

Beyond the Vertebrate Model: Insights from Insect Stress Responses

Emily Gilford^{1*}, Sinead English^{2,3}, Tim W. Fawcett⁴, Stuart Townley⁵, Tom Tregenza¹, Bram Kuijper¹.

1. Centre for Ecology and Conservation, University of Exeter, Penryn, Cornwall, U.K.

2. Institute of Organismic and Molecular Evolutionary Biology, Johannes Gutenberg University Mainz, Mainz, Germany.

3. School of Biological Sciences, University of Bristol, Bristol, UK

4. Centre for Research in Animal Behaviour, University of Exeter, Exeter, U.K.

5. Department of Earth and Environmental Sciences, University of Exeter, Penryn, Cornwall, U.K.

* Corresponding author, erg220@exeter.ac.uk, ORCID [0000-0003-2038-9570](https://orcid.org/0000-0003-2038-9570)

Abstract

Stress responses are essential for survival, coordinating behavioural, physiological and molecular adjustments that enable organisms to cope with challenges. Most research has focused on vertebrates, leaving invertebrate stress physiology comparatively underexplored, particularly in insects. In this review, we compare insect and vertebrate stress responses to examine what insects reveal about the evolution and ecology of stress regulation. There is a striking mismatch between the ecological and evolutionary diversity of insects and their representation in stress response research. Only 4% of recent empirical studies of stress responses focused on insects, with research concentrated in a small number of model and applied species. Despite major differences in neuroendocrine architecture, insects and vertebrates show convergence in several features of stress regulation, including rapid monoaminergic signalling, mobilisation of metabolic resources, neuroendocrine-immune interactions, and downstream molecular programmes associated with cellular protection and

recovery. Vertebrates coordinate these responses through relatively centralised neuroendocrine systems such as the hypothalamo-pituitary-adrenal (HPA) and sympathetic-adreno-medullary (SAM) axes, whereas insects rely on more distributed interactions among biogenic amines, peptide hormones, neurosecretory tissues and visceral neural circuits, including interactions described in the proposed octopamine-adipokinetic hormone (OAH) axis.

Developmental mode, life-history strategy and social organisation further generate variation in insects that is poorly captured by vertebrate-centred models of stress. We argue that cross-taxon generalisation is most informative at the level of ecological function rather than mechanistic equivalence. Rather than serving as simplified models of vertebrate stress physiology, insects provide complementary systems for testing how alternative regulatory architectures evolve under diverse ecological conditions.

Keywords

Stress response; comparative stress physiology; vertebrates; insects; neuroendocrine regulation; octopamine; adipokinetic hormone; developmental plasticity; life-history strategy.

Introduction

Across taxa, organisms must detect and respond to environmental challenges. These coordinated physiological and behavioural adjustments, collectively referred to as the stress response, integrate neural, endocrine, immune, and behavioural pathways (McEwen, 2007; Romero et al., 2009; Taborsky et al., 2021). Stress responses are typically fast acting and reversible, but can carry significant physiological costs, including reduced reproductive success, suppressed immune function, inhibited growth, oxidative damage, and depletion of energy reserves (Adamo, 2017; Bonier et al., 2009; Picard et al., 2018). Stressors (stimuli that trigger a stress response) vary widely in their nature and duration, ranging from brief predator encounters to chronic environmental instability or social conflict, each placing different demands on an organism's stress response mechanisms (Romero et al., 2009). Comparing stress responses across diverse taxa provides important insights into how these systems have evolved in response to different ecological challenges (Adamo, 2017; Koolhaas et al., 2011; McEwen, 2007).

We focus on insects as an exceptionally diverse and experimentally tractable group, while recognising that other invertebrate groups, particularly crustaceans and cephalopods, have also yielded important insights into stress physiology (Elwood et al., 2009; Fiorito et al., 2015). Their small size, short generation times and ease of manipulation, combined with enormous diversity in ecological niches, life-history strategies and social systems, make insects particularly well suited to studying stress responses (Adamo, 2017; Cinel et al., 2020). Established insect model systems, particularly *Drosophila melanogaster*, have also underpinned major advances across genetics, developmental biology, neuroscience and evolution (Jennings, 2011). Insects are also ecologically and economically important: many species are agricultural pests, disease vectors or pollinators, and responses to insecticides are themselves mediated partly by stress physiology (Gong et al., 2023; Miyashita and Adamo,

2020). Understanding these responses can therefore advance comparative stress biology while informing agriculture, pest management and conservation.

Stress responses can produce broadly similar behavioural and physiological outcomes in vertebrates and insects, but the systems coordinating those responses differ (Cinel et al., 2020; Herman et al., 2016; Nässel and Zandawala, 2020). Vertebrate stress responses are coordinated partly through organised neuroendocrine axes, including the hypothalamo-pituitary-adrenal (HPA) and sympathetic-adreno-medullary (SAM) axes. In insects, stress responses involve more distributed interactions among neural, neuromodulatory and endocrine systems, including signalling by octopamine (OA) and adipokinetic hormone (AKH). Comparing these systems allows us to ask which features of stress responses are shared across taxa and which reflect different evolutionary solutions to similar challenges.

Despite their value as comparative systems, insects remain markedly underrepresented in stress response research. This taxonomic imbalance is evident in our mapping of stress response research published over the last five years: of 472 applicable primary empirical studies, 74% investigated vertebrates, compared with only 4% investigating insects (Fig. 1A; see Appendix 1 for methodology and literature details). Mammals and fish alone accounted for 63% of all included studies, with particular focus on laboratory rodents and humans.

