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"Why (Zebra)fish May Get Ulcers": Cognitive and Social Modulation of Stress in Fish

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Abstract
Background: In the bestseller book "*Why Zebras Don't Get Ulcers*", Robert Sapolsky argues that animals do not suffer from stress-related diseases like humans because for them, stress is episodic, while humans in contrast suffer from chronic psychological stress. In particular, the idea that fish cannot experience psychological stress is still prevalent, partly due to the lack of a homologous brain area to the neocortex. However, emerging evidence suggests that teleosts can undergo psychological stress, defined as a subjective and perceptual experience of the stressor, and in recent years, the underlying mechanisms started to be unveiled. ***Summary:*** The occurrence of cognitive appraisal in the assessment of stressors has been demonstrated in fish, indicating that the subjective evaluation of stimulus valence and salience, rather than absolute intrinsic characteristics of the stimulus itself, play a key role in the activation of the stress response. Moreover, individual biases (i.e., cognitive bias) in the cognitive appraisal of stimuli have also been described in fish, with some individuals consistently evaluating ambiguous stimuli as positive (aka optimists) whereas other individuals (aka pessimists) appraise them as negative. As a result, optimists and pessimists show consistent differences in stress reactivity and susceptibility/resilience to disease. Finally, social context has also been shown to modulate the response to aversive stimuli with the behavior of conspecifics either buffering or enhancing the response (i.e., social buffering vs. social contagion). ***Key Messages:*** Cognitive appraisal of stressors occurs in fish, implying that the stress response is modulated by a subjective and perceptual experience of the stressor. Moreover, interindividual consistent cognitive biases in the appraisal of stressors are also present in fish making some individuals more susceptible to stress-related diseases. Therefore, psychological stress has a health toll in fish, and psychologically stressed fish can potentially have ulcers.

Introduction

"*Why Zebras Don't Get Ulcers*" [1] is a bestseller popular science book by Robert Sapolsky that develops the argument that in contrast to wild animals, such as zebras, in which stress is mostly acute, in humans and few other primates the occurrence of psychological stress promotes a nonadaptive chronic stress response, leading

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to human stress-related disorders, such as ulcers. However, in recent years the occurrence of psychological stress, defined as a perceptual and subjective experience triggering the stress response, has also been documented in a wide range of evolutionarily diverse species, from fish to mammals, suggesting that these animals may also experience the detrimental effects of stress-related diseases. Therefore, in contrast to Sapolsky's claim, in this review, we will make the argument that also fish, "may get ulcers," in the sense that they may suffer from chronic/psychological stress-related diseases. This claim is based on three blocks of evidence that will be reviewed in this paper: (1) the occurrence of cognitive appraisal in fish, which provides a subjective experience of stressors; (2) the occurrence of consistent interindividual differences in cognitive appraisal of stimuli, which leads to the evolution of divergent cognitive bias styles (aka optimists vs. pessimists); and (3) the modulation of the stress response by the social environment, which can buffer (aka social buffering) or enhance (aka social contagion) the response. It is important to make it clear at this point that the subjective experience of stress in fish that we refer to in this paper means that due to cognitive appraisal mechanisms involved in stimuli evaluation, different individuals, or even the same individual in different moments in time, may experience the same stressor in different ways, and it does not necessarily imply that appraisal mechanisms result in conscious experience of the stressor. The relationship between cognitive appraisal, psychological stress, and consciousness will be addressed at the Conclusion section of this paper.

Cognitive Appraisal

Ever since Hans Selye introduced the term stress in Biology [2], it has been the target of different conceptualizations [3–8]. Despite the diversity of stress models, they all share the idea that stress is a response to actual or perceived threats (stressors) to organismal homeostasis, with an emphasis on the importance of anticipatory responses. Among these, the cognitive appraisal theory has emerged as a unifying model that conceptualizes stress as a transactional process in which the significance of the event (stressor) must be detected and assessed by the individual [9, 10]. According to appraisal theory, the stress response is not merely explained by the intrinsic characteristics of the stimuli but rather by the implications of the stimulus to the individual's needs, resources, and abilities as evaluated by the individual [10–12]. A key point in appraisal theory is to conceive appraisal as a recursive process reflecting the constant inflow of information characteristic of changing environments, which must be monitored to update previous appraisals and generate flexible responses [12–14]. The components of appraisal that have been identified both in humans and other animals are related to the ability of the individual to determine if the stimulus is significant enough to elicit further processing (i.e., stimulus relevance [15]).

