Zebrafish as a model of neurodevelopmental disorders

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Abstract

Neurodevelopmental disorders (NDDs) caused by aberrant brain growth and development are life-long, debilitating illnesses that markedly impair the quality of life. Animal models are a valuable tool for studying NDD pathobiology and therapies. Mounting evidence suggests the zebrafish (*Danio rerio*) as a useful model organism to study NDDs with high physiological homology to humans and sensitivity to pharmacological and genetic manipulations. Here, we summarize experimental models of NDDs in zebrafish and highlight the growing translational significance of zebrafish NDD-related phenotypes. We also emphasize the need in further development of zebrafish models of NDDs to improve our understanding of their pathogenesis and therapeutic treatments.

Key words: animal models; autism; attention-deficit/hyperactivity disorder; neurodevelopment; genetic models.

Introduction

Neurodevelopmental disorders (NDDs) are life-long debilitating conditions caused by aberrant growth and development of the central nervous system (CNS) (Thapar A et al., 2017;Young S et al., 2018). Currently recognized major clinical NDDs, to be discussed here, include communication disorders, autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), intellectual disability (ID), specific learning disorder and motor/tic disorders (American Psychiatric A, 2013). For example, ASD causes robust behavioral (e.g., hyperactivity, repetitive behaviors), emotional (e.g., low affectivity/empathy) and social deficits (American Psychiatric A, 2013;Elsabbagh M et al., 2012;Lainhart JEJIRoP, 1999;Simonoff E et al., 2013). ADHD causes hyperactivity and inattention (e.g., easy distraction and impulsivity) (American Psychiatric A, 2013;Mayes SD et al., 2000;Mayes SD and Calhoun SLJCN, 2007). Global developmental delay (Moeschler JB and Shevell M, 2014) is characterized by delay in motor, speech/language, cognitive, social/personal, and activities of daily living (Shevell MI et al., 2003). Another common NDD, ID presents as reduced intellectual functioning and adaptive behavior, impaired conceptual, social and practical adaptive skills (Schalock RL et al., 2007), as well as deficits in cognitive capacities (American Psychiatric A, 2013).

The etiology of NDDs is multi-factorial, complex and poorly understood (Gathercole SE et al., 2006;Krakowiak P et al., 2012;Lewis DA and Levitt PJAron, 2002;Newcorn JH et al., 2015;Thapar A,Cooper M and Rutter MJTLP, 2017). For instance, ADHD is associated with complications at birth, as well as genetic and environmental factors (e.g., chemical exposure or drug intake during gestation) (Lou HJAP, 1996;Millichap JGJP, 2008;Nigg JTJJoCC and Psychology A, 2012;Thapar A et al., 2013). ASD is linked to metabolic pathologies during pregnancy (e.g., obesity, diabetes) and immune disorders (Currenti SAJC and neurobiology m, 2010;Krakowiak P,Walker CK,Bremer AA,Baker AS,Ozonoff S,Hansen RL and Hertz-Picciotto IJP, 2012;Pessah IN et al., 2008). Genetic factors also play a role in NDDs, for example, causing specific NDD (e.g., Down, Smith-Magenis and William's-Beuren) syndromes (Martens G and

van Loo KJCg, 2007). However, the underlying mechanisms of NDDs remain unclear (Martens G and van Loo KJCg, 2007;Miles JHJGiM, 2011), necessitating further research in this field.

Animal models have been used to evaluate the etiology and develop new therapies for NDDs and associated comorbidities (Gatto CL and Broadie KJCoin, 2011;Kalueff AV et al., 2014;Meyer U et al., 2009;Tropepe V et al., 2003). Complementing rodent models, the zebrafish (*Danio rerio*) is emerging as a valuable model organism in CNS research and drug screening (Best J et al., 2008;Khan KM et al., 2017;MacRae CA and Peterson RTJNrDd, 2015;Rihel J and Schier AFJDn, 2012). Here, we summarize the mounting evidence for modeling NDDs in zebrafish, focusing on important translational lessons from using this model organism and selected NDDs chosen based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V (American Psychiatric A, 2013)).