Insect research was not only comparatively scarce, but also taxonomically sparse: *Drosophila melanogaster* was the most frequently represented insect species, accounting for six of the 19 insect studies, while each of the remaining insect taxa was represented by only a single study (Fig. 1B). Beyond *D. melanogaster*, the insect literature was concentrated in species of applied importance, particularly agricultural pests, disease vectors and pollinators (Potts et al., 2010; Sánchez-Bayo and Wyckhuys, 2019), with only one study identified in non-model wild insects.

Mapping stress-response research reveals a strong vertebrate bias and a narrow focus within insect studies

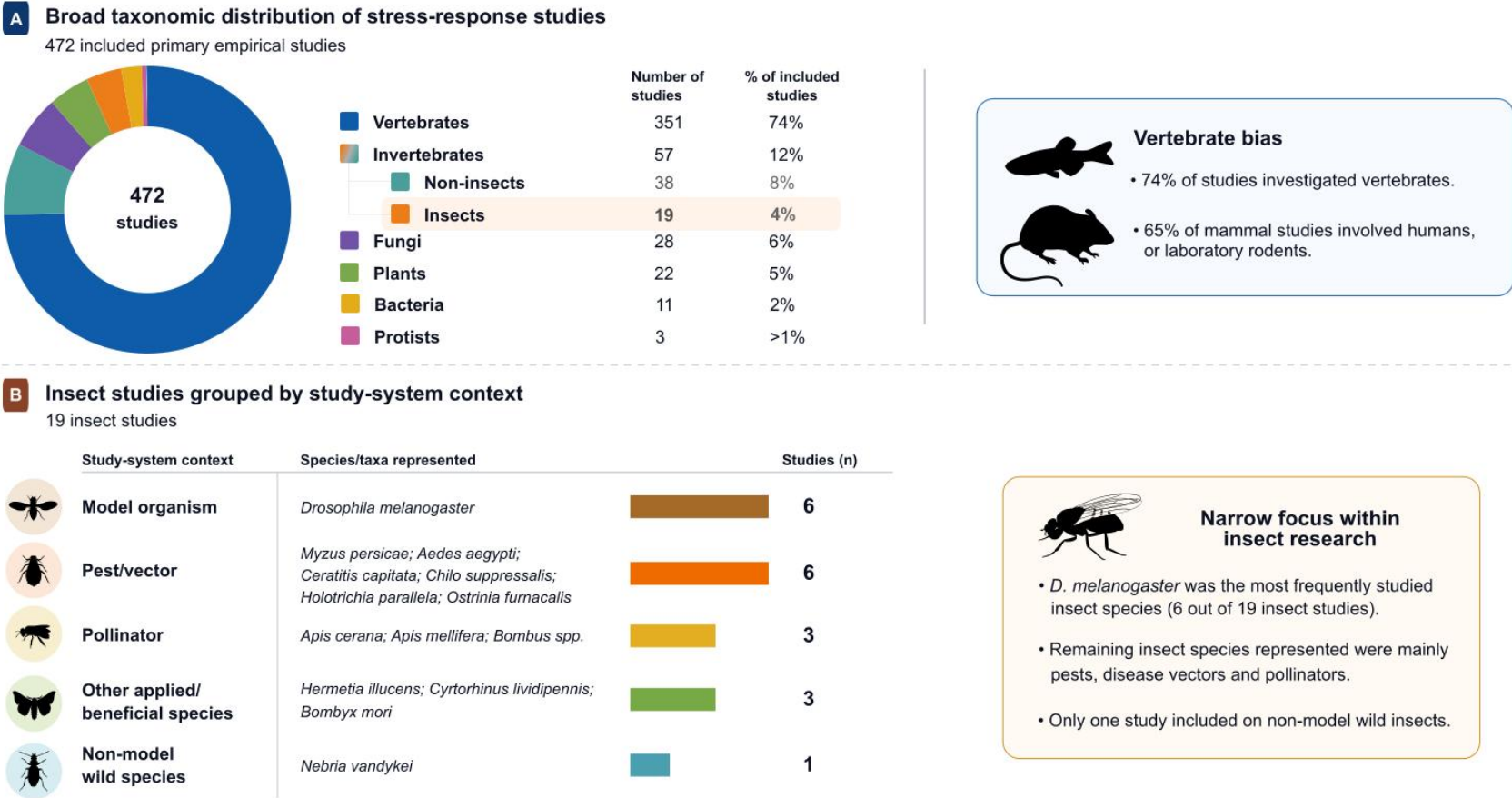


Figure 1. Taxonomic representation in stress response research from July 2021 – July 2026. Studies were identified through a Web of Science Core Collection topic search combining “stress” or “stress response” with terms referring to animals, vertebrates, insects, fish, birds or mammals. The mapping included 472 eligible primary empirical studies (see Appendix 1 for the full search strategy and inclusion criteria). (A) Broad taxonomic distribution of eligible studies, grouped according to their primary study system. Percentages represent the proportion of the 472 studies within each taxonomic group. (B) Insect taxa represented in the 19 insect studies, grouped by study-system context. Counts indicate the number of studies investigating each species. Species silhouettes are used under a public domain license from [PhyloPic](#).

This taxonomic imbalance extends beyond studies of neuroendocrine and molecular architecture to research examining organisms' responses to environmental stressors (MacLeod et al., 2023; McEwen, 2007; Taborsky et al., 2021). Vertebrate research encompasses responses to a broad range of environmental stressors, including predation (Fardell et al., 2020), pollutants and other anthropogenic disturbances (Tarlow and Blumstein, 2007), social interactions (MacLeod et al., 2023), and abiotic challenges such as climatic extremes and resource limitation (Wingfield, 2013); whereas in insects, research on different stressor types remains comparatively fragmented and uneven. The most recent dedicated review of insect stress responses focused primarily on predation risk (Cinel et al., 2020), with less emphasis on other ecologically and anthropogenically relevant stressors, such as pesticides, climate change, and interactions with conspecifics. Recent theoretical frameworks addressing the adaptive value of stress responses (Ellis and Giudice, 2019; Koolhaas et al., 2011; Taborsky et al., 2021) have been highly influential in vertebrate research, but their applicability to insects remains comparatively underexplored, partly because empirical and conceptual frameworks in stress biology have historically been shaped by vertebrate systems.