Two major components of appraisal are stimulus salience and valence, such that individuals adjust their internal state to the perceived state of the outside world. The salience of a stimulus is usually a function of its novelty, and animals respond to novelty/familiarity with adaptive behavioral changes. For example, when zebrafish is placed in a novel tank, it increases swimming and freezing behavior [16]. However, with repeated exposures to the same tank over consecutive days, fish spent more time in explorative swimming and decreased freezing, suggesting that zebrafish has become familiar with the new tank hence decreasing its saliency and the concomitant behavioral response. The valence, positive or negative, of a stimulus is a function of its pleasantness to the individual and drives approach/withdrawal responses, respectively [17–20]. Both conditioned place preference (CPP) and conditioned place aversion (CPA) protocols have been validated for fish to assess their perception of stimuli valence (e.g., sea bass, [19]; sea bream [20]). These tests allow the assessment of the reward/punishment values that individuals attribute of different stimuli. Motivation tests, in which animals have to pay to get access to stimuli or resources have also been used. For example, male Mozambique tilapia (*Oreochromis mossambicus*) have been trained to open a transparent pendular door to get access to a compartment where different resources were placed (e.g., food, social partner) [21]. By attaching different weights to the door, the animal had to dispend different amounts of physical effort to enter the compartment and access the desired resource. It was shown that the motivational state of the animals and their social status regulated the price they were willing to pay to access different resources, hence allowing the measurement of motivational needs and their perception of resource valence and salience [21]. Both CPP/CPA and motivation tests have the advantage that not only the perception of valence of stimuli can be assessed but also its salience since one can quantify reward/punishment value in a quantitative scale in the case of CPP/CPA or establish a price curve in motivation tests where animals have to pay, in form of physical work, to get access to the presented stimuli/resource. This allows to apply economic theory to animal motivation and

