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## **Abnormal repetitive behaviors in zebrafish and their relevance to human brain disorders**

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## **Abstract**

Abnormal repetitive behaviors (ARBs) are a prominent symptom of numerous human brain disorders and are commonly seen in rodent models. As rodent studies of ARBs continue to dominate the field, mounting evidence suggests that zebrafish (*Danio rerio*) also display ARB-like phenotypes and may therefore be a novel model organism for ARB research. In addition to practical research advantages, zebrafish share high genetic and physiological homology to humans and rodents, including multiple ARB-related genes and stereotypic behaviors relevant to ARB. Here, we discuss a wide spectrum of stereotypic repetitive behaviors in zebrafish, data on their genetic and pharmacological modulation, and the overall translational relevance of fish ARBs to modeling human brain disorders. Overall, the zebrafish is rapidly emerging as a new promising model to study ARBs and their underlying mechanisms.

**Keywords:** zebrafish; abnormal repetitive behavior; stereotypy; animal models; human brain disorders

## 1. Introduction

Abnormal repetitive behaviors (ARBs) commonly occur in neuropsychiatric diseases, including obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), trichotillomania, Parkinson's disease, as well as Tourette's, Rett, Fragile X and Prader-Willi syndromes [1-3]. Typical ARBs include abnormal motor behavior, disrupted social interactions, aberrant goal-oriented behavior and self-injurious cycled actions [4]. In humans, the most frequent ARBs include skin-picking, head-hitting, repetitive manipulation of objects (spinning, twirling), repetitive use of language, body rocking, hand flapping, finger flicking and tics [5, 6]. Highly relevant clinically [1, 7, 8], some ARBs (e.g., skin-picking, hair-pulling) may also cause physical harm [9, 10]. Together, this emphasizes the growing clinical importance of ARBs and the need for their broad-scale translational research.

Animal experimental models are a powerful tool in neuroscience and biological psychiatry, markedly improving our understanding of CNS function and dysfunction [11-13]. Behaviorally, ARBs can be divided into two groups – motor stereotypies and impulsive/compulsive behaviors [14-16]. The former include the repetition of purposeless movements and/or body postures, whereas the latter involve cognitive inflexibility and aberrant goal-oriented behaviors [17-20]. Clinical motor stereotypies include repetitive stereotypical motor movements (SMMs), critical for neuropsychiatric diagnostics. Common SMMs include body rocking, hand flapping and finger moving, often seen in patients with ASD, Fragile X syndrome, Rett syndrome, Parkinson's disease (e.g., periodic fast/slow finger movements), and Huntington's disease [21-27]. Other common ARBs are tics, often occurring in Tourette's syndrome [28] as unconscious, abrupt, periodical and arrhythmic movements or vocalizations [1, 29]. OCD symptoms include complex ARBs stemming from persistent recurrent compulsive ideas [30], combining composite behavioral acts (compulsions or rituals) with repeated behaviors (e.g., washing and cleaning) that, unlike tics, are conscious [1].

Given a wide spectrum of ARBs and multiple distinct CNS disorders with ARB-like phenotypes, the complex neurobiology of repetitive behaviors is poorly understood [31, 32]. However, the basic neuroanatomy and neuronal circuitry are beginning to unravel for some ARBs in both clinical and animal studies. For example, magnetic resonance imaging (MRI) in both humans and rodents has

revealed core brain structures involved in the regulation of motor behavioral patterns, including sensory motor and anterior cingulate cortex, cerebellum, thalamus and the basal ganglia [33-39]. Paralleling clinical findings, several rodent models with overt spontaneous stereotypies (e.g. deer mice, BTBR T+tf/J, C57BL/10, C57BL/6, C58 mice) are widely used to study ARBs, in which affected animals display repetitive jumping and self-grooming [40-43]. Neurochemical and clinical volumetric studies of the basal ganglia pathways implicate all major neurotransmitters in ARBs [44]. For example, OCD responds to selective serotonin reuptake inhibitors (SSRIs) [45], and disturbances in the serotonin transporter (SERT) are common in humans with OCD [46] and in animal models of this disorder [47, 48]. Likewise, gamma-aminobutyric acid (GABA), glutamate, noradrenaline, histamine, acetylcholine, cannabinoids, endogenous opioids and hypothalamic-pituitary-adrenal (HPA) axis hormones serve as reliable biomarkers of repetitive behavior [44, 49].

Various CNS disorders comorbid with ARBs have strong genetic determinants, including neuroligin (*NLGN*), GABA A-receptor  $\beta 3$  gene (*GABRB3*), methyl-CpG-binding protein 2 (*MeCP2*), the fragile X mental retardation (*FMRI*), contactin-associated protein-like 2 (*Cntnap2*), *SHANK* family, tuberous sclerosis complex 1 (*TSC1*), neurexin 1a (*NRXN1*) [50-52] and dopamine D3 receptor genes (*DRD3*) [53, 54]. Neuroligin genes (e.g., *NLGN3*) modulate dopaminergic signaling in ventral striatum [55], and mouse knockouts in *NLGN3* display robust motor stereotypies [55]. Other genes essential for GABA- and glutamatergic signaling are implicated in ARB pathogenesis [56]. For example, *MeCP2* (encoding transcriptional regulator MeCP2) and *GABRB3* (encoding the  $\beta 3$  subunit of the GABA<sub>A</sub> receptor) are associated with Rett and Prader-Willi syndromes [57-59]. Likewise, *GABRB3* knockout mice display repetitive circling and tail chasing [60, 61], whereas *MeCP2*-deficient mice exhibit impaired GABA signaling with forelimb stereotypies [62]. Genes related to aberrant glutamatergic signaling include *SHANK2* and other *SHANK* genes (responsible for stability of excitatory synapses [56]), and their disturbances may trigger repetitive jumping [63]. Mice lacking genes affecting glutamate NMDA receptors (e.g., *ninjurin 1/ning1*) and *grin1* (*glutamate ionotropic receptor NMDA type subunit 1*) exhibit compulsive grooming resembling clinical OCD [64, 65].

In summary, the genetic contribution to ARBs, established in preclinical and clinical genetics

studies (Table 1), confirm shared core mechanisms of ARB pathogenesis in humans and rodent models [66-68], calling for further translational research in this field. However, as humans and rodents share 80-85% genetic homology, it is logical to ask whether shared ARB pathways are generally evolutionarily conserved across vertebrate taxa? For example, while mutant mice with DAT genetic ablation show multiple repetitive behaviors [69-72], zebrafish (*Danio rerio*) with DAT genetic knockout can become a powerful model of DAT-mediated behavioral deficits. Generated recently, these mutant zebrafish display thigmotaxis (swimming closely to the walls of the tank, Fig. 3) [73] which may represent an ARB-like phenotype. Given a 70-75% of genetic homology between humans and zebrafish [74], their generally similar CNS [75] and core neurotransmitters, neurohormones [76], and their molecular targets [77-79], can experimental modeling of ARBs be extended to include fish models? In other words, can fish have ARBs? And, if they do, - how can ARBs of animals, separated from humans by thousands of years of evolution, inform us about core mechanisms underlying ARB pathogenesis?

## **2. ARB lessons from zebrafish**

While the vast majority of pre-clinical ARB data have been obtained from rodent models [43, 80-86] (Table 1), the growing understanding of evolutionarily conserved core mechanisms of CNS disorders [12] necessitates novel models, new model organisms, and translational cross-species comparisons in the field of ARB research [87]. A small teleost fish, the zebrafish is rapidly gaining popularity in preclinical studies modeling human brain diseases [88] as a low-cost and research-efficient vertebrate organism [89] with fast development highly suitable for CNS research [90]. Notably, transparency of embryos allows the observation of zebrafish CNS *in vivo*, further enhanced by zebrafish brain using imaging tools [91]. Finally, remarkable genetic and physiological similarity to humans, simply quantifiable overt behavioral responses, shared neural circuits and sensitivity to psychotropic drugs make zebrafish an appropriate model species in preclinical studies of human CNS disorders [91, 92].

Similar to rodent models, many basic behavioral patterns of zebrafish can be assessed in observation tanks similar to rodent open field tests, such as novel tank tests [93, 94]. Albeit not showing

some common rodent open field stereotypies (e.g., self-grooming), fish have their own set of stereotypic movements that can be recognized, quantified and modulated experimentally [95]. For example, zebrafish stereotypies are often observed in response to pharmacological intervention, and include repeated back-and-forth swimming at a particular part of the tank (e.g., at the bottom, middle, or top of the tank) [96], but may also include more specific behavioral pattern, such as stereotypic circling - repetitive round trajectory swimming, that is common for ketamine and other glutamatergic antagonists [97, 98] (Table 2). Furthermore, adult zebrafish may display repetitive thigmotaxis often seen following psychostimulant (e.g., nicotine) administration, and manifested as stereotypic swimming along the walls of the tank near the surface (similar to stereotypic locomotion of other model species in the open field test [99]).

However, it is premature to interpret such behavioral patterns without thorough mechanistic analyses and complementing behavioral observations with pharmacological and genetic challenges to target ARBs. For example, recent studies of the neurophysiological underpinnings of repetitive turning and other ARB-like behavior have focused on zebrafish larvae, revealing an important role of hindbrain in such fish phenotypes [100-102]. Likewise, assessing thigmotaxis and its relevance to ARBs in rodents [103] and zebrafish [99], such responses can be also related to alternation in luminance, and represent a tendency to swim outward (rather than the preference for the edges) [104].

### ***2.1. Autism-related models***

Like in rodents, disruption of some ASD-related genes provokes ARB-like phenotypes in zebrafish. For example, *SHANK3* knockout zebrafish display aberrant circling, thigmotaxis, corner-to-corner swimming and ‘looped’ figure-8 swimming [105]. With high homology of *SHANK3* between rodents and zebrafish (Table 2), such fish ARBs resemble stereotypies in mouse mutants of this gene [106-108]. *SYNGAP1* encoding synaptic Ras GTPase activating protein 1 is a critical regulator of glutamatergic NMDA-receptors [109] implicated in ASD [109, 110]. Zebrafish *SYNGAP1* knockouts display remarkable stereotypic movements, including prolonged undulating swimming with frequent C-bends, accompanied by aberrant mid- and hindbrain development [111]. Contactin-associated protein-like 2 gene (*CNTNAP2*) triggers epilepsy and ASD [112, 113] by disrupting inhibitory GABA-

ergic neurotransmission [114, 115]. In line with ASD-like ARBs in *CNTNAP2* knockout mice [116, 117], zebrafish *CNTNAP2* mutants also display higher responsivity to GABA-A receptor inhibitors, causing circling and burst-like movements [118]. Thus, the disruption of key ASD-related genes leads to the development of stereotypic movements in zebrafish.