To address the insect-vertebrate divide in research effort, stressor coverage and conceptual framing, we synthesise current understanding of insect stress responses by integrating neuroendocrine mechanisms with ecological and evolutionary perspectives, using insects as comparative systems for understanding the evolution of stress biology more broadly. In doing so, we provide a framework for identifying when insights from vertebrate stress research can be generalised to insects, and when important biological differences should be expected. We first examine the regulatory architecture of vertebrate and insect stress responses in greater detail, then consider what molecular approaches reveal about insect responses, before turning to their ecological and evolutionary variation.

Architecture: how do stress responses differ between vertebrates and insects?

Vertebrate and insect stress responses draw on monoaminergic and peptidergic signalling systems with deep evolutionary roots in bilaterian animals (Bauknecht and Jékely, 2017; Ottaviani and Franceschi, 1996). Both insects and vertebrates use amines and peptide hormones to mobilise energy, redirect behaviour and adjust internal physiology under threat (McEwen, 2007; Nässel and Zandawala, 2020), but these signals are embedded within substantially different anatomical and regulatory architectures (Bobrovskikh and Gruntenko, 2023; Lubawy et al., 2020; McEwen, 2007; Miyashita and Adamo, 2020; Nässel and Zandawala, 2020).

Vertebrate stress axes

Across vertebrates, stress responses involve evolutionarily conserved hypothalamic-pituitary glucocorticoid and sympathetic–catecholaminergic pathways, represented in mammals by the HPA and SAM axes, although their anatomical organisation differs among lineages (Denver, 2009). Taking mammals as a well-characterised example, stressor-related neural inputs converge on hypothalamic neurons that release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These stimulate secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn promotes the release of glucocorticoids, such as cortisol or corticosterone, from the adrenal cortex (Delahunt and Mellsop, 1987; McEwen, 2007; Sapolsky et al., 2000). Glucocorticoids mobilise energy and modulate metabolic, immune, and behavioural processes, while exerting negative feedback on the hypothalamus and pituitary (Herman and Cullinan, 1997; Sapolsky et al., 2000). In parallel, the sympathetic division of the autonomic nervous system acts directly on internal organs and stimulates the adrenal medulla to release adrenaline and noradrenaline through the

sympathetic-adreno-medullary (SAM) axis (Godoy et al., 2018; Goldstein, 2010; McCorry, 2007). Together, these neural and hormonal signals increase cardiovascular activity, alter thermoregulation, and rapidly prepare the body for action (Carrive, 2006; Nakamura, 2015; Oka, 2018) (Fig. 2). The precise anatomical organisation described above is not shared by all vertebrates. For example, in teleost fishes, glucocorticoid release is mediated by the hypothalamo-pituitary-interrenal (HPI) axis, while catecholamines are released from chromaffin tissue associated with the head kidney rather than from a discrete adrenal medulla (Wendelaar Bonga, 1997).