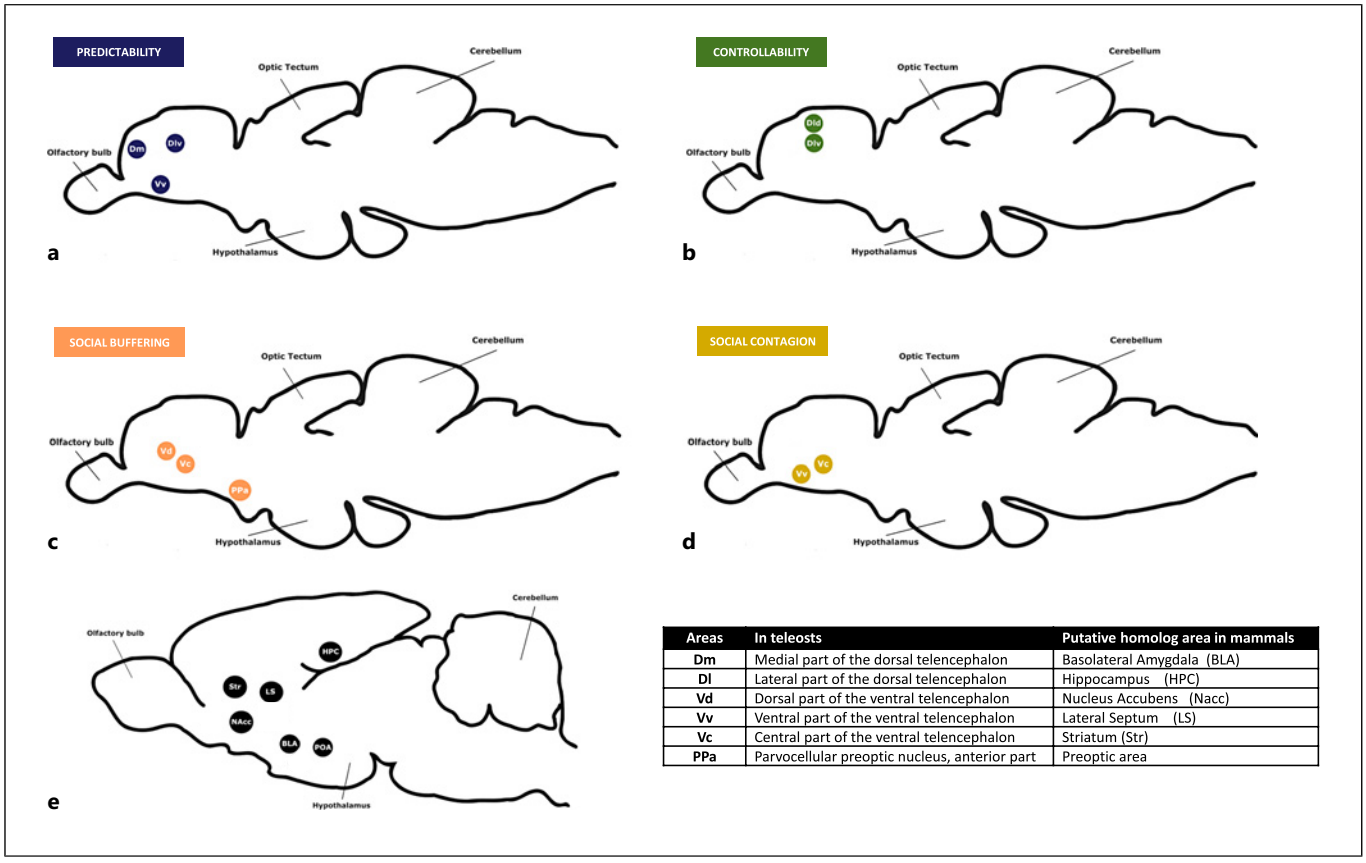
to distinguish between necessities, in the case that work expressed by the individual always increases with an increase in price, from luxuries, when the work stops increasing with an increase in price. This distinction is particularly relevant when assessing welfare needs of animals.

On top of the evaluation of stimulus salience and valence, animals can also appraise stimulus based on associative learning between two stimuli, such that one stimulus predicts the occurrence of another (aka predictability), or based on operant learning between a stimulus and a behavioral response (aka controllability). Predictability allows individuals to detect contingencies between stimuli in the environment, enabling them to anticipate the occurrence of specific events, thus reducing the uncertainty of the external environment. In general, predictability reduces the stress response to negatively valenced events (i.e., stressors; e.g., [22–24]). On the other hand, controllability allows animals to evaluate the implications of a situation and control it, resulting in lowered stress responses; hence, it can be seen as a coping strategy [13, 15, 25, 26]. A seminal study conducted in rats [27] showed that individuals preferred an operant-obtained food reward instead of a free reward (contrafreeloading), suggesting that controllability may be rewarding by itself. Examples of contrafreeloading phenomena have been shown in many other species, including birds [28, 29], goats [30], and monkeys [31, 32].

In recent years, the effects of both predictability and controllability on fish stress responses have been documented. Cichlid fish (*O. mossambicus*), aka tilapia [24], exposed to predictable and unpredictable events with varying valences (negative vs. positive), exhibited differences in behavior (avoidant vs. appetitive) and cortisol response based on the predictability and valence of the stimuli. In this experiment, during the training phase, a visual cue (conditioned stimulus [CS]) was paired with an unconditioned stimulus (US: food on the positive valence treatment or physical confinement in the negative valence treatment). As the control treatment during the training phase, individuals were also exposed to the CS, but it was unpaired with the US. Subsequently, at the test phase, individuals in the stressor (i.e., confinement) predictable (i.e., CS-US paired training) treatment displayed less aversive behavior, and a lower cortisol response than those with in the stressor unpredictable treatment (i.e., CS-US unpaired training). Interestingly, the exposure to unpredictable feeding events also elicited a higher cortisol response and anticipatory behavior, when compared to the predictable feeding event (i.e., CS-US paired training), indicating that cortisol is a better marker of affective arousal than of affective valence. Together, these results indicate that tilapia are able of appraising events and adjust their behavior and internal state accordingly and that predictability plays a key role in these responses [24]. Similar results have been obtained for sea bream (*Sparus aurata*) [33] and for European sea bass (*Dicentrarchus labrax*) [34], which confirmed the effect of predictability in lowering the stress response in both species.