A small teleost fish, the zebrafish has a short reproductive cycle and transparent embryos and larvae, enabling an easy assessment of their neurodevelopment (Kimmel CB et al., 1995;Singleman C and Holtzman NGJZ, 2014). Zebrafish have four developmental stages: embryo (until the *protruding mouth,* ~72 hours past fertilization, hpf); larva (3-30 days past fertilization, dpf); juvenile fish (attaining a complete pattern of scales and completely losing the larval fin fold; 1-3 months), and adult fish (defined by the production of viable gametes and ability to breed) (Kimmel CB,Ballard WW,Kimmel SR,Ullmann B and Schilling TFJDd, 1995).

The structural and anatomical formation of zebrafish CNS initiates early (Kimmel CB,Ballard WW,Kimmel SR,Ullmann B and Schilling TFJDd, 1995;Papan C and Campos-Ortega JAJRsaodb, 1994), with neuronal formation beginning at 16 hpf (Kimmel CB et al., 1991). By 17 hpf, zebrafish brain forms its sub-regions, including the midbrain-hindbrain boundary, cerebellum and thalamus (Gutzman JH et al., 2008;Hanneman E et al., 1988;Kimmel CB,Ballard WW,Kimmel SR,Ullmann B and Schilling TFJDd, 1995;Kimmel CBJAron, 1993). The blood-brain barrier begins to form at 20 hpf, demonstrating the well-developed microglia and complete barrier structure at 3 dpf (Herbomel P et al., 1999;Quiñonez-Silvero C et al., 2019). The neural signaling systems, which are ontogenetically homologous to mammalian systems,

form between 18-32 hpf and include the catecholaminergic (Holzschuh J et al., 2001;Mueller T and Wullimann M, 2015), gamma-aminobutyric acid (GABA)-ergic and glutamatergic systems (Higashijima SI et al., 2004).

Zebrafish model of selected neurodevelopmental disorders

Zebrafish are actively used to model various aspects of ASD, including sociocognitive deficits and behavioral perseverations (Meshalkina DA et al., 2018;Stewart AM et al., 2014). For example, mimicking ASD-like phenotypes, dizocilpine (MK-801), a non-competitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, evokes social deficits (impaired shoaling) in adult fish (Seibt KJ et al., 2011;Zimmermann FF et al., 2016). Zebrafish mimic pathological effects of ASD following larval valproate exposure during neurodevelopment (Dwivedi S et al., 2018), causing overt deficits in social interaction as adults (Zimmermann FF et al., 2017). Valproate exposure during early life also alters brain development, promotes cell proliferation and neurogenesis (including in regions that may contribute to brain overgrowth and macrocephaly), and causes behavioral (e.g., hyperactivity and ASD-like social deficits) and genomic (i.e., gene expression-based; e.g., upregulated *adsl* (*adenylosuccinate lyase*) and *mbd5* (*methyl-CpG binding domain protein 5*), downregulated *shank3a* (*SH3 and multiple ankyrin repeat domains 3a*) and *tsc1b* (*tuberous sclerosis complex 1*)) responses in embryonic and larval zebrafish (Chen J et al., 2018;Lee S et al., 2018).

Environmental factors that may promote AD clinically include pesticides, solvents and air pollutants (Rossignol DA et al., 2014;Ye BS et al., 2017). Suggesting some predictive validity, zebrafish NDD-related phenotypes can also be corrected by clinically active drugs. For example, risperidone, an atypical antipsychotic used to reduce anxiety and aggression in ASD children (McCracken JT et al., 2002), lowers anxiety-like behavior and cortisol levels caused by acute stress (net chasing) in zebrafish (Idalencio R et al., 2015). Aripiprazole, another atypical antipsychotic used to control irritability, hyperactivity and stereotypies in ASD (Accordino RE et al., 2016), similarly reduces stress response in zebrafish (Barcellos HHD et al., 2016).