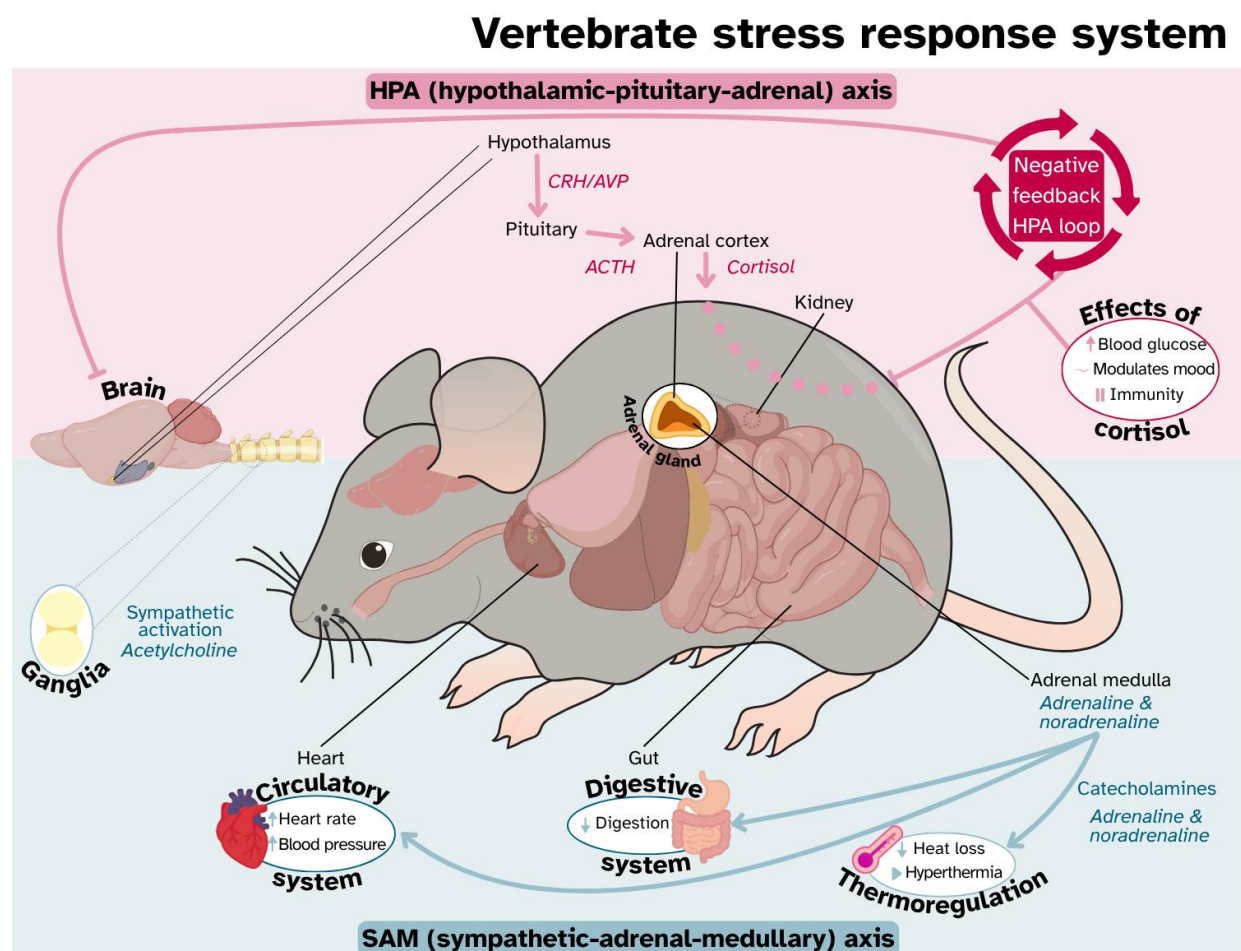


Figure 2. Overview of the vertebrate stress response system, using a mammalian example, showing the HPA (pink) and SAM (light blue) axes. The HPA axis mediates a slower endocrine response through glucocorticoid release, while the SAM axis mediates rapid sympathetic and endocrine responses through neural signalling and catecholamine release. Solid arrows indicate neural or endocrine signalling pathways, blunt-ended lines indicate negative feedback or inhibition, and

dotted lines indicate internal anatomical structures or hormonal pathways not externally visible in the schematic. Symbols within the physiological-effect summaries indicate increases (↑), decreases (↓), modulation (~), suppression (■) or activation/mobilisation (▶). Only selected downstream physiological effects are illustrated. Diagram not to scale.

Distributed neuroendocrine architecture in insects

In insects, stress responses emerge from interactions among distributed neurosecretory tissues and visceral neural circuits, mediated partly by neuromodulators, neuronally released chemical messengers that alter neuronal excitability or synaptic strength. These neuromodulators in turn modify the activity and output of neural circuits (Katz, 1999; Marder, 2012), rather than being organised around a directly equivalent central endocrine axis (Fig. 3).

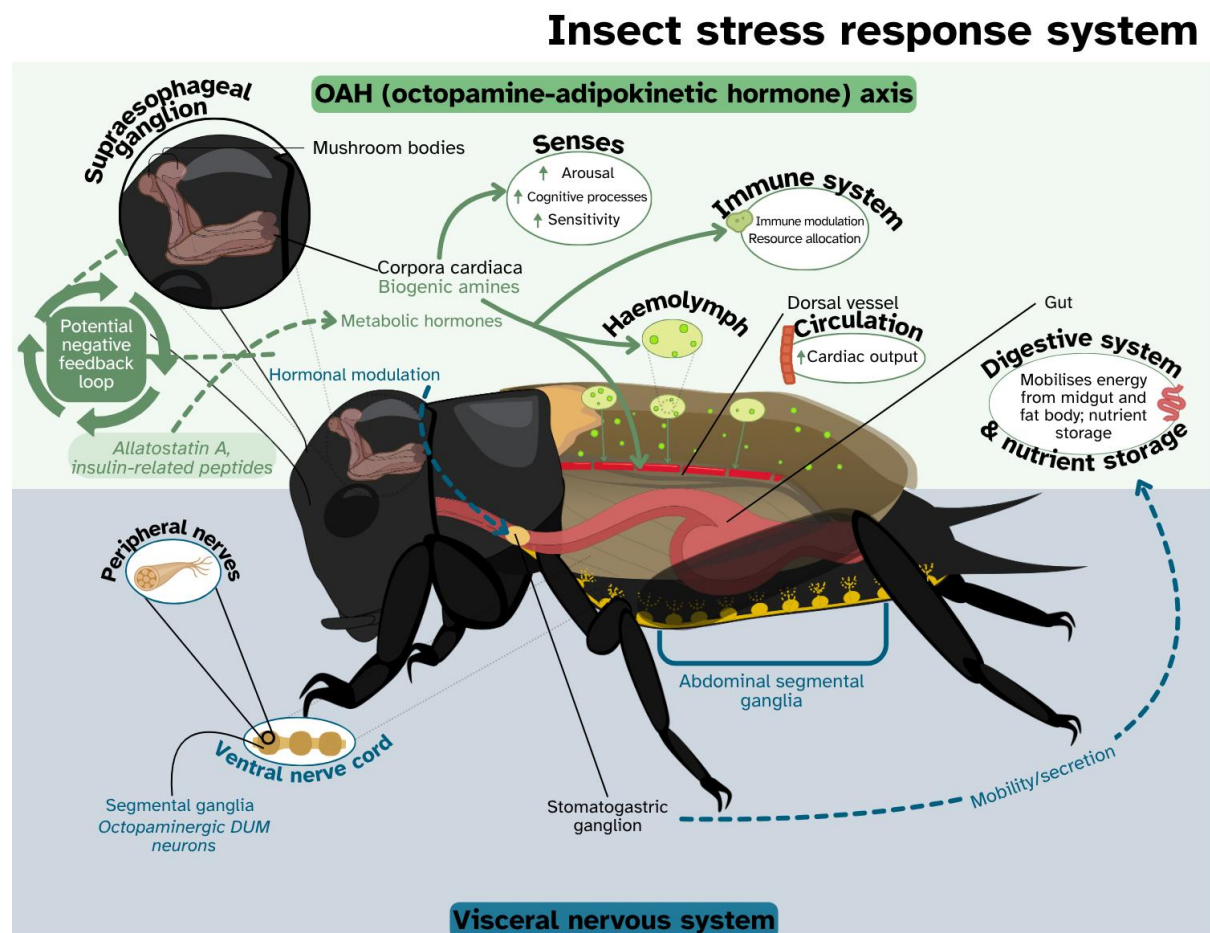


Figure 3. Overview of the insect stress response system showing the proposed octopamine–adipokinetic-hormone (OAH) axis (green) and the visceral nervous system (dark blue). The proposed OAH axis coordinates endocrine and