The fragile X syndrome, clinically distinct from ASD, has an overlapping ARB phenotype with typical stereotypic movements, hand flapping and biting [119-121] triggered by aberrant activity of an X chromosome gene *FMRI* (fragile X mental retardation 1) crucial for CNS development, neurotransmission and synaptic stability [122, 123]. *FMRI* knockout rodents display aberrant jumping, circling, digging and increased self-grooming [124, 125]. Although zebrafish *FMRI* knockouts and knockdowns have craniofacial alterations, aberrant neurotransmission (e.g., cholinergic in motor neurons, glutamatergic in the CNS) and behavioral changes (e.g., hyperactivity [126-129]), their ARBs have not yet been noted [127], necessitating further studies using this model organism.

Rett syndrome is another debilitating disorder genetically related to the X chromosome, mainly affecting females and manifesting in stereotyped hand wringing, rubbing or clapping movements [130]. The main candidate gene for Rett syndrome is *MeCP2* [131], and *MeCP2* knockout mice display similar neurological deficits [132], including ARB-like hindlimb clasping and altered dopamine and glutamate signaling [133, 134]. Zebrafish *MeCP2* knockouts display abnormal thigmotaxis, likely associated with neurodevelopmental abnormalities in the hindbrain [135], and the *MeCP2* knockdown impairs neurodevelopment and neurodifferentiation in larval fish [136].

## ***2.2. Modeling obsessive-compulsive disorder in zebrafish***

There are strong parallels between OCD and other ARB-related conditions, and animal models of OCD proposed based on their phenotypic stereotypy profiles, include genetic models (e.g., hyperdopaminergic mutant deer mice [137, 138] and *Sapap*, *Slitrk5* and *HoxB8* knockout mice [139]), drug-induced and some other models [43, 140, 141]. Zebrafish models of OCD are gaining value in neuropsychiatric research [142-145]. Currently, there are many behavioral tasks that can be used to assess OCD phenotypes in zebrafish and that may be differently classified when using larvae or adult animals. Larvae OCD-like phenotypes are commonly analyzed by video-tracking software and



comprise subtle stereotypic movements such as dashing, freezing and repetitive rotational turns [142]. A recent method to analyze swimming behavior in zebrafish larvae [146] improves the analysis of their behavioral profiles and can be used as an important tool for OCD drug discovery assays. In addition to larvae, OCD phenotypes can be measured in adult zebrafish by assessing their stereotypic movements and compulsive choice [93, 142] (see further).

The early studies using adult zebrafish focused on drug-induced locomotor effects to better understand OCD-related stereotypic behavior in zebrafish novel tank test, a paradigm similar to the open field in rodents [93]. For example, this has revealed stereotypic behavior in adult zebrafish expressed as repetitive rotations or “circling behavior”, such as those induced by NMDA receptor antagonists (e.g., ketamine) [147]. This approach has clear translational concordance with OCD and its treatment [148, 149], as ketamine and other NMDA antagonists often evoke stereotypic circling in humans and rodents. Zebrafish exposed to ibogaine (a hallucinogen with some NMDA antagonist activity that induces stereotypic behavior in rodents [150]) display circling behavior and repetitive corner-to-corner swimming [151]. Repetitive, unvarying perseverative behavior without goal or function has been described in zebrafish following cocaine withdrawal [130]. The predictive validity of stereotypic behavior in translational models is based on response to SSRIs which ameliorate OCD symptoms [152]. Notably, 5-HT<sub>1B</sub> receptor antagonists can induce repetitive behavior in zebrafish [153] that can be reversed by known OCD treatments (e.g., fluoxetine [154]) with striatal activation modulated only by specific OCD treatments [153].

Compulsive choice is another important OCD-related behavior frequently studied in rodent models [69] by subjecting the rodent to the spontaneous alternation test [155] and using the “signal attenuation” model [82]. In zebrafish, a compulsive choice can be studied in a T- or Y-maze assessing habit formation. Briefly, during acquisition of a learning task, normal animals will use both olfactory and visual stimuli to learn the location of food. Once the task is well learned, the animal will develop a ‘habit’ in which the amount of cognitive processing of the array of stimuli in the environment will be lower, as evidenced by lower sensitivity to devaluation, and by reduced sensitivity to contingency degradation [156-158]. Importantly, alterations in habit-forming have been observed in OCD patients

[159], suggesting that such behavior is an important marker of this disorder [160, 161]. In line with this, zebrafish exposed to alcohol during early brain development form habits early in the learning process in an adaptation of the T-maze “place-response” test Parker, Evans [162]. Such tests can be further validated by drugs traditionally used to treat OCD-related symptoms (e.g., fluoxetine), thus providing face and predictive validity for zebrafish models of stereotypic behavior and habit formation in OCD-like phenotypes [93, 142].

### ***2.3. Cognitive inflexibility***

Cognitive flexibility is the ability to adjust and adapt cognitive processing strategies in response to new, unexpected challenges [163]. Conceptually, it is the opposite end of the spectrum to ARBs, which are rigid and fixed. Therefore, understanding the biology of cognitive and behavioral flexibility may offer much to the study of ARBs, and vice versa [85]. Thus, to more closely translate the animal model to human OCD [1], assessment of cognitive flexibility-rigidity needs to be related to observed compulsive behaviors [164]. One method of measuring behavioral flexibility is attention set shifting tasks, which requires learning the response to a simple ‘rule’ applied to a complex stimulus, to identify relevant or non-relevant cues, and then modifying the response when the rule is changed, i.e. responding to the previously irrelevant (instead of the relevant, reinforced) cue [165]. Reductions in cognitive flexibility are seen in patients suffering from various neuropsychiatric disorders, including OCD and ASD [166], making it an important endophenotype to observe and model [167, 168].

Many neuropsychiatric diseases affecting the frontal cortex have deficits in cognitive flexibility signified by increased perseveration for the previous rule and increased errors shifting from one rule to the next [166]. Notably, the severity of the condition (i.e., in OCD patients) correlates with the deficit in reversal learning [166, 169]. Another paradigm, similar to that in primates and rodents [165, 170], has been adapted for zebrafish. For example, zebrafish are able to discriminate two colored cues (using a food reinforcer), demonstrating the capacity for to make ‘choices’ about differently valued stimuli. Zebrafish are also capable of cognitive flexibility, in terms of their responses to reversal learning and intra-dimensional set-shifting [171]. During a typical reversal learning protocol, an animal initially is trained (Phase 1) on a discrete-trial protocol to discriminate between two

differentially reinforced stimuli (e.g., colors: RED =  $S+$  [reinforced], GREEN =  $S-$  [non-reinforced]). Once it has reached a criterion of response allocation to the reinforced alternative (e.g., 6-correct responses in a row), the reinforced and non-reinforced alternatives are reversed (GREEN =  $S+$ , RED =  $S-$ ; Phase 2). During Phase 2, the animal initially shows low correct responses, but gradually learns that  $S-$  from phase 1 is now  $S+$ , and reaches criterion on Phase 2. In Phase 3, the colors are switched to a new pair (intra-dimensional set shift; e.g., BLUE =  $S+$ , YELLOW =  $S-$ ). In the final phase (Phase 4), the two new colors are reversed. If the animal is showing cognitive flexibility, the hypothesis in a reversal learning experiment such as this is that the animal will reach criteria more quickly as the phases continue, on account of their switching the 'rule' by which they are performing responses on the task in an adaptive manner. Zebrafish require progressively fewer trials to reach learning criterion as a function of phase, confirming that this species can be cognitively flexible [172]. Thus, zebrafish performance on tasks of cognitive flexibility renders them ideal for the study of ARB, as cognitive inflexibility is a hallmark of ARBs. Together with the ease of genetic and pharmacological manipulations, zebrafish may further our knowledge on the cognitive-psychobiological aspects of cognitive flexibility in ARB-related disorders.

Another area of executive function that can be measured is working (e.g., spatial) memory [173]. The Y-maze (Fig. 4), a three-armed maze to record spontaneous alternation [174], has been adapted for zebrafish [175] as a useful tool for testing fish. Mazes can be set up in the presence or absence of any motivational or emotional factors, therefore permitting measures of motivation and learning or pure novelty seeking with minimal confound [175]. Automation of this task has enabled minimum user interaction and ease of recording several different variables from a single trial. A recent study employing the Y-maze used an analysis of overlapping tetragrams (i.e., in 100 trials, 16 overlapping tetragrams ranging from RRRR to LLLL [176]) to determine how zebrafish explore the maze in a 1-h trial, revealing aberrant alternations in fish developmentally exposed to ethanol. Thus, the Y-maze has the potential of a flexible and relatively high-throughput method for assessing executive functions associated with learning and working memory. With some further investigation, the Y-maze can be an excellent tool for evaluating neuropsychiatric disorders with both extreme and

more subtle ARBs, thus broadening our ability to model cognitive dysfunction in zebrafish. Indeed, age-related changes in patterns of alternation and repetition have been found in zebrafish (Fig. 4). Given overt stereotypies as part of the typical behavioral repertoire of infant humans (reducing with age in normative development) [177, 178], repetitive movements in the aquatic Y-maze may mimic ARBs observed in human development.

### **3. Existing challenges, model limitations, and future directions**

Clearly, numerous challenges exist in the development of zebrafish models of ARBs. For example, how to properly translate animal repetitive behaviors into human ARBs? Indeed, several of clinical ARB symptoms are difficult, if not impossible, to observe in zebrafish. Therefore, the question is whether the behaviors selected in order to determine ARB are sufficient to call these animal behaviors ARBs. Another problem concerns the overall reliability of behavioral tests recognized recently and requiring an urgent solution [179, 180]. One way to solve it is to ensure that standard protocols are published and utilized by groups using the same behavioral endpoints. Another strategy is to ensure automation is used as widely as possible. As stated earlier, this will be expedited by the recent advent and availability of commercially available automated testing hardware. Third, laboratories should adhere to standardized reporting protocols, such as the ARRIVE guidelines [181], to ensure that intra-laboratory procedures are transparent and fully repeatable, aiming to maximize interlaboratory reliability. Fourth, laboratories should be encouraged to share data and protocols in a timely manner, even from negative experiments, via preprint online servers, to enable fast and accurate reproduction of protocols across the community, and facilitate interlaboratory collaboration, if necessary.

