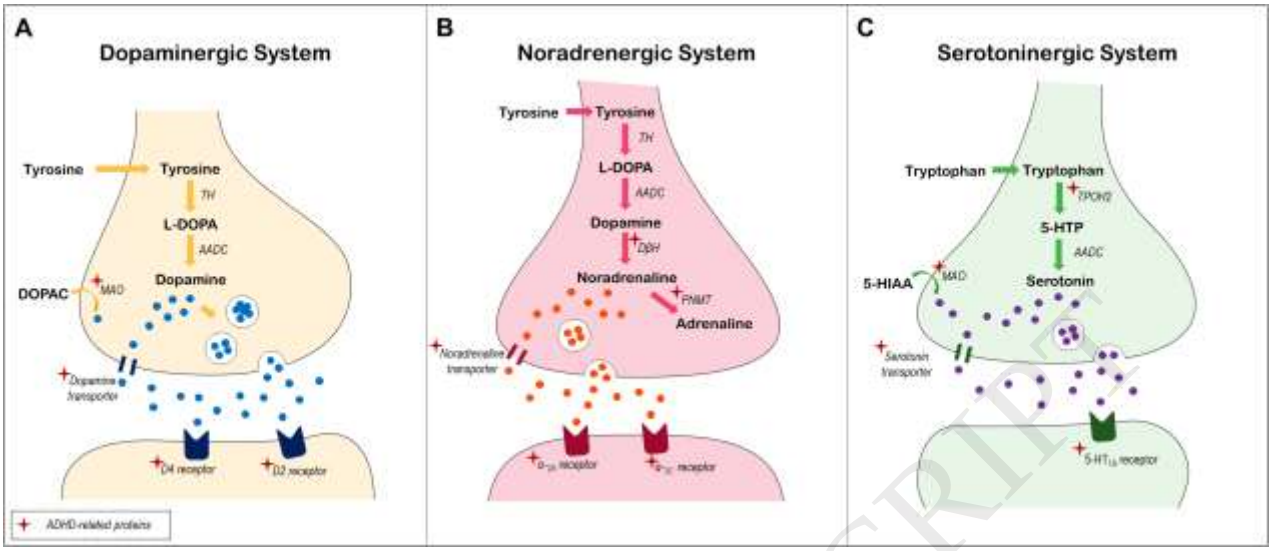

Figure 2. Schematic diagram outlining advantages of using zebrafish models to investigate ADHD.

