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Identifying knowledge gaps in understanding the effects of selective serotonin reuptake inhibitors (SSRIs) on fish behaviour

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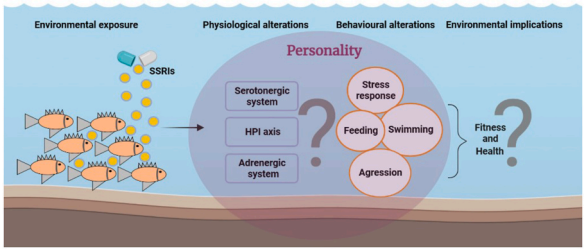
HIGHLIGHTS

- The reported effects of SSRIs on fish fitness-related behaviours were reviewed.
- Most of the performed studies lack environmental relevance and consistency in the reported effects.
- Little is known on how personality influences experimental outcomes.
- Antidepressants exposure may lead to alteration on personality traits.
- Research gaps are highlighted.

GRAPHICAL ABSTRACT



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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants increasingly prescribed to treat patients with clinical depression. As a result of the significant negative impact of the COVID-19 pandemic on the population's mental health, its consumption is expected to increase even more. The high consumption of these substances leads to their environmental dissemination, with evidence of their ability to compromise molecular, biochemical, physiological, and behavioural endpoints in non-target organisms. This study aimed to provide a critical review of the current knowledge regarding the effects of SSRI antidepressants on fish ecologically relevant behaviours and personality-dependent traits. A literature review shows limited data concerning the impact of fish personality on their responses to contaminants and how such responses could be influenced by SSRIs. This lack of information may be attributable to a lack of widely adopted standardized protocols for evaluating behavioural responses in fish. The existing studies examining the effects of SSRIs across various biological levels overlook the intra-specific variations in behaviour and physiology associated with different personality patterns or coping styles. Consequently, some effects may remain undetected, such as variations in coping styles and the capacity to handle environmental stressors. This oversight could potentially result in long-term effects with ecological implications.

Data support the need for more studies to understand the impact of SSRIs on personality-dependent traits and how they may impair fitness-related behaviours. Given the considerable cross-species similarity in the personality dimensions, the collected data may allow new insights into the correlation between personality and animal fitness.

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1. Introduction

Pharmaceutical consumption is a global-scale practice, projected to increase further due to population growth and ageing (Saaristo et al., 2019; Moreira et al., 2022). This has spurred intensive research into the development of new and more potent drugs for preventive and symptomatic treatment of human ailments, including mental disorders (Mezzelani et al., 2018; Fekadu et al., 2019). Upon administration, pharmaceuticals undergo metabolism, exert their intended therapeutic effects by targeting specific biological pathways, and are excreted through urine and/or faeces, either in their original form or as metabolites, thereby entering the sewage system (Branchet et al., 2021; Madikizelaa et al., 2020; Klatte et al., 2017; Sehonova et al., 2018). However, current sewage treatment processes often fail to effectively remove these substances, leading to their dissemination in the aquatic environment (Saaristo et al., 2019; Madikizelaa et al., 2020; Klatte et al., 2017; Sehonova et al., 2018; Desbiolles et al., 2018; Hossain et al., 2021). This emergence of pharmaceuticals as environmental contaminants poses a growing challenge with potential risks to ecosystems and human health (Saaristo et al., 2019; Desbiolles et al., 2018; Puckowski et al., 2016). Consequently, pharmaceuticals have garnered increasing concern as emerging environmental contaminants (Moreira et al., 2022; Desbiolles et al., 2018; Hossain et al., 2021; Puckowski et al., 2016). Despite being detected at relatively low concentrations, typically ranging from nanograms per litre (ng/L) to micrograms per litre (μg/L), their continuous release into the environment requires careful attention (Puckowski et al., 2016). Even at these low concentrations, they can induce harmful effects on aquatic organisms due to the high degree of structural similarity between the primary targets of SSRIs in fish and humans (Hossain et al., 2021; Puckowski et al., 2016; Nguyena et al., 2021; Burkina et al., 2015). Pharmaceuticals have already been detected in aquatic environments at concentrations exceeding those known to induce toxic effects (Nguyena et al., 2021). Overall, available data indicate that the risks posed by pharmaceuticals to fish are influenced by multiple factors, including the nature and concentration of the drug and characteristics of the organisms (such as species, life stage, sex, and previous exposure to other environmental contaminants) (Burkina et al., 2015; Huang et al., 2019, 2020; Bachour et al., 2020; Sehonova et al., 2019).