Animal models are important tools for studying the genetic complexity of NDDs (Banerjee S et al., 2014;Hoffman EJ, 2014). For example, the contactin associated protein-like 2 (*CNTNAP2*) gene is up-regulated in ASD patients (Arking DE et al., 2008;Strauss KA et al., 2006). In line with this, zebrafish *CNTNAP2* mutants display nocturnal hyperactive behavior and GABAergic deficits, which can be reversed by treatment with estrogens (e.g., estradiol cypionate and Biochanin A) (Hoffman EJ et al., 2016). A homozygous founder mutation in *TRAPPC6B* is also associates with human ASD (Marin-Valencia I et al., 2018), and zebrafish *trappc6b* morphants parallel some human NDD phenotype, displaying microcephaly and neuronal hyper-excitability (Marin-Valencia I,Novarino G,Johansen A,Rosti B,Issa MY,Musaev D,Bhat G,Scott E,Silhavy JL and Stanley V, 2018). Zebrafish knockouts of synaptic ras gtpase activating protein 1 (*SYNGAP1*) and the SH3 and multiple ankyrin repeat domains 3 (*SHANK3*) genes recapitulates developmental delay in ASD (Kozol RA et al., 2015), including delayed mid/hindbrain development, motor deficits (unproductive swim attempts) and spontaneous seizure-like behaviors (Kozol RA,Cukier HN,Zou B,Mayo V,De Rubeis S,Cai G,Griswold AJ,Whitehead PL,Haines JL and Gilbert JRJHmg, 2015). The *shank3b* mutant fish display morphological and behavioral deficits (e.g., reduced locomotion an social interaction) (Liu C-x et al., 2018). *Dyrk1aa* knockout zebrafish exhibit social impairments that reproduce human phenotypes of ASD, as well as lower *c-fos* in hypothalamus vs. wild type, suggesting that the knockout fish brain is less activated by social contexts (Kim O-H et al., 2017). Morpholino *shank3b* knockdown zebrafish exhibit reduced social interaction, spend less time near conspecifics, and repetitive swimming behaviors in both larvae and adults (Liu C-x et al., 2018).

Common phenotypes associated with ADHD include inattention, impulsiveness and hyperactivity (Winstanley CA et al., 2006), which all can be evaluated in zebrafish (Fontana BD et al., 2019). Both adult and larvae zebrafish can also be useful to model pathological hyperactivity and impulsivity, common in ADHD (Blaser R et al., 2010;Ellis LD et al., 2012;Fontana BD,Franscescon F,Rosemberg DB,Norton WHJ,Kalueff AV and Parker MO, 2019;Saili KS et al., 2012). For example, exposure to 1% alcohol evokes zebrafish motor

hyperactivity following dopaminergic stimulation (Nowicki M et al., 2015). Likewise, models have been developed to assess the ability of adult zebrafish to respond to impulsiveness and attention stimulus (Parker MO et al., 2014;Parker MO et al., 2013), as well as to evaluate neurochemical (e.g., monoaminergic) mechanisms of impulsivity in these fish (Parker MO,Brock AJ,Sudwarts A and Brennan CH, 2014).

Genetic risks of ADHD include the gene variants in the *latrophilin 3 (LPHN3)* gene (Martinez AF et al., 2016), whose *lphn3.1* ortholog down-regulation in zebrafish evokes hyperactivity and impulsivity, similarly to ADHD patients (Lange M et al., 2012). The nocturnal hyperactivity behaviors in ADHD are associated with clock genes polymorphisms (Kissling C et al., 2008;Mogavero F et al., 2018). As neuromedin U (Nmu) promotes hyperactivity and inhibits sleep in larvae, the *nmu* mutant animals present hypoactive phenotype (Chiu CN et al., 2016). In addition, zebrafish knockouts of the clock gene period1b (*per1b*) exhibit similar hyperactivity, impulsivity and circadian disturbances to clinical ADHD (Huang J et al., 2015). The zebrafish *Depdc5* knockdown and *period1b* mutants can also be used as ADHD model in zebrafish, showing both hyperactivity and cognitive deficits (de Calbiac H et al., 2018;Wang T et al., 2018) (note, however, that hyperactivity is a rather non-specific behavioral alteration, and its presence alone may not be sufficient to mimic ADHD). Zebrafish can also help evaluate new treatments for AHDH. For example, auriculasin, a prenylated isoflavones from *Flemingia philippinensis*, reduces hyperactivity and increases melatonin and dopamine in period1b-/- zebrafish (Wang T,Liu Y,Liu H,Li C and Wang Y, 2018). Likewise, zebrafish *contactin associated protein-like 2 (cntnap2)* mutants display ADHD-like hyperactivity and GABAergic deficits in the forebrain, which can be reversed by phytoestrogen biochanin A (Hoffman EJ et al., 2016).

