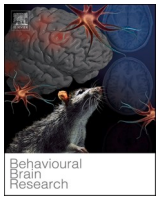
Behavioural Brain Research 453 (2023) 114607

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr



Towards experimental models of delirium utilizing zebrafish

Gleb O. Maslov [a,g], Konstantin N. Zabegalov [b], Konstantin A. Demin [c,d], Tatiana O. Kolesnikova [a,d], Yuriy M. Kositsyn [d], Murilo S. de Abreu [h,*], Elena V. Petersen [h], Allan V. Kalueff [a,c,d,e,f,g,**]

[a] Neurobiology Program, Sirius University of Science and Technology, Sochi, Russia
[b] National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan
[c] Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia
[d] Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia
[e] Novosibirsk State University, Novosibirsk, Russia
[f] Laboratory of Preclinical Bioscreening, Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia
[g] Ural Federal University, Ekaterinburg, Russia
[h] Laboratory of Cell and Molecular Biology and Neurobiology, Moscow Institute of Physics and Technology, Moscow, Russia

ARTICLE INFO

Keywords:
Zebrafish
Delirium
Experimental models
Drug screening

ABSTRACT

Delirium is an acute neuropsychiatric condition characterized by impaired behavior and cognition. Although the syndrome has been known for millennia, its CNS mechanisms and risk factors remain poorly understood. Experimental animal models, especially rodent-based, are commonly used to probe various pathogenetic aspects of delirium. Complementing rodents, the zebrafish (*Danio rerio*) emerges as a promising novel model organism to study delirium. Zebrafish demonstrate high genetic and physiological homology to mammals, easy maintenance, robust behaviors in various sensitive behavioral tests, and the potential to screen for pharmacological agents relevant to delirium. Here, we critically discuss recent developments in the field, and emphasize the developing utility of zebrafish models for translational studies of delirium and deliriant drugs. Overall, the zebrafish represents a valuable and promising aquatic model species whose use may help understand delirium etiology, as well as develop novel therapies for this severely debilitating disorder.

1. Introduction

Delirium is an acute mental condition characterized by impaired behavior, attention, perception and orientation due to rapidly occurring decompensation of brain function [1] (Table 1). Previously described as "clouding of consciousness", delirium is characterized by altered consciousness in terms of context (e.g., time and space) and the intensity (i.e., hyper- or hypo-arousal) of brain activation [2]. Delirium treatment costs >200 million dollars yearly in major Europe countries [3], and can also be associated with lethal outcomes [4]. However, the exact clinical symptoms, pathogenetic causes, risk factors, and treatment strategies of this syndrome remain poorly understood. Some classifications (e.g., Diagnostic and Statistical Manual of Mental Disorders, DSM-5) describe delirium as rapidly developing attention deficits and impaired cognitive functions, including memory, orientation, language and perception of images and space [5]. Other commonly used psychiatric classifications (e.g., International Classification of Diseases, ICD-11) list delirium among neurocognitive disorders, together with mild cognitive impairment, amnesia and dementia, whose shared key symptoms include impaired attention, orientation and consciousness [1]. Additional common clinical signs of delirium include motor agitation, thought disorder and impaired sleep-wakefulness (Table 1).

Delirium is typically associated with multiple pathogenic factors (Table 2), either evoking cognitive dysfunctions directly or disturbing major neurotransmitter (e.g., dopamine- or cholinergic) systems [6]. Delirium is also often caused by neurodegenerative diseases, infections, brain traumas and by various drugs [1], especially opiates, benzodiazepines, anticholinergics and dopaminergic mimetics (Table 2) [7]. Moreover, delirium has a progressive nature (e.g., occurring in 50 % of patients >65), and can be triggered by rapid severe clinical conditions

* Corresponding author.
** Corresponding author at: Institute of Experimental Medicine, Almazov National Medical Research Centre, St. Petersburg, Russia.
E-mail addresses: abreu_murilo@hotmail.com (M.S. de Abreu), avkalueff@gmail.com (A.V. Kalueff).

https://doi.org/10.1016/j.bbr.2023.114607
Received 25 May 2023; Received in revised form 28 July 2023; Accepted 29 July 2023
Available online 29 July 2023

Table 1
Main clinical symptoms and factors causing clinical delirium [122].

Symptoms	Details	References
Core		
Disturbance of attention	Difficulty with focusing, holding and transferring attention	[123]
Cognitive impairment	Memory disturbances, clouding of consciousness	[123]
Perceptual impairment	Disorientation in space* and impaired image perception, including visual, auditory and tactile hallucinations	[1,5123]
Language disorder	Speech problems	[1,5]
Additional		
Abnormal behaviors	Actions and behaviors unusual for the situation (see below)	[1,5]
Locomotion disorder	Hyper- or hypoactivity	[1,5]
Disrupted sleep-wake cycle	Sleep deterioration, including prodromal (in 2–3 days)**	[1,5]
Related		
Aggression	Increased aggression and self-destructive behavior	[1,5]
Anxiety	Fears, anxiety and / or paranoia	[124,125]
Depression and apathy	Apathy and inaction* **	[125]
Frequent mood swings	Frequent transition from aggression/ hyperactivity to joy or sadness	[125]
Agitation	Motor and emotional excitement****, irritability and euphoria	[125]

*Develop within hours, less often - within days
**Delirium is ameliorated during the day, and hyperactivity and recurrence of symptoms occur at night
*** Symptoms are less common with delirium
**** Often accompanied by fear and anxiety

Table 2
Selected neuroactive drugs that can cause pharmacogenic delirium clinically [126–129]. Note that zebrafish are sensitive to all classes of these drugs (denoted by *).

Drug classes (sensitivity in zebrafish)	Drugs
Antipsychotics *	Clozapine, haloperidol, fluphenazine, thioridazine
Opiates *	Fentanyl, meperidine, morphine, prednisone
Antiarrhythmics *	Lidocaine, amiodarone
Anticonvulsants *	Phenytoin, lamotrigine, pregabalin
Antidepressants *	Desipramine, fluoxetine, bupropion, clomipramine
Dopamine receptor agonists *	Amantadine, bromocriptine
Benzodiazepines *	Lorazepam, diazepam
Non-steroidal anti-inflammatory drugs (NSAIDs) *	Diclofenac, ibuprofen, ketoprofen
Calcium channel blockers *	Nifedipine, verapamil
Beta-adrenergic blockers *	Atenolol, metoprolol
H2-histamine receptor blockers *	Cimetidine, ranitidine
Anticholinergics *	Atropine, scopolamine

(e.g., seen in 80 % of patients in emergency medical care) [8].

Overall, delirium is a complex multifaceted and severely debilitating syndrome [6] whose treatment represents an important unmet biomedical problem. Experimental animal models, especially rodent-based, are commonly used to probe various central nervous system (CNS) disorders. Complementing rodents, a small freshwater teleost fish, the zebrafish (*Danio rerio*), is also rapidly emerging as a promising model organism to study brain disorders. Recognizing clinical and societal importance of delirium, here we critically discuss recent developments in experimental modeling of this disorder, and emphasize the utility of zebrafish models for its translational studies and the search for its therapy.

Table 3
Selected signs of experimental delirium in rodents.

Symptoms	Details	References
Perceptual impairment	Refusal to perceive external stimuli, instilled in learning process	[20,26]
Memory impairment	The lack of adequate response to learned stimuli	[20,26]
Inappropriate behavior	Behavior uncharacteristic of the situation	[24]
Impaired context memory	Failure to distinguish novel vs. previously remembered contexts	[20]
Disruption of activity	Daytime hyperactivity	[20]
Disrupted sleep-wake cycle	Aberrant circadian rhythms	[130]

2. Experimental models of delirium

Albeit recognized clinically for nearly 3000 years [9], the pathogenesis and causes of delirium remain poorly understood [6]. Currently accepted theories of delirium pathogenesis involve aberrant neurotransmitter circuits, neuroinflammation, impaired blood-brain barrier (BBB) and neuroendocrine deficits [6]. For example, cholinergic deficits impair cognitive functions [10], and anticholinergic drugs represent a specific class of deliriant hallucinogens [11]. Delirium can also be linked to neuroinflammation [12], as interleukin (IL) IL-8 and cortisol rise prior to delirium onset [13], whereas delirious patients with high IL-8 and calcium-binding protein β (S-100β) levels show increased mortality [14]. Likewise, elevated levels of another cytokine, tumor necrosis factor (TNF)-alpha, or its receptors correlate with delirium symptoms [15–17], and high cortisol is associated with high risk of post-surgery delirium [18,19].

Animals models, especially based on laboratory rodents, are a valuable tool to study individual symptoms and mechanisms of delirium [20]. For example, activation of the peripheral immune system in rodents during systemic peripheral inflammation (caused by lipoproteins or pathogenic microorganisms) evokes microglial immune responses [21] with altered BBB permeability and neuronal oxygenation that collectively trigger cognitive deficits in conditioned avoidance and contextual memory tasks [22], strikingly resembling impaired cognitive functions in clinical delirium [23]. Other rodent models involve delirium-like states caused by anesthesia and surgery [20,24]. Both experimental procedures affect mouse behavior (e.g., increasing the latency of finding food in the buried food test, and worsening rat performance in the Y-maze task, as they show fewer visits to the novel arms), suggesting deficient dopaminergic control of locomotor and novelty-seeking behavior [25], see Table 3 for details.