Selective serotonin reuptake inhibitor (SSRI) antidepressants are one of the major classes of pharmaceuticals, widely and increasingly prescribed in the last decades to treat patients diagnosed with clinical depression, also being used to treat obsessive-compulsive disorder, panic disorders, social phobias, and attention-deficit disorder (Mole and Brooks, 2019; Silva et al., 2012). These pharmaceuticals have received particular attention as they can be particularly potent and hazardous since they are specifically designed to modulate human behaviour (Huang et al., 2019, 2020; Mole and Brooks, 2019). Therefore, they may induce behavioural alterations in non-target organisms, like fish, with severe fitness consequences (Martin et al., 2021). Several studies have already demonstrated that sublethal exposure to SSRIs can significantly alter fish behaviour, physiology, and gene expression (Hedgespeth et al., 2014; Kellner et al., 2015; Bisesi et al., 2016; Pelli and Connaughton, 2015; Weinberger and Klaper, 2014; Yang et al., 2021; Menon et al., 2020). This class of antidepressants has often been detected in water systems (Fekadu et al., 2019; Burkina et al., 2015; Menon et al., 2020; Fernandez-Rubio et al., 2019; Silva et al., 2015; Sumpter and Margiotta-Casaluci, 2022), and their environmental levels are expected to increase significantly due to the negative impact of the COVID-19 pandemic on mental health (Singh et al., 2022). SSRIs exert their therapeutic effect by blocking the serotonin reuptake transporter (SERT) in the presynaptic cell, thus inducing an increase in serotonin levels within the central nervous system (CNS) (Salahinejad et al., 2022; Kellner and Olsén, 2020; McDonald, 2017). Environmental risk assessments focusing on ecologically relevant sublethal endpoints related to chronic exposures, such as altered behaviour, have been considered a suitable and reliable approach to characterize the ecotoxicological potential of these biologically active chemicals, ubiquitous at low concentrations (Mezzelani et al., 2018; Huang et al., 2019; Mole and Brooks, 2019; Martin et al., 2021).

Behaviour modification, resulting from complex and interconnected levels of biological organization (Saaristo et al., 2019; Martin et al., 2021; Bertram et al., 2022; Ford et al., 2021), has emerged as a sensitive indicator of environmental contaminants, carrying ecological significance. However, exposure to stress can elicit distinct intraspecific behavioural and physiological responses to environmental and toxicological stressors, known as coping styles (Demin et al., 2019; Wong et al., 2019; Bergmuller, 2020; Yuan et al., 2018). This individual sensitivity within a species can influence susceptibility to diseases and environmental contaminants (Demin et al., 2019; Wong et al., 2019). Extensive research involving humans and non-human animals has revealed variations in coping abilities when confronted with environmental challenges (Koolhaas, 2008; Xin et al., 2017; Santarnecchi et al., 2018). Humans, for instance, exhibit diverse coping styles when faced with stressful situations in their daily lives (Xin et al., 2017), representing unique sets of mental and behavioural strategies employed to navigate stress and traumatic experiences (Santarnecchi et al., 2018). Notably, individuals differ significantly in their responses to stress, with some displaying maladaptive reactions while others exhibit resilience (Xin et al., 2017), suggesting varying susceptibility to stress and, consequently, to diseases. Avoidance-based coping styles have been associated with a predisposition to developing psychiatric disorders like post-traumatic stress disorder (PTSD), anxiety, and major depression, whereas problem-oriented coping skills have shown positive correlations with well-being and a higher quality of life (Santarnecchi et al., 2018).

Similarly, it is recognized that organisms from many species, ranging from insects to humans, exhibit different coping styles, differing from their conspecifics in stress responsiveness to the environment when exposed to environmental stressors (Koolhaas, 2008; Demin et al., 2019; Wong et al., 2019). These individual coping styles occur within a population as acontinuum axis between two extreme phenotypes, called bold (proactive) and shy (reactive), along with intermediate phenotypes (Ferrari et al., 2020; Tudorache et al., 2013, 2018). Nonetheless, there is a considerable lack of information about how coping styles/personality influence organisms' response to contaminant-induced stress, fitness, and health and vice versa. This can be studied in organisms like zebrafish (*Danio rerio*) that display two well-defined and distinct personality patterns. An additional advantage of using this species is its high genetic homology and significant conservation of monoaminergic systems with humans (Adhish and Manjubala, 2023; Xie et al., 2022; Gould et al., 2021).

Thus, this review aimed to provide an overview of the current knowledge on the sub-lethal effects induced by SSRIs on fish, focusing on behaviour and fish personality/coping styles, tested under ecologically relevant scenarios, and provide a critical discussion on the relevance of these findings.

2. SSRIs as emerging contaminants

The consumption of antidepressants significantly increased in the last few years, particularly in Europe. In 2000, consumption did not exceed 20 Defined Daily Doses (DDD)/1000 inhabitants/day, while in 2018 it almost reached 110 DDD/1000 inhabitants/day (Estrela et al., 2020). The recent pandemic of COVID-19 had a considerable impact on the population's mental health (Singh et al., 2022). According to the Organization for Economic Co-operation and Development (OECD), the incidence of anxiety and depression increased significantly from March 2020 onwards (Fig. 1) (Organization for Economic Co).

