Review Article

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Fight or flee? Lessons from insects on aggression

https://doi.org/10.1515/nf-2017-0040

Abstract: Aggression between members of the same species serves to secure resources, but the costs can quickly outweigh benefits. Hence, for aggression to be evolutionarily adaptive, animals must decide when best to flee, rather than fight. How its done, is arguably best understood in crickets. These insects implement the decision by simply modulating the behavioural threshold to flee. This threshold is raised by potentially rewarding experiences (e. g. resource possession), via the amine octopamine, so that the animal is less prone to flee and persists longer in fighting. Conversely, the threshold is lowered by nitric oxide, released in response to aversive stimuli (e. g. the opponent's agonistic signals), thus increasing the tendency to flee. A cricket then flees, when the sum of its opponent's actions exceeds the threshold. Subsequently, serotonin keeps the threshold low, so that losers remain submissive; possibly by inhibiting dopamine, which is necessary for recovery of aggression in losers.

Keywords: serotonin, octopamine, nitric oxide, social behaviour, decision making

Introduction

Darwin (1859) recognised that the struggle for existence was most severe between individuals of the same species – after all they compete for the same niches, foods and sexual partners. Although intra-specific aggression can ensure survival, it's a dangerous game, and the costs of injury can quickly exceed the potential gains. Hence, for aggression to be evolutionarily adaptive, all animals must know when it would be more opportune to fight or to flee. But how? Behavioural game theory (Maynard-Smith and Price, 1973; Hardy and Briffa, 2013) posits that the ritualised fighting strategies common in animals and even indigenous peoples, with impressive threats preceding blows, have evolved as a low-risk means to assess win chances. Win chances largely depend on physical attributes such as strength and weaponry (teeth, claws, horns), but also on an individual's aggressive motivation, or tendency to invest energy in fighting. Aggressive motivation, in turn, is largely experience dependent. It is promoted by the presence of resources, which can differ in value for each contestant, and fuel the weaker to prevail, for example, in defence of offspring (Maynard-Smith and Parker, 1976; Hsu et al., 2006). Winners also tend to become more aggressive and win subsequent interactions, whereas losers become submissive, even towards unfamiliar opponents (the loser effect). Defeat is also often coupled with depression-like symptoms in animals and humans that can become severe, particularly after repeated defeats (de Boer et al., 2016) and can even shorten lifespan (Razzoli et al., 2018). But what are the proximate mechanisms underlying experience-dependent changes in aggressive motivation and in the assessment of costs, benefits and win chances? How, exactly, do animals decide when to fight or flee?

The answers of course lie in the brain. Aggression is influenced by numerous neurotransmitters, modulators and hormones and the drugs that affect them (Trainor et al., 2017). These signalling systems, with widespread innervation patterns and multiple, functionally unique receptors as mediators are highly complex (Carhart-Harris and Nutt, 2017), and it has thus proven elusive to decipher their natural, behavioural functions in aggression (Oliver, 2015).

Here, we summarise how experiences control the decision to fight or flee via the action of neurotransmitters in insects, primarily adult male crickets (*Gryllus bimaculatus*). But first, why crickets? In addition to having a comparatively simpler nervous system, their spectacular fighting behaviour is highly stereotyped, and hence easily quantified (Figure 1). Even so, as in mammals, aggression in crickets is promoted by physical activity, winning, the presence of resources, and is suppressed by defeat, particularly multiple defeats, with potentially lifelong consequences (Stevenson and Rillich, 2017). Furthermore, our work illustrates that crickets can make seemingly complex social decisions without conscious reasoning, and this is arguably their greatest experimental advantage. Work on