Relevant to modeling ID, ethanol exposure during neurodevelopment induces learning and memory deficits in zebrafish (Carvan III MJ et al., 2004;Fernandes Y et al., 2014;Luchiari AC et al., 2015), strikingly resembling human fetal alcohol syndrome (FAS). The bromodomain PHD finger transcription factor (BPTF) variants are found in patients with global developmental delay/ID, speech delay, postnatal microcephaly, and dysmorphic features (Stankiewicz P et al.,

2017). Zebrafish knockout of *bptf* causes smaller head size and abnormal craniofacial patterning (Stankiewicz P,Khan TN,Szafranski P,Slattery L,Streff H,Vetrini F,Bernstein JA,Brown CW,Rosenfeld JA and Rednam S, 2017). The X-linked genetic syndrome associated with mutations in TAF1 gene presents global developmental delay and ID. Zebrafish morpholino of *taf1* ortholog reduces the optic tectum, demonstrating that mutations in *TAF1* play a critical role in the development of this X-linked ID (O'Rawe JA et al., 2015). In addition, mutations in *exosome component 3* (*EXOSC3*) are associated with global developmental delay, cerebellar atrophy, progressive microcephaly and pontocerebellar hypoplasia type 1 (Wan J et al., 2012). Morpholino knockdown of *exosc3* in zebrafish embryos causes embryonic microcephaly and poor motility, resembling some of clinical features (Wan J,Yourshaw M,Mamsa H,Rudnik-Schöneborn S,Menezes MP,Hong JE,Leong DW,Senderek J,Salman MS and Chitayat D, 2012). Patients with dysfunction of Cyclin K (CCNK) display developmental delay, ID and language defects (Fan Y et al., 2018). Functional assay in zebrafish larvae show that *Ccnk* knockdown impairs brain and spinal cord development (Fan Y,Yin W,Hu B,Kline AD,Zhang VW,Liang D,Sun Y,Wang L,Tang S and Powis Z, 2018). Another candidate gene for reading problems and mild ID is *CTNND2*, and both humans and zebrafish with haploinsufficiency of this gene present cognitive dysfunction (Hofmeister W et al., 2015).

As several motor disorders are also classified as NDDs, zebrafish emerge as a useful tool to unravel possible aberrant control of the motor system (Schilling TFJZ, 2002). For example, larvae exposure to ketamine evokes anxiety-like behavior and lower swimming speed (Félix LM et al., 2017) – the effects diminished by acetyl l-carnitine, which promotes neuroprotective effects and reduces the degeneration of Rohon-Beard sensory neurons in zebrafish (Cuevas E et al., 2013). The Rett syndrome is an X-linked neurodevelopmental disorder with mental retardation and a rapid regression of motor and cognitive skills. Mutations in the transcription factor *MECP2* gene are present in >90% of Rett syndrome patients (Amir RE et al., 1999), and the *Mecp2* knockout zebrafish display reduced swimming activity (Pietri T et al., 2013) and aberrant CNS brain-derived neurotrophic factor (*bdnf)* gene expression (Nozawa K et al., 2017).

Microcephaly is a general comorbidity of many NDDs (Watemberg N et al., 2002;Woods CGJCoin, 2004), and zebrafish may help examine genetic implications and the molecular mechanisms of this disorder (Kim H-T et al., 2011;Novorol C et al., 2013). The autosomal recessive primary microcephaly (MCPH) is characterized by smaller cortices, which can be evaluated by expression of the abnormal spindle-like microcephaly associated gene (*aspm*) in zebrafish (Kim H-T,Lee M-S,Choi J-H,Jung J-Y,Ahn D-G,Yeo S-Y,Choi D-K,Kim C-HJB and communications br, 2011). Similarly, *Fancd2* (fanconi anemia complementation group D2) mutants zebrafish also present microcephaly and microphthalmia, paralleling clinical phenotypes (Liu TX et al., 2003). The loss-of-function and missense variants in KIAA1109 are associated to autosomal-recessive multi-system Alkuraya-Kucinskas syndrome, and knockdown of the orthologous gene in zebrafish causes embryonic hydrocephaly (Gueneau L et al., 2018). Kabuki syndrome is a rare multiple congenital anomaly syndrome characterized by global developmental delay and ID due to mutations in the *KMT2D* and *KDM6A* genes. Zebrafish knockdown of *kmt2d* and the two zebrafish paralogues *kdm6a* and *kdm6al* present developmental abnormalities similar to Kabuki syndrome, as kdm6a and kmt2d morphants exhibit severe abnormalities in brain development (Van Laarhoven PM et al., 2015).