Therefore, the prescription and consumption of antidepressants are expected to increase even more, particularly of SSRIs, the most prescribed antidepressant drugs (Estrela et al., 2020; Zacarías et al., 2021),

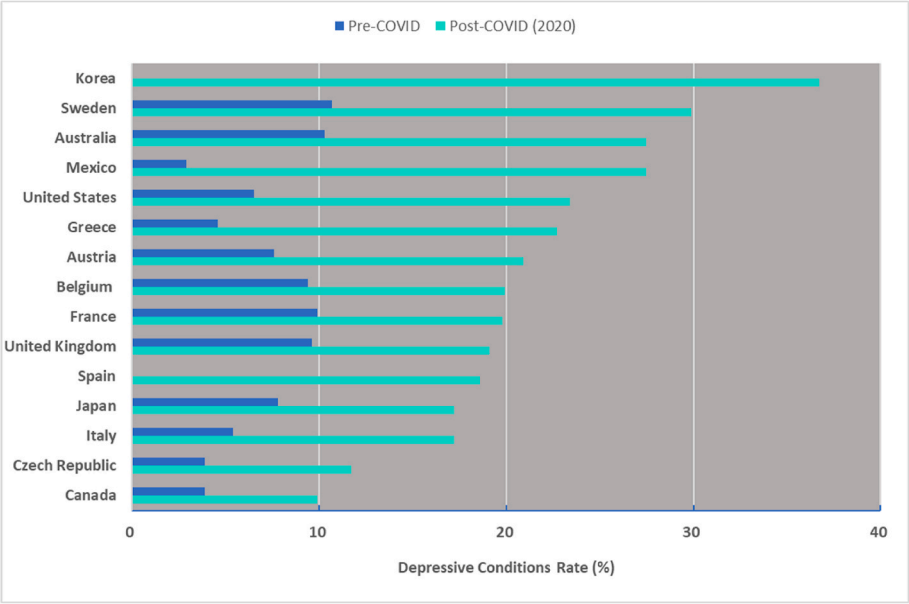

Fig. 1. Prevalence of depression conditions in different countries, before the COVID-19 pandemic and in early 2020. (Data source: OECD, 2021).

representing an environmental and public health concern (Diaz-Camal et al., 2022), as some of these drugs are detected in drinking water (Zacarías et al., 2021).

Following oral ingestion, SSRIs are primarily subjected to hepatic metabolization, exerting their therapeutical effect by blocking the serotonin reuptake transporter (SERT) in the presynaptic neuron and inducing an increase in serotonin (5-HT; 5-hydroxytryptamine) extracellular concentrations within the CNS, thus leading to the relief of the symptomatology associated with depression and anxiety conditions (Sumpter and Margiotta-Casaluci, 2022; Salahinejad et al., 2022). These pharmaceuticals may be eliminated through urine and/or faeces as parent compounds and/or as their metabolites (Silva et al., 2012), resulting in their release to sewage systems (Sehonova et al., 2018). Due to incomplete removal during wastewater treatment, these active substances reach and spread along environmental matrices, such as water systems (Sumpter and Margiotta-Casaluci, 2022; Hughes et al., 2012) and, therefore, are frequently detected in surface waters (Mole and Brooks, 2019; Salahinejad et al., 2022). Once in the environment, they exhibit relatively low susceptibility to environmental degradation (e.g., hydrolysis, photolysis, biodegradation) which is translated.

Into their environmental persistence (Silva et al., 2012). They remain pharmaceutically active with the ability to cause detrimental effects on non-target organisms, even at low concentrations, due to the evolutionary conservation of the serotonergic system across vertebrates, along with their bioaccumulation potential (Silva et al., 2012; Martin et al., 2021; Sumpter and Margiotta-Casaluci, 2022; Salahinejad et al., 2022; Gould et al., 2021; Hughes et al., 2012; Kaushik and Thomas, 2019; Grabicova et al., 2017), associated with their lipophilic nature. pH plays an important role in the toxicokinetic and uptake of these antidepressants as it strongly influences their ionization state, with a general toxicity increase observed for higher pH values (Ford and Fong, 2016).

The most frequently detected SSRIs in surface waters are citalopram, fluoxetine, sertraline, and paroxetine, with reported levels up to 427, 330, 75 and 90 ng/L, respectively (Mole and Brooks, 2019; Silva et al., 2012; Sumpter and Margiotta-Casaluci, 2022). In this manuscript, the authors consider environmentally relevant those levels close to the levels reported in the environment.

Until the past decade, the predominant focus of studies examining the toxicity of SSRIs on organisms revolved around fluoxetine and sertraline. This emphasis was due to their significant consumption rates, physicochemical properties that affect their bioaccumulation and metabolism in humans, as well as their capacity to influence behaviour (Brooks, 2014). The current environmental levels of SSRIs appear to reflect changes in consumption patterns as citalopram and paroxetine have also been increasingly and frequently detected in surface waters worldwide (Mole and Brooks, 2019; Silva et al., 2012; Sumpter and Margiotta-Casaluci, 2022) and, therefore, are also considered contaminants of emerging concern. Given that the class of antidepressants known as SSRIs encompasses substances with distinct pharmacokinetics and physicochemical properties, it is crucial to avoid generalizing scientific findings regarding their potential effects and toxicity. Variations in affinity for serotonin receptors have been observed among different SSRIs (Salahinejad et al., 2022; Esa-Pekka Palvimaki et al., 1999), and their interaction with fish detoxification systems may also differ. After uptake by fish, SSRIs, like other xenobiotics, are primarily subjected to a biotransformation process mediated by liver cytochrome P450 enzymes (CYP450) (Burkina et al., 2015). However, according to *in vitro* studies performed with fish cell fractions, the effects of SSRIs on the CYP450 system are distinct as they can act as inhibitors or inducers depending on the specific interaction between the SSRI itself and the enzymatic activity in question (Thibaut and Porte, 2008).