neuromodulatory responses through biogenic amines and peptide hormones, whereas the visceral nervous system mediates rapid autonomic-like regulation of visceral organs. Octopaminergic pathways also modulate skeletal muscle and other peripheral targets. Solid arrows indicate neural or hormonal signalling pathways, dashed arrows indicate hypothesised or incompletely characterised interactions and blunt-ended lines indicate potential feedback regulation. Only selected downstream physiological effects are illustrated. Diagram not to scale.

Insects lack a direct equivalent of the SAM axis or the discrete endocrine glands that underpin the HPA system (Godoy et al., 2018; MacLeod et al., 2023; McCorry, 2007). Instead, rapid neural regulation of visceral organs is mediated partly through the visceral nervous system, including stomatogastric circuits that regulate the gut and other internal organs. Insect visceral neural circuits are functionally analogous to parts of the vertebrate autonomic and enteric nervous systems (Copenhaver, 2007; Hernández et al., 2015). Local neural regulation operates alongside systemic signalling by circulating biogenic amines, particularly octopamine, and peptide hormones such as adipokinetic hormone and insulin-like peptides (Lubawy et al., 2020; Nässel and Zandawala, 2020). At the phenotypic level, such a distributed organisation combines rapid, organ-specific adjustments with broader metabolic and behavioural coordination, rather than implying that insect responses are uniformly faster or less systemic than vertebrate responses (Adamo, 2012; Lubawy et al., 2020).

Insect neuroendocrine signalling is distributed across several neural and peripheral tissues. Neurosecretory cells in the brain and ventral nerve cord produce chemical messengers that may be released locally within the nervous system or into the haemolymph, sometimes through neurohemal release sites such as the corpora cardiaca. These messengers include neuropeptides such as adipokinetic hormone (AKH) and insulin-like peptides, and biogenic amines such as octopamine and tyramine (Nässel and Zandawala, 2020; Orchard and Lange, 2024). The corpora cardiaca also contains endocrine cells that produce and release AKH, whereas the corpora allata produces juvenile hormone (JH). Additional hormonal signals originate from peripheral tissues, including the gut, fat body and ovaries, while octopamine

(OA) and tyramine are released by neurons and can act locally as neurotransmitters or neuromodulators, or systemically as neurohormones (Bobrovskikh and Gruntenko, 2023). The corpora cardiaca and corpora allata are therefore important components of insect neuroendocrine regulation, but they are not its sole control or release centres. Together with the visceral nervous system, these distributed neural and endocrine tissues coordinate local and whole-body components of the insect stress response (Farooqui, 2012; Lubawy et al., 2020; Nässel and Zandawala, 2020; Orchard and Lange, 2024).

It has been proposed that insects possess an octopamine–adipokinetic-hormone (OAH) axis, that is functionally analogous in some respects to the vertebrate HPA axis (Cinel et al., 2020). Following stressor detection, neural processing can activate octopaminergic pathways, with OA acting both locally and, following release into the haemolymph, systemically. In locusts, OA can stimulate AKH release from the corpora cardiaca through mechanisms involving cyclic adenosine monophosphate and calcium signalling (Orchard et al., 1993; Pannabecker and Orchard, 1987, 1986). However, AKH release is not solely downstream of octopamine: AKH-producing cells can sense circulating sugar concentrations directly and integrate additional neural, endocrine and metabolic inputs (Hughson, 2021; Nelson et al., 2021). Once released, AKH acts principally on the fat body to mobilise stored carbohydrates and lipids, increasing circulating fuel availability to support energetically demanding behaviour and subsequent recovery (Toprak, 2020). A broader sequence has been proposed in honeybees (Even et al., 2012), in which early OA and dopamine signalling is followed by the release of metabolic hormones, including AKH. This remains a proposed model rather than an established order of release. Honeybee foragers also carry nectar sugars in the crop, which can supply energy during flight, while AKH appears to have a weaker effect on circulating trehalose in honeybees than in some other insects (Even et al., 2012). Thus, the contribution

of AKH to energy metabolism may differ among species even where OA and AKH are both present.

OA also influences neural, muscular and physiological processes outside of the proposed OAH axis. Octopaminergic dorsal unpaired median neurons (DUM) coordinate skeletal and visceral muscle activity (Verlinden et al., 2010), while OA increases cardiac output through effects on the dorsal vessel (Pflüger and Stevenson, 2005). OA and its precursor tyramine are structurally related to vertebrate adrenergic catecholamines and are similarly derived from tyrosine, albeit through distinct biosynthetic branches (Bauknecht and Jékely, 2017; Roeder, 2005). This shared biochemical and evolutionary background provides context for their analogous roles in coordinating arousal, activity and energy metabolism, despite substantial differences in the system-level organisation of insect and vertebrate stress responses (Roeder, 2020). Alongside OA and AKH, signalling molecules such as corazonin, diuretic hormone, allatostatin A and insulin-like peptides influence overlapping aspects of metabolism, gut activity, arousal and energy mobilisation (Even et al., 2012; Nässel, 2025; Nässel and Zandawala, 2020). Insect stress regulation is therefore not reducible to a single OA–AKH cascade but involves interacting pathways distributed across neural and peripheral tissues.

