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Zebrafish as a Prodigious Tool in Neuropsychiatric Research: Current Perspectives and Future Potential

Saileela Varadammagari, Rekha Dasari, Anjali Gujjala, Prema Mugannagari, Praveen Kumar Pasala* and Somasekhar Reddy Kanala

Department of Pharmacology, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous K.R.Palli Cross, Chiyyedu, Anantapuramu district, Andhra Pradesh 515721, India.

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ABSTRACT:

A major worldwide health burden is attributed to neuropsychiatric illnesses, which include autism spectrum disorders, schizophrenia, depression, and anxiety. The intricate interaction of genetic, environmental, and neurological factors makes it difficult to comprehend their complex genesis and find effective treatments, even after decades of research. Even while they are instructive, traditional animal models frequently fail to accurately represent the entire range of human mental illnesses and restrict high-throughput methods.Because of its extensive behavioral repertoire, conserved neurotransmitter systems, and genetic similarity to humans, the zebrafish (Danio rerio) has become a potent and adaptable model in neuropsychiatric research. It is the perfect organism for connecting molecular mechanisms with behavioral phenotypes because of its special characteristics, which include optical transparency during early development, a short life cycle, ease of genetic modification, and adaptability for high-throughput screening.Recent research has shown that zebrafish can be used to represent a range of neuropsychiatric disorders using both pharmacological and genetic treatments. Zebrafish-specific behavioral paradigms make it possible to evaluate fundamental symptoms like anxiety, social impairments, and hyperactivity, which helps find new treatment targets.In the future, the zebrafish model's contribution to translational neuroscience will be significantly strengthened by the combination of cutting-edge imaging methods, CRISPR-based genetic editing, and machine learning for behavioral analysis. Zebrafish present a viable route for deciphering the pathophysiology of neuropsychiatric illnesses and expediting the creation of tailored therapies as the science develops further.

I. INTRODUCTION:

Hundreds of millions of people worldwide suffer from neuropsychiatric diseases, which include a broad range of illnesses like attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, depression, anxiety, and autism spectrum disorder (ASD). These conditions have significant effects on healthcare systems, socioeconomic structures, and quality of life, making them one of the main causes of disability globally. Because they are multidimensional and involve intricate interactions between genetic, epigenetic, neurochemical, and environmental factors, the underlying mechanisms are still poorly understood despite their prevalence.The absence of dependable, predictive, and scalable animal models impedes the development of efficient diagnosis and treatments for neuropsychiatric diseases(1). The use of traditional mammalian models—especially those involving rodents—has greatly advanced our knowledge of behavior and brain function. Nevertheless, they have a number of drawbacks, including high maintenance expenses, low drug screening throughput, difficulties with real-time imaging, and extensive genetic modification. The scientific community has been compelled by these limitations to investigate alternate models that can supplement or improve current methodologies (2).The zebrafish (Danio rerio) has become a well-known model organism in behavioral and brain studies in recent years (3). Zebrafish were first used in developmental biology, but because of their special set of traits—a well-characterized genome with high human homology, conserved neuroanatomical structures and neurotransmitter systems, and a wide range of measurable behaviors—they have quickly spread into neuropsychiatric research(4). They are especially appealing for analyzing brain function and simulating human neuropsychiatric disorders because of their optical transparency throughout

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early development, quick embryogenesis, and susceptibility to high-throughput pharmacological and genetic screening.The growing demand for integrative models that enable a systems-level understanding of brain-behavior interactions is another factor fueling the growing interest in zebrafish (5). As the field of neuropsychiatric research advances toward personalized treatment plans and precision medicine, zebrafish present an exciting, scalable, and morally sound platform for research and validation (6). The function of zebrafish in neuropsychiatric research is examined in this review, which also highlights important behavioral paradigms, molecular techniques, translational implications, and potential future initiatives.