Therefore, we need to enhance our understanding of the pharmacokinetics and pharmacodynamics of SSRIs in fish. This knowledge will facilitate the improvement of environmental impact assessments related to these emerging contaminants.

3. Effects of SSRIs on fitness-related traits in fish

As SSRIs occur in the environment at very low or even at trace levels, they are more likely to cause sub-lethal chronic effects since they are specifically designed to elicit effects in their target organisms at low concentrations, and their biological targets are highly conserved across vertebrate taxa (Martin et al., 2021). SSRIs have already been identified in fish tissues, especially in the brain, highlighting their bioaccumulation potential (Moreira et al., 2022; Puckowski et al., 2016; Menon et al., 2020; Sumpter and Margiotta-Casaluci, 2022; Gould et al., 2021; Hughes et al., 2012). Arnnok et al. (2017) (Arnnok et al., 2017) reported high bioaccumulation of norsertraline (sertraline metabolite) in the liver and brain of fish. Grabicova et al. (2014) (Grabicova et al., 2014), observed that citalopram and sertraline were present in the brains and livers of most fish exposed to undiluted effluent from a sewage treatment plant, but not in blood, plasma or muscle. In human

patients, the brain-to-plasma ratio of fluoxetine is 2.6:1 (Karson et al., 1993). Long-term consumption of fish (including the entire body) may carry a potential risk to human health. Nonetheless, it should be highlighted that the only available study addressing human risk assessment related to SSRI exposure through food, concluded no evidence of considerable risk to human health associated with the consumption of marine mussels contaminated with SSRIs (Silva et al., 2017).

Current evidence highlights the ability of these environmental contaminants to cause maladaptive stress responses in fish, as they can also act and impact fish serotonergic system (Sehonova et al., 2018; Burkina et al., 2015; Sumpter and Margiotta-Casaluci, 2022; Sumpter et al., 2014) leading to impairment of diverse behavioural responses such as swimming, aggression, stress, fear responses and consequent fitness reduction (Sumpter and Margiotta-Casaluci, 2022; Salahinejad et al., 2022; Vinterstare et al., 2021). This is of particular concern since fishes play an ecological key role in aquatic ecosystems and, therefore, any SSRIs-induced behaviour changes can cause top-down effects on lower trophic levels affecting the whole ecosystem (Sehonova et al., 2018; Fernandez-Rubio et al., 2019).

Evidence suggests that due to the functional conservation of SSRI's therapeutical targets between humans and teleost fish, and SSRIs bioaccumulation potential, behavioural changes in fish are more likely to occur at plasma or tissue concentrations comparable to that inducing effects on humans (between 50 μg/L and 300 μg/L (Salahinejad et al., 2022; McDonald, 2017; Tanoue et al., 2019; Pan et al., 2018; Correia et al., 2023)). However, physiological, biochemical, and behavioural alterations have been reported on embryos/larvae of zebrafish exposed to fluoxetine levels as low as 0.1 μg/L, when the predicted plasma concentrations of fluoxetine were below human therapeutic doses (Salahinejad et al., 2022). Species with higher homology with humans, such as zebrafish, may be more sensitive to SSRIs (Salahinejad et al., 2022). Pan et al. (2018) (Pan et al., 2018) found evidence of tissue accumulation and concentration-dependent effects in two fish species (*D. rerio* and *Carassius auratus*) after short-term (6 days) exposure to the SSRI fluoxetine (0.1, 1, 10, 100 and 1000 μg/L). After long-term exposure, a more environmentally representative scenario, Pan et al. (2018) (Pan et al., 2018) detected the highest fluoxetine bioconcentration factor (BCF) in *C. auratus* at the lowest tested concentration (0.1 μg/L), suggesting that bioaccumulation levels may be higher in the natural environment where the concentrations are typically lower.

Among the SSRIs most detected in the environment, fluoxetine is considered to have the highest acute toxicity (Puckowski et al., 2016; Silva et al., 2012; Correia et al., 2023). This SSRI is the most investigated due to its environmental persistence and unique pharmacokinetics associated with a readily ionizable and toxic metabolite, norfluoxetine (Silva et al., 2012; Singh et al., 2022; Correia et al., 2023). Accordingly, extensive data concerning fluoxetine sub-lethal (acute and chronic) effects on fish are available (Menon et al., 2020; Fernandez-Rubio et al., 2019; Correia et al., 2023). Available data show that 7–28 days of exposure to environmentally relevant concentrations of fluoxetine (10–100 μg/L) induce anxiolytic responses in a variety of fish species (e.g., *D. rerio*, *Gasterosteus aculeatus, Oryzias latipes, Gambusia holbrooki*, *Poecilia reticulata*, *Pimephales promelas*) leading to maladaptive anxiety and fear responses which may impact ecologically relevant behaviours conditioning survival, such as feeding and predator escape (Pelli and Connaughton, 2015; Weinberger and Klaper, 2014; de Farias et al., 2020; Meijide et al., 2018; Ansai et al., 2016; Wong et al., 2013). Several studies associated acute and chronic exposures to fluoxetine (from 10 μg/L up to 10 mg/L) with altered (decreased) feeding behaviour in several fish species (e.g., *Cichlasoma dimerus*, *P. promelas, Pomatoschistus microps*) (Yang et al., 2021; Dorelle et al., 2020; Duarte et al., 2019). However, a lack of effects on feeding behaviour has also been reported. de Farias et al. (2020) found no effects on *D. rerio* feeding behaviour after 15 days of exposure to 100 μg/L fluoxetine (de Farias et al., 2020).