The effect of controllability on the stress response in fish has also been studied in the European sea bass, by anticipatory signaling (CS – light) the stressor that would allow the individual to escape the signaled stressor (US – confinement) [35]. Three different conditions were presented along with the conditioning protocol: (1) a controllable stressor, where the signal (CS) was presented together with the US and with the possibility to escape through a door; (2) an uncontrollable stressor, with no possibility to escape; and (3) a loss of control, consisting of five training trials of controllable stressor followed by two trials of uncontrollable stressor. The perception of control decreased freezing behavior and the number of escapes, and increased exploration behavior and shoal cohesion. The cortisol response to the signaled stressor that can be avoided was significantly lower than that to an unescapable signaled stressor [35]. Interestingly, loss of control in animals that were first trained with a signaled stressor and then switched to a signaled stressor treatment elicited the highest cortisol response, suggesting that it is perceived as a more negative situation than having no control from the beginning.

In the studies of predictability and controllability in sea bream and sea bass, besides behavioral and physiological (i.e., cortisol circulating levels) responses, brain activation patterns have also been measured, providing an insight in the brain regions engaged in predictability and controllability in fish [33, 34]. For this purpose, the expression of immediate early genes (*c-fos*, *egr-1*, *bdnf*, and *npas4*) was used as a molecular proxy for neuronal activation [36, 37]. In Sea bass, the dorsomedial telencephalon (Dm), which is considered the fish homolog of the mammalian basal amygdala [38], showed an increase in activation in response to an unpredictable stressor, whereas the ventral area of the dorsolateral telencephalon (Dlv), a putative homolog of the hippocampus [38], showed a lack of response to a predictable stressor which is not observed in response to an unpredictable one [34]. In sea bream, Dm is also activated in response to unpredictable appetitive stimuli, and the ventral area of the ventral pallium (Vv)



Areas	In teleosts	Putative homolog area in mammals
Dm	Medial part of the dorsal telencephalon	Basolateral Amygdala (BLA)
Dl	Lateral part of the dorsal telencephalon	Hippocampus (HPC)
Vd	Dorsal part of the ventral telencephalon	Nucleus Accubens (Nacc)
Vv	Ventral part of the ventral telencephalon	Lateral Septum (LS)
Vc	Central part of the ventral telencephalon	Striatum (Str)
PPa	Parvocellular preoptic nucleus, anterior part	Preoptic area

Fig. 1. Schematic representation of the different fish brain areas involved in predictability (**a**), controllability (**b**), social buffering (**c**), and social contagion (**d**), and the corresponding homologous areas in mammals (**e**).

responds both to appetitive and aversive unpredictable stimuli [33]. Therefore, overall predictability seems to be associated in the fish brain with activation of Dm and Vv and an inactivation of Dlv (Fig. 1a). On the other hand, controllability in sea bass is associated with decreased activity in the dorsal area of the dorsolateral telencephalon (Dld) and increased activity in the Dlv, suggesting a specific involvement of the Dl in controllability ([35]; Figure 1b). Finally, it should be highlighted that on top of specific differences of activation in each of these brain regions, predictability and controllability also induced specific patterns of co-activation across brain regions indicating specific patterns of functional connectivity in the fish brain that parallel these behavioral states [33–35]. Together, these results indicate an involvement of the pallial amygdala and hippocampus-like areas in the teleost brain in cognitive appraisal, suggesting an evolutionarily conserved role of these two brain regions in information processing related to stressor appraisal across vertebrates.