Paralleling clinical surgery-evoked delirium, impaired innate and learned behaviors are observed in rats 6–9 h after anesthesia or surgery [26]. Assessing this experimental postoperative delirium shows that anesthesia and surgery increase the latency of finding the correct arm in the mouse Barnes maze [27], and cause poorer performance and attention in a serial 5-choice reaction test. The latter phenotype is accompanied by altered hippocampal morphology and microgliosis [28], as well as increased translocation of the transcription factor EB (TFEB), likely due to neuroinflammation [24] and generally consistent with the proinflammatory concept of delirium pathogenesis [21].

In mice with experimental dementia, reduced blood glucose following insulin administration also causes delirium-like conditions, including poorer memory and spatial navigation [29]. The latter phenotypes also rapidly deteriorate following administration of atropine, a classic muscarinic anticholinergic drug and a potent traditional *deliriant* hallucinogen [20]. Delirium-like state induced in rats by biperiden (a muscarinic/nicotinic anticholinergic agent) within 20 min after injection includes hyperactivity (e.g., restlessness, stereotypic walking in circles near walls and impulsive movements) in some animals, and hypoactivity (e.g., stops, drowsiness and ptosis) in some others [30].

Table 4
Selected molecular biomarkers of delirium (adopted from [131]).

Biomarkers	References
Serum anticholinergic activity	[10]
Amino acids	[132,133]
Melatonin	[134]
Interleukins (IL-1, 2, 6 and 8)	[135–137]
Insulin-like growth factor	[138]
C-reactive protein (CRP)	[139]
S–100 β	[140]
Apolipoprotein- E (APO-E)	[141]
Cortisol	[142]
Estradiol	[143]
TNF-alpha	[144]
Neuron-specific enolase	[145]

Their subsequent electroencephalography (EEG) analyses reveal increased delta, theta-1, alpha-1 and beta-rhythms in hyperactive rats, and delta rhythm (characteristic of sleep) in hypoactive rats [30]. As such, altered EEG patterns (i.e., alpha- and beta- rhythms desynchronization or slowing theta-rhythms) and immune (e.g., IL) responses [28, 30] may serve as putative prognostic biomarkers of experimental and clinical delirium (Table 4).

Although experimental rodent models have long been in translational neurobiology, they have multiple limitations, such as high cost of care and testing, low throughput and limited translatability of their phenotypes into complex human neuropsychiatric conditions [31]. At the same time, compared to rodents, zebrafish models may have several advantages to be considered. For example, zebrafish genetic models are easier to generate due to specific aspects of zebrafish (vs. rodent) genetics and the greater availability of modern gene-editing tools in zebrafish. Zebrafish models may be more resilient to behavioral

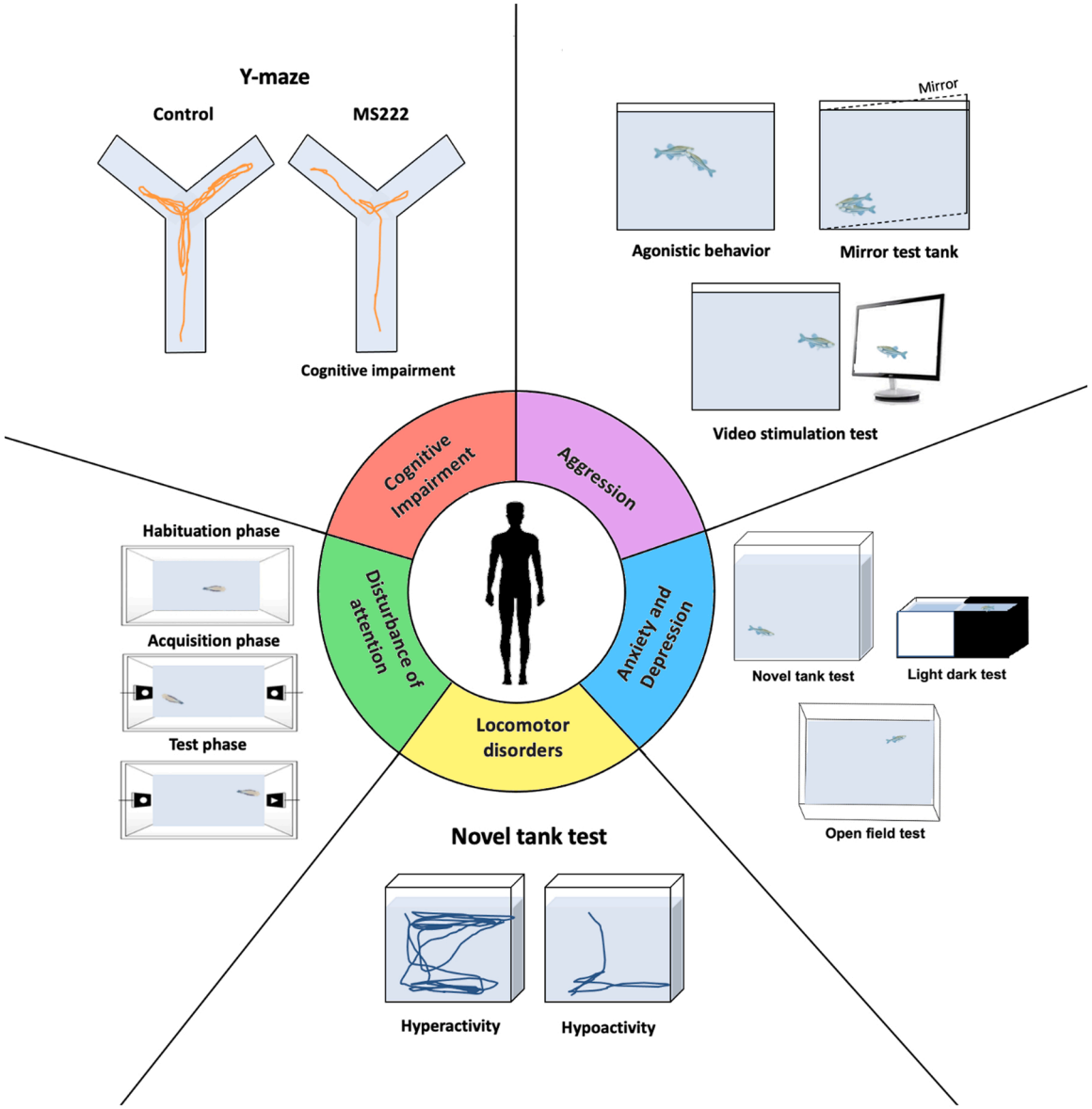


Fig. 1. Clinical delirium and its modeling in zebrafish. Cognitive and attention deficits are common in clinical delirium, and can both be assessed in zebrafish [70, 71]. For example, acute anesthetics (e.g., tricaine methanesulfonate, MS222) induce poorer performance in zebrafish Y-maze [146]. In zebrafish attention assay, the animals are typically subjected to a familiarization trial, and after different time delays (5 min to 96 h) assessed in a novel object recognition trial [72]. Several zebrafish assays have been developed to assess other delirium-related behavioral domains, such as aggression (e.g., in the agonistic behavior test, mirror test, and video stimulation test [98,99]), anxiety (e.g., in the novel tank test, light-dark test, and open field test) [100,101]) and general locomotion (e.g., hyper- and hypoactivity) [102].

variation influenced by environmental factors (e.g., experimenter identity), which contributes to increased reproducibility and reliability of laboratorial data obtained with these fish [32]. Zebrafish models also have some regulatory advantages (e.g., better following the 3 R principles of replacement, reduction and refinement of bioexperimentation than more advanced/sophisticated mammals), and since their drug treatment by water immersion is a less stressful/invasive procedure than injections in rodents [33]. Furthermore, to better understand the evolutionarily conserved, 'core' pathogenic mechanisms of a CNS disorder, using a wider range of model species (beyond mammals) becomes critical. Likewise, zebrafish are a valuable model species in CNS drug discovery due to their high sensitivity to major classes of CNS drugs, amenability to sophisticated automated behavioral analyses of both individual fish and groups (e.g., shoals), significant high-throughput drug screening potential, and the availability of both larval and adult zebrafish-based drug screening assays [34].

3. Zebrafish as an efficient model organism in CNS research

Zebrafish is a useful powerful model system in translational neurobiological research [35]. A fully sequenced genome, the availability of multiple well-characterized inbred, outbred, mutant and transgenic strains, and high (>70 %) genetic homology with humans, collectively make zebrafish particularly useful in this field [36]. The zebrafish brain, like in all teleost fishes, demonstrates morphological features common for all vertebrates. Small size, short reproductive period, high fecundity, the possibility of screening transparent embryos at all stages of development, and the ease of behavioral analyses, also support their utility for studying brain pathogenesis [37] and generating large sets of behavioral data that can be used in high-throughput preclinical screening [38]. Substantial physiological similarity with humans further enables zebrafish-based modeling of various CNS disorders [39], testing a wide range of psychoactive substances [40], studying neurotoxicity and probing development and functions of excitatory and inhibitory neurons, microglia and oligodendrocytes [41].

4. Zebrafish susceptibility to factors causing delirium

Several classes of psychoactive substances, directly related to delirium or its therapy, have already been tested in zebrafish (Table 2). For example, an atypical antipsychotic clozapine at high concentrations increases swimming time in the top of the tank [42]. A traditional neuroleptic haloperidol reduces zebrafish locomotor activity at high (20–80 nM), and increases at low (5 nM), concentrations [43]. Another antipsychotic, fluphenazine, reduces swimming speed of zebrafish larvae at concentrations of 0.98–1.57 nM, and, when combined with haloperidol, impairs motor coordination and orientation, causing characteristic erratic and patterned movements (e.g., swimming up and down and/or side-to-side) [44]. Thus, like in humans, antipsychotic agents can induce delirium-like behavioral patterns and cause impaired attention, memory and motor activity in zebrafish (Fig. 1).