Changes in stress response, characterized by reduced anxiety and fear, are likely attributed to the effect of altered hormone levels, such as cortisol and catecholamines. These effects may be related to interactions between the serotonergic and adrenergic systems and between the serotonergic system and the hypothalamus-pituitary-interrenal (HPI) axis (Sumpter and Margiotta-Casaluci, 2022; Kreke and Dietrich, 2008). Fluoxetine has been associated with effects on aggression and boldness across fish taxa (e.g., *D. rerio*, *Betta splendens*, *O. latipes*, *Neogobius melanostomus*), often with a negative correlation between the level of aggression and boldness and fluoxetine exposure concentrations (Eisenreich et al., 2017; Theodoridi et al., 2017; McCallum et al., 2017; Greene and Szalda-Petree, 2022; Dzieweczynski and Hebert, 2012). Nevertheless, the disruptive effect of fluoxetine on aggressive behaviour tends to be more consistent in exposures lasting between 5 and 21 days, with 75% of the studies demonstrating a reduction in aggression. In contrast, acute exposures (less than 5 days) show lower consistency, with 50% of the studies indicating decreased aggressiveness (McDonald, 2017).

An intraperitoneal administration of 25 and 50 μg fluoxetine/g of fish has been shown to affect processes such as branchial nitrogen excretion and intestinal osmoregulation in the teleost fish *Opsanus beta* (Morando et al., 2009). Richards et al. (2009) (Richards et al., 2009) demonstrated the ability of fluoxetine 100 and 1000 μg/L to constrict the arterio-arterial branchial vasculature, leading to impaired gas exchange and hypoxia, and ultimately to death, within the first 96 h of exposure to 1000 μg/L and after 35-day exposure to 100 μg/L fluoxetine. The ability of fluoxetine (50 ng/L) to modify circadian rhythm by reducing melatonin content in 5 days *D. rerio* larvae, has been reported with locomotor activity decrease in daytime associated with down-regulation of the clock genes clock1a and bmal1b (Wei et al., 2022). Nonetheless, fluoxetine ecotoxicity data focusing on ecologically relevant exposure conditions (e.g., concentrations and exposure duration) and ecologically relevant sublethal endpoints, such as altered behaviour, still lack consistency when it comes to correlating specific behaviours (e.g., predator avoidance, swimming, feeding) to risk assessment and management (Sumpter et al., 2014; Correia et al., 2023). Non-monotonic dose responses have been observed, with effects detected at low concentrations not being found at high concentrations, along with higher variations of investigated endpoints, mainly behavioural, at lower-level exposure and with species-specific and sex-dependent response (Pelli and Connaughton, 2015; Weinberger and Klaper, 2014; Yang et al., 2021; Salahinejad et al., 2022; Pan et al., 2018; Correia et al., 2023; de Farias et al., 2020; Meijide et al., 2018; Ansai et al., 2016; Kreke and Dietrich, 2008; Eisenreich et al., 2017; Theodoridi et al., 2017; McCallum et al., 2017; Greene and Szalda-Petree, 2022; Martin et al., 2017, 2019; Fursdon et al., 2019; Mennigen et al., 2010).

Compared to fluoxetine, the available data concerning the effects of citalopram, sertraline and paroxetine on fish are considerably limited. This fact is more evident for paroxetine. Short-term exposure to sertraline and citalopram seems to consistently result in a reduction of feeding behaviour in different fish species (Hedgespeth et al., 2014; Kellner et al., 2015; Hubena et al., 2021). A decrease in locomotor activity along with alterations in aggressiveness after 7–30 days of exposure to a wide range of citalopram and sertraline concentrations [0.38–100 μg/L] have also been reported (Yang et al., 2021; Kellner and Olsén, 2020; Hubena et al., 2021; Kania and Wrońska, 2015) in different fish species. As for fluoxetine, these findings require further studies for their validation, as different sensitivity between species has been reported, along with a significant variation in exposure conditions. The available data for paroxetine suggest acute toxicity comparable to fluoxetine (e.g., paroxetine and fluoxetine 96 h median lethal concentration (LC_{50}) for the amphibian *Xenopus laevis* are 5.12 mg/L and 7.5 mg/L, respectively) (Silva et al., 2015). According to probabilistic environmental hazard assessments based on the calculation of therapeutic hazard values and fish plasma modelling approaches, paroxetine can be considered a contaminant of emerging concern and, thus, its ecotoxicity assessment is required to increase understanding of its potential environmental impacts (Mole and Brooks, 2019).