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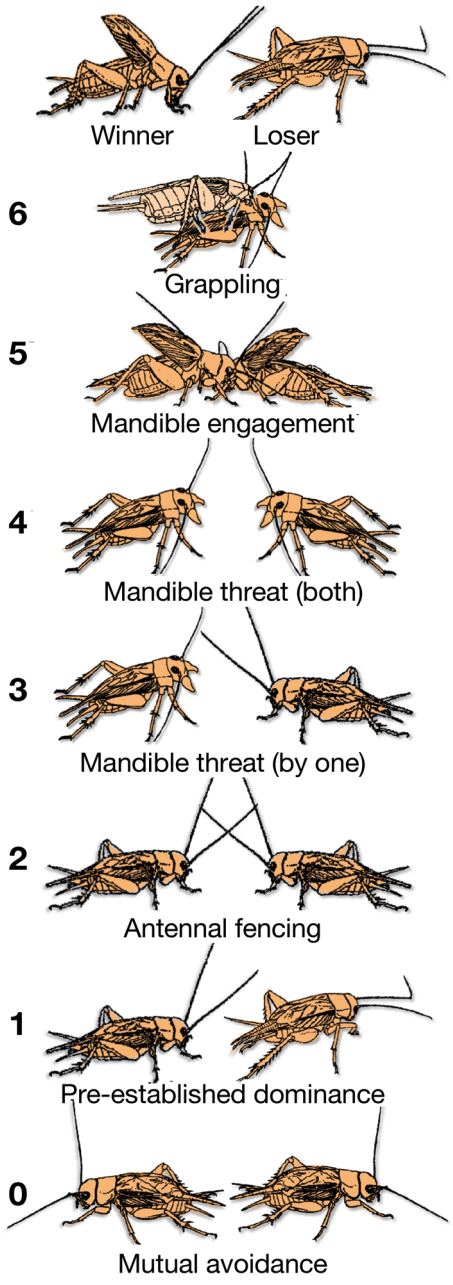

Figure 1 Levels of escalating aggression in crickets. Fights can conclude at any level, when one opponent retreats, but they usually escalate to level 5 and last several seconds. Losers exhibit reduced aggression for about 3 h after defeat, whereas winners become hyper-aggressive. Modified from Stevenson et al., 2000.

insects, also point to some remarkable similarities in the mechanism underlying aggression in insects, rodents and man (Thomas et al., 2015; Stevenson and Rillich, 2017), that will be mentioned here. Our main aim, however, is to point out novel insights into how crickets make the actual decision to fight or flee, which is less well understood in other model animals.

Controlling the decision to fight – the role of octopamine (OA)

In his pioneering work on crickets, Franz Huber (1955) found that elements of aggressive behaviour can be elicited by electrical stimulation of the brain. The natural aggression-releasing stimulus, however, is antennal contact between male crickets during fencing behaviour, and comprises both mechanical and olfactory components (Sakura and Aonuma, 2013; Rillich and Stevenson, 2015). Male-male contact leads to release of the amine octopamine (OA) in crickets (Adamo et al., 1995; Figure 2) and to direct excitation of OA neurones by pheromone sensitive receptors in *Drosophila* (Andrews et al., 2014). Much like the related amines noradrenaline (NA) and adrenaline (AD) in vertebrates, OA acts in insects as a stress hormone, released to cope with high energy demand and to support fight or flight responses (Verlinden et al., 2010). Whereas a consistent relationship between NA/AD and mammalian aggression has yet to be established (Nelson, 2006), pharmacological and genetic manipulations show that OA increases aggression in crickets (Stevenson et al., 2005) and fruit flies (Hoyer et al., 2008; Zhou et al., 2008). However, pharmacological depletion revealed that neither OA, nor any other amine, is necessary to actually initiate aggression (Stevenson et al., 2000). Furthermore, although simply lashing a male cricket's antennae with the cut antennae of another male is sufficient to elicit an aggressive response (rival song production, mandible spreading, cf. Figure 1), this is not altered by aminergic drugs (Rillich and Stevenson, 2015). After antennal stimulation, however, the crickets escalate higher, and persist longer in actual fights and this effect is dependent on OA. This is just one example illustrating that OA mediates the aggression-promoting effects of a variety of experiences (Figure 3).