Finally, schizophrenia is a critical, severely debilitating disorder, which is relevant to NDDs, affects approximately 1% globally and causes cognitive, emotional, social and perceptual dysfunctions (Association AP, 2013). Schizophrenia-like phenotypes can be studied in zebrafish using various tests to assess fish locomotor activity (Daggett J, 2016;Kysil EV et al., 2017;Wang L et al., 2016), as well as social (Wang L,Jiang W,Lin Q,Zhang Y and Zhao C, 2016), cognitive (Daggett J, 2016;Meshalkina DA et al., 2017) and aggressive behaviors (de Abreu MS et al., 2019;Zabegalov KN et al., 2019), all commonly observed in schizophrenic patients. Schizophrenia-like states can also be induced experimentally, for example, mimicking the hypofunction of glutamatergic N-methyl-D-aspartate (NMDA) signaling (Farber NB, 2003). In zebrafish, a pro-psychotic drug dizocilpine (MK- 801) potently modulates a wide range of behavioral phenotypes, including those directly relevant to psychoses, such as motor

hyperactivity and social deficits, which are also reversed by clinically active antipsychotics sulpiride and olanzapine (Seibt KJ et al., 2010;Seibt KJ et al., 2011). In addition, several brain genes are associated with schizophrenia and can be evaluated in zebrafish, including the disrupted in schizophrenia 1 (*disc1*) and neuregulin 1 (*nrg1*) genes (Owen MJ et al., 2009), as well as glutamatergic and GABA-ergic genes, such as *dysbindin (DTNBP1), catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH), Metabotropic glutamate receptor-3 (GRM3; mGluR3)*, *regulator of G-protein signaling 4 (RGS4)* (Harrison PJ and Weinberger DRJMp, 2005;O'Tuathaigh CMP et al., 2007).

General discussion

Evidence summarized here suggests that zebrafish emerge as an important new model to study NDDs. Possessing several practical advantages, such as chorion transparency that allows easy observation of development, low cost and rapid development (Beliaeva N et al., 2010;Tavares B and Lopes SSJAmp, 2013) (Fig. 1), zebrafish also present conserved GABAergic (Hortopan GA et al., 2010;Roy B and Ali DWJN, 2014), monoaminergic (Irons T et al., 2013;Souza BR and Tropepe VJRitn, 2011;Yamamoto K et al., 2010), purinergic (Piato AL et al., 2011;Zimmermann FF,Gaspary KV,Siebel AM,Leite CE,Kist LW,Bogo MR and Bonan CDJMn, 2017), glutamatergic (Rico EP et al., 2010;Vitale W, 2012) and melatonergic (Genario R et al., 2019) systems, as well as well-defined neuronal complexes (Jin Y et al., 2018;Kabashi E et al., 2011;Panula P et al., 2006). In addition, zebrafish is an important model to assess chemical, neurotoxic and genetic insults during neural development (Giordani S and d'Amora MJFiN, 2018;Wang S et al., 2018). Zebrafish are further suitable for studying NDDs (Dorsemans A-C et al., 2017) due to high neuroplasticity, enabling the analyses of multiple neuronal adaptations (Ghosh S and Hui SP, 2016) and their behavioral (e.g., sociality or emotionality) correlates (Teles MC et al., 2016) controlled by relatively well-defined circuits (Perathoner S et al., 2016). The growing number of zebrafish genes whose orthologs have been implicated in human NDDs (Fontana BD,Franscescon F,Rosemberg DB,Norton WHJ,Kalueff AV and Parker MO, 2019;Meshalkina DA et al., 2018;Vaz R et al., 2019) supports the value of

this organism for developing new CNS targets. Finally, important advantages of zebrafish models of NDDs (over mammals) include their high-throughput potential (Jordi J et al., 2018) and better compliance, as lower vertebrates, with bioethical animal experimentation and 3R principles (de Abreu MS et al., 2019).