Overall, there are still considerable discrepancies in the available literature concerning behavioural effects on fish exposed to this class of antidepressants. Understanding the potential adverse impacts of SSRIs on fish behaviour is, undoubtedly, ecologically crucial as behavioural expression translates the interaction between an organism's internal status and its surrounding environment, and alterations in behaviour might impact fitness directly (Martin et al., 2019, 2021; Bertram et al., 2022; Ford et al., 2021). Indeed, behaviour can be considered a highly sensitive and useful endpoint in ecotoxicology assessment, being a multi-level indicator of biological effects and an early warning tool (Martin et al., 2021; Bertram et al., 2022; Ford et al., 2021; Orozco--Hernandez et al., 2022; Gaaied et al., 2020; Silva et al., 2020). However, behavioural assessment can itself be a source of variability as behaviour is not an easy endpoint to quantify, requiring a careful selection and execution of the tests considering the suitability and feasibility towards the behaviour it is intended to measure (Sumpter et al., 2014). This requires assessment criteria and standardized methods (e.g., US EPA, OECD) for fish toxicity studies with the inclusion of behavioural endpoints (Gould et al., 2021), as already done for other toxicological endpoints, to increase data consistency and thus improve reproducibility and reliability of the obtained results (Ford et al., 2021).

Future studies should focus on long-term and multigenerational exposures to increase understanding of sub-lethal SSRI-induced alterations under environmentally relevant scenarios. In humans, chronic SSRI treatment results in a profound reduction in serotonin transporter (SERT) expression and function, despite increased extracellular serotonin levels (Homberg et al., 2007). This complex pharmacokinetics of chronic SSRI exposure within humans suggests that to fully understand the implications of waterborne SSRI exposure on aquatic organisms, exposures should last at least for 21 days, as long-term compensatory mechanisms such as the desensitization of serotonin may occur (McDonald, 2017). Moreover, fish are more likely to be chronically exposed to complex mixtures of SSRIs which also requires further evaluation of the potential synergistic effects of combined SSRIs mixtures.

4. SSRIs and their impact on fish personality/coping styles

Different individuals cope with environmental challenges in different ways. This individual behavioural variance, like stress coping styles (SCS), has been associated with personality aspects (Tudorache et al., 2015; Fatsinia et al., 2020; Carbonara et al., 2019). Indeed, not all individuals within a species react the same way when subjected to the same conditions, even if they share the same age, size, sex, and place of origin (Grzesiuk and Pawelec, 2021). This variation in individual sensitivity may affect susceptibility to disease and/or environmental contaminants (Demin et al., 2019; Wong et al., 2019). However, the interaction between SCS, environmental stressors and disease susceptibility is still largely unknown.

Coping styles are suites of behavioural and physiological responses to stress that remain consistent over time and across contexts (Ferrari et al., 2020; Koolhaas et al., 2010a; Höglund et al., 2020). Such intraspecific behavioural variability is a well-documented phenomenon across vertebrates, including teleost fish and humans. Individuals of many species exhibit different SCS when subjected to stressful or risky situations, which may vary along a proactive-reactive *continuum* axis (Tudorache et al., 2015; Fatsinia et al., 2020; Carbonara et al., 2019; Thörnqvist et al., 2019). These behavioural patterns represent a relevant variable that may directly interfere with experimental outcomes in various behavioural tasks (Mackenzie et al., 2009). The existence of divergent SCS (proactive and reactive) among individuals and within a population is part of a fitness and survival strategy to optimize and ensure a correct adaptive response to changing environmental conditions (Ferrari et al., 2020). Different coping styles can already be present at a larval stage as shown by Tudorache et al. (2015) (Tudorache et al., 2015) in 8 days old zebrafish larvae.

Variations in coping styles are related and partially conditioned by heritable factors due to different gene expression patterns (Mackenzie et al., 2009; Fior et al., 2018a; Oswald et al., 2012), as well as consistent and divergent physiological and neuroendocrine responses to stress (Ferrari et al., 2020; Vinterstare et al., 2021; Höglund et al., 2020). Proactive fish are bolder, less plastic, more risk-taking, aggressive, territorial, and more predictable than shy fish. They are characterized by actively engaging stressors in a fight-flight strategy, exploring the environment quickly and superficially, with lower hypothalamic-pituitary-interrenal (HPI) axis reactivity and lower basal cortisol levels and higher sympathetic reactivity compared to reactive fish (Ferrari et al., 2020; Vinterstare et al., 2021; Höglund et al., 2020; Baker et al., 2018; Korte et al., 2005; Jolles et al., 2019). This behavioural pattern is better suited for predictable and stable environments. Conversely, reactive individuals are less aggressive and more cautious, exhibiting a conservation-withdrawal strategy that includes a freeze-hide response, with high HPI axis reactivity and baseline cortisol levels, and higher behavioural flexibility (Höglund et al., 2020; Korte et al., 2005), allowing them to cope with more unexpected and fluctuating environments (Carbonara et al., 2019; Baker et al., 2018). This different predisposition towards risk-prone behaviour in proactive-reactive individuals has proven effective in selecting fish, based on their personality, using standardized individual-based and/or group-based tests. Within this framework, various well-established protocols can be employed to differentiate proactive from reactive individuals and evaluate the consistency of coping styles over time. The group risk-taking test is one of the most successfully used tests when considering fish social species, that consists in measuring the time an individual takes to leave a group in the safety of a sheltered area to a new environment (area), thus exhibiting a risk-prone behaviour reflecting boldness level (Castanheira et al., 2013; Ferrari et al., 2015; Alfonso et al., 2019). The novel tank test is a valuable behavioural assay often utilized to distinguish between proactive and reactive individuals. This test shares a similar protocol with the previously described group risk-taking test, but with the notable difference that it is done with one individual at a time (Wong et al., 2012). The feeding latency test and the novel object test are other examples of individual-based assays that allow measuring fish boldness (Wong et al., 2012). Most of the performed studies in this scope have used different combinations of both individual and group-based tests to assess the repeatability and consistency of individual behavioural traits over short periods (from 1 to 14 days) (Castanheira et al., 2013; Ferrari et al., 2015; Alfonso et al., 2019; Wilson and Stevens, 2005; Øverli et al., 2007; Wilson and Godin, 2009). Indeed, the reproducibility of the outcomes seems to be higher for measurements that are repeated in short periods as individuals are more consistent in behaviour over short periods in comparison to long ones (Ferrari et al., 2015; Bell et al., 2009). Several factors, encompassing predation pressure, food availability, social interactions, temperature, hypoxia, and learning, have the potential to shape coping styles (Ferrari et al., 2015). Castanheira et al. (2016) (Castanheira et al., 2016) observed SCS behaviour consistency in *Sparus aurata* only before sexual maturation and highlighted the importance of considering life history. Thus, the behavioural aspect of coping styles is not stationary and may change according to life history events (Castanheira et al., 2016), besides appearing to be species-specific (Carbonara et al., 2019).