A less insect-specific effect is that of physical exertion, a naturally reinforcing and rewarding activity in rodents (Herrera et al., 2016) that also enhances aggression in man (Wood and Stanton, 2012). In crickets, flying induces OA release (Adamo et al., 1995) and a subsequent transient increase in aggression (Hofmann and Stevenson, 2000), that is blocked by OA-receptor antagonists and mimicked by the OA agonist chlordimeform (CDM; Stevenson et al., 2005). Although the pesticide CDM binds almost irreversibly to OA receptors, the crickets are not protected from losing a contest. Hence, the decision to flee must be controlled independent of OA.

Winning increases aggression in numerous animals (Hsu et al., 2006). In rodents, this winner effect is mediated by androgens (Oliviera et al., 2011) and dopamine

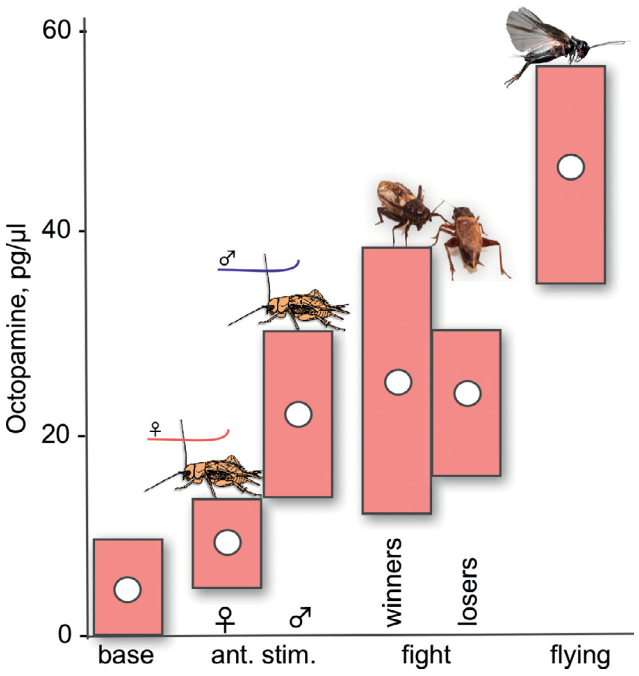

Figure 2 Haemolymph levels of octopamine in male crickets (µg/µl medians and interquartile ranges) at rest (base) and following antennal stimulation with either a male or female antenna (ant. stim. ♂, blue stroke, ♀, red stroke), after fighting in winners and losers, and after flying. Adapted from Adamo et al., 1995.

(DA, Becker and Marler, 2015), but in crickets by OA (Rillich and Stevenson, 2011). Physical fighting in crickets increases OA levels (Adamo et al., 1995; Figure 2) and interrupting fights before their conclusion revealed that the physical exertion of fighting alone can establish a winner effect (Rillich and Stevenson, 2011). Surprisingly though, crickets also show a winner effect after only observing an opponent retreat, without physical exertion. This is reminiscent of the case in humans, where testosterone levels rise after watching a previous victory in sports (Carre and Putnam, 2010).

Possession of a resource, such as territory, enhances aggression in rodents, but the cause is little understood (Fuxjager et al., 2010). In crickets, burrows are valuable resources that protect from predators, attract females, and are vigorously defended (Rodriguez-Munoz et al., 2008). In the laboratory, crickets given a shelter to occupy, show a transient increase in aggression, that is dependent on OA (Rillich et al., 2011). Since shelter residency, or watching an opponent retreat, requires little energy and is hardly stressful, OA is not acting here simply as a stress hormone. It seems rather to function as a central neuromodulator to mediate the aggression-promoting effects of experiences that are potentially rewarding, or at least not aversive. OA conveys reward signals in appetitive learning para-

