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Research report

Modeling PTSD in the zebrafish: Are we there yet?

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HIGHLIGHTS

- PTSD is a rapidly growing anxiety disorder with deleterious symptomology.
- There is not an all encompassing, efficacious treatment for the disorder.
- We provide a brief overview of PTSD using human and rodent models.
- We summarize the available literature on stress using the zebrafish model.
- We present the benefits of creating a PTSD paradigm using zebrafish.

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ABSTRACT

Post-traumatic stress disorder is an anxiety disorder that can develop following one or more traumatic events that threaten one's safety or make the victim feel helpless. Currently there are an increasing number of cases in the population in part due to the number of soldiers returning from combat. The disorder is characterized by symptoms that include hypervigilance, sleep disturbances, social and cognitive degradation, and memory flashbacks. Most of the research has been centered on the human and rodent as subjects but recently another viable contender has emerged – the zebrafish (*Danio rerio*). The zebrafish is a strong comparative model with the ability to exhibit a wide variety of behaviors, complex learning, and neurobiological changes that can be extrapolated to the human condition. The zebrafish is an ideal organism to study pharmacological treatments as well as the neurological underpinnings of the disorder. Here we review a sampling of the human and rodent model literature on post-traumatic stress disorder focusing on symptomology, current treatments, and stress paradigms. We also make the argument for the inclusion of the zebrafish model in future studies investigating the causes, symptoms, and treatments of post-traumatic stress disorder.

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1. Introduction

The discussion of post-traumatic stress disorder (PTSD), a debilitating anxiety disorder, is becoming more prevalent within the scientific literature [1,2]. With large numbers of soldiers returning from combat exhibiting symptoms of the disease, and a 6.8% lifetime prevalence among citizens from the United States, the need for research into not only the treatment of the disorder but also the etiology of PTSD has become paramount [3]. PTSD is an affliction that is characterized by the development of negative symptoms after experiencing or witnessing a traumatic event. Such symptoms include flashbacks, nightmares, emotional numbing, hypervigilance and arousal, and sleep disturbances (DSM-V; [4]). PTSD is often co-morbid with depression, substance abuse, altered sleep patterns, decreased cognitive abilities, and memory impairment [5].

While research into the topic is ever increasing, there remains the need for more exploration as a truly effective treatment, especially with regards to co-morbid disorders, remains elusive. Much of the research on the disorder is focused on the human condition: testing for biomarkers, moderators, co-morbid disorders, various symptomology, and potential treatments [6–8]. Additionally, researchers have also examined PTSD using several rodent models (Table 1). The use of rodents has allowed for a more extensive look into not only possible pharmaceutical treatments of the disorder but also the neurobiological underpinnings of the disease.

In recent years the zebrafish has gained favor as an additional model organism, in the study of both diseased and normal states. Zebrafish display robust behaviors, which have become increasingly simple to quantify due to advances in video-tracking tools.

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Table 1
Rodent stress tasks.