However, as other *in vivo* models, zebrafish present certain limitations in regard to modeling NDDs. For example, zebrafish show overt differences in physiology compared to mammals, such as the external fertilization that does not mimic uterine development in mammals (d'Amora M and Giordani S, 2018). Another problem is that zebrafish present rather limited range of behavioral phenomena (e.g., it is unclear if depression-like states exist in zebrafish (de Abreu MS et al., 2018)) compared to other, much better studied (e.g., rodent) NDDs models. Moreover, unlike mammals, zebrafish does not exhibit some critical brain areas (most notably, cerebral cortex (Kalueff AV et al., 2014)). It is also impossible to mimic some NDDs in zebrafish (e.g., speech sound disorder, stuttering, developmental coordination disorder, tic disorders, communication/language disorder), or to evaluate the role of neurodevelopment during gestation (due to external fertilization in fish). While zebrafish do present a complex behavioral repertoire (Ariyomo TO et al., 2013;Blaser R,Chadwick L and McGinnis GJBbr, 2010;Dreosti E et al., 2015;Kalueff AV et al., 2013), the face validity of zebrafish models for NDDs remains unclear, and it is unlikely that all NDD symptoms can be recapitulated. In addition, unlike mammals, some zebrafish genes are duplicated as a result of teleost-specific genome duplication event (Howe K et al., 2013), with an average of 20–24% of genes duplicated (Howe K, Clark MD, Torroja CF, Torrance J, Berthelot C, Muffato M, Collins JE, Humphray S, McLaren K, Matthews L, McLaren S, Sealy I, Caccamo M, Churcher C, Scott C, Barrett JC, Koch R, Rauch GJ, White S, Chow W, Kilian B, Quintais LT, Guerra-Assunção JA, Zhou Y, Gu Y, Yen J, Vogel JH, Eyre T, Redmond S, Banerjee R, Chi J, Fu B, Langley E, Maguire SF, Laird GK, Lloyd D, Kenyon E, Donaldson S, Sehra H, Almeida-King J, Loveland J, Trevanion S, Jones M, Quail M, Willey D, Hunt A, Burton J, Sims S, McLay K, Plumb B, Davis J, Clee C, Oliver K, Clark R, Riddle C, Elliot D, Eliott D, Threadgold G, Harden G, Ware D, Begum S, Mortimore B, Mortimer B, Kerry

G, Heath P, Phillimore B, Tracey A, Corby N, Dunn M, Johnson C, Wood J, Clark S, Pelan S, Griffiths G, Smith M, Glithero R, Howden P, Barker N, Lloyd C, Stevens C, Harley J, Holt K, Panagiotidis G, Lovell J, Beasley H, Henderson C, Gordon D, Auger K, Wright D, Collins J, Raisen C, Dyer L, Leung K, Robertson L, Ambridge K, Leongamornlert D, McGuire S, Gilderthorp R, Griffiths C, Manthravadi D, Nichol S, Barker G, Whitehead S, Kay M, Brown J, Murnane C, Gray E, Humphries M, Sycamore N, Barker D, Saunders D, Wallis J, Babbage A, Hammond S, Mashreghi-Mohammadi M, Barr L, Martin S, Wray P, Ellington A, Matthews N, Ellwood M, Woodmansey R, Clark G, Cooper J, Tromans A, Grafham D, Skuce C, Pandian R, Andrews R, Harrison E, Kimberley A, Garnett J, Fosker N, Hall R, Garner P, Kelly D, Bird C, Palmer S, Gehring I, Berger A, Dooley CM, Ersan-Ürün Z, Eser C, Geiger H, Geisler M, Karotki L, Kirn A, Konantz J, Konantz M, Oberländer M, Rudolph-Geiger S, Teucke M, Lanz C, Raddatz G, Osoegawa K, Zhu B, Rapp A, Widaa S, Langford C, Yang F, Schuster SC, Carter NP, Harrow J, Ning Z, Herrero J, Searle SM, Enright A, Geisler R, Plasterk RH, Lee C, Westerfield M, de Jong PJ, Zon LI, Postlethwait JH, Nüsslein-Volhard C, Hubbard TJ, Roest Crollius H, Rogers J and Stemple DL, 2013). This can result in redundant functions of various key brain genes related to NDDs, and may provide phenotypic buffering and/or complicating the generation of gene-targeted (knockout or knockdown) diseases models (Kozol RA et al., 2016;Sakai C et al., 2018).