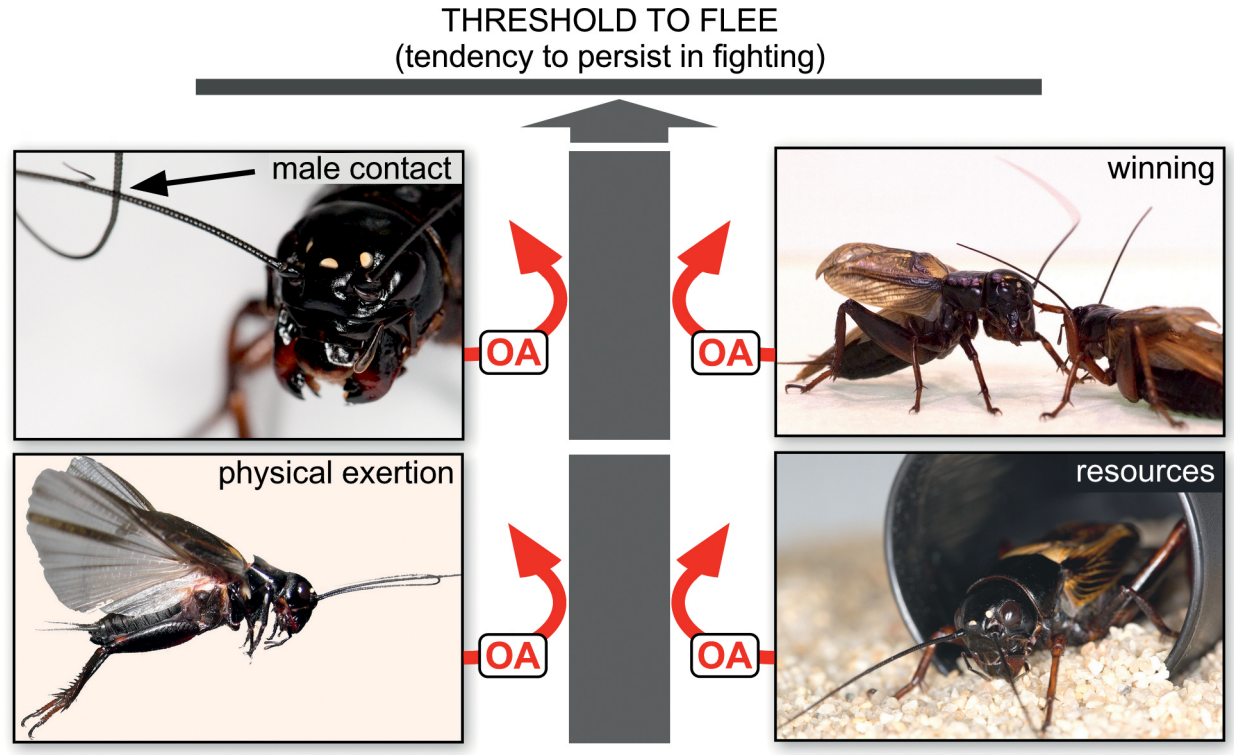

Figure 3 Schema to illustrate that the experiences in crickets of male contact, physical exertion (flying), winning and resource possession (burrow residency) each lead to the release of octopamine (OA), which then acts as a neuromodulator to promote aggression by raising the threshold to flee. The cricket thus becomes less likely to flee in response to the agonistic actions of an opponent (see Figure 4) and as a result tends to persist longer in fighting. Modified from Stevenson and Rillich, 2017.

digms in crickets (Mizunami and Matsumoto, 2017). Furthermore, neurones identified as important for aggression in *Drosophila* (Zhou et al., 2008), appear to be of the same type that signal sucrose reward in honeybee olfactory learning (Hammer, 1993). However, as the experiments with antennal stimulation illustrate, OA does not increase the tendency to actually initiate aggression. As discussed below, OA appears rather to promote aggression by raising the threshold to flee, which in effect increases the propensity to persist longer in fighting (Figure 3). In this respect, OA can be considered to represent the motivational component of aggression in insects.

Controlling the decision to flee – the role of nitric oxide (NO)

Very little is known about how animals make the decision to flee from an opponent in an aggressive interaction (see, however, Certel et al., 2010 on novel insights into how *Drosophila* implements the decision to court or fight a conspecific, and Evans et al., 2018 concerning a synaptic threshold mechanism for the decision to escape from harmful stimuli in rodents).