Feedback in insect stress regulation

Compared with vertebrate stress axes, empirical support for coordinated feedback in insect stress regulation is less extensive, and the interactions underlying it remain incompletely characterised, particularly within the proposed OAH system. Nevertheless, evidence from *Drosophila melanogaster* demonstrates that insect neuroendocrine regulation can include feedback among neurosecretory cells, peripheral sensors, target tissues and hormonal pathways (Nässel and Zandawala, 2020). In *D. melanogaster*, experimentally supported relationships include interactions within insulin and insulin-like growth factor signalling, and among insulin-like peptides, peripheral tissues and other stress-related hormones. These

relationships have been summarised as feedback loops connecting the brain, fat body, corpora cardiaca, corpora allata and ovaries (Bobrovskikh and Gruntenko, 2023). However, several connections within the broader network remain inferred, and it has not been established whether these interactions operate together as a coordinated feedback system during stress. It is difficult to establish complete feedback loops because individual relationships have often been investigated in different tissues, developmental stages and stress contexts, while the same signalling molecules can act as neurotransmitters, local neuromodulators or circulating hormones in different contexts (Bobrovskikh and Gruntenko, 2023; Nässel and Zandawala, 2020). Evidence therefore supports the presence of neuroendocrine feedback in insects, but whether and how feedback directly regulates OA and AKH release and recovery remain unclear.

A mechanistic example of how feedback may emerge from distributed stress regulation is provided by *Drosophila* studies on short-term heat stress. In adult female *Drosophila melanogaster*, heat exposure causes the Forkhead box O transcription factor (*dFOXO*), which regulates the expression of genes involved in metabolism and stress responses, to enter fat-body cell nuclei. In fat-body cells, *dFOXO* is implicated in reduced expression of the *dilp6* gene, which encodes fat-body insulin-like peptide 6 (*DILP6*), and increased expression of the insulin receptor gene *dInR* (Eremina et al., 2021, 2019). Suppression of *DILP6* has been proposed to relieve the inhibition on insulin-producing cells in the brain, increasing brain-derived insulin-like peptide signalling through the insulin receptor in the fat body. This signalling could return *dFOXO* to the cytoplasm, completing a proposed short negative-feedback loop between the brain and fat body (Bobrovskikh and Gruntenko, 2023). Mutations reducing *dFOXO* or *DILP6* function disrupted heat-induced changes in insulin-pathway gene expression and prevented the subsequent reduction in lipid reserves (Eremina et al., 2021, 2019). These findings implicate insulin signalling in the heat-stress response in *D.*

272 *melanogaster*, but do not demonstrate the complete short loop during heat stress or establish
273 whether it occurs in other insects. A wider proposed network links this loop to JH and 20-
274 hydroxyecdysone production, dopamine and OA signalling, and AKH-mediated mobilisation
275 of carbohydrates and lipids (Bobrovskikh and Gruntenko, 2023). The proposed longer
276 feedback loop combines evidence from experiments conducted across different stressors,
277 developmental stages and timescales. Whether these interactions operate together as a
278 coordinated feedback system under the same conditions remains to be established.

279 Direct haemolymph measurements can provide information about the temporal response but
280 cannot, by themselves, resolve its regulatory mechanism. In the insect species studied,
281 circulating OA concentrations are generally low under unstressed conditions but can increase
282 several-fold following an acute challenge, before returning towards baseline. In the cricket
283 *Gryllus bimaculatus*, haemolymph OA increases during aggressive encounters, flight and
284 other high-arousal behaviours, while octopaminergic signalling contributes to experience-
285 dependent modulation of aggression (Adamo et al., 1995; Stevenson et al., 2005).

286 Comparable increases occur in locusts and other insects following flight, handling or
287 restraint, consistent with a broader role in coordinating behavioural and metabolic responses
288 to demanding situations (Davenport and Evans, 1984; Verlinden et al., 2010). Repeated
289 exposure to predator-like disturbances can also produce a more sustained elevation in
290 baseline OA concentrations in *Gryllus texensis* (Adamo and Baker, 2011). These temporal
291 dynamics could arise from phasic, stimulus-dependent OA release followed by its removal
292 from circulation, with or without additional negative feedback. In locusts, circulating OA is
293 rapidly removed from the haemolymph by peripheral tissues, including the Malpighian
294 tubules (Goosey and Candy, 1982). Release and clearance dynamics could therefore produce
295 a transient elevation without requiring negative feedback, but they neither exclude nor
296 demonstrate additional regulation through the broader feedback relationships described

above. Although this rise-and-recovery pattern resembles the expected functional form of an acute vertebrate stress response (Taborsky et al., 2021), temporal similarity does not establish equivalence in its regulatory mechanism. Distinguishing these possibilities would require experiments that manipulate candidate feedback pathways while repeatedly measuring circulating OA and AKH.

Overall, comparisons between vertebrate and insect stress responses reveal convergence in functional outcomes, despite substantial differences in the underlying mechanisms as outlined above. In vertebrates, responses are organised around the HPA and SAM axes, with systemic hormonal feedback to hormone-releasing tissues. In insects, regulation is distributed across various interacting neural, neuromodulatory and endocrine systems. Individual feedback relationships among neurosecretory cells, peripheral tissues and hormonal pathways have been demonstrated, but its organisation within stress-specific systems, particularly the proposed OAH system, remains incompletely characterised (Bobrovskikh and Gruntenko, 2023; Nässel and Zandawala, 2020). It remains unclear how these architectural differences influence the timing, flexibility and physiological costs of stress responses. Similar behavioural or physiological outcomes across taxa should not be assumed to reflect equivalent underlying mechanisms, and cross-taxon generalisation is likely to be most informative at the level of regulatory function. Comparative approaches that distinguish functional outcomes from mechanistic architecture are therefore essential for determining which features of stress regulation are evolutionarily conserved and which represent lineage-specific solutions.