Current evidence demonstrates the association between behavioural, physiological, and neurological differences in proactive and reactive coping styles in fish and different expressions of central serotonin function (Koolhaas et al., 2010a; Coppens et al., 2010; Tran et al., 2016; Backström and Winberg, 2017). Additionally, brain serotonin is causally implicated in both aggression and behavioural flexibility, as lower prefrontal cortex serotonin levels have been linked to heightened aggression and impulsive behaviour (Coppens et al., 2010). Aggressive and impulsive control disorders in humans have been strongly correlated with low levels of brain serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) along with up-regulation of the auto-receptors

(5-HTR1A and 5-HTR1B) located in presynaptic neurons that act as an additional self-regulatory mechanism of aggressive behaviour with inhibitory effects on the serotonin neurotransmission (Pavlov et al., 2012; Koolhaas et al., 2010b). Although it is well established that SSRIs can interfere with fish behaviour, data on differential responses to this type of antidepressant depending on fish personality, is very limited (Salahinejad et al., 2022). In humans, the suppression of certain personality traits due to SSRI treatment has been reported to occur in some cases (Grzesiuk and Pawelec, 2021).

As aggression and boldness are fish personality traits correlated with serotonin levels, it is expected that drugs that interfere with the expression of the serotonergic system, such as SSRIs, may lead to behavioural phenotype modulation (Fior et al., 2018a). Indeed, the modulation of bold (proactive) behaviour by the SSRI fluoxetine (0.5 μg–50 μg/L) into a shyer phenotype has been recently reported in some fish species (*B. splendens, D. rerio*) (Fior et al., 2018b; Dzieweczynski et al., 2016a, 2016b). Nonetheless, Grzesiuk and Pawelec (2021) (Grzesiuk and Pawelec, 2021), in a study performed with two freshwater wild fish species (*N. fluviatilis* and *Gobio*), observed an increase in the proportion of bold individuals after 21 days of exposure to an environmentally relevant concentration of fluoxetine (360 ng/L). In a two-year multigenerational assay with *P. reticulata*, Polverino et al. (2021) (Polverino et al., 2021) reported that exposure to environmentally realistic levels of fluoxetine (40 and 366 ng/L) suppresses behavioural differences between individuals by diluting the individual activity level and risk-taking behaviour. Tan et al. (2020) (Tan et al., 2020) also observed a reduction in among-individual phenotypic variation in *P. reticulata* females after a long-term (15 months) exposure to environmentally relevant levels of fluoxetine (30 and 300 ng/L). These outcomes can be considered a first line of evidence that should guide further studies for a comprehensive insight into the ecological adverse implications that may arise from SSRIs-suppressive effects on individual coping strategies, by reducing intraspecific behavioural variance, which may ultimately compromise the ability of the whole population to adapt in an ever-changing environment. The potential implications are considerable if individuals experience increased shyness due to SSRI exposure. Shy individuals are typically less prone to explore and take risks, which could hinder their ability to venture into new environments with improved conditions and resources. Furthermore, increased susceptibility to disease may also be a consequence of their cautious nature. Data concerning other SSRIs of environmental concern such as citalopram, sertraline and paroxetine are even more scarce or non-existent. Kellner et al. (2020) (Kellner and Olsén, 2020) observed a suppressive effect of citalopram on *G. aculeatus* aggressiveness, with no effects on personality-dependent behaviours (no significant correlation between feeding behaviour and aggressive behaviour) found in response to citalopram exposure. To the best of our knowledge, there are no studies performed so far concerning the potential adverse effects of sertraline or paroxetine on fish personality.