Behavioural theories agree that an animal's decision to flee is based on its assessment of offensive, agonistic signals exchanged during fighting, but it is debated whose signals are assessed: the signaller's own, the opponent's, or both (Arnott and Elwood, 2009). The secret in crickets was revealed by imposing handicaps to impair agonistic signalling (Rillich et al., 2007). We first noted that crickets still fight, without significant change in win chances, with either fully disabled mandibles or blackened eyes. Surprisingly though, blinded crickets practically always (98 %) beat opponents with disabled mandibles. This, seemingly odd finding, conforms fully with the Cumulative Assessment Hypothesis of Payne (1998). This posits that individuals evaluate only their opponent's actions in a contest, and flee when the accumulated sum exceeds a critical threshold. Accordingly, in our experiment, the blinded cricket persists longer and eventually wins since it perceives no visual threats and greatly reduced physical impact from an opponent with disabled mandibles. The latter by contrast, experiences the full brunt of the blinded opponent's actions, and hence flees earlier.

Later experiments revealed that the NO signalling pathway plays a leading role in opponent assessment and controlling when to flee (Stevenson and Rillich, 2015; Figure 4). As in mammals (Bedrosian and Nelson, 2014), NO appears to dampen aggression in crickets. When this system is pharmacologically activated, crickets rarely escalate to physical fights (cf. Figure 1), and they last only half as long (2–6 s). By contrast, when blocked, crickets fight for up to a minute or more (Stevenson and Rillich, 2015). Handicapping revealed that NO does not reduce aggressive motivation. For example, blinded crickets treated with a NO-donor fight opponents with lamed mandibles with unchanged ferocity and persistence, but they now win less than 50 % of fights instead of nearly always in controls. Conversely, instead of nearly always losing against blinded opponents, crickets with disabled mandibles won half the fights when treated with a NO synthesis inhibitor. These compensatory effects of nitridergic drugs indicate that NO mediates the impact of the opponent's agonistic signals. This was verified by testing how a potentially aversive stimulus, not normally experienced during fighting, affects subsequent contest behaviour. Whereas light wind stimulation of the abdominal cerci had no effect on its own, when preceded by male antennal stimulation, the wind stimulus induced normally aggressive crickets to behave like losers, and retreat on contacting another male without fighting. However, if they received a NO synthesis blocker, the antennal/wind stimulus regime no longer induced loser behaviour (Rillich and Stevenson, 2017). Thus, male contact sets the behavioural context during which a cricket begins to evaluate external stimuli as aversive. These external stimuli then promote behaviour via the action of NO.

If true, that crickets add up their opponents' actions and flee when the accumulated sum exceeds some critical level, then winners must also have a memory of the sum of their opponents' actions. Indeed, winners that receive aversive (wind) stimuli just after winning, subsequently behave like losers on confronting a fresh opponent (Stevenson and Rillich, 2015). Again, this effect is not evident

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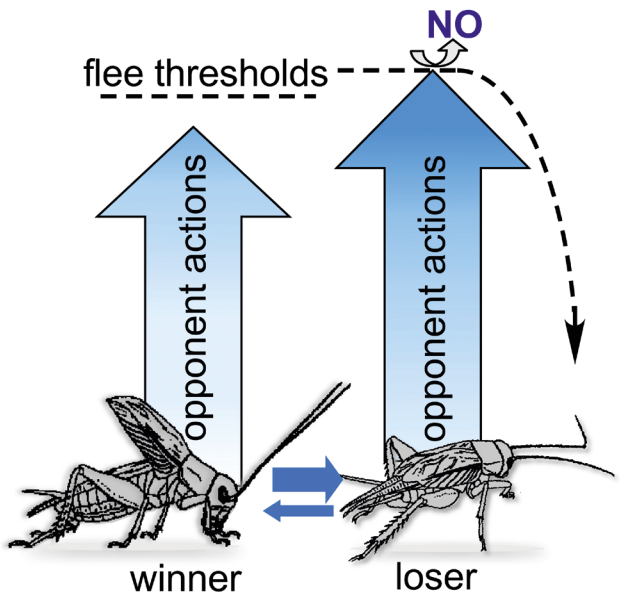