Exposure to morphine reduces zebrafish freezing and increases time in aversive compartment with added alarm substance, suggestive of impaired memory, inattention and loss of orientation in space [45]. In turn, morphine withdrawal in zebrafish produces robust anxiogenic-like effects, increasing freezing time, latency to top and reducing time in top of the novel tank test [46]. A prototypical deliriant anticholinergic hallucinogen, atropine, at 90 mg/L enhances locomotor activity (distance traveled and speed) in zebrafish, while another deliriant hallucinogen from this group, scopolamine, at 120 mg/L reduces the number of top entries and maximum swimming speed, thereby resembling hypoactivity and anxiety seen in delirium clinically [47]. Zebrafish treated with scopolamine are also less susceptible to learning [48], which may also be relevant to cognitive deficits in clinical delirium.

An anti-glutamatergic 'dissociative' hallucinogenic drug, dizocilpine (MK-801), well-known to worsen memory and learning in humans and rodents, at high doses evokes pronounced cognitive impairments in zebrafish, accompanied by stereotypic 'circling' swimming behavior [49]. Another anti-glutamatergic drug, ketamine, evokes similar circling swimming in zebrafish [50], raising the possibility that such phenotype may be relevant to disorientation and/or locomotor signs of delirium mediated via central glutamatergic system. Often causing clinical delirium itself [51], ethanol also evokes delirium in patients upon its withdrawal [52]. In zebrafish, ethanol withdrawal [53] reduces exploration of novel objects, suggestive of impaired attention [54] which may resemble clinical delirium (Table 1). Taken together, this indicates that zebrafish models demonstrate generally high sensitivity to drugs with known delirium-related pharmacological profiles, hence supporting potential utility of these fish to study delirium.

As already mentioned, delirium is caused by multiple other factors beyond drugs [55,56]. For example, patients with type 2 diabetes often present with CNS deficits, including impaired cognitive functions and delirium [57]. Interestingly, zebrafish have gained popularity as a promising model for diabetes-related CNS disorders [58], since chronically exposed to high-sucrose diet fish demonstrate both hyperglycemia and poorer associative and spatial learning [59]. Finally, some other environmental manipulations can also cause delirium-like phenotypes. For instance, in both hypo- (18 °C) and hyper- (34 °C)-thermal conditions, zebrafish exhibit impaired cognitive abilities [60,61], somewhat resembling clinical delirium associated with thermal factors [62].

Zebrafish are also useful for studying delirium and for the development of novel therapies for this disorder, as they show high genetic homology to humans [63] and possess major hormones, neurotransmitters and receptors [64], as well as multiple orthologous dopaminergic, cholinergic and other neurotransmitter genes [65–67] associated with delirium. Zebrafish also display rich behavioral repertoire and neural biomarkers that parallel those altered in clinical delirium states. For instance, human delirium can be assessed by electrophysiological (e.g., EEG) assays [68] that have also been developed in zebrafish [69]. Experimentally induced cognitive- and attention deficits in zebrafish models can be used for predicting the efficacy of pharmacotherapies for cognitive and attention disorders [70,71] relevant to delirium. In zebrafish visual attention paradigm, animals are subjected to a familiarization trial, and after different time delays (from 5 min to 96 h) next tested in the novel object recognition assay [72]. This model enables screening drugs modulating attention and memory, since nicotine (0.02 mg/kg) increases, while scopolamine (0.025 mg/kg) and mecamylamine decrease, object discrimination [72]. Likewise, delirium is often comorbid with neurodegenerative disorders (e.g., Alzheimer's disease) that have successfully been modeled in zebrafish [73], and therefore merit further scrutiny in terms of recapitulating delirium-like states and their comorbidity in such fish models as well.

Given the role of melatonin in regulating sleep-waking cycle (often disrupted in delirium), the link between melatonin and delirium is also plausible [74]. Indeed, melatonin supplementation reduces occurrence of delirium in both adults and elderly patients [75,76]. Zebrafish already represent a promising model of behavioral dysregulation (e.g., sleep and anxiety) associated with melatonin [77], and may therefore be also relevant to delirium-like states. For example, zebrafish have been used as a model of sleep-related behavior and circadian rhythms [78–80], whose disruption by constant luminosity induces cognitive deficits [81] and anxiety [82], corrected by melatonin supplementation [77,83]. Collectively, this suggests melatonin as a putative novel target in translational studies of delirium, whereas zebrafish models can be used to bidirectionally modulate delirium-related phenotypes and screen for novel pro- and anti-deliriant drugs.

Despite clear advantages of using zebrafish to model delirium states, they also present some limitations and challenges. For instance, we recognize that zebrafish, like any animal model organism, cannot fully recapitulate the complex behavioral repertoire of human delirium phenotypes [84,85]. In addition, the zebrafish genome duplication may complicate studying some genes, yet offering interesting opportunities

for studying some others [38,86]. For instance, while the association of the dopamine D2 receptor gene with delirium has been reported clinically [87], this gene has two copies in zebrafish (e.g., *drd2a* and *drd2b*). The latter enables genetic knockout or knockdown of only one copy of the gene, keeping the other copy intact, hence offering a wider spectrum of genotypes (and the resultant behavioral phenotypes) that can be modeled in fish, compared to mammals.

Cross-species analyses of neuroanatomy and its relevance to delirium circuits are also important to consider. For example, in healthy humans, the activity of the dorsolateral prefrontal cortex negatively correlates with activity in the posterior cingulate cortex [88], which is part of the default mode network that is selectively active at rest and during internally directed thought, but becomes deactivated during externally directed tasks [89]. During delirium, this relationship between the two reciprocal circuits is reversed, perhaps contributing to some clinical features of delirium, such as inadequate shifting and focusing of attention [90]. In general, delirium alters multiple neural circuits, often reducing their connectivity strength, global efficiency, local clustering and modularity [91]. Although brain cell types and its major structures are generally similar between zebrafish and other vertebrates [92], some significant differences do exist between the zebrafish and the human brains [64]. For example, while human prefrontal cortex plays a key role in delirium states [91], zebrafish lack cortex [93] and CNS functions attributed to cortex may be controlled in fish by subcortical areas [94]. Collectively, this necessitates further side-by-side cross-taxon studies of neural circuits relevant to delirium-like states.

The search for novel behavioral and physiological biomarkers is another important strategic direction of clinical research of delirium [91]. For instance, clinical delirium can be detected based on monitoring of blinks and eye movements, as it induces fewer blinks and vertical eye movements, but longer blinking and horizontal eye movements [95]. Zebrafish eye development and physiology are similar to that of humans [96], and vision plays an important role in both taxa [97]. Thus, albeit unconventional, testing the idea of developing novel protocols that may assess delirium states by eye movements in zebrafish may indeed be interesting and feasible. Various zebrafish assays (Fig. 1) have been developed to assess several other delirium-related behavioral domains, such as aggression (e.g., the agonistic behavior test, mirror test, and video stimulation test [98,99]), anxiety (e.g., the novel tank, the light-dark, and the open field tests) [100,101]) and general locomotion (e.g., hyper- and hypoactivity) [102].

5. Discussion

Like other CNS disorders, delirium has several subtypes (e.g., ranging in severity from mild to severe, and presenting as either hypo or hyperactive delirium). However, distinguishing delirium from other similar common brain pathologies is both clinically and pre-clinically complicated, necessitating novel measures of delirium severity in future clinical and pre-clinical studies [103]. Genome-wide association studies have recently identified a novel locus for delirium risk on chromosome 2, spanning multiple genes, including two sodium/hydrogen exchange pumps (*SLC9A4* and *SLC9A2*) and three interleukin (IL)-related genes (*IL1RL1, IL18R1* and *IL18RAP*) [104]. Interestingly, zebrafish possess well-conserved IL-1 and IL-18 receptor family members [105] that may be genetically manipulated, and potentially lead to genetic models of delirium-like states in fish. Likewise, cross-species/cross-taxon analyses of other putative evolutionarily conserved (and especially differentially expressed) delirium genes, their clusters, and differentially represented DNA binding sites for transcription factors may help to understand shared molecular mechanisms of delirium pathogenesis.

In addition to neuronal cells, glia may also play an important role in delirium [91]. For example, the failure of the innate system to shut down may result in a cytokine storms seen in sepsis and sepsis-induced delirium. While intact astrocytes with proper cholinergic and anti-inflammatory effects control the innate immune system, astrocytal deficits can trigger exaggerated inflammation that may lead to delirium [106]. Given the importance of neuroglia in CNS disorders and in zebrafish CNS models [107,108], this aquatic organism may also be valuable for probing the role of glia in delirium pathogenesis.

Moreover, delirium has also been linked to epigenetic regulation [109]. For example, the expression of TNF-alpha increases with aging, and a transient acute delirium can be accompanied by elevated TNF-alpha levels [110]. In contrast, DNA methylation of pro-inflammatory cytokine (e.g., TNF-alpha and IL-6) genes decreases in glia [111], and DNA methylation of the TNF-alpha gene negatively correlates with age in patients with postoperative delirium, but not in non-delirium patients after neurosurgery [109]. Overall, these findings further implicate epigenetic mechanisms in pathophysiology of delirium, meriting further scrutiny, including in zebrafish models.

There are also robust and stable sex differences in clinical delirium. For instance, men have higher scores on motor agitation and affective lability, whereas women have a higher frequency of hypoactive delirium [112] but less frequent postoperative delirium following cardiac surgery [113]. In zebrafish models, sex differences are also found in behavior

Table 5
Selected open questions related to modeling delirium in zebrafish.