As a Model Organism, Zebrafish:

Human-like Genetic and Neuroanatomical Similarities:Zebrafish (Danio rerio) are an excellent model for researching the neurological underpinnings of behavior and neuropsychiatric diseases because of their striking genetic and neuroanatomical similarities to humans (7). There is at least one zebrafish ortholog for over 70% of human genes (8), and this conservation is significantly higher (~84%) when looking at genes linked to human illnesses, such as those linked to neurodevelopmental and psychiatric conditions (9). Crucially, the human central nervous system and the zebrafish brain share important anatomical and functional elements(10). Despite having a simpler design, the zebrafish brain preserves homologous areas involved in emotion regulation, memory, motor control, and social behavior. Major sections such as the forebrain, midbrain, hindbrain, and spinal cord are present.Neurotransmitter systems that are essential for mental processes are very preserved. Similar to mammals, zebrafish have dopaminergic, serotonergic, glutamatergic, GABAergic, and cholinergic pathways. These systems can be pharmacologically altered to mimic human-like traits including anxiety, depression, hyperactivity, or social impairments(11). They also regulate many of the same physiological and behavioral processes. The findings from zebrafish may be applied to higher animals, such as humans, thanks to this conservation(12).

Behavioral Frameworks Associated with Neuropsychiatric Conditions:

Numerous conserved behaviors in zebrafish can be objectively evaluated and altered to simulate key symptoms of neuropsychiatric diseases in humans(13). These behavioral paradigms offer important insights into the mechanisms underlying mental health disorders, especially when paired with genetic and pharmaceutical methods(14).

Models of Stress and Anxiety:

Novel tank test:One of the most widely used tests to gauge zebrafish anxiety-like behavior. Zebrafish exhibit behaviors similar to mammalian anxiety responses when they are introduced to a new tank, including bottom-dwelling, freezing, and thigmotaxis (keeping close to the edges). The assay's translational relevance is confirmed by the fact that anxiogenic chemicals enhance bottom-dwelling while anxiolytic medications, such as diazepam, decrease it(15).

Light and dark test**:**This test takes advantage of zebrafish's natural dislike of brightly light areas. Spending more time in the dark zone is seen as a sign of nervousness. It is extremely sensitive to pharmaceutical manipulation as well as environmental stresses(16).

Cortisol Measurements**:** Similar to cortisol in humans, cortisol is the main stress hormone in zebrafish. A physiological readout to supplement behavioral data can be obtained by measuring whole-body cortisol levels following acute or chronic stress(17).

States Like the Depression:

Unpredictable Chronic Stress (CUS):Depressive-like behaviors, such as decreased mobility, decreased social contact, and altered sleep/wake cycles, are brought on by repetitive, mild stressor exposure over a period of days or weeks. The effectiveness of antidepressants in zebrafish is assessed using CUS models(18).

Evaluations of Anhedonia and Social Interaction:Zebrafish depression models frequently exhibit decreased social preference or motivation to engage with conspecifics(19). Anhedonia-like behavior can be identified with the use of assays that gauge a person's preference for social areas or level of interest in reward-associated stimuli, such as food or light cues(20).

Models of Schizophrenia and Psychosis:

Antagonists of NMDA Receptors:Pharmacological substances that block NMDA receptors, including ketamine and MK-801, cause zebrafish to become hyperactive, exhibit disturbed social behavior, and have trouble with sensorimotor gating(21). Antipsychotic

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medications can reverse these phenotypes, which mirror positive and cognitive symptoms of schizophrenia(22).

The disturbance of social behavior: Generally speaking, zebrafish exhibit great social cohesiveness (shoaling). One of the main negative symptoms of schizophrenia is social disengagement, which is modeled by disruption in shoaling behavior following NMDA antagonist treatment or genetic modification(23).

Disorders of the Autism Spectrum (ASD):

Models ofgenetics (such as Shank3 and CNTNP2):CRISPR/Cas9 and morpholino knockdown have been used to simulate mutations in ASD-associated genes in zebrafish. These fish have abnormalities in sensory processing, changed repetitive habits, and poor social preference(24).

Studies of Social Preference and Communication:Tests measure how long a zebrafish spends in the vicinity of a conspecific group as opposed to an empty area(25). Reduced social orientation is frequently seen in larvae and adults with characteristics similar to those of ASD. As stand-ins for communication impairments, acoustic and visual cue responses are also investigated(26).

Hyperactivity and ADHD:

Dopamine-Related Modifications**:** Zebrafish hyperactivity and impulsivity are modulated by dopamine-system-targeting stimulants such as amphetamine and methylphenidate. Alterations in activity levels have also been connected to mutations in dopaminergic genes (e.g., drd4, dat)(27).