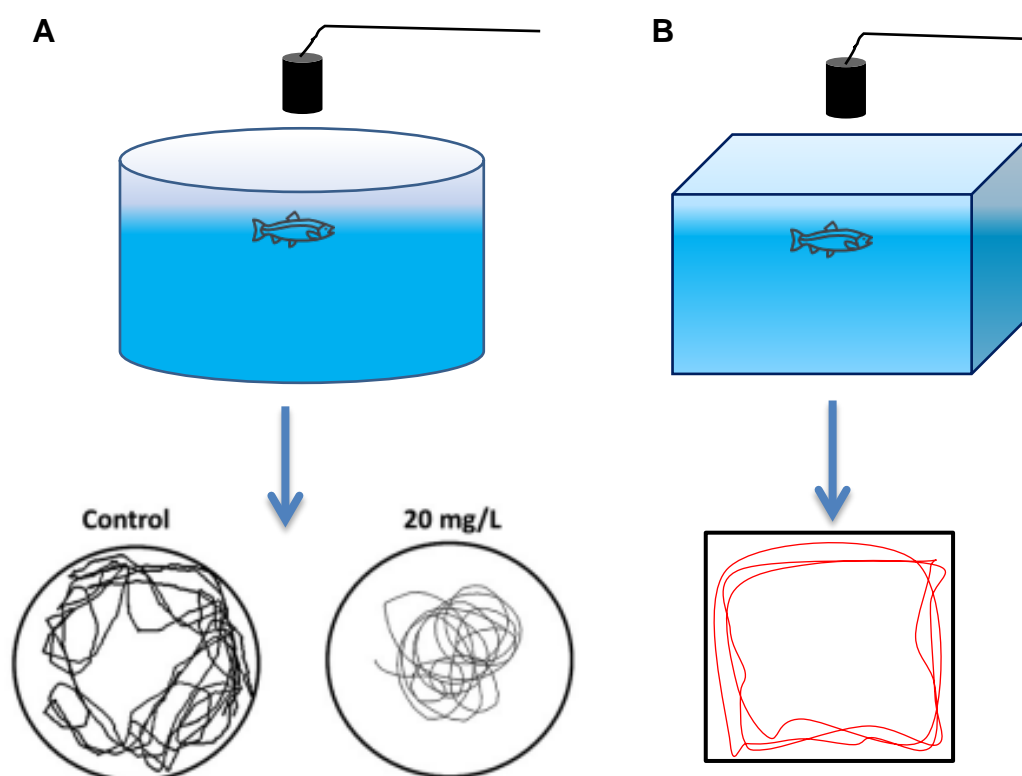
In addition to challenges mentioned above, one of the most useful aspects of the zebrafish model is the ability to carry out high-throughput testing in a vertebrate system. To a certain extent, this is possible in adult fish using protocols outlined above. However, there are some drawbacks to using adult zebrafish which are similar to those associated with mammalian model systems, including practical problems with cost of housing, space constraints, long-term isolation of a sentient social species, and individual behavioral variance. Therefore, the more active use of larvae should be

considered, especially given the development of larval assays of complex behaviors (e.g., impulsivity) [182] which may be useful in the early characterization of ARBs, with strong links between behavioral compulsions and impulse control [183, 184]. Finally, in order for zebrafish to prove useful to study mechanisms of ARBs, several fundamental questions need to be addressed. Indeed, the underlying mechanics of normal action selection in zebrafish remain unclear. For example, what neural circuits underlie choice behavior, behavioral flexibility, and balance between various basal ganglia pathways? Once we have the answers to this question, zebrafish will be extremely useful in understanding the neural circuits underlying ARB (also see Table 2 for strategic directions in the study of ARBs using this organism).

### **Acknowledgments**

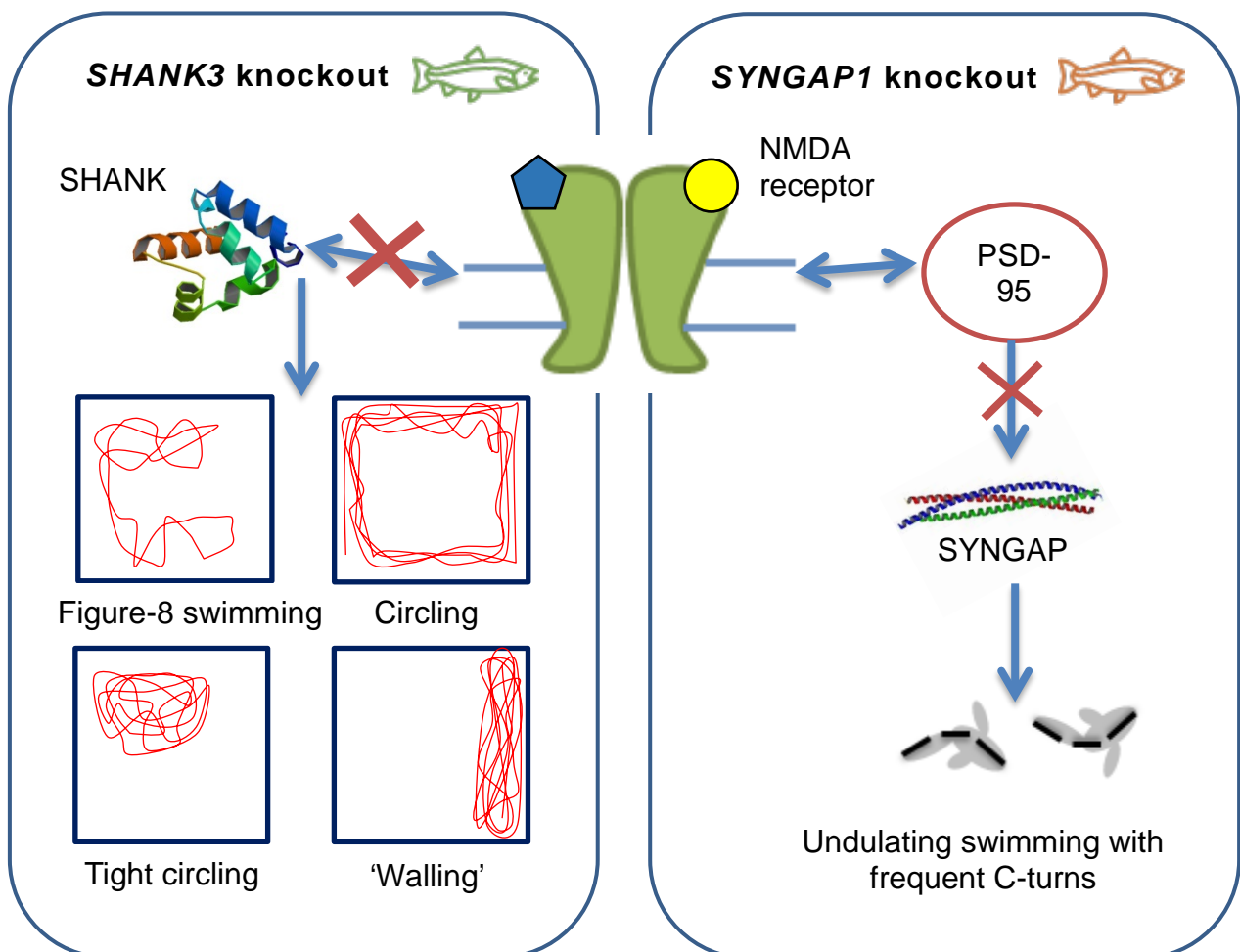
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**Figure 1. Selected repetitive behavior in zebrafish.** Panel A shows how drugs can affect zebrafish behavior in novel tank test. For example, acute ketamine exposure may induce characteristic repetitive behavioral patterns in zebrafish swimming, paralleling ketamine-evoked circling in rodents and clinical stereotypies (see [147] for details). Panel B illustrates thigmotaxis in adult zebrafish, as they typically prefer to swim close to the walls of the tank [185]. Albeit potentially reflecting increased anxiety-like behavior in some contexts (e.g., anxiogenic center avoidance), this response may also represent a pathological repetitive behavior (e.g., evoked by psychostimulants, such as nicotine) relevant to stereotypic peripheral hyperlocomotion, commonly seen in rodents (e.g., following psychostimulant drugs) (adapted from [186]).