Questions
• Can delirium be deconstructed into smaller subtypes (e.g., cognitive- vs. attention- vs motor-related vs. mixed) clinically? If yes, can these subtypes be separately modeled in both rodents and zebrafish?
• Are there reliable candidate human 'delirium' genes? If yes, do zebrafish possess their orthologs? What is their estimated genetic homology between humans and fish?
• Are there overt individual and population sex differences in clinical delirium? How variable are individual delirium-like responses in zebrafish?
• As there robust sex differences in clinical delirium, can zebrafish display similar stable sex differences in various delirium-related models?
• Do clinical cognitive and other (e.g., attentional, affective, motor) dimensions of delirium correlate with each other? How do these phenotypic clusters correlate in zebrafish models?
• Selected molecular biomarkers of delirium are listed in Table 4. Are physiological biomarkers of delirium shared between zebrafish, rodents and humans?
• Does delirium represent a common 'wholistic' syndrome based on shared mechanisms, or a constellation of similarly-looking syndromes that are caused by multiple overlapping, but otherwise rather unrelated, factors?
• Are there differences across age in zebrafish delirium responses, similar to the progressive nature of clinical delirium?
• Mounting evidence (discussed in the text) links both central and peripheral inflammation to clinical delirium. Do delirium-like and other inflammation-related (e.g., sickness behavior-like) phenotypes also overlap in zebrafish models?
• How does systemic inflammation and neuroinflammation correlate in clinical delirium? Can such models be also developed for zebrafish relevant to this pathological state?
• Are there characteristic delirium-related patterns of brain gene expression in humans and rodents? How does CNS gene expression correlate with delirium responses in zebrafish models, and with data in mammals?
• Can experimental delirium be epigenetically regulated? If yes, are the patterns of such regulation similar across mammals and fish?
• What are specific neural circuits involved in experimental delirium states? Are they similar for zebrafish models of delirium? Are there species differences that may be important to consider?
• Can zebrafish neurodegenerative (e.g., Alzheimer's or Parkinson's) disease models induce delirium-like phenotypes, with shared and/or disease-specific neurological and physiological effects?
• Can novel automated models and tests be developed to assess zebrafish delirium-like states (e.g., by EEG or eye movement tracking)?
• Can different levels of clinical delirium severity be modeled in zebrafish?
• Can novel molecular targets (e.g., based on melatonin signaling) be identified, and the respective drugs developed, to correct delirium-like states in zebrafish?
• Can artificial intelligence be used to screen specific 'deliriant' drugs and predict their CNS profile based on assessing delirium-related behavior in zebrafish models?
• How to distinguish delirium-like from other similar and common, but distinct pathologies (e.g., seizure) in zebrafish models?
• What is the role of neurons vs. glia in delirium clinically, and in zebrafish models?
• Delirium is often comorbid with schizophrenia and other prevalent neuropsychiatric disorders. Can specific zebrafish models be developed to address this comorbidity aspect of their pathogenesis and/or its therapy?

and neuropharmacology responses [114], as female are more anxious than males [115], and acute exposure to scopolamine causes anxiolytic-like effects in females, and anxiogenic-like effects in males [116]. However, it remains unclear whether zebrafish display similar differences in delirium-related models, hence warranting further studies in this field.

Artificial intelligence (AI) approaches have been applied clinically to characterize and detect delirium-related behavioral signs [117,118]. For instance, AI can successfully predict delirium in patients following cardiac surgery [119]. In zebrafish, AI-driven behavioral analyses have already been developed, successfully detecting Parkinson's-like phenotypes [120] and characterizing a wide range of psychoactive drug responses [121]. For example, zebrafish are highly sensitive to classical deliriant hallucinogenic drugs (e.g., scopolamine and atropine) [47], and it is likely that novel specific 'deliriant' behavioral patterns can be extracted by AI by comparing control fish with those treated with multiple deliriant and non-deliriant drugs. Thus, the possibility of developing innovative AI-based zebrafish screens for detecting aberrant delirium-like behaviors and screening for novel drugs and genetic mutations relevant to delirium pathogenesis, may indeed be promising.

Overall, mounting evidence summarized here highlights key characteristics and recent findings that may foster modeling delirium-like states in zebrafish and support this aquatic species as a promising tool to probe the pathobiology of delirium. As multiple conceptual and practical questions regarding studying delirium in fish remain open (Table 5), this calls for developing further translational models of delirium and its novel therapies in zebrafish.

Data Availability

No data was used for the research described in the article.

Acknowledgements

This study is supported by Sirius University of Science and Technology (Sochi, Russia). A.V.K. is supported by St. Petersburg State University. The study utilized the facilities and equipment of the Resource Fund of Applied Genetics MIPT (support grant 075-15-2021-684).