Assays for locomotor function**:**A high-throughput way to measure hyperactivity is to quantify spontaneous swimming activity in various lighting or environmental settings(28). Compounds intended to treat symptoms similar to ADHD are frequently tested using these assays(29).

Pharmacological and Genetic Models of Neuropsychiatric Conditions:

Using Genetic Modification to Model Disease**:**Zebrafish are a potent model for researching the molecular causes of neuropsychiatric diseases because of their genetic tractability(30). Zebrafish can be genetically modified to express mutations in genes associated with human mental disorders using techniques including CRISPR/Cas9 genome editing, morpholino antisense oligonucleotides, and Tol2 transgenesis(31). Among the noteworthy instances are:Major depressive illness, bipolar disorder, and schizophrenia have all been linked to mutations in the DISC1 gene (Disrupted in Schizophrenia (32). Mutants in zebrafish disc1 show symptoms similar to human psychiatric symptoms, including abnormal brain development, impaired social behavior, and disturbed sleep-wake cycles.SHANK3: Autism spectrum disorders are closely associated with mutations in SHANK3, a gene essential for synaptic scaffolding. A good platform for studying ASD is provided by zebrafish with shank3 mutations, which exhibit decreased social interaction, increased stereotypical behavior, and altered synaptic function.MECP2: Zebrafish models with compromised mecp2 function exhibit hypoactivity, motor dysfunction, and developmental delay, resembling Rett syndrome, a neurodevelopmental condition sometimes included in the autism spectrum(33).

Drug-Induced Models That Resemble Mental Illnesses:Zebrafish are extremely sensitive to pharmacological interventions, which goes beyond genetics and makes it possible to create chemically induced models that mimic particular neuropsychiatric symptoms(34). These models are very helpful for examining neurotransmitter networks and evaluating possible treatments:

Disorders of Anxiety:Strong anxiety-like behaviors in zebrafish can be controlled with medication.In the novel tank diving test (NTT) and light/dark box test, anxiogenic substances like coffee, yohimbine, and FG-7142 cause a rise in bottom-dwelling, irregular swimming, and freezing, which are indicative of elevated anxiety(35).The predictive validity of zebrafish anxiety models is confirmed by the reversal of these behaviors by anxiolytics such as diazepam, buspirone, and clonazepam.n addition to being sensitive to GABAergic and serotonergic modulators, these assays replicate the brain circuits implicated in anxiety in humans(36).

States that resemble depressions:Chronic stress exposure or pharmaceutical targeting of monoaminergic pathways can both produce depressive phenotypes.Reserpine causes social disengagement and hypoactivity via depleting monoamines(37).Corticosteroids, like dexamethasone or cortisol, mimic long-term stress, which results in changed cortisol cycles and attenuated behavioral reactions.Translational importance is demonstrated by the normalization of these behaviors by antidepressants such desipramine, sertraline, and fluoxetine(38).To

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determine antidepressant-like activity, behavioral procedures such as the zebrafish forced swim test (zFST) and social interaction evaluations have been used(39).

Models of Schizophrenia and Psychosis:In zebrafish, psychotomimetic substances impair social behavior, sensory processing, and cognition, simulating the symptoms of schizophrenia(40MK-801, ketamine, and phencyclidine (PCP) are examples of NMDA receptor antagonists that cause hyperlocomotion, decreased social interaction, and deficiencies in prepulse inhibition (PPI), which is a commonly recognized endophenotype of schizophrenia(41).Zebrafish also exhibit hyperactivity and stereotypical behaviors when exposed to amphetamine, a dopamine agonist.These deficiencies can be reversed by antipsychotic medications such as clozapine, olanzapine, and haloperidol, thereby bolstering concept and predictive validity(42).The investigation of dopaminergic and glutamatergic contributions to psychotic symptoms is made possible by these models(43).

ASD, or autism spectrum disorder**:**Core characteristics of ASD, including social difficulties, repetitive behavior, and inappropriate communication, are displayed by zebrafish exposed to specific neurotoxicants and antiepileptic medications(44).Exposure to valproic acid (VPA) during embryogenesis interferes with neurodevelopment, leading to decreased social preference, elevated anxiety, and poor movement(45).Similar effects are produced by exposure to propionic acid (PPA) and methylmercury, frequently accompanied by oxidative stress and altered expression of synaptic proteins(46).These models enable assessment of neurodevelopmental toxicity and possible treatment drugs (such as oxytocin and risperidone) by simulating environmental risk factors for ASD(47).