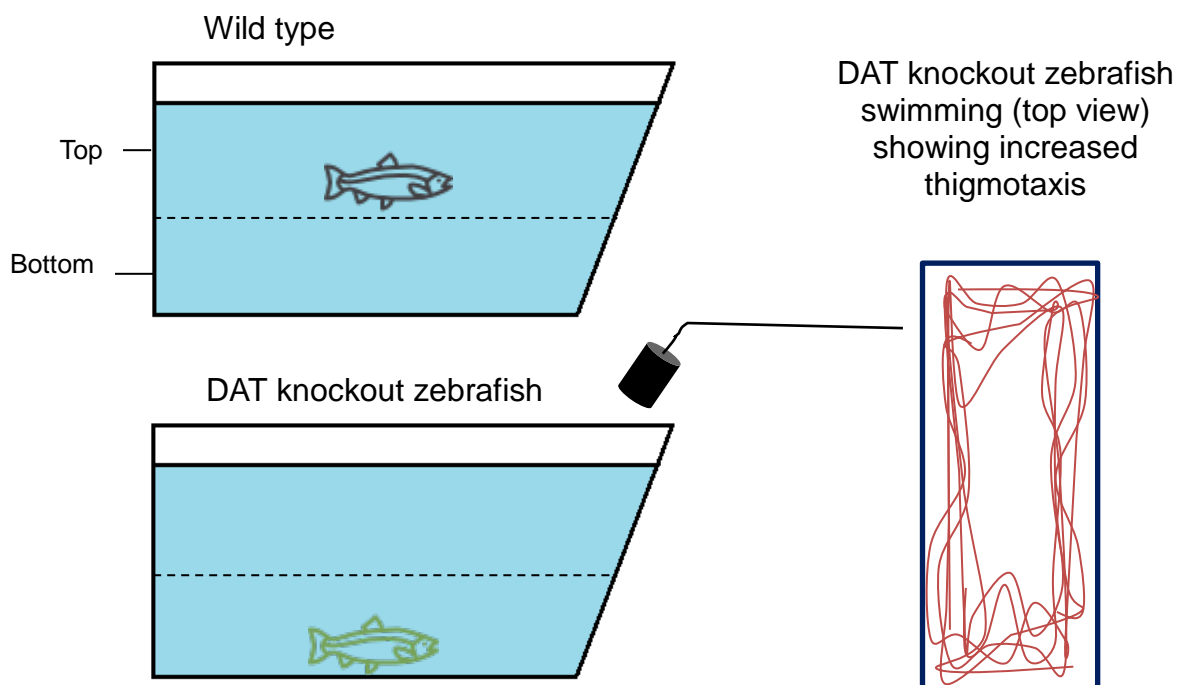


**Figure 2. Selected examples of genetic models of aberrant repetitive behaviors in zebrafish.**

SHANK3 (left panel) is an autism-related gene that encodes postsynaptic density protein (PSD, binding to glutamatergic NMDA receptors) whose ablation in mice impairs synaptic transmission. Knock-down of SHANK in zebrafish up-regulates NMDA receptor and evokes ARB-like repetitive circling, corner-to-corner and figure-8 swimming (top view), according to [105]. A synaptic ras GTPase-activating protein SYNGAP1 (right panel) is another key protein involved in synaptic transmission, whose hypofunction in mice induces precocious maturation of synapses and increases synaptic transmission. NMDA receptor interact with postsynaptic density-95 (PSD-95) protein, which binds to SYNGAP1. SYNGAP1 knockdown zebrafish demonstrate overt stereotypic movements, including prolonged undulating swimming with frequent C-turns (top view), according to [187]

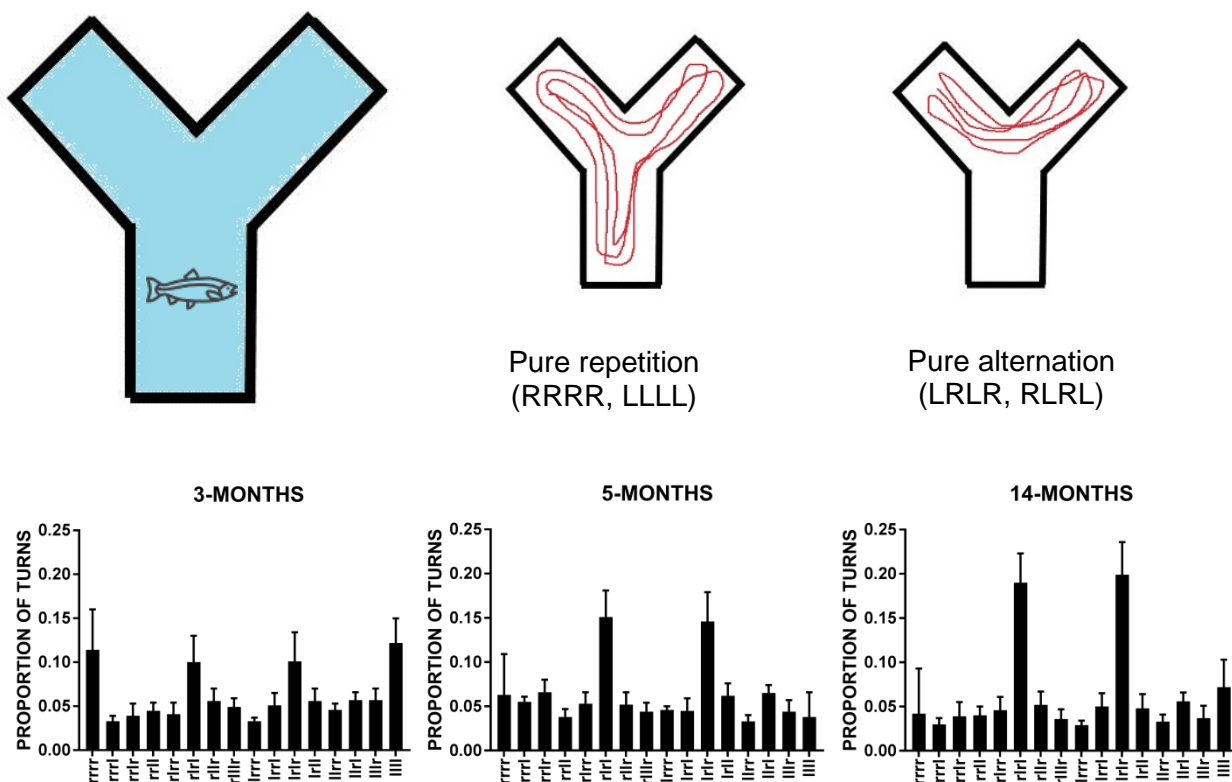


**Figure 3.** A brief summary of ARB-like behavioral phenotype of the dopamine transporter (DAT) knockout zebrafish, including swimming predominantly at the bottom of the tank with characteristic thigmotaxis (moving along the walls of the tank), according to [73]





**Figure 4. The use of Y-maze to assess behaviorally flexible patterns of swimming (alternation and repetition) in zebrafish.** This test also reveals certain developmental changes in zebrafish swimming, ranging from pure alternation (LRLR, RLRL) to pure repetition of previous response (RRRR, LLLL, Parker laboratory, unpublished data). Overall, young fish show high levels of pure repetition and pure alternation, whereas older zebrafish show lower levels of repetition relative to alternation.



**Table 1. Selected animal models that parallel clinical symptoms of ARBs**

<b>Rodents</b>		<b>Zebrafish</b>	
<b>ARB</b>	<b>Ref-er-ences</b>	<b>ARB</b>	<b>Refer-ences</b>
<b><i>Pharmacological</i></b>			
Rat ASD model (prenatal valproate) evokes repetitive locomotion (back-and-forth moving)	[188]	Acute ketamine* induces increased circling behavior, Fig. 1	[147]
Amphetamine exposure in C58/J mice evokes repeated cage-lid back-flipping	[65]	Acute dizocilpine (MK-801)* increased circling behavior	[98]
Rat 6-OHDA** brain lesions (a Parkinson's model) evoke compulsive lever-pressing under chronic pramipexole***	[189]	Phencyclidine (PCP)* increased circling behavior	[190]
Rat prenatal exposure to lipopolysaccharide (LPS) increases repetitive self-grooming	[191]	The mixture of crude oil with lead increases cycle swimming in 15 larvae	[192]
Deer mice exhibit increased repetitive jumping following apomorphine***	[193]	Stereotypic corner-to-corner swimming at the bottom of the tank under ibogaine	[151]
<b><i>Genetic</i></b>			
<i>Shank1</i> knockout mice display increased self-grooming	[194]	Adult <i>mecp2</i> mutants exhibit overt thigmotaxis	[135]
Histidine decarboxylase knockout mice display increased self-grooming	[195]	Shank3b knockouts display figure "8" swimming, circling, cornering and walling (Fig. 2)	[105]
Mice with deleted <i>Netrin-G ligand 2 (NGL-2)</i> gene display increased self-grooming	[196]	<i>Syngap1a</i> knockdowns escape responses with prolonged repetitive C-bends	[111]
<i>Hoxb8</i> KO mice (an OCD model) display pathological self-grooming	[139]	<i>CNTNAP2</i> mutant larvae display burst-like and circling movements	[118]
<i>MeCP2</i> deficient mice display stereotyped fore-paw movements and compulsive self-grooming	[62]	Adult DAT knockouts exhibit increased thigmotaxis	[73]

\*An antagonist of glutamate NMDA receptors

\*\*6-hydroxydopamine, a neurotoxic antidopaminergic agent

\*\*\*An agonist of several dopamine receptors

**Table 2. Comparative genetic homology between human, rodent and zebrafish ARB-related genes, based on the Basic Local Alignment Search Tool (BLAST, [www.blast.ncbi.nlm.nih.gov](http://www.blast.ncbi.nlm.nih.gov)) database**

Gene	Comparison: query coverage/homology		
	Human vs Mouse	Human vs Zebrafish	Mouse vs Zebrafish
<i>SLC6A3</i>	48%/87%	42%/79%	48%/78%
<i>FMR1</i>	96%/89%	30%/75%	30%/75%
<i>MeCP2</i>	82%/82%	5%/70%	5%/68%
<i>CNTNAP2</i>	64%/81%	38%/68%	54%/68%
<i>SHANK1</i>	73%/85%	28%/70%	35%/72%
<i>SHANK2</i> (zebrafish – shank2b gene)	48%/86%	35%/70%	27%/76%
<i>SHANK3</i> *	99%/85%	34-41%/71%	35-41%/73%
<i>TSC1</i> (zebrafish – tsc1a, tsc1b)	64%/81%	7-17%/69-72%	8-23%/69-73%
<i>GABRB3</i> **	97%/81%	20%/79%	21%/80%
<i>DRD3</i>	86%/88%	44%/74%	51%/75%
<i>5-HT2C</i>	96%/83%	15%/70%	16%/69%
<i>SYNGAP1</i> ***	67%/ 92%	43%/73%****	No similarity
<i>HOXB8</i> (zebrafish: hoxb8a, hoxb8b)	99%/90%	37%/71-75%	25%/70-75%
<i>SLC1A1</i>	82%/81%	37%/70%	38%/72%

\* Zebrafish shank3a – PREDICTED transcript variant X18, shank3b – PREDICTED transcript variant X4

\*\* Human/mouse – transcript variant 1, zebrafish – PREDICTED transcript variant X1

\*\*\* Human – transcript variant 1, zebrafish: syngap1a – PREDICTED transcript variant X2, syngap1b