Cognitive Bias

The occurrence of subjective cognitive appraisal in fish opens the possibility that biases in stimulus appraisal may occur across individuals, such that some individuals will assess ambiguous stimuli as negative (i.e., signaling punishment), whereas others may assess these same stimuli as positive (i.e., signaling reward). Such cognitive biases have been characterized in many different species from bees to mammals [39–41] and have been mainly seen as transient affective states that can be used as indicators of animal welfare [42]. Transient changes in cognitive bias have been described in monogamous cichlids, which display increased pessimistic assessment of ambiguous stimulus when separated from their partner [43]. In the Murray cod (*Maccullochella peelii*) [43], housing males with a larger aggressive individual for 24 h induced a pessimistic response in a judgment bias test. In three-spined sticklebacks (*Gasterosteus aculeatus*), both sex, personality (boldness), and lateralization

showed an association with cognitive bias with males and more lateralized individuals being more optimistic [44]. Finally, in captive juvenile European sea bass (*D. labrax*) [45], a baseline pessimistic bias resulting from living in laboratory conditions can be ameliorated by providing unexpected appetitive events (i.e., food). However, if these biases are consistent within the same individual across time, they can be seen as a personality phenotypic trait, with different individuals exhibiting specific phenotypes, leading to between-individual variability, with positive- and negative-bias (aka optimistic and pessimistic) [46].

The occurrence of trait cognitive bias has recently been documented in zebrafish using a cognitive bias setup that consists in a half radial maze, in which after being trained to discriminate between positive (i.e., associated with reward) and negative (i.e., associated with punishment) color-cued arms of the maze, individuals are faced with an ambiguous option. The latency to enter this ambiguous arm of the maze is taken as an indicator of the expectation to encounter a reward (i.e., optimistic bias) or a punishment (i.e., pessimistic bias) [47], with the results showing high individual bias repeatability across time [48]. The trait dimension of this phenotype has been further supported by three types of evidence: (1) a bimodal distribution of the trait in the population; (2) trait-specific fitness consequences; and (3) the existence of a genetic basis that explains interindividual variation in the trait. The bimodal distribution of the frequency of the judgment bias score, characterized by a lower modal extreme with optimistic-biased fish, and a higher modal extreme with pessimistic-biased fish suggests the action of disruptive selection for the evolution of alternative phenotypes in this judgment bias dimension [48]. Moreover, the judgment bias score has been shown to be correlated with the response to a novel object, positively linking the response to an ambiguous stimulus with risk-taking personality trait [48]. These alternative phenotypes of cognitive bias can reflect evolutionarily stable alternative adaptive behavioral strategies to deal with the frequency of rewards and threats in the environment, with the fitness of optimists being enhanced in reward-rich environments and the fitness of pessimists being higher in threat-rich environments. Thus, it can be predicted that under specific environmental conditions (e.g., high reward vs. high threat) optimists and pessimists must show differences in Darwinian fitness. The occurrence of such trait-specific fitness consequences has been demonstrated by a study in which optimistic and pessimistic zebrafish females exposed to unpredictable chronic stress were shown to allocate reproductive effort differently, with pessimistic females investing more in current reproduction as shown by increased vitellogenesis [49]. These results suggest that, as predicted by the adaptive hypothesis of cognitive bias, by increasing investment in current reproduction, pessimistic females have higher fitness than optimistic females in harsh environments. Finally, the genetic basis of cognitive bias in zebrafish was evidenced in a study in which individuals of a telomerase-deficient zebrafish mutant line ($tert^{AB/hu3430}$), which exhibit shorter telomeres from early in life and concomitantly shorter life spans, were more pessimistic in response to ambiguous stimuli than wild-type zebrafish [50].

To the best of our knowledge, the neural basis of trait cognitive bias has not been investigated in non-human animals. In humans, administration of dopaminergic drugs (L-DOPA) increases an optimism bias, due to an impaired ability to update undesirable information about the future [51]. Accordingly, the human mesolimbic reward circuitry was also found to selectively update knowledge about future desirable outcomes more often than undesirable ones, in contrast to the orbitofrontal cortex, which responds to the opportunity to update information regardless of its valence [52]. Therefore, the connectivity between the orbitofrontal cortex and mesolimbic reward circuit could be key for the observed cognitive biases. In animals lacking a neocortex, such as fish, other subcortical regions must be playing this role in articulation with the dopaminergic reward system.