Notably, the long-term effect of many zebrafish mutants is not characterized for adult zebrafish behavior, calling into question its predictive validity. Thus, studies aiming to characterize in detail the face and predictive validity of zebrafish NDDs models are still necessary if we are to understand the mechanisms of these disorders across the lifespan.

Nevertheless, mounting evidence suggests that zebrafish models can be used to screen novel treatments for various NDDs. For example, screening of behavioral effects of over 10000 drugs in larval zebrafish (Jordi J,Guggiana-Nilo D,Bolton AD,Prabha S,Ballotti K,Herrera K,Rennekamp AJ,Peterson RT,Lutz TA and Engert F, 2018) suggests several compounds which may help develop new ADHD therapies and improve our understanding of mechanisms and neural circuits involved in this disorder. Still, a large translational gap exists for animal models

of NDDs, including zebrafish models relevant to these conditions. In general, the translatability of findings obtained in animal models is generally associated with the range of mechanisms and phenotypic profiles that the animal model can address (Zeiss CJ and Johnson LK, 2017). The factors that may contribute to the reproducibility-translatability gap include relationships between the model choice (e.g., intended goal of the intervention) and the integration of biomarker data with outcome measures that are clinically relevant to humans (Zeiss CJJIj, 2017). Despite clear advantages as a model organism (discussed above), our present understanding of zebrafish NDD-related phenotypes and their molecular mechanisms remained limited, as is the number of established behavioral models and tests relevant to mimicking these disorders. Nevertheless, as animal models continue to play a key role in the identification of genetic and molecular targets to develop safer and more effective treatments for NDD, the zebrafish is emerging as a potentially promising species to generate important insights into pharmacological and genetic roles of NDDs. With many questions yet remaining open in this field (Table 1), this calls for further research utilizing zebrafish models of NDDs.

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Conflict of interest

The authors declare no conflict of interest

Figure 1. Schematic diagram emphasizing the advantages of using zebrafish to study neurodevelopmental disorders and their risk factors.