\*\*\*\* No similarity with syngap1b

**Table 3. Selected open questions in the field of zebrafish modeling of ARBs**

<b>Questions</b>
<b><i>Conceptual</i></b>
• What is entire spectrum of neurobehavioral ARB-like phenotypes in zebrafish?
• Which brain structures are implicated in zebrafish ARBs?
• Are there links between zebrafish ARB and social behavioral deficit?
• How is normal motor sequence selection modified (varied) based on prior motor sequence performance in zebrafish?
• How do alterations in mechanisms of motor sequence selection lead to repeated invariant behavioral sequences (ARBs)?
• Are ARBs a neurological phenomenon, or the result of alterations in interaction with the environment?
• Can ARBs spontaneously emerge in zebrafish (i.e., as a result of chronic isolation/under-stimulation)?
• Can a zebrafish be 'bored'?
• Can ARBs in zebrafish be qualitatively differentiated from 'normal' behavior, and modeled, mathematically?
• Do larval zebrafish display overt ARBs? Are they similar to those seen in adult fish?
• Is there a pathological link between ARBs, self-aggression, and aggression? Can this be modeled in zebrafish?
• Do ARBs display aging-related trajectories in zebrafish?
• How does stress affect zebrafish ARBs?
• Do zebrafish use ARBs in social or sexual contexts?
• Do zebrafish ARBs display circadian rhythms?
<b><i>Translational</i></b>
• What are the mechanisms of normal motor sequence selection and invigoration in zebrafish?
• What is the homology in mechanics and/or circuitry of motor sequence selection between zebrafish and mammals?
• If zebrafish ARB can be quantified into subunits or predictable patterns? Can they help test drugs or mimic human ARB?
• Is there a substantial homology between human and zebrafish ARB-related neurocircuitry?
• Do stress-evoked alterations in zebrafish ARBs resemble those evoked in human ARBs?
• Do zebrafish ARBs respond to various drugs similarly to human ARBs?
• How does impulsivity contribute to zebrafish ARB expression?
• How does zebrafish individuality ('personality') affect ARB-like phenotypic variance in zebrafish populations?
• Are there robust sex differences in some zebrafish ARBs similar to those in humans with certain CNS disorders?
• Are there common/shared epigenetic mechanisms of ARB regulation in mammals and zebrafish?
• Do aging-related ARBs in zebrafish resemble those observed in aging humans?
<b><i>Methodological</i></b>
• Can zebrafish ARBs be fractionated into quantifiable sub-units, in terms of predictable patterns of expression?
• What is the potential for the development of a zebrafish ARB ethogram?
• Can a zebrafish be trained to produce ARB?
• Can a zebrafish that shows ARB be trained to stop producing these patterns?
• What are neuroendocrine biomarkers of zebrafish ARBs?
• Are there well-established strain differences in zebrafish ARBs?
• Do zebrafish ARBs differ between the laboratories and/or between different vendors?
• Do wild-caught zebrafish display ARBs? Do ARBs increase during domestication?
• To what extent ARBs may concomitantly affect other neurobehavioral responses
• Are there reliable tools for automated quantification of ARBs in zebrafish?
• Are tools available for high-throughput multi-animal detection of ARBs in zebrafish groups?
<b><i>Others</i></b>
• Do zebrafish ARBs represent an animal welfare problem?
• Can improved welfare (e.g., by using environmental enrichment) reduce zebrafish ARBs?

## References

1. Association, A.P., *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. 2013. p. 947.
2. Langen, M., et al., *The neurobiology of repetitive behavior: ... and men*. Neuroscience and Biobehavioral Reviews, 2011. **35**(3): p. 356-365.
3. Lewis, M. and S.J. Kim, *The pathophysiology of restricted repetitive behavior*. Journal of Neurodevelopmental Disorders, 2009. **1**(2): p. 114-132.
4. Garner, J.P., et al., *Reverse-translational biomarker validation of Abnormal Repetitive Behaviors in mice: an illustration of the 4P's modeling approach*. Behav Brain Res, 2011. **219**(2): p. 189-96.
5. Bodfish, J.W., *Stereotypy, Self-Injury, and Related Abnormal Repetitive Behaviors*, in *Handbook of Intellectual and Developmental Disabilities*, J.W. Jacobson, J.A. Mulick, and J. Rojahn, Editors. 2007, Springer US: Boston, MA. p. 481-505.
6. Lewis, M.H. and J.W. Bodfish, *Repetitive behavior disorders in autism*. Mental Retardation and Developmental Disabilities Research Reviews, 1998. **4**(2): p. 80-89.
7. Levy, S.E., D.S. Mandell, and R.T. Schultz, *Autism*. Lancet, 2009. **374**(9701): p. 1627-1638.
8. Moss, J., et al., *The Prevalence and Phenomenology of Repetitive Behavior in Genetic Syndromes*. Journal of Autism and Developmental Disorders, 2009. **39**(4): p. 572-588.
9. Huisman, S., et al., *Self-injurious behavior*. Neuroscience and Biobehavioral Reviews, 2018. **84**: p. 483-491.
10. Roberts, S., K. O'Connor, and C. Belanger, *Emotion regulation and other psychological models for body-focused repetitive behaviors*. Clinical Psychology Review, 2013. **33**(6): p. 745-762.
11. Bennett, A.J. and D.L. Ringach, *Animal Research in Neuroscience: A Duty to Engage*. Neuron, 2016. **92**(3): p. 653-657.
12. McGonigle, P., *Animal models of CNS disorders*. Biochemical Pharmacology, 2014. **87**(1): p. 140-149.
13. Strickland, J.C. and M.A. Smith, *Animal models of resistance exercise and their application to neuroscience research*. J Neurosci Methods, 2016. **273**: p. 191-200.
14. Fineberg, N.A., et al., *Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review*. Neuropsychopharmacology, 2010. **35**(3): p. 591-604.
15. Mahone, E.M., et al., *Repetitive arm and hand movements (complex motor stereotypies) in children*. J Pediatr, 2004. **145**(3): p. 391-5.
16. Robbins, T.W. and B.J. Sahakian, *Translational Neuropsychopharmacology*. Vol. 28. 2016: Springer.
17. Garner, J.P., *Stereotypies and other abnormal repetitive behaviors: Potential impact on validity, reliability, and replicability of scientific outcomes*. Ilar Journal, 2005. **46**(2): p. 106-117.
18. Bechard, A.R. and M.H. Lewis, *Transgenerational effects of environmental enrichment on repetitive motor behavior development*. Behavioural Brain Research, 2016. **307**: p. 145-149.
19. Moy, S.S., et al., *Development of a mouse test for repetitive, restricted behaviors: Relevance to autism*. Behavioural Brain Research, 2008. **188**(1): p. 178-194.
20. Phillips, D., et al., *Cage-induced stereotypic behaviour in laboratory mice covaries with nucleus accumbens FosB/Delta FosB expression*. Behavioural Brain Research, 2016. **301**: p. 238-242.
21. Grosseckathofer, U., et al., *Automated Detection of Stereotypical Motor Movements in Autism Spectrum Disorder Using Recurrence Quantification Analysis*. Front Neuroinform, 2017. **11**: p. 9.
22. Zeef, D.H., et al., *An experimental model for Huntington's chorea?* Behav Brain Res, 2014. **262**: p. 31-4.
23. Stegemoller, E., et al., *Laterality of repetitive finger movement performance and clinical features of Parkinson's disease*. Hum Mov Sci, 2016. **49**: p. 116-23.
24. Kalia, L.V. and A.E. Lang, *Parkinson's disease*. The Lancet, 2015. **386**(9996): p. 896-912.
25. Tarquinio, D.C. and A.K. Percy, *Rett Syndrome*, in *Neuronal and Synaptic Dysfunction in*

- Autism Spectrum Disorder and Intellectual Disability*. 2016. p. 301-323.
26. Loftin, R.L., S.L. Odom, and J.F. Lantz, *Social interaction and repetitive motor behaviors*. *J Autism Dev Disord*, 2008. **38**(6): p. 1124-35.
  27. de Esch, C.E., S. Zeidler, and R. Willemsen, *Translational endpoints in fragile X syndrome*. *Neurosci Biobehav Rev*, 2014. **46 Pt 2**: p. 256-69.
  28. Hartmann, A. and B. Millet, *Repetitive movements and behaviors in neurological and psychiatric practice: Distinctions and similarities between Tourette disorder and obsessive-compulsive disorder*. *Rev Neurol (Paris)*, 2018. **174**(4): p. 199-202.
  29. Cavanna, A.E., *Gilles de la Tourette syndrome as a paradigmatic neuropsychiatric disorder*. *CNS Spectr*, 2018: p. 1-6.
  30. Eilam, D., *From an animal model to human patients: An example of a translational study on obsessive compulsive disorder (OCD)*. *Neurosci Biobehav Rev*, 2017. **76**(Pt A): p. 67-76.
  31. Supekar, K. and V. Menon, *Sex differences in structural organization of motor systems and their dissociable links with repetitive/restricted behaviors in children with autism*. *Mol Autism*, 2015. **6**: p. 50.
  32. Wolff, N., et al., *When repetitive mental sets increase cognitive flexibility in adolescent obsessive-compulsive disorder*. *J Child Psychol Psychiatry*, 2018.
  33. Anagnostou, E. and M.J. Taylor, *Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here*. *Molecular Autism*, 2011. **2**.
  34. Brennan, B.P., et al., *A Critical Review of Magnetic Resonance Spectroscopy Studies of Obsessive-Compulsive Disorder*. *Biological Psychiatry*, 2013. **73**(1): p. 24-31.
  35. Bruin, W., D. Denys, and G. van Wingen, *Diagnostic neuroimaging markers of obsessive-compulsive disorder: Initial evidence from structural and functional MRI studies*. *Prog Neuropsychopharmacol Biol Psychiatry*, 2018.
  36. Estes, A., et al., *Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder*. *Autism Res*, 2011. **4**(3): p. 212-20.
  37. Hollander, E., et al., *Striatal volume on magnetic resonance imaging and repetitive behaviors in autism*. *Biol Psychiatry*, 2005. **58**(3): p. 226-32.
  38. Saxena, S. and S.L. Rauch, *Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder*. *Psychiatric Clinics of North America*, 2000. **23**(3): p. 563-+.
  39. Wilkes, B.J. and M.H. Lewis, *The neural circuitry of restricted repetitive behavior: Magnetic resonance imaging in neurodevelopmental disorders and animal models*. *Neurosci Biobehav Rev*, 2018. **92**: p. 152-171.
  40. Muehlmann, A.M., et al., *Further characterization of repetitive behavior in C58 mice: Developmental trajectory and effects of environmental enrichment*. *Behavioural Brain Research*, 2012. **235**(2): p. 143-149.
  41. Pearson, B.L., et al., *Motor and cognitive stereotypies in the BTBR T+tf/J mouse model of autism*. *Genes Brain Behav*, 2011. **10**(2): p. 228-35.
  42. Tanimura, Y., S. Vaziri, and M.H. Lewis, *Indirect basal ganglia pathway mediation of repetitive behavior: attenuation by adenosine receptor agonists*. *Behav Brain Res*, 2010. **210**(1): p. 116-22.
  43. Wolmarans, D., et al., *Peromyscus maniculatus bairdii as a naturalistic mammalian model of obsessive-compulsive disorder: current status and future challenges*. *Metabolic Brain Disease*, 2018. **33**(2): p. 443-455.
  44. Katherine, M., *Stereotypic Movement Disorders*. *Semin Pediatr Neurol*, 2018. **25**: p. 19-24.
  45. Korff, S. and B.H. Harvey, *Animal models of obsessive-compulsive disorder: Rationale to understanding psychobiology and pharmacology*. *Psychiatric Clinics of North America*, 2006. **29**(2): p. 371-+.
  46. Matsumoto, R., et al., *Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: A [C-11]DASB PET study*. *Neuroimage*, 2010. **49**(1): p. 121-126.
  47. Wolmarans, D., et al., *Reappraisal of spontaneous stereotypy in the deer mouse as an animal model of obsessive-compulsive disorder (OCD): Response to escitalopram treatment and basal serotonin transporter (SERT) density*. *Behavioural Brain Research*, 2013. **256**: p. 545-553.