The establishment of judgment bias as a personality trait raises the possibility that individuals with different judgment bias phenotypes (i.e., optimists/pessimists) may respond differently to stressors and therefore express differential resilience to stress-related diseases. In rats, "pessimistic" individuals subjected to chronic restraint, developed depression-like symptoms (e.g., anhedonia) faster, and these symptoms lasted for longer than in "optimistic" animals [53]. Research on the role of cognitive bias on stress resilience in fish is still scarce. Recent research conducted in our laboratory indicates that pessimistic individuals have an enhanced response to chronic stress paralleled by a higher disease susceptibility [48]. Indeed, when exposed to unpredictable chronic stress for 1 month optimists and pessimists exhibit different brain transcriptomes in the telencephalon and diencephalon, suggesting that chronic stress, which is perceived differently by the two phenotypes, elicits different brain states. Moreover, differential activation of the hypothalamic-pituitary-interrenal axis was also observed, with the optimists having higher mineralocorticoid/

glucocorticoid ratios in specific brain regions, indicating that they have a lower stress reactivity. Accordingly, optimists seem to be more resilient to stress-related disease than pessimists, as shown by a lower tumorigenesis in a zebrafish melanoma line (Tg[mtifa:HRAS-GFP]) [48]. Together, these results suggest that cognitive bias regulates the stress response with implications for disease susceptibility/resilience.

Social Modulation

Finally, the social context in which animals live needs also to be considered. Many fish species are social, and the presence of conspecifics can influence their response to stressors. In particular, the identity and the state of conspecifics can modulate the stress response. Two phenomena have been described in this respect: (1) social buffering, where the presence of familiar and/or relaxed conspecifics decreases the response to aversive stimuli; and (2) social contagion, in which the presence of alarmed conspecifics enhances the stress/alarm response. These phenomena have been observed in several species [54, 55], including fish [56].

Social buffering has been documented in several fish species. In the group-living cichlid *Neolamprologus pulcher*, individuals recover better from air exposure as a stressor (i.e., show lower cortisol levels) when introduced into a social group during the recovery post-stress, when compared to individuals recovering alone [57]. Moreover, this buffering of the stress response is paralleled by a decreased expression of arginine vasotocin and oxytocin in the preoptic area, suggesting a lower activation of the stress axis [57]. Similarly, in an Italian cyprinid (*Telestes muticellus*), group-living individuals have lower cortisol and muscle oxidative stress levels and upregulation of antioxidant enzymes when compared to solitary individuals [58]. Social buffering was also observed in the gregarious lake sturgeon (*Acipenser fulvescens*) when recovering from thermal stress. Post-stress isolated fish show higher levels of whole-body cortisol and of mRNA expression of steroidogenic acute regulatory protein (StAR) and heat shock proteins (hsp90a, hsp90b, and hsp70) than grouped fish [59]. Higher cortisol levels have also been observed in individuals exposed alone to a stressor than when exposed in conspecific groups, both in the three-spined stickleback (*G. aculeatus*; exposure to a predator [60]); and in zebrafish (*Danio rerio*; exposure to a novel environment [61]). Finally, in zebrafish, social buffering has also been tested with the use of the alarm substance [62], a known fear-eliciting stimulus in this species [63]. A lower fear response (decreased freezing) was observed in focal fish tested in the presence of both olfactory and visual conspecific cues than in fish tested alone [62]. At the brain level, social buffering in zebrafish is associated with the absence of an activation of the central part of the ventral telencephalon (Vc; putative homolog of the striatum), the dorsal part of the ventral telencephalon (Vd; putative homolog of *nucleus accumbens*), and of the preoptic area (Ppa), which are observed when individuals respond alone to the alarm substance [64] (Fig. 1c). Among teleost fish, social contagion of fear/stress was first described in zebrafish, using alarm pheromone-induced behavior in demonstrators, which is characterized by a first phase of fast erratic swimming near the bottom followed by freezing, as a fear cue for observers that mimic the alarm response [65–67]. Fear contagion has been shown in several shoaling species other than zebrafish, but in most cases, chemical alarm cues are present and seem to be the main fear transmission signal [66, 68–70]. In zebrafish, social contagion of fear is paralleled by a decrease in activation of two brain regions: Vv and Vc (Fig. 1d) [71]. In the case of Vv, it was also demonstrated that a significant proportion of the activated cells were GABAergic, indicating that social contagion is associated with decreased activity of inhibitory synapses. In the case of Vc, most activated neurons were glutamatergic, suggesting that a secondary inhibitory circuit must be involved in the observed pattern.