Addiction and Substance Abuse:Zebrafish are appropriate for studying addiction because they exhibit drug-seeking and reward-related behaviors that are comparable to those of humans.Increased motility and conditioned place preference (CPP) are the results of exposure to nicotine, ethanol, cocaine, and morphine.Following cessation, withdrawal symptoms (such as anxiety-like behavior and decreased social contact) are also noted(48).The dopaminergic and opioid signaling pathways, which are preserved in zebrafish, regulate the reinforcing effects of these drugs.This is a useful method for identifying neurochemical changes in substance use disorders and screening anti-addiction medications(49).

Models of Bipolar Disorder and Mania**:**Some drug-induced zebrafish paradigms mimic manic-like states, however they are less frequently replicated.Amphetamine and modafinil are examples of psychostimulants that cause hyperactivity, impulsive conduct, and sleep disturbances, which are characteristics of manic episodes(50).These behaviors are normalized by the mood stabilizer lithium, which provides a platform for studying the biology of bipolar disorder and testing mood stabilizers(51).

Uses in Drug Screening and Discovery:

The zebrafish model has become a cornerstone in modern drug discovery pipelines, notably in neuropsychiatric research. For high-throughput screening and in vivo investigation of pharmacological effects on the brain and behavior, zebrafish are especially useful due to their small size, transparency during early development, and conserved neurochemical pathways. Zebrafish models offer a strong platform for early-stage drug screening as well as mechanism-of-action research, bridging the gap between in vitro systems and mammalian models(52).

High-volume behavioral tests**:**Zebrafish's size and compatibility with 96- or 384-well plate layouts make them ideal for automated, extensive behavioral screening(53). The quick evaluation of hundreds of chemicals for behavioral modification is made possible by these systems(54).Commonly used assays include:Anxiety-reducing novel tank diving test,Test of preference for light or dark,Assays for social interaction,Tracking locomotors,Preference for conditioned places (CPP),Video tracking and machine learning-based analysis can be used to quantify behavioral endpoints in order to identify minor phenotypic changes(55). This makes it possible to quickly identify neuroactive substances that have an impact on emotion, thought, or movement(56).

Neural Activity Imaging in Vivo During Drug Response:Real-time, non-invasive brain imaging is made possible by the optical transparency of zebrafish embryos and larvae(57). This enables the correlation of cellular-level effects of psychoactive substances and neural circuit activity with behavioral responses(58).High-resolution information on how medications affect neuronal excitability can be obtained using calcium imaging with genetically encoded markers such as GCaMP(59).Light-sheet microscopy and two-

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photon imaging can be used to create whole-brain activity maps, which provide information on how medications impact brain function worldwide(60).Mechanistic investigations of drug action and neurotoxicity benefit greatly from these methods(61).

Safety and Toxicology Profiling: In neurotoxicology, zebrafish are being utilized more and more to evaluate the adverse effects of psychoactive substances(62).Because they are susceptible to neurodevelopmental toxins, embryonic and larval stages are perfect for research on developmental neurotoxicity (DNT)(63).Endpoints consist of: Defects in morphology,Changes in neurobehavior,Circulation and heart rate,Teratogenicity and lethality (LC50).Zebrafish, as opposed to rat models, provide quick and economical screening of chemical libraries for safety and efficacy prior to clinical development(64).

Reusing Current Pharmaceuticals**:** Repurposing drugs is a useful tactic to speed up the development of new treatments, especially for complicated conditions like autism, schizophrenia, and depression.FDA-approved medications can be evaluated for off-label effectiveness in neuropsychiatric disorders using zebrafish behavioral models.In zebrafish models of depression, ASD, and psychosis, a number of currently available medications (such as fluoxetine, valproic acid, and minocycline) have demonstrated neuroprotective or behavioral-modulating effects(65).In zebrafish, phenotype-based screening frequently uncovers surprising modes of action, directing logical repurposing tactics.This method has already produced intriguing candidates for clinical review and cuts down on the time and expense involved in de novo drug development(66).