Measuring octopamine in insects: methods, proxies and limitations

Distinguishing local neuromodulatory activity, circulating hormonal responses and downstream molecular effects requires complementary measurement approaches. We

321 therefore briefly review current approaches for quantifying octopaminergic signalling before
322 considering how transcriptomics could provide a broader systems perspective.

323 Much of our current understanding of insect stress physiology centres on the biogenic amine
324 OA, which can act as a neurotransmitter, neuromodulator or circulating neurohormone.
325 Octopaminergic activity has been associated with adaptive responses to physical activity,
326 aggression, food deprivation, infection and encounters with predators (Mezheritskiy et al.,
327 2024). Interpreting this literature therefore requires an appreciation of how OA signalling is
328 measured, the proxies commonly used to infer its activity, and the limitations associated with
329 each approach.

330 Direct measurements of circulating OA remain technically challenging. Although acute
331 stressors can increase haemolymph OA concentrations several-fold, the absolute quantity of
332 OA available for analysis may remain small, as it occurs at picogram-scale concentrations
333 and the volume of haemolymph obtainable from an individual insect is limited (Adamo et al.,
334 1995; Badley et al., 2018; Davenport and Evans, 1984). A further analytical challenge is the
335 structural similarity between OA and its precursor tyramine. The ability of immunoassays to
336 distinguish these compounds depends on the antibody used: MAb-OA1 exhibited 21% cross-
337 reactivity with tyramine (Dacks et al., 2005), whereas an indirect competitive enzyme-linked
338 immunosorbent assay using MAb 3C11-E3 showed low cross-reactivity with related
339 compounds and was successfully applied to housefly samples (Liu et al., 2014). Therefore,
340 immunoassay specificity and sensitivity must be validated for the species and sample type
341 being studied. Chromatographic approaches, including high-performance liquid
342 chromatography (HPLC) with electrochemical detection (-ED) and liquid chromatography-
343 tandem mass spectrometry, can separate OA from tyramine and other monoamines, but
344 require specialised equipment and careful optimisation to avoid interference or co-elution
345 (Badley et al., 2018; Davla et al., 2023).

346 Given the difficulties of directly measuring octopaminergic activity, many studies use
347 indirect molecular proxies. Quantitative polymerase chain reaction (qPCR) and RNA
348 sequencing (RNA-seq) can quantify the expression of genes encoding biosynthetic enzymes,
349 including tyrosine decarboxylase, which converts tyrosine to tyramine, and tyramine β -
350 hydroxylase, which converts tyramine to OA, as well as OA and tyramine receptors (Roeder,
351 2005). Biosynthetic activity can also be assessed directly. In the cockroach *Periplaneta*
352 *americana*, tyramine β -hydroxylase (TBH) activity was measured by incubating nerve-cord
353 extracts with tyramine and quantifying the OA produced using an enzyme-linked
354 immunosorbent assay (ELISA). Mechanical stress increased TBH activity after both 1 and 24
355 hours, with a stronger increase after 1 hour (Châtel et al., 2013).

356 Further insight into the relationship between stress and octopaminergic signalling comes from
357 studies of OA-receptor transcript abundance. In *Drosophila melanogaster*, loss of the *logjam*
358 gene, a p24-family protein involved in cellular trafficking, elicited a cellular stress response
359 and was accompanied by decreased *OAMB* (an OA receptor) transcript abundance (Boltz and
360 Carney, 2008). Functional manipulation has nevertheless demonstrated the wider
361 physiological importance of this receptor: targeted reduction of *OAMB* expression in insulin-
362 producing cells has been shown to increase *DILP3* transcription, resistance to starvation and
363 oxidative stress, and food consumption, linking OA reception to insulin-related metabolic
364 regulation (Luo et al., 2014). In honeybee flight muscle, cold stress produced selective, age-
365 and time-dependent changes in OA receptor transcript abundance. The *AmOAR β 2X1A*
366 transcript increased after 30 and 120 minutes in 1-week-old workers but not in foragers,
367 whereas two other *AmOAR β 2* transcripts decreased after 120 minutes in foragers; most
368 receptor genes showed no consistent response to cold stress (Kaya-Zeeb et al., 2022). These
369 studies measured receptor-transcript abundance rather than receptor-protein levels, so it

remains unclear whether transcriptional changes produce corresponding changes in receptor abundance (Buccitelli and Selbach, 2020; Vogel and Marcotte, 2012).

Functional studies also illustrate the phenotypic consequences of octopaminergic signalling: suppressing OA release in *Drosophila melanogaster* prevented exercise-induced improvements in climbing, flight performance, cardiac stress resistance and fat-body lysosomal activity, whereas OA administration or periodic activation of octopaminergic neurons reproduced several adaptations normally induced by endurance exercise (Sujkowski et al., 2017). More broadly, transcriptomic approaches allow examination of coordinated changes across multiple components of octopaminergic and downstream stress-signalling pathways, as discussed below.

Transcriptomic perspectives on insect stress responses

Given the difficulties of directly measuring OA and other neurohormones, gene-expression studies offer a complementary way to characterise molecular responses to stress and identify candidate links between neuroendocrine signalling and downstream pathways. Vertebrate stress transcriptomics have been more extensively studied than insect responses, raising the question of which transcriptional features recur across these differently organised systems.