Given the documented sex-dependent responses to SSRIs concerning behavioural traits such as feeding and aggression (Kellner and Olsén, 2020), it is plausible to hypothesize that a similar response pattern might extend to specific behaviours associated with personality traits. In this context, the involvement of estradiol in shaping female behavioural expression has been proposed (Dzieweczynski et al., 2016a). Studies by Mennigen et al. (2010) (Mennigen et al., 2010) and Lister et al. (2009) (Lister et al., 2009) revealed decreased estradiol levels in female goldfish (*C. auratus*) and zebrafish following fluoxetine exposure, which could potentially impact personality-dependent sexual behaviours and, subsequently, reproductive success. Clearly, there is still a long way ahead as we are only starting to understand to what extent SSRI's effects on personality-dependent traits may impair fitness-related behaviours leading to progressive physiological dysregulation that can ultimately result in disease and mortality (Christensen et al., 2019). Fish are more likely to be chronically exposed to contaminants throughout their life cycle. Thus, given that SSRI's therapeutical effects on people are observed following 3–4 weeks of treatment, future studies should focus on exposures of not less than 21–28 days, particularly to concentrations often detected on surface waters.

A growing line of evidence highlights the importance of personality as a significant factor to be considered in farmed fish when to improve the management and welfare of aquaculture populations (Castanheira et al., 2017). Therefore, the potential economic impact of SSRI's effects on personality-dependent traits should not be neglected as farmed fish may be exposed to these environmental contaminants as they are commonly reared in natural water resources in several aquaculture farms. This fact may affect vulnerability and susceptibility to disease, making it difficult to optimize mitigation measures to minimise stressors that may act as triggers for disease.

Furthermore, there is also the need to increase knowledge concerning the potential transgenerational implications of SSRIs-suppressive effects on phenotypic variation in fish. As bold and aggressive personality traits are heritable with a significant maternal inheritance proportion, the potential interference of SSRIs on this heritable character should also be studied (Ariyomo et al., 2013).

5. Translational research: fish as a proxy for individual disease vulnerability

Current evidence highlights a relationship between personality traits and health (Zozulya et al., 2008; Murray and Booth, 2015). Under stressful conditions, both human personality traits and specific behavioural patterns in animals are prominently exhibited (Mehta and Gosling, 2008). Several studies have demonstrated that individuals from many species, including teleost fish and humans, deal with stress differently by adopting different behavioural strategies to overcome stress (Wong et al., 2019). This variation in individual sensitivity may affect disease susceptibility (McDonald, 2017; Demin et al., 2019). Despite the myriad differences in morphology, physiology, behaviour and biological complexity within humans and non-human animals, translational research has proven to be very helpful in understanding personality, immunity, and health. Humans share with other species many molecular and biochemical pathways involved in behavioural expression that are highly conserved across animal taxa (Ford et al., 2021; Wilson and Godin, 2009; Castanheira et al., 2016). The study of various behavioural models has shown that coping style determines, to a large degree, the reaction of the neuroendocrine system to stress, therefore influencing several aspects of the stress response such as activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-interrenal/adrenal (HPI/HPA) axis, both systems affecting the immune system (Wilson et al., 2019). In this context, zebrafish has emerged as a promising model for the study of behaviour and personality due to high genetic and physiological homology with humans along with two well-defined personality patterns (proactive/bold and reactive/shy) and the same modulatory neurotransmitters found in the mammalian brain (e.g., serotonergic, and dopaminergic systems) (Adhish and Manjubala, 2023; Xie et al., 2022; Gould et al., 2021). Therefore, assessing the effects of SSRIs on zebrafish personality may be very helpful in understanding the potential effects of these antidepressants on human personality, which is clinically and environmentally relevant. The silencing of personality traits is sometimes a consequence of SSRI's therapeutical treatment (Homberg et al., 2007). However, its potential influence on human response to environmental stressors (e.g., contaminants) and disease susceptibility is unknown. Additionally, effects related to unintentional exposure to these antidepressants should also be addressed as SSRIs have already been detected in some countries in drinking water (McDonald, 2017).

5. Final considerations

As current data highlight the potential of SSRIs to modulate personality by erasing intraspecific behavioural variance within a

population, it is environmentally relevant to understand how this can impact an organism's ability to cope with additional environmental stressors (e.g., temperature, chemicals, micro (nano)plastics and their combination) in such challenging and ever-changing environment. Considering the widespread consumption of antidepressants and the increasing exposure of humans to a diversity of environmental stressors, this approach could prove beneficial and potentially applicable to humans as well. The presence of non-monotonic responses in studies with SSRIs underscores the importance of prioritizing the development of environmentally relevant tests. These tests are essential for achieving a comprehensive understanding of the environmental consequences associated with SSRIs. Given that behaviour is influenced by integrated effects at multiple biological levels, it is crucial to include long-term and multigenerational assessments, incorporating various types of SSRIs, in behavioural assays due to their environmental relevance. By adopting this approach, we can accurately evaluate the long-term impacts of SSRIs on the environment.

Credit author statement

Carla Ferreira: Conceptualization, Investigation, Writing – Original Draft, Writing – Review & Editing; Sandra C. Soares: Review & Editing, Supervision; Peter Kille: Review & Editing, Supervision; Miguel Oliveira: Conceptualization, Writing – Review and Editing, Visualization, Supervision and Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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