Prospects & Innovations for the Future:

Zebrafish are positioned to become even more important in revealing the intricacies of mental disease and brain function as neuroscience and psychiatry research advance. By enabling systems-level analysis, human-model interaction, and precision medicine techniques, emerging technologies are greatly extending the potential of zebrafish models beyond conventional behavioral experiments. The major developments influencing the upcoming wave of zebrafish-based neuropsychiatric research are listed below(67).

Combining behavioral analysis with AI:The use of machine learning and artificial intelligence (AI) is transforming zebrafish behavioral phenotyping:These days, deep learning algorithms can analyze intricate behavioral patterns with great throughput, sensitivity, and accuracy.Tools like DeepLabCut, idTracker.ai, and Zebrafish Tracker allow for accurate, real-time tracking of social interactions, movement, and minute variations in posture or trajectory that would be missed by humans.Drug screening resolution is improved by AI-assisted behavioral state categorization, which also enables phenotypic clustering of drugs according to their mechanisms of action.This technique enables more in-depth examination of psychiatric phenotypes, speeds up discovery, and lessens human bias(68).

Zebrafish Brains: Multi-omics and Single-cell Transcriptomics**:**The use of zebrafish in omics-based methods to identify the molecular basis of mental illnesses is growing:Comprehensive information on changes in gene expression, signaling pathways, and metabolic alterations linked to illness or medication response can be obtained using transcriptomics, proteomics, and metabolomics.The variety of neuronal and glial cell types in the zebrafish brain has been made clear using single-cell RNA sequencing (scRNA-seq), which provides a high-resolution map of gene expression specific to individual cell types.Particularly when combined with behavioral and imaging data, these databases make it easier to identify new treatment targets, biomarkers, and disease-associated pathways.Combining multi-omic techniques can improve model interpretability and establish a direct connection between molecular changes and observable phenotypes(69).

Human Brain Organoid Interactions with Zebrafish**:**Novel attempts are being made to develop hybrid systems that combine organoids of the human brain with zebrafish models:Real-time in vivo imaging of human neural development, disease progression, and drug reaction is made possible by transplanting human brain organoids into the yolk sac or brain of zebrafish.Through the integration of human cellular architecture and genetic material into the zebrafish model, these systems aid in overcoming species-specific restrictions.This "chimeric modeling" creates new opportunities for research on neurodevelopmental and neurodegenerative disorders and allows for the direct assessment of patient-derived cells in a living brain environment.These systems have the potential to improve translational accuracy and comprehend disease mechanisms unique to humans(70).

Using Zebrafish Avatars to Advance Customized Psychiatry:By creating patient-specific

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avatars, zebrafish are becoming instruments for precision medicine in psychiatry:Researchers can replicate unique illness symptoms by breeding zebrafish lines that express genetic mutations unique to each patient.By selecting substances that are most likely to help a particular patient based on their genetic and molecular profile, these avatars enable individualized drug screening.Standardized treatments are frequently useless for rare or treatment-resistant psychiatric diseases, where this method is very helpful.When combined with pharmacogenomic and genomic information, zebrafish avatars could play a key role in customized treatment plans for mental health issues in the future(71,72).

II. CONCLUSION:

Zebrafish have been a potent and adaptable model organism in neuropsychiatric research during the last few decades. They are a vital tool for analyzing the intricate etiology of neuropsychiatric disorders because of their special set of benefits, which include genetic and neurochemical homology with humans, transparent embryonic development, a quick life cycle, and suitability for high-throughput behavioral and pharmacological screening.Our knowledge of behavioral traits linked to addiction, schizophrenia, anxiety, depression, and autism spectrum disorders has greatly benefited from the use of zebrafish models. The breadth and complexity of zebrafish-based research are growing due to the growing availability of genetic editing tools and transgenic lines, as well as sophisticated imaging and omics technology. These models are bridging the gap between fundamental neuroscience and clinical applications by speeding up the identification of new drug targets and providing a platform for quick screening of therapeutic molecules.Looking forward, the integration of zebrafish with emerging fields such as machine learning-based behavioral analysis, personalized medicine, and humanized genetic models holds immense promise. While challenges remain—particularly in translating complex cognitive and emotional traits across species—continued refinement and standardization of zebrafish methodologies will undoubtedly enhance their relevance and reliability.In conclusion, zebrafish represent a prodigious tool in the neuropsychiatric research toolbox—poised to play an increasingly central role in unraveling brain-behavior relationships and driving innovation in mental health therapeutics.

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