References

[1] P.S. Sachdev, D. Blacker, D.G. Blazer, M. Ganguli, D.V. Jeste, J.S. Paulsen, R. C. Petersen, Classifying neurocognitive disorders: the DSM-5 approach, Nat. Rev. Neurol. 10 (11) (2014) 634–642.
[2] M. van den Boogaard, A.J.C. Slooter, Delirium in critically ill patients: current knowledge and future perspectives, BJA Educ. 19 (12) (2019) 398–404.
[3] S.K. Inouye, R.G. Westendorp, J.S. Saczynski, Delirium in elderly people, Lancet 383 (9920) (2014) 911–922.
[4] D. Ignjatovic-Ristic, N. Rancic, S. Novokmet, S. Jankovic, S. Stefanovic, Risk factors for lethal outcome in patients with delirium tremens - psychiatrist's perspective: a nested case-control study, Ann. Gen. Psychiatry 12 (1) (2013), 39-39.
[5] A. European Delirium, S. American Delirium, The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer, BMC Med. 12 (2014) 141.
[6] J.R. Maldonado, Neuropathogenesis of delirium: review of current etiologic theories and common pathways, Am. J. Geriatr. Psychiatry 21 (12) (2013) 1190–1222.
[7] A.P. Pereverzev, O.D. Ostroumova, R.I. Isaev, O.N. Tkacheva, Y.V. Kotovskaya, [Drug-induced delirium in elderly and senile patients], Zh. Nevrol. Psikhiatr Im. S S Korsakova 119 (7) (2019) 120–127.
[8] B. Setters, L.M. Solberg, Delirium, Prim. Care 44 (3) (2017) 541–559.
[9] D. Adamis, A. Treloar, F.C. Martin, A.J. Macdonald, A brief review of the history of delirium as a mental disorder, Hist. Psychiatry 18 (72 Pt 4) (2007) 459–469.
[10] T.T. Hshieh, T.G. Fong, E.R. Marcantonio, S.K. Inouye, Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 63 (7) (2008) 764–772.
[11] K.M. Zimmerman, M. Salow, L.M. Skarf, T. Kostas, A. Paquin, M.J. Simone, J. Rudolph, Increasing anticholinergic burden and delirium in palliative care inpatients, Palliat. Med. 28 (4) (2014) 335–341.
[12] J.L. Rudolph, B. Ramlawi, G.A. Kuchel, J.E. McElhaney, D. Xie, F.W. Sellke, K. Khabbaz, S.E. Levkoff, E.R. Marcantonio, Chemokines are associated with delirium after cardiac surgery, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 63 (2) (2008) 184–189.
[13] B.C. van Munster, A.H. Zwinderman, S.E. de Rooij, Genetic variations in the interleukin-6 and interleukin-8 genes and the interleukin-6 receptor gene in delirium, Rejuvenation Res. 14 (4) (2011) 425–428.
[14] B.A. Khan, A.J. Perkins, S. Gao, S.L. Hui, N.L. Campbell, M.O. Farber, L.L. Chlan, M.A. Boustani, The CAM-ICU-7 delirium severity scale: a novel delirium severity instrument for use in the intensive care unit, Crit. Care Med. 45 (5) (2017) 851.
[15] S.M. Vasunilashorn, L. Ngo, S.K. Inouye, T.A. Libermann, R.N. Jones, D.C. Alsop, J. Guess, S. Jastrzebski, J.E. McElhaney, G.A. Kuchel, E.R. Marcantonio, Cytokines and postoperative delirium in older patients undergoing major elective surgery, J. Gerontol. A Biol. Sci. Med. Sci. 70 (10) (2015) 1289–1295.
[16] C. Ritter, C.D. Tomasi, F. Dal-Pizzol, B.B. Pinto, A. Dyson, A.S. de Miranda, C. M. Comim, M. Soares, A.L. Teixeira, J. Quevedo, M. Singer, Inflammation biomarkers and delirium in critically ill patients, Crit. Care 18 (3) (2014) R106.
[17] T.D. Girard, L.B. Ware, G.R. Bernard, P.P. Pandharipande, J.L. Thompson, A. K. Shintani, J.C. Jackson, R.S. Dittus, E.W. Ely, Associations of markers of inflammation and coagulation with delirium during critical illness, Intensive Care Med. 38 (12) (2012) 1965–1973.
[18] J. Kazmierski, A. Banys, J. Latek, J. Bourke, R. Jaszewski, Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study, Crit. Care 17 (2) (2013) 1–10.
[19] Y. Colkesen, S. Giray, Y. Ozenli, N. Sezgin, I. Coskun, Relation of serum cortisol to delirium occurring after acute coronary syndromes, Am. J. Emerg. Med. 31 (1) (2013) 161–165.
[20] P.T. Trzepacz, M. Leavitt, K. Ciongoli, An animal model for delirium, Psychosomatics 33 (4) (1992) 404–415.
[21] I.C. Hoogland, C. Houbolt, D.J. van Westerloo, W.A. van Gool, D. van de Beek, Systemic inflammation and microglial activation: systematic review of animal experiments, J. Neuroinflamm. 12 (2015) 114.
[22] T. Kawano, D. Yamanaka, B. Aoyama, H. Tateiwa, M. Shigematsu-Locatelli, A. Nishigaki, H. Iwata, F.M. Locatelli, M. Yokoyama, Involvement of acute neuroinflammation in postoperative delirium-like cognitive deficits in rats, J. Anesth. 32 (4) (2018) 506–517.
[23] K.M. Rieck, S. Pagali, D.M. Miller, Delirium in hospitalized older adults, Hosp. Pr. 48 (Supl 1) (2020) 3–16 (1995).
[24] R. Velagapudi, S. Subramaniyan, C. Xiong, F. Porkka, R.M. Rodriguiz, W. C. Wetsel, N. Terrando, Orthopedic surgery triggers attention deficits in a delirium-like mouse model, Front Immunol. 10 (2019) 2675.
[25] A.J. Duszkiewicz, C.G. McNamara, T. Takeuchi, L. Genzel, Novelty and dopaminergic modulation of memory persistence: a tale of two systems, Trends Neurosci. 42 (2) (2019) 102–114.
[26] M. Peng, C. Zhang, Y. Dong, Y. Zhang, H. Nakazawa, M. Kaneki, H. Zheng, Y. Shen, E.R. Marcantonio, Z. Xie, Battery of behavioral tests in mice to study postoperative delirium, Sci. Rep. 6 (2016) 29874.
[27] N. Liufu, L. Liu, S. Shen, Z. Jiang, Y. Dong, Y. Wang, D. Culley, G. Crosby, M. Cao, Y. Shen, E. Marcantonio, Z. Xie, Y. Zhang, Anesthesia and surgery induce age-dependent changes in behaviors and microbiota, Aging (Albany NY) 12 (2) (2020) 1965–1986.
[28] M. Cibelli, A.R. Fidalgo, N. Terrando, D. Ma, C. Monaco, M. Feldmann, M. Takata, I.J. Lever, J. Nanchahal, M.S. Fanselow, M. Maze, Role of interleukin-1beta in postoperative cognitive dysfunction, Ann. Neurol. 68 (3) (2010) 360–368.
[29] J. Kealy, C. Murray, E.W. Griffin, A.B. Lopez-Rodriguez, D. Healy, L.S. Tortorelli, J.P. Lowry, L.O. Watne, C. Cunningham, Acute inflammation alters brain energy metabolism in mice and humans: role in suppressed spontaneous activity, impaired cognition, and delirium, J. Neurosci. 40 (29) (2020) 5681–5696.
[30] Y. Tamura, S. Chiba, H. Takasaki, K. Tabata, Y. Ishimaru, T. Ishimoto, Biperiden-induced delirium model in rats: a behavioral and electroencephalographic study, Brain Res. 1115 (1) (2006) 194–199.
[31] J.F. Cryan, A. Holmes, The ascent of mouse: advances in modelling human depression and anxiety, Nat. Rev. Drug Discov. 4 (9) (2005) 775–790.
[32] M.S. de Abreu, A.V. Kalueff, Of mice and zebrafish: the impact of the experimenter identity on animal behavior, Lab Anim. 50 (1) (2021), 7-7.
[33] M.S. de Abreu, A.C.V.V. Giacomini, D.J. Echevarria, A.V. Kalueff, Legal aspects of zebrafish neuropharmacology and neurotoxicology research, Regul. Toxicol. Pharmacol. 101 (2019) 65–70.
[34] F.V. Costa, T.O. Kolesnikova, D.S. Galstyan, N.P. Ilyin, M.S. de Abreu, E. V. Petersen, K.A. Demin, K.B. Yenkoyan, A.V. Kalueff, Current state of modeling human psychiatric disorders using zebrafish, Int. J. Mol. Sci. 24 (4) (2023) 3187.
[35] K.M. Khan, A.D. Collier, D.A. Meshalkina, E.V. Kysil, S.L. Khatsko, T. Kolesnikova, Y.Y. Morzherin, J.E. Warnick, A.V. Kalueff, D.J. Echevarria, Zebrafish models in neuropsychopharmacology and CNS drug discovery, Br. J. Pharm. 174 (13) (2017) 1925–1944.
[36] D.G. Howe, Y.M. Bradford, T. Conlin, A.E. Eagle, D. Fashena, K. Frazer, J. Knight, P. Mani, R. Martin, S.A. Moxon, H. Paddock, C. Pich, S. Ramachandran, B.J. Ruef, L. Ruzicka, K. Schaper, X. Shao, A. Singer, B. Sprunger, C.E. Van Slyke, M. Westerfield, ZFIN, the zebrafish model organism database: increased support for mutants and transgenics, Nucleic Acids Res. 41 (2013) D854–D860 (Database Issue).
[37] C.B. Kimmel, Genetics and early development of zebrafish, Trends Genet. 5 (8) (1989) 283–288.
[38] A.V. Kalueff, A.M. Stewart, R. Gerlai, Zebrafish as an emerging model for studying complex brain disorders, Trends Pharmacol. Sci. 35 (2) (2014) 63–75.
[39] D.R.W. Burrows, E. Samarut, J. Liu, S.C. Baraban, M.P. Richardson, M.P. Meyer, R.E. Rosch, Imaging epilepsy in larval zebrafish, Eur. J. Paediatr. Neurol. 24 (2020) 70–80.