48. Korff, S., D.J. Stein, and B.H. Harvey, *Stereotypic behaviour in the deer mouse: Pharmacological validation and relevance for obsessive compulsive disorder*. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2008. **32**(2): p. 348-355.
49. Tochen, L. and H.S. Singer, *Tourette Syndrome and Tic Disorders*, in *Handbook of Basal Ganglia Structure and Function, Second Edition*. 2017. p. 951-970.
50. Kim, H., C.S. Lim, and B.K. Kaang, *Neuronal mechanisms and circuits underlying repetitive behaviors in mouse models of autism spectrum disorder*. Behavioral and Brain Functions, 2016. **12**.
51. Martins, G.J., *Neurobiology of Autism Spectrum Disorders*, in *Autism Spectrum Disorders in Adults*, B. Barahona Corrêa and R.-J. van der Gaag, Editors. 2017, Springer International Publishing: Cham. p. 29-93.
52. Mossa, A., et al., *SHANK genes in autism: Defining therapeutic targets*. Prog Neuropsychopharmacol Biol Psychiatry, 2018. **84**(Pt B): p. 416-423.
53. Langen, M., et al., *The neurobiology of repetitive behavior: of mice*. Neurosci Biobehav Rev, 2011. **35**(3): p. 345-55.
54. Staal, W.G., *Autism, DRD3 and repetitive and stereotyped behavior; an overview of the current knowledge*. European Neuropsychopharmacology, 2015. **25**(9): p. 1421-1426.
55. Rothwell, P.E., et al., *Autism-Associated Neuroligin-3 Mutations Commonly Impair Striatal Circuits to Boost Repetitive Behaviors*. Cell, 2014. **158**(1): p. 198-212.
56. Heise, C., et al., *Heterogeneity of Cell Surface Glutamate and GABA Receptor Expression in Shank and CNTN4 Autism Mouse Models*. Frontiers in Molecular Neuroscience, 2018. **11**.
57. Hogart, A. and J.M. LaSalle, *Epigenetic Dysregulation of 15q11-13 GABAA Receptor Genes in Autism*, in *The Neurochemical Basis of Autism: From Molecules to Minicolumns*, G.J. Blatt, Editor. 2010, Springer US: Boston, MA. p. 113-127.
58. Lewis, M.H., et al., *Animal models of restricted repetitive behavior in autism*. Behav Brain Res, 2007. **176**(1): p. 66-74.
59. Wu, Y., et al., *Characterization of Rett Syndrome-like phenotypes in Mecp2-knockout rats*. J Neurodev Disord, 2016. **8**: p. 23.
60. DeLorey, T.M., et al., *Mice lacking the beta3 subunit of the GABAA receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome*. J Neurosci, 1998. **18**(20): p. 8505-14.
61. DeLorey, T.M., et al., *Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: a potential model of autism spectrum disorder*. Behav Brain Res, 2008. **187**(2): p. 207-20.
62. Chao, H.T., et al., *Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes*. Nature, 2010. **468**(7321): p. 263-9.
63. Modi, M.E., et al., *Hyperactivity and Hypermotivation Associated With Increased Striatal mGluR1 Signaling in a Shank2 Rat Model of Autism*. Front Mol Neurosci, 2018. **11**: p. 107.
64. Le, H., et al., *Disruption of Ninjurin1 Leads to Repetitive and Anxiety-Like Behaviors in Mice*. Molecular Neurobiology, 2017. **54**(9): p. 7353-7368.
65. Moy, S.S., et al., *Repetitive behavior profile and supersensitivity to amphetamine in the C58/J mouse model of autism*. Behav Brain Res, 2014. **259**: p. 200-14.
66. Chiocchetti, A.G., H.S. Bour, and C.M. Freitag, *Glutamatergic candidate genes in autism spectrum disorder: an overview*. J Neural Transm (Vienna), 2014. **121**(9): p. 1081-106.
67. Larsen, E., et al., *A systematic variant annotation approach for ranking genes associated with autism spectrum disorders*. Mol Autism, 2016. **7**: p. 44.
68. Liu, L., et al., *DAWN: a framework to identify autism genes and subnetworks using gene expression and genetics*. Molecular Autism, 2014. **5**.
69. Cinque, S., et al., *Behavioral Phenotyping of Dopamine Transporter Knockout Rats: Compulsive Traits, Motor Stereotypies, and Anhedonia*. Front Psychiatry, 2018. **9**: p. 43.
70. Fox, M.A., et al., *An evaluation of the serotonin system and perseverative, compulsive, stereotypical, and hyperactive behaviors in dopamine transporter (DAT) knockout mice*. Psychopharmacology (Berl), 2013. **227**(4): p. 685-95.
71. Rodriguiz, R.M., et al., *Aberrant responses in social interaction of dopamine transporter*

- knockout mice*. Behavioural Brain Research, 2004. **148**(1-2): p. 185-198.
72. Yamashita, M., et al., *Impaired cliff avoidance reaction in dopamine transporter knockout mice*. Psychopharmacology (Berl), 2013. **227**(4): p. 741-9.
  73. Kacprzak, V., et al., *Dopaminergic control of anxiety in young and aged zebrafish*. Pharmacol Biochem Behav, 2017. **157**: p. 1-8.
  74. Howe, K., et al., *The zebrafish reference genome sequence and its relationship to the human genome*. Nature, 2013. **496**(7446): p. 498-503.
  75. Sager, J.J., Q. Bai, and E.A. Burton, *Transgenic zebrafish models of neurodegenerative diseases*. Brain Structure and Function, 2010. **214**(2-3): p. 285-302.
  76. Panula, P., et al., *The comparative neuroanatomy and neurochemistry of zebrafish CNS systems of relevance to human neuropsychiatric diseases*. Neurobiol Dis, 2010. **40**(1): p. 46-57.
  77. Lillesaar, C., *The serotonergic system in fish*. J Chem Neuroanat, 2011. **41**(4): p. 294-308.
  78. Rico, E.P., et al., *Zebrafish neurotransmitter systems as potential pharmacological and toxicological targets*. Neurotoxicol Teratol, 2011. **33**(6): p. 608-17.
  79. Yamamoto, K. and P. Vernier, *The evolution of dopamine systems in chordates*. Front Neuroanat, 2011. **5**: p. 21.
  80. Eilam, D. and H. Szechtman, *Psychostimulant-induced behavior as an animal model of obsessive-compulsive disorder: An ethological approach to the form of compulsive rituals*. Cns Spectrums, 2005. **10**(3): p. 191-202.
  81. Garner, J.P. and G.J. Mason, *Evidence for a relationship between cage stereotypies and behavioural disinhibition in laboratory rodents*. Behavioural Brain Research, 2002. **136**(1): p. 83-92.
  82. Joel, D., *The signal attenuation rat model of obsessive-compulsive disorder: a review*. Psychopharmacology, 2006. **186**(4): p. 487-503.
  83. Patterson, P.H., *Modeling Autistic Features in Animals*. Pediatric Research, 2011. **69**(5): p. 34r-40r.
  84. Sesia, T., B. Bizup, and A.A. Grace, *Evaluation of animal models of obsessive-compulsive disorder: correlation with phasic dopamine neuron activity*. International Journal of Neuropsychopharmacology, 2013. **16**(6): p. 1295-1307.
  85. Tanimura, Y., M.C. Yang, and M.H. Lewis, *Procedural learning and cognitive flexibility in a mouse model of restricted, repetitive behaviour*. Behavioural Brain Research, 2008. **189**(2): p. 250-256.
  86. Taylor, J.L., et al., *Dopamine receptor modulation of repetitive grooming actions in the rat: Potential relevance for Tourette syndrome*. Brain Research, 2010. **1322**: p. 92-101.
  87. Joel, D., *Current animal models of obsessive compulsive disorder: a critical review*. Prog Neuropsychopharmacol Biol Psychiatry, 2006. **30**(3): p. 374-88.
  88. Lieschke, G.J. and P.D. Currie, *Animal models of human disease: zebrafish swim into view*. Nat Rev Genet, 2007. **8**(5): p. 353-67.
  89. Kalueff, A.V., D.J. Echevarria, and A.M. Stewart, *Gaining translational momentum: More zebrafish models for neuroscience research Preface*. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2014. **55**: p. 1-6.
  90. Burne, T., et al., *Big ideas for small brains: what can psychiatry learn from worms, flies, bees and fish?* Molecular Psychiatry, 2011. **16**(1): p. 7-16.
  91. Stewart, A.M., et al., *Zebrafish models for translational neuroscience research: from tank to bedside*. Trends in Neurosciences, 2014. **37**(5): p. 264-278.
  92. Kalueff, A.V., A.M. Stewart, and R. Gerlai, *Zebrafish as an emerging model for studying complex brain disorders*. Trends in Pharmacological Sciences, 2014. **35**(2): p. 63-75.
  93. Egan, R.J., et al., *Understanding behavioral and physiological phenotypes of stress and anxiety in zebrafish*. Behav Brain Res, 2009. **205**(1): p. 38-44.
  94. Rosemberg, D.B., et al., *Differences in spatio-temporal behavior of zebrafish in the open tank paradigm after a short-period confinement into dark and bright environments*. PLoS One, 2011. **6**(5): p. e19397.
  95. Buske, C., *Zebrafish Social Behavior Testing in Developmental Brain Disorders*, in *Organism Models of Autism Spectrum Disorders*, P.L. Roubertoux, Editor. 2015, Springer New York:



- New York, NY. p. 303-316.
96. Parker, M., *Modeling OCD Endophenotypes in Zebrafish*, in *The rights and wrongs of zebrafish: Behavioral phenotyping of zebrafish*, A.V. Kalueff, Editor. 2017, Springer International Publishing: Cham. p. 131-143.
  97. Kalueff, A.V., *Illustrated Zebrafish Neurobehavioral Glossary*, in *The rights and wrongs of zebrafish: Behavioral phenotyping of zebrafish*, A.V. Kalueff, Editor. 2017, Springer International Publishing: Cham. p. 291-317.
  98. Swain, H.A., C. Sigstad, and F.M. Scalzo, *Effects of dizocilpine (MK-801) on circling behavior, swimming activity, and place preference in zebrafish (Danio rerio)*. *Neurotoxicology and Teratology*, 2004. **26**(6): p. 725-729.
  99. Schnorr, S.J., et al., *Measuring thigmotaxis in larval zebrafish*. *Behavioural Brain Research*, 2012. **228**(2): p. 367-374.
  100. Fero, K., T. Yokogawa, and H.A. Burgess, *The Behavioral Repertoire of Larval Zebrafish*, in *Zebrafish Models in Neurobehavioral Research*, A.V. Kalueff and J.M. Cachat, Editors. 2011, Humana Press: Totowa, NJ. p. 249-291.
  101. Wolf, S., et al., *Sensorimotor computation underlying phototaxis in zebrafish*. *Nat Commun*, 2017. **8**(1): p. 651.
  102. Dunn, T.W., et al., *Brain-wide mapping of neural activity controlling zebrafish exploratory locomotion*. *Elife*, 2016. **5**: p. e12741.
  103. Hodgson, S.R., et al., *Morphine-induced stereotyped thigmotaxis could appear as enhanced fear and anxiety in some behavioural tests*. *Journal of Psychopharmacology*, 2010. **24**(6): p. 875-880.
  104. Horstick, E.J., et al., *Search strategy is regulated by somatostatin signaling and deep brain photoreceptors in zebrafish*. *Bmc Biology*, 2017. **15**.
  105. Liu, C.X., et al., *CRISPR/Cas9-induced shank3b mutant zebrafish display autism-like behaviors*. *Mol Autism*, 2018. **9**: p. 23.
  106. Copping, N.A., et al., *Touchscreen learning deficits and normal social approach behavior in the Shank3B model of Phelan-McDermid Syndrome and autism*. *Neuroscience*, 2017. **345**: p. 155-165.
  107. Dhamne, S.C., et al., *Replicable in vivo physiological and behavioral phenotypes of the Shank3B null mutant mouse model of autism*. *Mol Autism*, 2017. **8**: p. 26.
  108. Duffney, L.J., et al., *Autism-like Deficits in Shank3-Deficient Mice Are Rescued by Targeting Actin Regulators*. *Cell Rep*, 2015. **11**(9): p. 1400-1413.
  109. Clement, J.P., et al., *Pathogenic SYNGAP1 Mutations Impair Cognitive Development by Disrupting Maturation of Dendritic Spine Synapses*. *Cell*, 2012. **151**(4): p. 709-723.
  110. Carvill, G.L., et al., *Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1*. *Nature Genetics*, 2013. **45**(7): p. 825-U158.
  111. Kozol, R.A., et al., *Two knockdown models of the autism genes SYNGAP1 and SHANK3 in zebrafish produce similar behavioral phenotypes associated with embryonic disruptions of brain morphogenesis*. *Human Molecular Genetics*, 2015. **24**(14): p. 4006-4023.
  112. Alarcon, M., et al., *Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene*. *American Journal of Human Genetics*, 2008. **82**(1): p. 150-159.
  113. Penagarikano, O., et al., *Absence of CNTNAP2 Leads to Epilepsy, Neuronal Migration Abnormalities, and Core Autism-Related Deficits*. *Cell*, 2011. **147**(1): p. 235-246.
  114. Coghlan, S., et al., *GABA system dysfunction in autism and related disorders: From synapse to symptoms*. *Neuroscience and Biobehavioral Reviews*, 2012. **36**(9): p. 2044-2055.
  115. Petralia, R.S., et al., *Ontogeny of postsynaptic density proteins at glutamatergic synapses*. *Molecular and Cellular Neuroscience*, 2005. **29**(3): p. 436-452.
  116. Jurgensen, S. and P.E. Castillo, *Selective Dysregulation of Hippocampal Inhibition in the Mouse Lacking Autism Candidate Gene CNTNAP2*. *Journal of Neuroscience*, 2015. **35**(43): p. 14681-14687.
  117. Selimbeyoglu, A., et al., *Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice*. *Science Translational Medicine*, 2017. **9**(401).
  118. Hoffman, E.J., et al., *Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the*

- Autism Risk Gene, CNTNAP2*. Neuron, 2016. **89**(4): p. 725-733.
119. Garber, K.B., J. Visootsak, and S.T. Warren, *Fragile X syndrome*. European Journal of Human Genetics, 2008. **16**(6): p. 666-672.
  120. Hagerman, R.J., et al., *Advances in the Treatment of Fragile X Syndrome*. Pediatrics, 2009. **123**(1): p. 378-390.
  121. Neri, G., *The Clinical Phenotype of the Fragile X Syndrome and Related Disorders*, in *Fragile X Syndrome: From Genetics to Targeted Treatment*. 2017. p. 1-16.
  122. Davis, J.K. and K. Broadie, *Multifarious Functions of the Fragile X Mental Retardation Protein*. Trends in Genetics, 2017. **33**(10): p. 703-714.
  123. Nelson, D.L., M.R. Santoro, and S.T. Warren, *Fragile X Syndrome Genetics*, in *Fragile X Syndrome: From Genetics to Targeted Treatment*. 2017. p. 19-39.
  124. Melancia, F. and V. Trezza, *Modelling fragile X syndrome in the laboratory setting: A behavioral perspective*. Behavioural Brain Research, 2018. **350**: p. 149-163.
  125. Lai, J.K.Y., et al., *Regional Brain Volumes Changes in Adult Male Fmr1-Ko Mouse on the Fvb Strain*. Neuroscience, 2016. **318**: p. 12-21.
  126. den Broeder, M.J., et al., *Generation and Characterization of Fmr1 Knockout Zebrafish*. Plos One, 2009. **4**(11).
  127. Kim, L., et al., *Anxiety, hyperactivity and stereotypy in a zebrafish model of fragile X syndrome and autism spectrum disorder*. Prog Neuropsychopharmacol Biol Psychiatry, 2014. **55**: p. 40-9.
  128. Ng, M.C., Y.L. Yang, and K.T. Lu, *Behavioral and Synaptic Circuit Features in a Zebrafish Model of Fragile X Syndrome*. Plos One, 2013. **8**(3).
  129. Shamay-Ramot, A., et al., *Fmrp Interacts with Adar and Regulates RNA Editing, Synaptic Density and Locomotor Activity in Zebrafish*. Plos Genetics, 2015. **11**(12).
  130. Chahrour, M. and H.Y. Zoghbi, *The story of Rett syndrome: From clinic to neurobiology*. Neuron, 2007. **56**(3): p. 422-437.
  131. Amir, R.E., et al., *Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2*. Nature Genetics, 1999. **23**(2): p. 185-188.
  132. Guy, J., et al., *A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome*. Nature Genetics, 2001. **27**(3): p. 322-326.
  133. Allemang-Grand, R., et al., *Neuroanatomy in mouse models of Rett syndrome is related to the severity of Mecp2 mutation and behavioral phenotypes*. Molecular Autism, 2017. **8**.
  134. Jorge-Torres, O.C., et al., *Inhibition of Gsk3b Reduces Nfkb1 Signaling and Rescues Synaptic Activity to Improve the Rett Syndrome Phenotype in Mecp2-Knockout Mice*. Cell Reports, 2018. **23**(6): p. 1665-1677.
  135. Pietri, T., et al., *The first mecp2-null zebrafish model shows altered motor behaviors*. Front Neural Circuits, 2013. **7**: p. 118.
  136. Gao, H., et al., *Mecp2 regulates neural cell differentiation by suppressing the Id1 to Her2 axis in zebrafish*. Journal of Cell Science, 2015. **128**(12): p. 2340-2350.
  137. Stein, D.J., *Neurobiology of the obsessive-compulsive spectrum disorders*. Biological psychiatry, 2000. **47**(4): p. 296-304.
  138. Berridge, K.C., et al., *Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's*. BMC biology, 2005. **3**(1): p. 4.
  139. Ahmari, S.E., *Using Mice to Model Obsessive Compulsive Disorder: From Genes to Circuits*. Neuroscience, 2016. **321**: p. 121-137.
  140. Hoffman, K.L. and R.I.R. Morales, *Toward an understanding of the neurobiology of "just right" perceptions: Nest building in the female rabbit as a possible model for compulsive behavior and the perception of task completion*. Behavioural Brain Research, 2009. **204**(1): p. 182-191.
  141. Szechtman, H., W. Sulis, and D. Eilam, *Quinpirole induces compulsive checking behavior in rats: A potential animal model of obsessive-compulsive disorder (OCD)*. Behavioral Neuroscience, 1998. **112**(6): p. 1475-1485.
  142. D'Amico, D., X. Estivill, and J. Terriente, *Switching to zebrafish neurobehavioral models: The obsessive-compulsive disorder paradigm*. Eur J Pharmacol, 2015. **759**: p. 142-50.