Figure 4 Schema depicting current understanding of how crickets decide when to flee. Each cricket enters into a fight with a set threshold to flee (dashed line), that is determined by previous experience (Figure 3) and can thus be different for each individual, and possibly even higher in the prospective loser, as in this figure. During fighting, the contestants exchange agonistic signals (solid blue arrows), which can vary in frequency and intensity between individuals (as indicated by arrow thickness). Crickets evaluate their opponent's actions as aversive stimuli, and flee the moment when the accumulated sum experienced during a contest (vertical arrows) exceeds a critical amount, which corresponds to the threshold to flee. Aversive stimuli experienced in an aggressive context induce the release of nitric oxide (NO), which acts as a neuromodulator to promote retreat, by lowering the threshold to flee. Losers thus appear to be submissive, since they retreat in response to even the slightest contact with an aggressive male. Details in Stevenson and Rillich 2015; Rillich and Stevenson, 2018.

when NO synthesis is blocked, or when the aversive stimuli are given 1 min or more after winning. Thus, winners need to accumulate only a few more aversive stimuli within a brief susceptible period to recruit NO and become subordinate. We speculate that winners of other species including our own, may be similarly susceptible to post-conflict depression, particularly in the absence of a rewarding experience normally associated with victory.

Social defeat and the loser effect

After fleeing, loser crickets remain submissive for some 3 h and retreat on contacting another male, even if unfamiliar (Stevenson and Rillich, 2013). Such loser effects are common in invertebrates and vertebrates including humans, but the underlying physiological mechanisms remain unclear for most animals (Hsu et al., 2006; Oliveira et al., 2009). In crickets, NO seems to be necessary for both initiating retreat and establishing loser depression. Inhibiting NO signalling prolongs the loser effect, whereas activators induce early recovery (Iwasaki et al., 2007; Stevenson and Rillich, 2015). Recovery from the loser effect also occurs immediately after flying, or burrow residency, and both these effects depend on OA (Hofmann and Stevenson, 2000; Stevenson et al., 2005; Rillich et al., 2011). However, although the OA agonist CDM induces early recovery, natural recovery is not affected by blocking OA receptors. Contrasting this, dopamine (DA), which appears to have no effect on the aggression exhibited by socially naive crickets, is both sufficient and necessary for natural recovery of aggression after defeat (Rillich and Stevenson, 2014).

Since OA is not necessary for initiating aggression, or recovery from defeat, it is unlikely that it promotes aggression by increasing the propensity to fight *per se*. The most parsimonious explanation is that OA raises the threshold to flee, in response to an opponent's agonistic signalling efforts, so that the animal in effect persists longer at fighting the opponent. Supporting this, losers respond to male antennal stimulation with the mandible threat display equally well as socially naive crickets (Rillich and Stevenson, 2015) and will attack another loser, if this loser retreats on sight, before contact (Rillich et al., 2007; Stevenson and Rillich, 2013). Thus, losers remain potentially aggressive, and only appear to be non-aggressive because they have a low threshold to flee, and accordingly retreat immediately when they contact an aggressive male.

Serotonin and aggression – insects are not so different

Serotonin (5-hydroxytryptamine, 5HT) is an evolutionarily ancient and well conserved neurotransmitter that is considered to function as the primary orchestrator of aggressive behaviour in invertebrates and vertebrates including humans (de Boer et al., 2015). While the mechanism is highly complex, 5HT in vertebrates is thought mainly to dampen aggression, e. g. by promoting withdrawal via 5HT1A and or 5HT1B receptors in the dorsal Raphe nucleus (Olivier, 2015). In invertebrates, however, 5HT is generally attributed with the reverse effect: 5HT, its precursor 5-hydroxytryptophan, 5HT1A agonists and genetic activation of specific 5HT neurones are reported to increase aggression and win chances, while reducing the tendency to flee

in crustaceans (Kravitz, 2000), fruit flies (Johnson et al., 2009; Alekseyenko et al., 2014) and stalk-eyed flies (Bubak et al., 2014).