Finally, it should be mentioned that oxytocin, which has been implicated in the regulation of social contagion and social buffering in mammals [72, 73], has also been demonstrated to be necessary and sufficient for the expression of these behaviors in zebrafish [64, 71]. These results indicate an evolutionarily conserved role for this nonapeptide in the social modulation of the stress response.

To the best of our knowledge, social buffering/contagion has always been tested in social species. To what extent these phenomena are also observed in asocial species is still unknown and would provide context regarding the species-specificity of these effects. A hint of a possible result comes from work on social buffering in social species (e.g., voles) that shows that familiarity with the conspecific plays a major role on its effect as a stress buffer [55]. Also in rats, the context in which animals are present to each other may have opposite effects (i.e., "enhancing or buffering stress") [55]. Therefore, it can be predicted that in asocial species, the presence of conspecifics should most probably elicit social stress, but empirical tests are needed.

Conclusion

Here we have reviewed evidence that supports the view that teleost fish use cognitive appraisal to mount a stress response, which gives rise to the evolution of alternative cognitive bias phenotypes (optimists vs. pessimists) that respond differently to stressors in a consistent way. Moreover, we have also reviewed the literature on the social modulation of the stress response at the behavioral and physiological levels.

Interestingly, these different cognitive and social mechanisms that regulate the stress response engage specific brain circuits. Stress predictability is paralleled by changes in activation in Dm and Vv, and a lack of response in Dlv, suggesting an amygdala-lateral septum-hippocampus circuit (Fig. 1a). On the other hand, stress controllability is associated with changes in activation of Dlv and Dld, indicating its regulation by a local hippocampal circuit (Fig. 1b). Thus, two key dimensions of cognitive appraisal in fish, predictability and controllability, seem to engage specific brain circuitry. Similarly, the two mechanisms of social regulation of stress also seem to have different underlying circuits that share a node (Vc), which is a putative homolog of the mammalian striatum: social buffering engages Vc, Vd, and Ppa, indicating a striatum-nucleus accumbens-preoptic area circuitry, whereas social contagion engages Vc and Vv, suggesting a striatum-lateral septum circuit. In comparison, these same processes engage both cortical and non-cortical structures in mammals. For example, in rodents, the ventromedial prefrontal cortex mediates cognitive appraisal of stressors and the activation of the physiological stress response [74], and social contagion of emotional states engages the insula and the anterior cingulate cortex, as well as subcortical areas such as the ventral hippocampus, the mediodorsal thalamus, the amygdala, and the nucleus accumbens [75]. Therefore, the results reviewed here indicate that cognitive operations that are implemented by cortical-subcortical circuitry in mammals are exclusively implemented by non-cortical pallial structures in teleost fish. This pattern suggests that, similarly to other cognitive domains, with the evolution of the neocortex in mammals, functions previously computed in subcortical structures have been coopted totally or partially by cortical circuits (e.g., optic tectum processing of color vision in fish vs. cortical processing of color vision in primates [76]). These results also have implications for the fish sentience debate, in which the argument that the absence of a neocortex, which is required for the awareness and ability to report subjective experiences (aka sensory consciousness) in humans, proves the absence of consciousness in fish has been often used [77]. Our results further support the view already expressed by others that similar cognitive functions can be independently implemented by convergent brain circuits, or even at a different level by more ancestral subcortical circuits within the same clade [78, 79].

In summary, cognitive appraisal of stressors and potential individual biases in their processing have a demonstrated impact on fish health (e.g., melanoma onset and progression in zebrafish). Therefore, psychological stress, defined as a subjective and perceptual experience of the stressor, has a health toll, and psychologically stressed fish can potentially have ulcers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Bianca Fusani and Rui Oliveira wrote together the first draft of the manuscript and reviewed the manuscript.

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