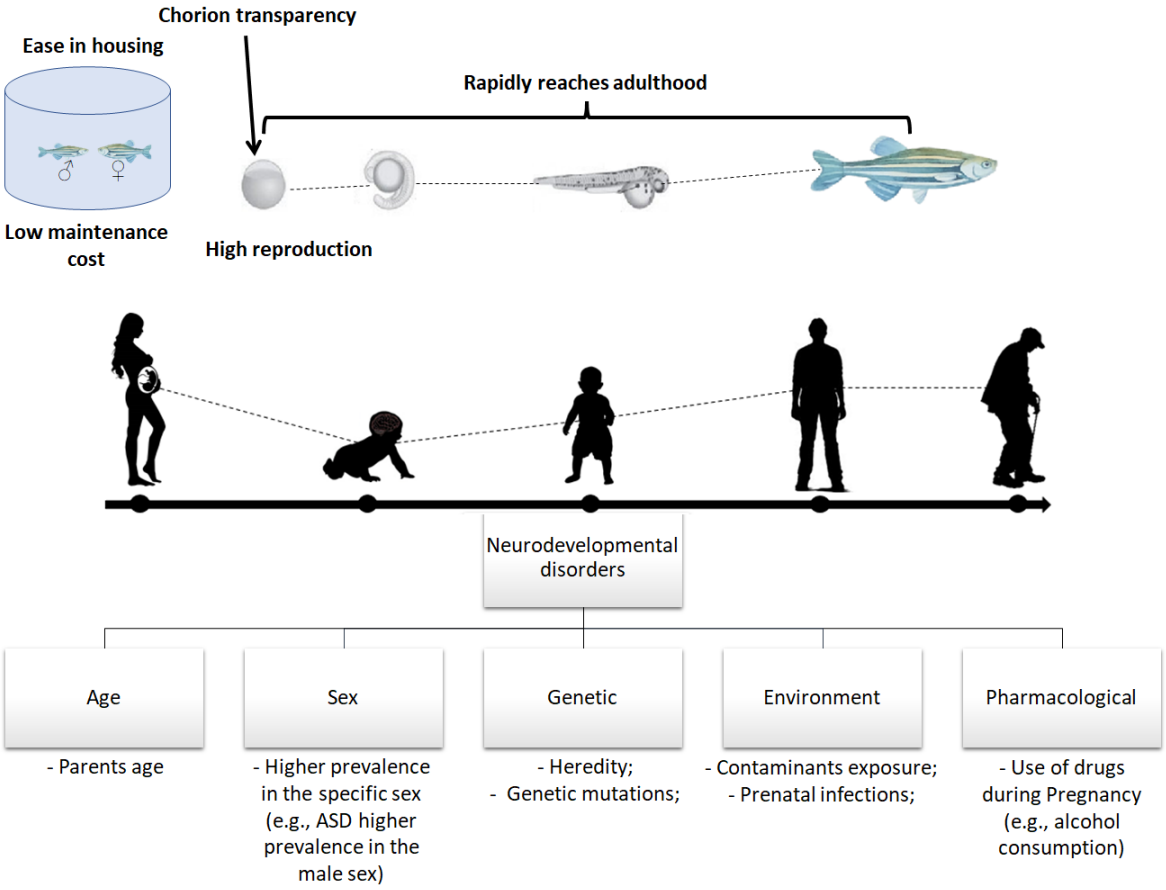

Table 1. Selected open translational questions related to modeling neurodevelopmental disorders (NDDs) using zebrafish.

Model-related
• How to obtain zebrafish models that are most robust to study NDDs? • How can stress affect or trigger NDD pathogenesis in zebrafish? • What is the best genetic model for each NDDs in zebrafish? • Are there differences in genetic determinants of NDDs in humans *vs.* zebrafish? • What is the role of epigenetic modulations in NDDs? • Can gene-environment interactions and genetic predisposition factors in clinical NDDs be modeled in zebrafish? • What is the impact of sex differences in NDD models in zebrafish? • How to develop zebrafish models of NDDs that display sex differences in pathogenesis similar to those in humans? • How does zebrafish 'personality' contribute to the expression of NDD behaviors in various aquatic tests? • Can computer technologies (e.g., behavioral software) lead to automatic recognition and extraction of zebrafish NDD-related behaviors? • Do gut microbiota factors contribute to zebrafish NDD pathogenesis? • Do various zebrafish 'NDDs' respond similarly to clinically effective drugs as human NDDs? • How can current genetic tools (e.g., CRISPR) assist in the understanding of NDDs mechanisms? • Are there individual and strain differences of NDDs phenotypes in zebrafish? Are they stable/consistent between strains for all major NDD subtypes? • How to best differentiate phenotypes of each NDD in zebrafish (e.g., disrupted social behavior (ADHD *vs.* ASD)? • Which behavioral endpoints are shared/common in tasks assessing NDDs behaviors in zebrafish *vs.* other models? • Can zebrafish NDD models also mimic their frequent comorbidity with non-NDD (e.g., affective) disorders? • Are there species differences (e.g., *Danio albolineatus vs*. *Danio rerio*) in responsivity to drugs used in NDD treatment?
Treatment-related
• What is the impact of environmental enrichment therapy on zebrafish NDD models? • Can environmental factors modulate (e.g., decrease or potentiate) drug effects on zebrafish NDD-related phenotypes? • Can physiological treatments (e.g., diet interventions, exercise) so widely used to treat NDDs clinically exert similar therapeutic effects in zebrafish NDD models? • What are prospects of stem cell-based therapy of NDDs? • What is the clinical replicability of the NDD-related pharmacological effects in zebrafish? • What nootropic drugs are effective for NDDs treatment? • Can extensive regenerative capacity of zebrafish brain become a basis for novel NDD therapies? • How can neuroimmune mechanisms modulate zebrafish NDD-related phenotypes? • What are novel, principally new targets for NDD therapy? Can these novel drug targets be identified through high-throughput screening using zebrafish?

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