The precise role of 5HT during normal fighting behaviour in socially naive crickets is uncertain (Dyakonova and Kruschinsky, 2013; Stevenson and Rillich, 2017). So far, we have failed to find a clear effect of serotonergic drugs on normal fighting behaviour of socially naive crickets (Stevenson et al., 2000; Rillich and Stevenson, 2015, 2017). Losers, however, are severely affected (Rillich and Stevenson, 2018). For example, blocking 5HT2-like receptors inhibits the acquisition of submissiveness in losers, while blocking re-uptake of endogenous 5HT with fluoxetine prohibits recovery from social defeat. This indicates that 5HT is released specifically after defeat to maintain the low threshold to flee that typifies loser behaviour. In *Drosophila*, 5HT was recently found to modulate stress-induced behavioural depression (Ries et al., 2017), but it is not known to influence post defeat depression in these insects. In rodents, however, submissive behaviour after defeat is reduced by 5HT2A antagonists injected into the amygdala (Clinard et al., 2015) and there is recent evidence for a similar aggression-suppressing effect of 5HT in crayfish after defeat (Bacque-Cazenave et al., 2017). It thus appears, that 5HT2-like receptors are involved in maintaining submissive behavior after social defeat in mammals, insects and possibly crustaceans. In crickets, work in progress suggests that this action of 5HT depends on prior release of NO, and could be implemented by inhibiting DA-mediated recovery of aggression after defeat (Figure 5).