[40] T.E. Muller, B.D. Fontana, K.T. Bertoncello, F. Franscescon, N.J. Mezzomo, J. Canzian, F.V. Stefanello, M.O. Parker, R. Gerlai, D.B. Rosemberg, Understanding the neurobiological effects of drug abuse: lessons from zebrafish models, Prog. Neuropsychopharmacol. Biol. Psychiatry 100 (2020), 109873.
[41] N.R. Martin, J.S. Plavicki, Advancing zebrafish as a model for studying developmental neurotoxicology, J. Neurosci. Res. 98 (6) (2020) 981–983.
[42] J. Viana, N. Wildman, E. Hannon, A. Farbos, P.O. Neill, K. Moore, R. van Aerle, G. Paull, E. Santos, J. Mill, Clozapine-induced transcriptional changes in the zebrafish brain, NPJ Schizophr. 6 (1) (2020) 3.
[43] G. Bruni, A.J. Rennekamp, A. Velenich, M. McCarroll, L. Gendelev, E. Fertsch, J. Taylor, P. Lakhani, D. Lensen, T. Evron, P.J. Lorello, X.P. Huang, S. Kolczewski, G. Carey, B.J. Caldarone, E. Prinssen, B.L. Roth, M.J. Keiser, R.T. Peterson, D. Kokel, Zebrafish behavioral profiling identifies multitarget antipsychotic-like compounds, Nat. Chem. Biol. 12 (7) (2016) 559–566.
[44] N.J. Giacomini, B. Rose, K. Kobayashi, S. Guo, Antipsychotics produce locomotor impairment in larval zebrafish, Neurotoxicol Teratol. 28 (2) (2006) 245–250.
[45] M. Sivalingam, S. Ogawa, I.S. Parhar, Habenula kisspeptin retrieves morphine impaired fear memory in zebrafish, Sci. Rep. 10 (1) (2020) 19569.
[46] B.S. Khor, M.F. Jamil, M.I. Adenan, A.C. Shu-Chien, Mitragynine attenuates withdrawal syndrome in morphine-withdrawn zebrafish, PLoS One 6 (12) (2011), e28340.
[47] A.D. Volgin, O.A. Yakovlev, K.A. Demin, P.A. Alekseeva, A.V. Kalueff, Acute behavioral effects of deliriant hallucinogens atropine and scopolamine in adult zebrafish, Behav. Brain Res. 359 (2019) 274–280.
[48] Y.H. Kim, Y. Lee, D. Kim, M.W. Jung, C.J. Lee, Scopolamine-induced learning impairment reversed by physostigmine in zebrafish, Neurosci. Res. 67 (2) (2010) 156–161.
[49] F. Franscescon, T.E. Muller, K.T. Bertoncello, D.B. Rosemberg, Neuroprotective role of taurine on MK-801-induced memory impairment and hyperlocomotion in zebrafish, Neurochem. Int. 135 (2020), 104710.
[50] S.M. Zakhary, D. Ayubcha, F. Ansari, K. Kamran, M. Karim, J.R. Leheste, J. M. Horowitz, G. Torres, A behavioral and molecular analysis of ketamine in zebrafish, Synapse 65 (2) (2011) 160–167.
[51] J. Perälä, K. Kuoppasalmi, S. Pirkola, T. Härkänen, S. Saarni, A. Tuulio-Henriksson, S. Viertiö, A. Latvala, S. Koskinen, J. Lönnqvist, J. Suvisaari, Alcohol-induced psychotic disorder and delirium in the general population, Br. J. Psychiatry 197 (3) (2010) 200–206.
[52] D.W. Kim, H.K. Kim, E.K. Bae, S.H. Park, K.K. Kim, Clinical predictors for delirium tremens in patients with alcohol withdrawal seizures, Am. J. Emerg. Med. 33 (5) (2015) 701–704.
[53] S.N. da Silva Chaves, G.R. Felicio, B.P.D. Costa, W.E.A. de Oliveira, M.G. Lima-Maximino, D.H. Siqueira Silva, C. Maximino, Behavioral and biochemical effects of ethanol withdrawal in zebrafish, Pharm. Biochem. Behav. 169 (2018) 48–58.
[54] J.T. Krook, E. Duperreault, D. Newton, M.S. Ross, T.J. Hamilton, Repeated ethanol exposure increases anxiety-like behaviour in zebrafish during withdrawal, PeerJ 7 (2019), e6551.
[55] R.C. van der Mast, Pathophysiology of delirium, J. Geriatr. Psychiatry Neurol. 11 (3) (1998) 138–145, discussion 157-8.
[56] S. Sahoo, A. Mehra, S. Grover, Acute hyperglycemia associated with psychotic symptoms in a patient with type 1 diabetes mellitus: a case report, Innov. Clin. Neurosci. 13 (11–12) (2016) 25–27.
[57] R. Lopes, B.D. Pereira, Delirium and psychotic symptoms associated with hyperglycemia in a patient with poorly controlled type 2 diabetes mellitus, Innov. Clin. Neurosci. 15 (5–6) (2018) 30–33.
[58] A.M. Lakstygal, M.S. de Abreu, D. Lifanov, E.A. Wappler-Guzetta, N. Serikuly, E. T. Alpsychov, D. Wang, M. Wang, Z. Tang, N. Yan, Zebrafish models of diabetes-related CNS pathogenesis, Prog. Neuro-Psychopharmacol. Biol. Psychiatry (2018).
[59] S. Ranjan, P.K. Sharma, Study of learning and memory in type 2 diabetic model of zebrafish (Danio rerio), Endocrine Metab. Sci. 1 (3–4) (2020), 100058.
[60] M. Toni, E. Angiulli, G. Miccoli, C. Cioni, E. Alleva, F. Frabetti, F. Pizzetti, F. G. Scalvini, S. Nonnis, A. Negri, Environmental temperature variation affects brain protein expression and cognitive abilities in adult zebrafish (*Danio rerio*): a proteomic and behavioural study, J. Proteom. 204 (2019), 103396.
[61] S. Nonnis, E. Angiulli, E. Maffioli, F. Frabetti, A. Negri, C. Cioni, E. Alleva, V. Romeo, G. Tedeschi, M. Toni, Acute environmental temperature variation affects brain protein expression, anxiety and explorative behaviour in adult zebrafish, Sci. Rep. 11 (1) (2021) 1–21.
[62] W.P. Cheshire, Thermoregulatory disorders and illness related to heat and cold stress, Autonom. Neurosci. 196 (2016) 91–104.
[63] K. Howe, M.D. Clark, C.F. Torroja, J. Torrance, C. Berthelot, M. Muffato, J. E. Collins, S. Humphray, K. McLaren, L. Matthews, S. McLaren, I. Sealy, M. Caccamo, C. Churcher, C. Scott, J.C. Barrett, R. Koch, G.J. Rauch, S. White, W. Chow, B. Kilian, L.T. Quintais, J.A. Guerra-Assunção, Y. Zhou, Y. Gu, J. Yen, J. H. Vogel, T. Eyre, S. Redmond, R. Banerjee, J. Chi, B. Fu, E. Langley, S.F. Maguire, G.K. Laird, D. Lloyd, E. Kenyon, S. Donaldson, H. Sehra, J. Almeida-King, J. Loveland, S. Trevanion, M. Jones, M. Quail, D. Willey, A. Hunt, J. Burton, S. Sims, K. McLay, B. Plumb, J. Davis, C. Clee, K. Oliver, R. Clark, C. Riddle, D. Elliot, D. Eliott, G. Threadgold, G. Harden, D. Ware, S. Begum, B. Mortimore, B. Mortimer, G. Kerry, P. Heath, B. Phillimore, A. Tracey, N. Corby, M. Dunn, C. Johnson, J. Wood, S. Clark, S. Pelan, G. Griffiths, M. Smith, R. Glithero, P. Howden, N. Barker, C. Lloyd, C. Stevens, J. Harley, K. Holt, G. Panagiotidis, J. Lovell, H. Beasley, C. Henderson, D. Gordon, K. Auger, D. Wright, J. Collins, C. Raisen, L. Dyer, K. Leung, L. Robertson, K. Ambridge, D. Leongamornlert, S. McGuire, R. Gilderthorp, C. Griffiths, D. Manthravadi, S. Nichol, G. Barker, S. Whitehead, M. Kay, J. Brown, C. Murnane, E. Gray, M. Humphries, N. Sycamore, D. Barker, D. Saunders, J. Wallis, A. Babbage, S. Hammond, M. Mashreghi-Mohammadi, L. Barr, S. Martin, P. Wray, A. Ellington, N. Matthews, M. Ellwood, R. Woodmansey, G. Clark, J. Cooper, A. Tromans, D. Grafham, C. Skuce, R. Pandian, R. Andrews, E. Harrison, A. Kimberley, J. Garnett, N. Fosker, R. Hall, P. Garner, D. Kelly, C. Bird, S. Palmer, I. Gehring, A. Berger, C.M. Dooley, Z. Ersan-Ürün, C. Eser, H. Geiger, M. Geisler, L. Karotki, A. Kirn, J. Konantz, M. Konantz, M. Oberländer, S. Rudolph-Geiger, M. Teucke, C. Lanz, G. Raddatz, K. Osoegawa, B. Zhu, A. Rapp, S. Widaa, C. Langford, F. Yang, S.C. Schuster, N.P. Carter, J. Harrow, Z. Ning, J. Herrero, S.M. Searle, A. Enright, R. Geisler, R.H. Plasterk, C. Lee, M. Westerfield, P.J. de Jong, L.I. Zon, J.H. Postlethwait, C. Nüsslein-Volhard, T.J. Hubbard, H. Roest Crollius, J. Rogers, D.L. Stemple, The zebrafish reference genome sequence and its relationship to the human genome, Nature 496 (7446) (2013) 498–503.
[64] P. Panula, Y.-C. Chen, M. Priyadarshini, H. Kudo, S. Semenova, M. Sundvik, V. Sallinen, The comparative neuroanatomy and neurochemistry of zebrafish CNS systems of relevance to human neuropsychiatric diseases, Neurobiol. Dis. 40 (1) (2010) 46–57.
[65] J. Schweitzer, W. Driever, Development of the dopamine systems in zebrafish, in: R.J. Pasterkamp, M.P. Smidt, J.P.H. Burbach (Eds.), Development and Engineering of Dopamine Neurons, Springer, New York, New York, NY, 2009, pp. 1–14.
[66] D. Clemente, A. Porteros, E. Weruaga, J.R. Alonso, F.J. Arenzana, J. Aijón, R. Arévalo, Cholinergic elements in the zebrafish central nervous system: histochemical and immunohistochemical analysis, J. Comp. Neurol. 474 (1) (2004) 75–107.
[67] F.J. Arenzana, D. Clemente, R. Sánchez-González, Á. Porteros, J. Aijón, R. Arévalo, Development of the cholinergic system in the brain and retina of the zebrafish, Brain Res. Bull. 66 (4) (2005) 421–425.
[68] S. Jacobson, H. Jerrier, EEG in delirium, Semin Clin. Neuropsychiatry 5 (2) (2000) 86–92.
[69] Y. Lee, K.J. Lee, J.-W. Jang, S. Kim, An EEG system to detect brain signals from multiple adult zebrafish, Biosens. Bioelectron. 164 (2020), 112315.
[70] D.J. Echevarria, D.J. Jouandot, C.N. Toms, Assessing attention in the zebrafish: are we there yet? Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (6) (2011) 1416–1420.
[71] D.A. Meshalkina, M.N. Kizlyk, E.V. Kysil, A.D. Collier, D.J. Echevarria, M. S. Abreu, L.J.G. Barcellos, C. Song, A.V. Kalueff, Understanding zebrafish cognition, Behav. Process. 141 (2017) 229–241.
[72] D. Braida, L. Ponzoni, R. Martucci, M. Sala, A new model to study visual attention in zebrafish, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 55 (2014) 80–86.
[73] S. Saleem, R.R. Kannan, Zebrafish: an emerging real-time model system to study Alzheimer's disease and neurospecific drug discovery, Cell Death Discov. 4 (1) (2018) 1–13.
[74] S.G. Joseph, Melatonin supplementation for the prevention of hospital-associated delirium, Ment. Health Clin. 7 (4) (2017) 143–146.
[75] S. Chen, L. Shi, F. Liang, L. Xu, D. Desislava, Q. Wu, J. Zhang, Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials, Mol. Neurobiol. 53 (6) (2016) 4046–4053.
[76] K.T. Ng, W.Y. Teoh, A.J. Khor, The effect of melatonin on delirium in hospitalised patients: a systematic review and meta-analyses with trial sequential analysis, J. Clin. Anesth. 59 (2020) 74–81.
[77] R. Genario, A.C.V.V. Giacomini, K.A. Demin, B.E. dos Santos, N.I. Marchiori, A. D. Volgin, A. Bashirzade, T.G. Amstislavskaya, M.S. de Abreu, A.V. Kalueff, The evolutionarily conserved role of melatonin in CNS disorders and behavioral regulation: translational lessons from zebrafish, Neurosci. Biobehav. Rev. 99 (2019) 117–127.
[78] I.V. Zhdanova, Sleep and its regulation in zebrafish, Rev. Neurosci. 22 (1) (2011) 27–36.
[79] G.M.J.C. Cahill, T. Research, Clock mechanisms in zebrafish 309 (1) (2002) 27–34.
[80] I. Elbaz, N. Foulkes, Y. Gothilf, L. Appelbaum, Circadian clocks, rhythmic synaptic plasticity and the sleep-wake cycle in zebrafish 7 (9) (2013).
[81] J. Pinheiro-da-Silva, S. Tran, P.F. Silva, A.C. Luchiari, Good night, sleep tight: the effects of sleep deprivation on spatial associative learning in zebrafish, Pharmacol. Biochem. Behav. 159 (2017) 36–47.
[82] A. Singh, N. Subhashini, S. Sharma, B.N. Mallick, Involvement of the α1-adrenoceptor in sleep–waking and sleep loss-induced anxiety behavior in zebrafish, Neuroscience 245 (2013) 136–147.
[83] A.C.V.V. Giacomini, K.H. Teixeira, L. Marcon, N. Scolari, B.W. Bueno, R. Genario, N.S. de Abreu, K.A. Demin, D.S. Galstyan, A.V. Kalueff, M.S. de Abreu, Melatonin treatment reverses cognitive and endocrine deficits evoked by a 24-h light exposure in adult zebrafish, Neurosci. Lett. 733 (2020), 135073.
[84] T.D. Girard, J.L. Thompson, P.P. Pandharipande, N.E. Brummel, J.C. Jackson, M. B. Patel, C.G. Hughes, R. Chandrasekhar, B.T. Pun, L.M. Boehm, M.R. Elstad, R. B. Goodman, G.R. Bernard, R.S. Dittus, E.W. Ely, Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study, Lancet Respir. Med 6 (3) (2018) 213–222.
[85] E.M.L. Bowman, E.L. Cunningham, V.J. Page, D.F. McAuley, Phenotypes and subphenotypes of delirium: a review of current categorisations and suggestions for progression, Crit. Care 25 (1) (2021) 1–13.
[86] D.A. Meshalkina, M.N. Kizlyk, E.V. Kysil, A.D. Collier, D.J. Echevarria, M. S. Abreu, L.J.G. Barcellos, C. Song, J.E. Warnick, E.J. Kyzar, A.V. Kalueff, Zebrafish models of autism spectrum disorder, Exp. Neurol. 299 (Part A) (2018) 207–216.
[87] B.C. van Munster, S. de Rooij, M. Yazdanpanah, P.J. Tienari, K.H. Pitkälä, R. J. Osse, D. Adamis, O. Smit, M.S. van der Steen, M. van Houten, T. Rahkonen,