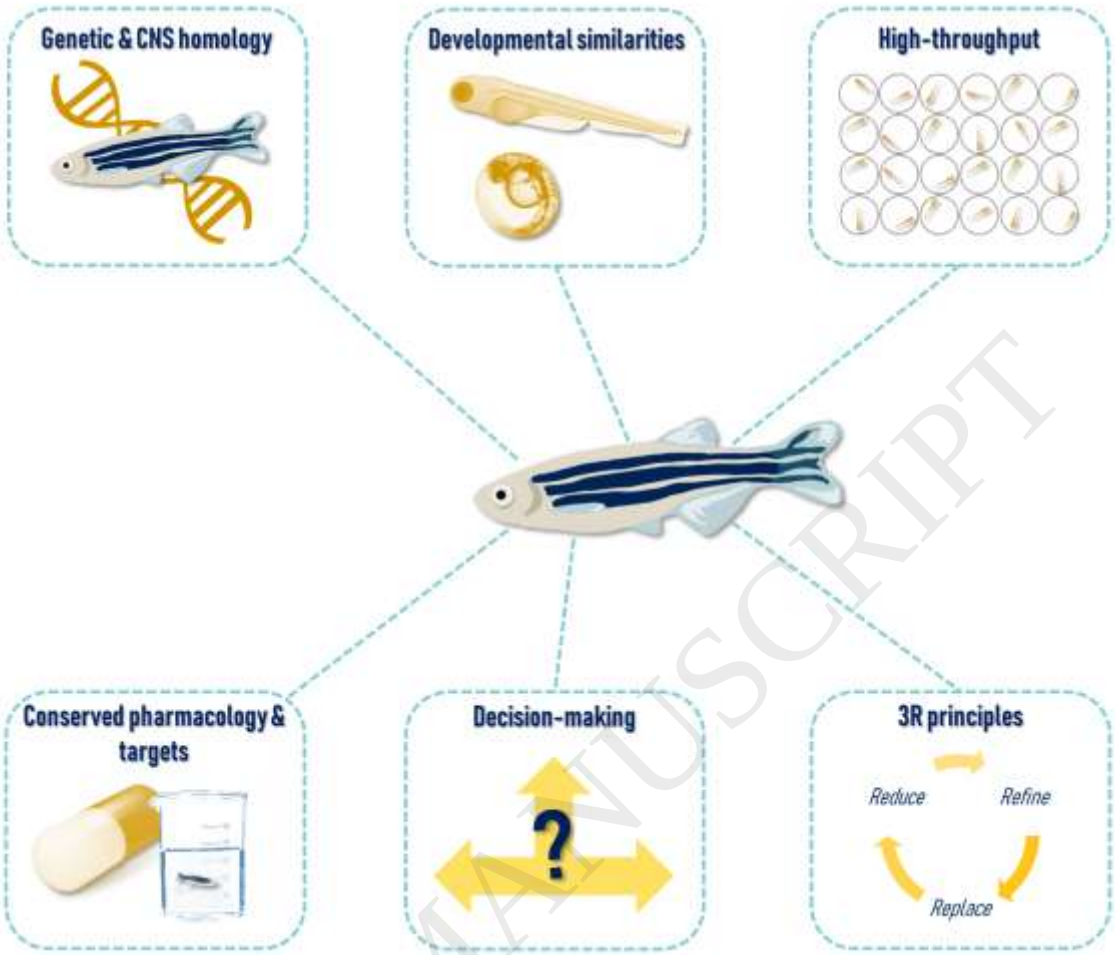

Table 1. Overview of the neurotransmitter systems involved in ADHD and their genetic homology to zebrafish.

Neuronal Pathways	Genes	Encoded proteins	Biological Role	Zebrafish orthologs genes	Nucleotide identity rate (%)		
					Zebrafish *vs* Human	Zebrafish *vs* Mice	Humans *vs* Mice
Dopaminergic System	*SLC6A3* (C:5)	Dopamine transporter	Mediates the reuptakes of dopamine from the synapses.	*slc6a3* (C:16)	89	84	87
	DRD4 (C:11)	Dopamine receptor 4	GPCR activated by the neurotransmitter dopamine.	*drd4a* (C:25) & *drd4b* (C:7)	71 & 86	69 & 73	91
	DRD2 (C:11)	Dopamine receptor 2	GPCR activated by the neurotransmitter dopamine.	*drd2a* (C:15) & *drd2b* (C: 5)	76 & 72	78 & 78	89
	MAO-A (C:X)	Monoamine oxidase A	Key role in degradation of serotonin, noradrenalin and dopamine.	*mao* (C:9)	83	83	80
Noradrenergic System	*SLC6A2* (C:16)	Noradrenaline Transporter	Mediates the reuptakes of noradrenaline from the synapses.	*slc6a2* (C:7)	83	81	87
	ADRA2A (C:10)	Alpha-2A adrenergic receptor	GPCR activated by the neurotransmitter noradrenalin.	*adra2a* (C:22)	77	77	84
	ADRA2C (C:4)	Alpha-2C adrenergic receptor	GPCR activated by the neurotransmitter noradrenalin.	*adra2c* (C:1)	87	85	87
	DBH (C:9)	Dopamine beta-hydroxylase	Synthetizes noradrenaline from dopamine.	*dbh* (C:10)	70	69	81
	PNMT (C:17)	Phenylethanolamine N-methyltransferase	Converts noradrenaline to adrenaline.	*pnmt* (C:12)	76	93	84