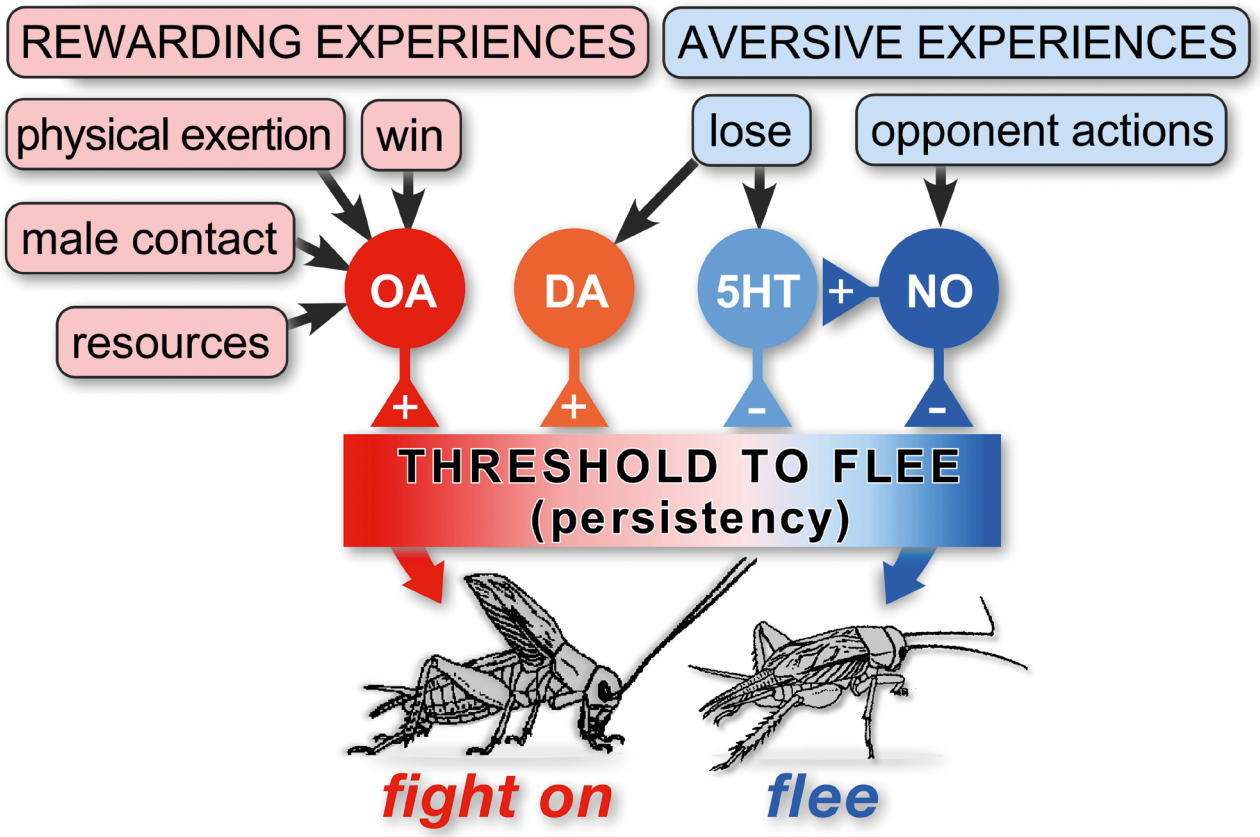

Figure 5 Hypothetical schema of the neurochemical control of aggression in crickets that best fits current data. Potentially rewarding, or at least non-aversive experiences promote fighting via the action of octopamine (OA, +), which raises the threshold to flee so that the animal tends to persist longer in fighting. Aversive experiences accumulated during fighting (e. g. opponent actions) promote retreat by lowering the threshold to flee *via* nitric oxide (NO, –). After defeat, serotonin acts via $5HT_2$-type receptors to maintain submissiveness (loser effect) by keeping the threshold to flee low (5HT, –) and thus preventing recovery of aggression in losers. The natural recovery of aggression after defeat requires dopamine, which acts by raising the threshold to flee (DA, +). Reproduced from Rillich and Stevenson, 2018.

Aggression and "personality" in crickets?

In mammals and man, social defeat, and particularly repeated intermittent defeat (chronic social defeat), is widely recognised as a major stressor that induces depression-like symptoms with long lasting general behavioural consequences (de Boer et al., 2016). Individuals of invertebrate species also show consistent behavioural differences (animal "personality"), that are thought to be both a cause and a consequence of variations in contest behaviour (Briffa et al., 2015). In crickets, winners are significantly more proactive than losers as a result of previous aggressive experience (Rose et al., 2017a, 2017b). In particular, chronic social defeat dramatically increases the duration of the loser effect, and has potentially lifelong effects on the expression of diverse behaviours. We suspect that 5HT is involved. For example, 5HT2 receptor antagonism increases resilience to multiple defeat, whereas blocking 5HT uptake increases the susceptibility to chronic defeat stress (Rillich and Stevenson, 2018).

Conclusions and outlook

Work on crickets has revealed that animals can implement the seemingly complex social decision of when best to fight or flee, quite simply, by exploiting the powers of neuromodulation. By using OA and NO to differentially modulate the threshold to flee, our model (Figures 4 and 5) satisfies the basic requirements of setting the propensity to persist in fighting, in balance with the perceived value of a disputed resource, previous agonistic experience, and the aggressive potential of the opponent as disclosed during combat. This is achievable without need of conscious reasoning, which is at least food for thought on

how more complex brains, such as our own, make similar judgements. Particularly so in view of some notable similarities in the neurochemical control of aggression in insects and mammals, such as 5HT's part in maintaining submissiveness after defeat (Rillich and Stevenson, 2018). Furthermore, the key roles revealed for OA and NO in controlling the decision to fight or flee in crickets, may also spark new thought on how the corresponding amines NA and AD and NO function in mammalian aggression which is far from clear. In crickets, though, we know practically nothing about the involved neurones. However, by exploiting genetic techniques, neurones that contain biogenic amines and influence aggression have been identified in fruit flies, and progress continues here on how they function naturally in aggressive behaviour. Now that these techniques are becoming available for crickets (Watanabe et al., 2018), it can be expected that similar advances will be made in this model system.

Dedicated to Franz Huber, whose advice I (PAS) still recall: "*don't forget the behaviour Paul – don't forget the behaviour!*"

Acknowledgements: We thank Julia Balsam and Stefan Schöneich for commenting on the manuscript and two anonymous referees for helpful suggestions.

Funding: Our work on aggression is funded by the Deutsche Forschungsgemeinschaft (STE 714/4–1, STE 714/5–1; RI 2728/2–1) and is greatly appreciated.

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