R. Sulkava, J.V. Laurila, T.E. Strandberg, J.H.M. Tulen, L. Zwang, A.J. D. MacDonald, A. Treloar, E.J.G. Sijbrands, A.H. Zwinderman, J.C. Korevaar, The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium, a meta-analysis, Am. J. Med. Genet. B Neuropsychiatr. Genet. 153b (2) (2010) 648–655.
[88] S.-H. Choi, H. Lee, T.-S. Chung, K.-M. Park, Y.-C. Jung, S.I. Kim, J.-J. Kim, Neural network functional connectivity during and after an episode of delirium, Am. J. Psychiatry 169 (5) (2012) 498–507.
[89] M.E. Raichle, The brain's default mode network, Annu. Rev. Neurosci. 38 (2015) 433–447.
[90] C.J. Stam, Modern network science of neurological disorders, Nat. Rev. Neurosci. 15 (10) (2014) 683–695.
[91] J.E. Wilson, M.F. Mart, C. Cunningham, Y. Shehabi, T.D. Girard, A.M. J. MacLullich, A.J.C. Slooter, E.W. Ely, Delirium, Nat. Rev. Dis. Prim. 6 (1) (2020) 1–26.
[92] P. Blader, U. Strähle, Zebrafish developmental genetics and central nervous system development, Hum. Mol. Genet. 9 (6) (2000) 945–951.
[93] M.O. Parker, A.J. Brock, R.T. Walton, C.H. Brennan, The role of zebrafish (*Danio rerio*) in dissecting the genetics and neural circuits of executive function, Front. Neural Circuits 7 (2013), 63-63.
[94] Y. Geng, R.T. Peterson, The zebrafish subcortical social brain as a model for studying social behavior disorders, Dis. Models Mech. 12 (8) (2019) dmm039446.
[95] A.W. van der Kooi, M.L. Rots, G. Huiskamp, F.A.M. Klijn, H.L. Koek, J. Kluin, F.S. S. Leijten, A.J.C. Slooter, Delirium detection based on monitoring of blinks and eye movements, Am. J. Geriatr. Psychiatry 22 (12) (2014) 1575–1582.
[96] R. Richardson, D. Tracey-White, A. Webster, M. Moosajee, The zebrafish eye—a paradigm for investigating human ocular genetics, Eye 31 (1) (2017) 68.
[97] D.M. Guthrie, Role of vision in fish behaviour, Behav. Teleost Fishes Springer (1986) 75–113.
[98] M.S. de Abreu, A.C.V.V. Giacomini, R. Genario, B.E. Dos Santos, L.G. da Rosa, K. A. Demin, E.A. Wappler-Guzzetta, A.V. Kalueff, Neuropharmacology, pharmacogenetics and pharmacogenomics of aggression: the zebrafish model, Pharm. Res. 141 (2019) 602–608.
[99] K.N. Zabegalov, T.O. Kolesnikova, S.L. Khatsko, A.D. Volgin, O.A. Yakovlev, T. G. Amstislavskaya, A.J. Friend, W. Bao, P.A. Alekseeva, A.M. Lakstygal, D. A. Meshalkina, K.A. Demin, M.S. de Abreu, D.B. Rosemberg, A.V. Kalueff, Understanding zebrafish aggressive behavior, Behav. Process. 158 (2019) 200–210.
[100] K.A. Demin, A.S. Taranov, N.P. Ilyin, A.M. Lakstygal, A.D. Volgin, M.S. de Abreu, T. Strekalova, A.V. Kalueff, Understanding neurobehavioral effects of acute and chronic stress in zebrafish, Stress (2020) 1–48.
[101] M.S. de Abreu, K.A. Demin, T.G. Amstislavskaya, T. Strekalova, A.V. Kalueff, - Zebrafish models for stress research, in: G. Fink (Ed.), Stress: Genetics, Epigenetics and Genomics, Academic Press, 2021, pp. 263–268.
[102] A.V. Kalueff, M. Gebhardt, A.M. Stewart, J.M. Cachat, M. Brimmer, J.S. Chawla, C. Craddock, E.J. Kyzar, A. Roth, S. Landsman, S. Gaikwad, K. Robinson, E. Baatrup, K. Tierney, A. Shamchuk, W. Norton, N. Miller, T. Nicolson, O. Braubach, C.P. Gilman, J. Pittman, D.B. Rosemberg, R. Gerlai, D. Echevarria, E. Lamb, S.C. Neuhauss, W. Weng, L. Bally-Cuif, H. Schneider, Towards a comprehensive catalog of zebrafish behavior 1.0 and beyond, Zebrafish 10 (1) (2013) 70–86.
[103] C.G. Hughes, N.E. Brummel, E.E. Vasilevskis, T.D. Girard, P.P. Pandharipande, Future directions of delirium research and management, Best. Pract. Res. Clinical Anaesthesiol. 26 (3) (2012) 395–405.
[104] T.H. McCoy Jr, K. Hart, A. Pellegrini, R.H. Perlis, Genome-wide association identifies a novel locus for delirium risk, Neurobiol. Aging 68 (2018) 160–e9.
[105] M.O. Huising, R.J.M. Stet, H.F.J. Savelkoul, B.M.L. Verburg-van Kemenade, The molecular evolution of the interleukin-1 family of cytokines; IL-18 in teleost fish, Dev. Comp. Immunol. 28 (5) (2004) 395–413.
[106] A. Sfera, C. Osorio, A.I. Price, R. Gradini, M. Cummings, Delirium from the gliocentric perspective, Front. Cell. Neurosci. 9 (2015) 171.
[107] N. Jurisch-Yaksi, E. Yaksi, C. Kizil, Radial glia in the zebrafish brain: Functional, structural, and physiological comparison with the mammalian glia, Glia 68 (12) (2020) 2451–2470.
[108] K.N. Zabegalov, D. Wang, L. Yang, J. Wang, G. Hu, N. Serikuly, E.T. Alpyshov, S. L. Khatsko, A. Zhdanov, K.A. Demin, D.S. Galstyan, A.D. Volgin, M.S. de Abreu, T. Strekalova, C. Song, T.G. Amstislavskaya, Y. Sysoev, P.E. Musienko, A. V. Kalueff, Decoding the role of zebrafish neuroglia in CNS disease modeling, Brain Res. Bull. 166 (2021) 44–53.
[109] T. Yamanashi, T. Nagao, N.E. Wahba, P.S. Marra, K.J. Crutchley, A.A. Meyer, A. J. Andreasen, M.M. Hellman, S.S. Jellison, C.G. Hughes, DNA methylation in the inflammatory genes after neurosurgery and diagnostic ability of post-operative delirium, Translational, Psychiatry 11 (1) (2021) 1–10.
[110] S.K. Inouye, R.G.J. Westendorp, J.S. Saczynski, Delirium in elderly people, Lancet (Lond., Engl.) 383 (9920) (2014) 911–922.
[111] G. Shinozaki, P.R. Braun, B.W.Q. Hing, A. Ratanatharathorn, M.J. Klisares, G. N. Duncan, S.S. Jellison, J.T. Heinzman, Y. Nagahama, L. Close, Epigenetics of delirium and aging: potential role of DNA methylation change on cytokine genes in glia and blood along with aging, Front. Aging Neurosci. 10 (2018) 311.
[112] P.T. Trzepacz, J.G. Franco, D.J. Meagher, Y. Lee, J.-L. Kim, Y. Kishi, L. M. Furlanetto, D. Negreiros, M.-C. Huang, C.-H. Chen, Delirium phenotype by age and sex in a pooled data set of adult patients, J. Neuropsychiatry Clin. Neurosci. 30 (4) (2018) 294–301.
[113] H. Wang, X. Guo, X. Zhu, Y. Li, Y. Jia, Z. Zhang, S. Yuan, F. Yan, Gender differences and postoperative delirium in adult patients undergoing cardiac valve surgery, Front. Cardiovasc. Med. 8 (2021) 1737.
[114] R. Genario, M.S. de Abreu, A.C.V.V. Giacomini, K.A. Demin, A.V. Kalueff, Sex differences in behavior and neuropharmacology of zebrafish, Eur. J. Neurosci. 52 (1) (2020) 2586–2603.
[115] R. Genario, A.C.V.V. Giacomini, M.S. de Abreu, L. Marcon, K.A. Demin, A. V. Kalueff, Sex differences in adult zebrafish anxiolytic-like responses to diazepam and melatonin, Neurosci. Lett. 714 (2020), 134548.
[116] B.E. dos Santos, A.C.V.V. Giacomini, L. Marcon, K.A. Demin, T. Strekalova, M. S. de Abreu, A.V. Kalueff, Sex differences shape zebrafish performance in a battery of anxiety tests and in response to acute scopolamine treatment, Neurosci. Lett. (2021), 135993.
[117] C. Hercus, A.-R. Hudaib, Delirium misdiagnosis risk in psychiatry: a machine learning-logistic regression predictive algorithm, BMC Health Serv. Res. 20 (1) (2020) 1–7.
[118] H. Ocagli, D. Bottigliengo, G. Lorenzoni, D. Azzolina, A.S. Acar, S. Sorgato, L. Stivanello, M. Degan, D. Gregori, A machine learning approach for investigating delirium as a multifactorial syndrome, Int. J. Environ. Res. Public Health 18 (13) (2021) 7105.
[119] J. Fliegenschmidt, N. Hulde, M.G. Preising, S. Ruggeri, R. Szymanowski, L. Meesseman, H. Sun, V. von Dossow, Artificial intelligence predicts delirium following cardiac surgery: a case study, J. Clin. Anesth. 75 (2021), 110473.
[120] A.A.O. Bashirzade, S.V. Cheresiz, A.S. Belova, A.V. Drobkov, A.D. Korotaeva, S. Azizi-Arani, A. Azimirad, E. Odle, E.-Y.V. Gild, O.V. Ardashov, MPTP-treated zebrafish recapitulate 'Late-Stage'Parkinson's-like cognitive decline, Toxics 10 (2) (2022) 69.
[121] D.V. Bozhko, V.O. Myrov, S.M. Kolchanova, A.I. Polovian, G.K. Galumov, K. A. Demin, K.N. Zabegalov, T. Strekalova, M.S. de Abreu, E.V. Petersen, A. V. Kalueff, Artificial intelligence-driven phenotyping of zebrafish psychoactive drug responses, Prog. Neuro-Psychopharmacol. Biol. Psychiatry (2021), 110405.
[122] J.R. Maldonado, Delirium in the acute care setting: characteristics, diagnosis and treatment, Crit. Care Clin. 24 (4) (2008) 657–722.
[123] J.H. Flaherty, J. Yue, J.L. Rudolph, Dissecting delirium: phenotypes, consequences, screening, diagnosis, prevention, treatment, and program implementation, Clin. Geriatr. Med. 33 (3) (2017) 393–413.
[124] J. Gaertner, S. Eychmueller, T. Leyhe, D. Bueche, E. Savaskan, M. Schlogl, Benzodiazepines and/or neuroleptics for the treatment of delirium in palliative care?-a critical appraisal of recent randomized controlled trials, Ann. Palliat. Med. 8 (4) (2019) 504–515.
[125] S.K. Inouye, Delirium in older persons, N. Engl. J. Med. 354 (11) (2006) 1157–1165.
[126] T.D. Girard, J.L. Thompson, P.P. Pandharipande, N.E. Brummel, J.C. Jackson, M. B. Patel, C.G. Hughes, R. Chandrasekhar, B.T. Pun, L.M. Boehm, M.R. Elstad, R. B. Goodman, G.R. Bernard, R.S. Dittus, E.W. Ely, Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study, Lancet Respir. Med. 6 (3) (2018) 213–222.
[127] L.E. Tune, S. Egeli, Acetylcholine and delirium, Dement Geriatr. Cogn. Disord. 10 (5) (1999) 342–344.
[128] J.E. Wilson, M.F. Mart, C. Cunningham, Y. Shehabi, T.D. Girard, A.M. J. MacLullich, A.J.C. Slooter, E.W. Ely, Delirium, Nat. Rev. Dis. Prim. 6 (1) (2020) 90.
[129] A.M. Lakstygal, T.O. Kolesnikova, S.L. Khatsko, K.N. Zabegalov, A.D. Volgin, K. A. Demin, V.A. Shevyrin, E.A. Wappler-Guzzetta, A.V. Kalueff, DARK classics in chemical neuroscience: atropine, scopolamine, and other anticholinergic deliriant hallucinogens, ACS Chem. Neurosci. 10 (5) (2019) 2144–2159.
[130] R.C. Arora, C. Cunningham, Losing sleep over delirium, Crit. Care Med. 46 (6) (2018) 1036–1038.
[131] S.S. Dunne, J.C. Coffey, S. Konje, S. Gasior, C.C. Clancy, G. Gulati, D. Meagher, C. P. Dunne, Biomarkers in delirium: a systematic review, J. Psychosom. Res. 147 (2021), 110530.
[132] R.J. Osse, D. Fekkes, J.H. Tulen, A.I. Wierdsma, A.J. Bogers, R.C. van der Mast, M. W. Hengeveld, High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults, J. Am. Geriatr. Soc. 60 (4) (2012) 661–668.
[133] P.P. Pandharipande, A. Morandi, J.R. Adams, T.D. Girard, J.L. Thompson, A. K. Shintani, E.W. Ely, Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients, Intensive Care Med. 35 (11) (2009) 1886–1892.
[134] K. Piotrowicz, A. Klich-Raczka, A. Pac, A. Zdzienicka, T. Grodzicki, The diurnal profile of melatonin during delirium in elderly patients–preliminary results, Exp. Gerontol. 72 (2015) 45–49.
[135] J. Hirsch, S. Vacas, N. Terrando, M. Yuan, L.P. Sands, J. Kramer, K. Bozic, M. M. Maze, J.M. Leung, Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery, J. Neuroinflamm. 13 (1) (2016) 211.
[136] J. Kazmierski, A. Banys, J. Latek, J. Bourke, R. Jaszewski, Raised IL-2 and TNF-alpha concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery, Int. Psychogeriatr. 26 (5) (2014) 845–855.
[137] E. Cape, R.J. Hall, B.C. van Munster, A. de Vries, S.E. Howie, A. Pearson, S. D. Middleton, F. Gillies, I.R. Armstrong, T.O. White, C. Cunningham, S.E. de Rooij, A.M. MacLullich, Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture, J. Psychosom. Res. 77 (3) (2014) 219–225.
[138] K. Wilson, C. Broadhurst, M. Diver, M. Jackson, P. Mottram, Plasma insulin growth factor—1 and incident delirium in older people, Int. J. Geriatr. Psychiatry: J. Psychiatry Late Life Allied Sci. 20 (2) (2005) 154–159.
[139] R.A. Pol, B.L. van Leeuwen, G.J. Izaks, M.M. Reijnen, L. Visser, I.F. Tielliu, C. J. Zeebregts, C-reactive protein predicts postoperative delirium following vascular surgery, Ann. Vasc. Surg. 28 (8) (2014) 1923–1930.