Task	Definition/procedure	Reference(s)
Attentional Set Shifting	A rat is placed into a start box before it is allowed to enter the testing environment. Using small terra-cotta pots that are filled with different material and scented with different fragrances, a rat must dig through the pots to get to a food reward, such as a cheerio. The object of the task is to learn which medium and which scents are connected to the reward. Once the rat learns these cues, the cues are changed and the rat must learn the new reward producing combination. The task can go through multiple rule changes, which forces the rat to change to a new cognitive set and forget the previous one. Such a cognitive change is rather demanding and relies on functioning frontal brain areas. Stress mediated performance deficits have been reported.	[66,71]
Elevated Plus Maze	A rat is placed into an elevated plus shaped maze with two open arms and two that are closed in by walls. The rat is then given time to explore the maze. Naturally, when given the choice to explore an open alley in a maze and a closed arm in the maze, the animal will spend significantly more time exploring the closed arm. The model focuses on the inner conflict in the rat to want to explore all areas and their innate fear of open spaces. Anxiolytic treatments tend to result in more open area exploration.	[64,65]
Fear Conditioning	A rodent is placed into a novel environment and is allowed to explore for at least 27 s. After this exploratory period has passed, a moderately painful foot shock is administered. The shock cannot be administered immediately upon entering the environment, as a sufficient amount of time must be given to allow for true conditioning to occur. In doing this, the fear of receiving the foot shock is associated with the new environment. By re-exposing the rat to the environment where the shock was administered, symptoms of PTSD are thought to be simulated.	[62]
Inescapable Tail Shock	The rat is restrained in a ventilated tube and receives 40 tail shocks at random intervals of 150–210 s over a 2-h period. These sessions happen once a day for 3 consecutive days.	[63]
Light/Dark Exploration Test	After a 1 h habituation to the testing room in their home cage, a rat is placed individually into the center of the white compartment facing the dark compartment of the L/D test apparatus, an open box with 1/3rd painted black (illuminated by dim red light) and 2/3rd painted white (illuminated by bright white light). These two areas were separated by a wooden partition. A 5 min testing session commenced where the rat was videotaped and the amount of time spent in each area was quantified. Increased stress would have the rat spending more time in the dark area of the box.	[70]
Novelty-Induced Hypophagia	After a training period of eight days where the rat is familiarized with a certain food such as graham cracker, the rodent is placed into a novel environment, one in which its never been before, for 15 min. The rat is then presented with the familiar graham crackers and allowed to eat. After the 15-min session, food intake is then measured by weighing the food bowl before and after testing. Hypophagia (reduction of feeding) is said to occur as an anxiety response to the novel environment. One of the benefits of this test is that substances such as antidepressants can be tested in relation to the anxiety response.	[67,68]
Social Interaction Test	Two rats of similar build, one experimental and one stimulus, are placed at opposite corners facing away from each other in a wooden box. For 5 min, the amount of time the experimental rat spends engaged in social behavior with the stimulus rat is collected. Anxiogenic treatments tend to decrease social interaction time.	[66]
Single Prolonged Stress	Rats are exposed to an extreme, singular stressful event. Such as being restrained for 2 h. After the restraint period, the rats, in groups of eight, are forced to swim for 20 min in 24 °C water. After forced swim, the rats are rendered unconscious via ethyl ether anhydrous. The rats regain consciousness in 5–15 min and then are returned to their housing unit. Their behaviors are quantified no less than seven days after the exposure. Typically, reactions are behavioral (flashbacks, hyperarousal, and avoidance of similar situations) and neurochemical (HPA axis).	[60,61]
Stress Re-Stress Model	Similar to the SPS task, the rats are restrained, forced to swim, and rendered unconscious via ether. Unlike the SPS task, they are then made to endure the same stressful event again seven days later.	[72]

They have a well-characterized, simple nervous system (compared to humans) and a fully characterized genome displaying a nucleotide sequence similar to most other vertebrates [9]. As such, zebrafish are a viable model for exploring the molecular and genetic mechanisms of behavior in addition to being a powerful comparative model to better understand PTSD [10–12]).

2. Human model

2.1. Symptomology

The manifestation of the PTSD is quite extensive and the diagnosis can include deleterious changes to memory and/or anxiogenesis. The symptoms most often associated with PTSD are flashbacks, nightmares, emotional numbing, increased startle response, and sleep disturbances (DSM-V; [4]). In addition, there is often an accompanying decline in working memory and, more specifically, emotional memory [8].

Cognitive deficits may be associated with not only neural networks that control emotional responses, but also the prefrontal cortex (PFC; [13]). Vasterling et al. [14] suggests that PTSD may have some connection to the frontal lobe, as those who suffer from PTSD perform in a fashion similar to frontal lobe injury patients on cognitive tasks. A decline in cognitive functioning may be related to stress induced malfunctioning of monoamine neurotransmission in the PFC [15]. In addition, Honzel et al. [8] report that individuals with PTSD perform similarly to control subjects on singular tasks but when they were asked to perform multiple tasks at one time, specifically those related to working memory, performance was significantly impaired. One explanation for this is that the emotional difficulties experienced by PTSD patients and their inability to regulate memories related to their trauma provided distraction or interference that is severe enough to cause declines in cognition [14].

Substance abuse is often comorbid with PTSD. Approximately 10–40% of substance abusers show signs of PTSD [16]. Individuals who suffer from both PTSD and alcohol dependence show more severe PTSD symptoms compared to those who do not have both disorders [17]. Fuehrlein et al. [7] reported that alcohol dependent individuals show more frequent drinking patterns than those with comorbid PTSD. However, those with comorbidity reported more alcohol-related symptoms on the Alcohol Dependency Scale (ADS; [18]) than the former. These symptoms include: staggering, frequency of hangovers, shaking, blackouts, etc. Patients suffering

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