Serotoninergic System	*SLC6A4* (C:17)	Serotonin transporter	Mediate the reuptake of serotonin being Na+ and Cl dependent.	*slc6a4a* (C:15) & *slc6a4b (*C:5)	72 & 70	73 & 72	83
	HTR1B (C:6)	Hydroxytryptamine receptor 1B	GPCR activated by the neurotransmitter serotonin.	*htr1b* (C:17)	71	69	89
	TPH2 (C:12)	Tryptophan hydroxylase-2	Rate-limiting enzyme that synthetizes serotonin in brain.	*tph2* (C:18)	75	76	75
Other ADHD-related mechanisms	*LPHN3* (C:4)	Latrophilin 3 receptor	GCPR that acts in signal transduction and cell adhesion.	*lphn3.1* (C:1) & *lphn3.2* (Unmapped)	71	76	87
	NOS1 (C:12)	Nitric oxide synthase 1	Enzyme that synthetizes nitric oxide mediating several processes in brain.	*nos1* (C:5)	82	85	97
	SNAP25 (C:20)	Synaptosomal-associated protein 25	Key role in axonal growth, synaptic plasticity and neurotransmitter release.	*snap25a* (C:20)	79	82	83
	ARRB2 (C:17)	Beta-arrestin-2 protein	Agonist-mediated desensitization of GCPR and role in cellular responses to different stimulus.	*arrb2a* (C:10)	72	73	84
	SYP (C:X)	Synaptophysin protein	Membrane protein of small synaptic vesicles in brain and endocrine cells.	*sypa* (C:8)	67	69	78
	HES1 (C:3)	Transcription factor HES1	Transcriptional repressor of genes that require a helix-loop-helix protein for their transcription	*her6* (C:6)	77	76	88
Average homology rate (%)					**76.5**	**77.2**	**85.2**

Abbreviations: ADHD = Attention deficit hyperactivity disorder; C: = chromosome location; GCPR = G-coupled protein receptor; Na^+ = Sodium anion; Cl = Chlorine. ***Note:*** *NCBI database was used to assess the nucleotide sequence and to obtain the nucleotide identity rate (%) through blast analysis.*

Questions
Conceptual
• Can different ADHD types be model using zebrafish?
• Is zebrafish a valid model for study ADHD phenotypes related to the monoamine systems?
• How ADHD behavioral phenotypes change across lifespan (e.g., larvae *versus* adults)?
• How does aging affect zebrafish ADHD-like responses?
• Is the genetic homology of zebrafish high enough for ADHD translational research?
• What are shared biochemical or/and molecular markers related to ADHD in humans, rodents and zebrafish?
• Do sex differences play a key role in zebrafish models of ADHD?
• Are there epigenetics processes that contribute to ADHD?
• Can zebrafish models target clinical comorbidity of ADHD with other brain disorders?
• Does zebrafish 'personality' affect the expression of ADHD-like phenotypes?
Specific
• Can stress affect the severity of (or mask) ADHD-like phenotypes in zebrafish models?
• Are there individual differences in ADHD phenotypes in zebrafish populations?
• Are there robust sex differences in ADHD severity (like those observed in humans)?
• Can zebrafish and rodent genetic models of ADHD become basis of gene therapy?
• Can new ADHD drugs be discovered by using larvae zebrafish for large-scale screening?
• What are specific neural circuits involved in zebrafish ADHD models?
• How can the environment affect zebrafish ADHD-like responses ant their severity across the lifespan? Are there gene x environment interactions for zebrafish ADHD models?
• How RDoCs approaches could be used to model ADHD in zebrafish?
• What are the mechanisms involved in the disruption of circadian cycle that leads to ADHD-like symptoms?
• Are there any ADHD differences between zebrafish strains?

Table 2. Selected open questions in the field of zebrafish modeling ADHD