[140] B.C. van Munster, J.C. Korevaar, C.M. Korse, J.M. Bonfrer, A.H. Zwinderman, S. E. de Rooij, Serum S100B in elderly patients with and without delirium, Int. J. Geriatr. Psychiatry: J. Psychiatry Late Life Allied Sci. 25 (3) (2010) 234–239.
[141] M.J. Ignatius, P.J. Gebicke-Härter, J. Skene, J.W. Schilling, K.H. Weisgraber, R. W. Mahley, E.M. Shooter, Expression of apolipoprotein E during nerve degeneration and regeneration, Proc. Natl. Acad. Sci. 83 (4) (1986) 1125–1129.
[142] A. Pearson, A. de Vries, S.D. Middleton, F. Gillies, T.O. White, I.R. Armstrong, R. Andrew, J.R. Seckl, A.M. MacLullich, Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls, BMC Res. Notes 3 (2010) 33.
[143] J.A. Avila-Funes, J.P. Ledesma-Heyer, A.P. Navarrete-Reyes, R. Chavira-Ramírez, L. Boeck-Quirasco, S. Aguilar-Navarro, Association between high serum estradiol levels and delirium among hospitalized elderly women, Rev. De. Invest. Clín. 67 (1) (2015) 20–24.
[144] C. Jorge-Ripper, M.R. Aleman, R. Ros, S. Aguilera, E. Gonzalez-Reimers, E. Espelosin, F. Santolaria, Prognostic value of acute delirium recovery in older adults, Geriatr. Gerontol. Int. 17 (8) (2017) 1161–1167.
[145] C. Grandi, C.D. Tomasi, K. Fernandes, L. Stertz, F. Kapczinski, J. Quevedo, F. Dal-Pizzol, C. Ritter, Brain-derived neurotrophic factor and neuron-specific enolase, but not S100β, levels are associated to the occurrence of delirium in intensive care unit patients, J. Crit. Care 26 (2) (2011) 133–137.
[146] B.D. Fontana, N. Alnassar, M.O. Parker, Tricaine methanesulfonate (MS222) has short-term effects on young adult zebrafish (Danio rerio) working memory and cognitive flexibility, but not on aging fish, Front. Behav. Neurosci. (2021) 177.