143. Fontana, B.D., et al., *The developing utility of zebrafish models of neurological and neuropsychiatric disorders: A critical review*. *Exp Neurol*, 2018. **299**(Pt A): p. 157-171.
144. Parker, M.O., *Modeling OCD endophenotypes in zebrafish*, in *The rights and wrongs of zebrafish: behavioral phenotyping of zebrafish*, A.V. Kalueff, Editor. 2016, Springer.
145. Kily, L.J., et al., *Gene expression changes in a zebrafish model of drug dependency suggest conservation of neuro-adaptation pathways*. *J Exp Biol*, 2008. **211**(Pt 10): p. 1623-34.
146. Palmer, T., et al., *Action sequencing in the spontaneous swimming behavior of zebrafish larvae - implications for drug development*. *Sci Rep*, 2017. **7**(1): p. 3191.
147. Riehl, R., et al., *Behavioral and physiological effects of acute ketamine exposure in adult zebrafish*. *Neurotoxicol Teratol*, 2011. **33**(6): p. 658-67.
148. Marinova, Z., D.M. Chuang, and N. Fineberg, *Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder*. *Current Neuropharmacology*, 2017. **15**(7): p. 977-995.
149. Rodriguez, C.I., et al., *Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder: Proof-of-Concept*. *Neuropsychopharmacology*, 2013. **38**(12): p. 2475-2483.
150. Szumlinski, K.K., et al., *Interactions between iboga agents and methamphetamine sensitization: studies of locomotion and stereotypy in rats*. *Psychopharmacology (Berl)*, 2000. **151**(2-3): p. 234-41.
151. Cachat, J., et al., *Unique and potent effects of acute ibogaine on zebrafish: the developing utility of novel aquatic models for hallucinogenic drug research*. *Behav Brain Res*, 2013. **236**(1): p. 258-69.
152. Shanahan, N.A., et al., *Essential role for orbitofrontal serotonin 1B receptors in obsessive-compulsive disorder-like behavior and serotonin reuptake inhibitor response in mice*. *Biol Psychiatry*, 2011. **70**(11): p. 1039-48.
153. Ho, E.V., et al., *Clinically effective OCD treatment prevents 5-HT1B receptor-induced repetitive behavior and striatal activation*. *Psychopharmacology (Berl)*, 2016. **233**(1): p. 57-70.
154. Shanahan, N.A., et al., *Chronic reductions in serotonin transporter function prevent 5-HT1B-induced behavioral effects in mice*. *Biol Psychiatry*, 2009. **65**(5): p. 401-8.
155. Ulloa, R.E., H. Nicolini, and A. Fernandez-Guasti, *Sex differences on spontaneous alternation in prepubertal rats: implications for an animal model of obsessive-compulsive disorder*. *Prog Neuropsychopharmacol Biol Psychiatry*, 2004. **28**(4): p. 687-92.
156. Dickinson, A., *Actions and Habits - the Development of Behavioral Autonomy*. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*, 1985. **308**(1135): p. 67-78.
157. Tsaltas, E., et al., *Reinforced spatial alternation as an animal model of obsessive-compulsive disorder (OCD): investigation of 5-HT2C and 5-HT1D receptor involvement in OCD pathophysiology*. *Biol Psychiatry*, 2005. **57**(10): p. 1176-85.
158. Meshalkina, D.A., et al., *Adult zebrafish in CNS disease modeling: a tank that's half-full, not half-empty, and still filling*. *Lab Anim (NY)*, 2017. **46**(10): p. 378-387.
159. Gillan, C.M., et al., *The role of habit in compulsivity*. *Eur Neuropsychopharmacol*, 2016. **26**(5): p. 828-40.
160. Gillan, C.M., et al., *Enhanced avoidance habits in obsessive-compulsive disorder*. *Biol Psychiatry*, 2014. **75**(8): p. 631-8.
161. Gillan, C.M., et al., *Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder*. *Am J Psychiatry*, 2011. **168**(7): p. 718-26.
162. Parker, M.O., et al., *Moderate alcohol exposure during early brain development increases stimulus-response habits in adulthood*. *Addict Biol*, 2016. **21**(1): p. 49-60.
163. Canas, J.J., et al., *Cognitive flexibility and adaptability to environmental changes in dynamic complex problem-solving tasks*. *Ergonomics*, 2003. **46**(5): p. 482-501.
164. Wolmarans, W., D.J. Stein, and B.H. Harvey, *A psycho-behavioral perspective on modelling obsessive-compulsive disorder (OCD) in animals: The role of context*. *Curr Med Chem*, 2017.
165. Birrell, J.M. and V.J. Brown, *Medial frontal cortex mediates perceptual attentional set shifting*

- in the rat*. Journal of Neuroscience, 2000. **20**(11): p. 4320-4324.
166. Weisholtz, D.S., et al., *Cognitive, Emotional, and Behavioral Inflexibility and Perseveration in Neuropsychiatric Illness*, in *Executive Functions in Health and Disease*. 2017, Elsevier. p. 219-248.
  167. Clarke, H., et al., *Cognitive inflexibility after prefrontal serotonin depletion*. Science, 2004. **304**(5672): p. 878-880.
  168. Dalley, J.W., R.N. Cardinal, and T.W. Robbins, *Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates*. Neuroscience and Biobehavioral Reviews, 2004. **28**(7): p. 771-784.
  169. Abbruzzese, M., S. Ferri, and S. Scarone, *The selective breakdown of frontal functions in patients with obsessive-compulsive disorder and in patients with schizophrenia: a double dissociation experimental finding*. Neuropsychologia, 1997. **35**(6): p. 907-912.
  170. Rygula, R., et al., *Role of Central Serotonin in Anticipation of Rewarding and Punishing Outcomes: Effects of Selective Amygdala or Orbitofrontal 5-HT Depletion*. Cerebral Cortex, 2015. **25**(9): p. 3064-3076.
  171. Colwill, R.M., et al., *Visual discrimination learning in zebrafish (Danio rerio)*. Behavioural Processes, 2005. **70**(1): p. 19-31.
  172. Parker, M.O., et al., *Discrimination reversal and attentional sets in zebrafish (Danio rerio)*. Behav Brain Res, 2012. **232**(1): p. 264-8.
  173. Conrad, C.D., et al., *Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine treatment*. Behavioral neuroscience, 1996. **110**(6): p. 1321.
  174. Hughes, R.N., *The value of spontaneous alternation behavior (SAB) as a test of retention in pharmacological investigations of memory*. Neuroscience & Biobehavioral Reviews, 2004. **28**(5): p. 497-505.
  175. Cognato, G.d.P., et al., *Y-Maze memory task in zebrafish (Danio rerio): the role of glutamatergic and cholinergic systems on the acquisition and consolidation periods*. Neurobiology of learning and memory, 2012. **98**(4): p. 321-328.
  176. Gross, A.N., et al., *Cage-induced stereotypies in female ICR CD-1 mice do not correlate with recurrent perseveration*. Behavioural brain research, 2011. **216**(2): p. 613-620.
  177. Thelen, E., *Rhythmical stereotypies in normal human infants*. Animal behaviour, 1979. **27**: p. 699-715.
  178. Foster, L.G., *Nervous habits and stereotyped behaviors in preschool children*. Journal of the American Academy of Child & Adolescent Psychiatry, 1998. **37**(7): p. 711-717.
  179. Gerlai, R., *Reproducibility and replicability in zebrafish behavioral neuroscience research*. Pharmacology Biochemistry and Behavior, 2018.
  180. Parker, M.O., *Adult vertebrate behavioural aquatic toxicology: reliability and validity*. Aquatic Toxicology, 2016. **170**: p. 323-329.
  181. Kilkenny, C., et al., *Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research*. PLoS biology, 2010. **8**(6): p. e1000412.
  182. O Parker, M. and C. H Brennan, *Translational pharmacology of a putative measure of motor impulsivity in larval zebrafish*. Current Psychopharmacology, 2016. **5**(2): p. 73-84.
  183. Belin, D., et al., *High impulsivity predicts the switch to compulsive cocaine-taking*. Science, 2008. **320**(5881): p. 1352-1355.
  184. Burbidge, C., et al., *The association between repetitive behaviours, impulsivity and hyperactivity in people with intellectual disability*. Journal of Intellectual Disability Research, 2010. **54**(12): p. 1078-1092.
  185. Schnorr, S.J., et al., *Measuring thigmotaxis in larval zebrafish*. Behav Brain Res, 2012. **228**(2): p. 367-74.
  186. Nema, S., et al., *A novel method for automated tracking and quantification of adult zebrafish behaviour during anxiety*. J Neurosci Methods, 2016. **271**: p. 65-75.
  187. Kozol, R.A., et al., *Two knockdown models of the autism genes SYNGAP1 and SHANK3 in zebrafish produce similar behavioral phenotypes associated with embryonic disruptions of brain morphogenesis*. Hum Mol Genet, 2015. **24**(14): p. 4006-23.
  188. Schneider, T. and R. Przewlocki, *Behavioral alterations in rats prenatally exposed to valproic*

- acid: animal model of autism*. Neuropsychopharmacology, 2005. **30**(1): p. 80-9.
189. Dardou, D., et al., *Chronic pramipexole treatment induces compulsive behavior in rats with 6-OHDA lesions of the substantia nigra and ventral tegmental area*. Behav Brain Res, 2017. **332**: p. 327-336.
  190. Kyzar, E.J., et al., *Effects of hallucinogenic agents mescaline and phencyclidine on zebrafish behavior and physiology*. Prog Neuropsychopharmacol Biol Psychiatry, 2012. **37**(1): p. 194-202.
  191. Kirsten, T.B. and M.M. Bernardi, *Prenatal lipopolysaccharide induces hypothalamic dopaminergic hypoactivity and autistic-like behaviors: Repetitive self-grooming and stereotypies*. Behav Brain Res, 2017. **331**: p. 25-29.
  192. Wang, Y., et al., *Maternal exposure to the water soluble fraction of crude oil, lead and their mixture induces autism-like behavioral deficits in zebrafish (Danio rerio) larvae*. Ecotoxicol Environ Saf, 2016. **134P1**: p. 23-30.
  193. Presti, M.F., S.B. Powell, and M.H. Lewis, *Dissociation between spontaneously emitted and apomorphine-induced stereotypy in Peromyscus maniculatus bairdii*. Physiology & Behavior, 2002. **75**(3): p. 347-353.
  194. Sungur, A.O., R.K.W. Schwarting, and M. Wöhr, *Behavioral phenotypes and neurobiological mechanisms in the Shank1 mouse model for autism spectrum disorder: A translational perspective*. Behav Brain Res, 2018. **352**: p. 46-61.
  195. Xu, M., et al., *Histidine decarboxylase knockout mice, a genetic model of Tourette syndrome, show repetitive grooming after induced fear*. Neurosci Lett, 2015. **595**: p. 50-3.
  196. Um, S.M., et al., *NGL-2 Deletion Leads to Autistic-like Behaviors Responsive to NMDAR Modulation*. Cell Rep, 2018. **23**(13): p. 3839-3851.