Vertebrate stress transcriptomics: a reference framework

In vertebrates, transcriptomic studies have revealed that stress responses involve temporally structured waves of changing gene-expression across neural and peripheral tissues. Acute stressors rapidly induce the expression of immediate early genes (IEGs), such as *c-fos* and *Egr1*, which act as early transcriptional regulators linking neuronal activation to broader genomic responses involved in neuronal plasticity and stress adaptation (Claydon and Conway–Campbell, 2022; de Nadal et al., 2011; Sheng and Greenberg, 1990; Vlasov et al., 2023). These early transcriptional events are followed by glucocorticoid-dependent changes

in the expression of metabolic, immune and synaptic pathways, many of which emerge during later recovery and adaptation phases rather than immediately following the stress response (Claydon and Conway–Campbell, 2022; Flati et al., 2020; Gray et al., 2017).

Studies of recovery have also identified changes associated with oxidative-stress regulation, metabolism and cellular repair (Aluru and Vijayan, 2009; Madaro et al., 2023). Evidence from rodents exposed to social, restraint or glucocorticoid-related challenges, and from fish exposed to thermal or osmotic stress, illustrates the importance of sampling time, tissue and stressor type when interpreting these transcriptional responses (Aluru and Vijayan, 2009; Flati et al., 2020; Jaszczyk et al., 2023).

Insect stress transcriptomics: current evidence and emerging patterns

Much of the transcriptomic evidence relating to insect stress responses derives from established model systems, particularly *Drosophila melanogaster* and the western honeybee *Apis mellifera* (Girardot et al., 2004; Li et al., 2018; Sørensen et al., 2005). In *A. mellifera*, targeted gene-expression experiments have assessed responses to heat exposure and wounding, providing mechanistic context for genome-wide studies by showing how cellular protection and immune pathways interact during the stress response. Heat exposure activated a conserved heat-shock response, increasing the expression of several genes encoding *HSP70*- and *HSP90*-family molecular chaperones and other putative targets of heat-shock factors across head, midgut, thoracic and abdominal tissues, although responses varied among genes and body region (McKinstry et al., 2017). While some genes associated with the unfolded-protein response also increased, the authors did not detect Xbp1 mRNA splicing, which generates the active form of X-box-binding protein 1 (XBP1), a transcription factor in the unfolded-protein response (McKinstry et al., 2017). This illustrates that expression of putative pathway targets does not necessarily establish activation of a particular signalling route. Heat shock also suppressed antimicrobial-peptide genes in abdominal tissue, whereas

wounding reduced the expression of several heat-shock-response genes in both proximal and distal tissues, indicating a mutually antagonistic relationship between the heat-shock and humoral immune responses (McKinstry et al., 2017). In *D. melanogaster*, transcriptomic approaches have been used to characterise responses to thermal stressors, oxidative stressors, starvation and infection (Landis et al., 2012). Early genome-wide studies revealed both shared and stressor-specific transcriptional organisation. Responses measured 24-hours after exposure to the herbicide paraquat, hydrogen peroxide or the antibiotic tunicamycin revealed a common long-term transcriptional response alongside substantial stressor-specific changes (Girardot et al., 2004). Following a one-hour heat-hardening treatment, genome-wide expression measured at eight time points over 64 hours revealed early-upregulated, early-downregulated and late-upregulated gene clusters, with most heat-responsive genes returning towards pre-stressor expression within eight hours. In comparisons with transcriptomic studies of other stressors in *D. melanogaster*, heat-responsive genes involved in chaperone and glutathione-transferase activity also featured in other stress responses, whereas protein-kinase cascades and gluconeogenesis appeared more specific to heat (Sørensen et al., 2005). Together, studies in these two species show that insect transcriptional stress responses can contain both shared and stressor-specific components and can be strongly structured through time.

Sequencing studies have also begun to show how stress-responsive regulators shape genome-wide patterns of gene expression. RNA-seq has been used to compare gene expression in control and *dFOXO* mutant adult *Drosophila melanogaster* exposed to normoxia or hypoxia (Ding et al., 2022). Hypoxia altered the expression of over 2,000 genes, 40% of which required *dFOXO*. *dFOXO*-dependent responses included increased expression of genes involved in cell signalling and suppression of genes associated with ribosome production, protein synthesis and mitochondrial activity (Ding et al., 2022). This combination of genome-

444 wide sequencing and functional genetic manipulation demonstrates how a stress-sensitive
445 transcription factor can connect neuroendocrine and metabolic signalling to organismal stress
446 tolerance.

447 More recent sequencing studies show how different molecular approaches can characterise
448 insect responses to environmental challenges. In the whitefly *Bemisia tabaci*, combined
449 measures of chromatin accessibility and gene expression identified changes in metabolic,
450 chaperone and stress-tolerance pathways following exposure to high and low temperatures
451 (Shen et al., 2023). Brain RNA-seq in fall armyworm (*Spodoptera frugiperda*) larvae
452 compared responses to cold and heat exposure with responses to water and food deprivation
453 (Gong et al., 2025). Expression patterns of genes encoding neuropeptide precursors and
454 receptors, and enzymes involved in dopamine and OA synthesis, varied among stressors. The
455 affected neuropeptides included those associated with ion balance and metabolism,
456 suggesting that neuroendocrine responses differed with the type of challenge (Gong et al.,
457 2025). In *S. frugiperda*, candidate neuropeptide and biogenic-amine signalling pathways have
458 been identified, associated with responses to cold, heat, water deprivation and food
459 deprivation (Gong et al., 2025), but changes in gene expression do not establish whether the
460 corresponding peptides or amines were released or whether their concentrations changed.
461 Direct measurements are therefore needed to determine hormone levels or the timing of
462 neuroendocrine responses.

463 Recent transcriptomic work has identified gene-expression responses that recur across
464 experiments, alongside differences among stressors. A meta-analysis of oxidative-stress
465 RNA-seq experiments in *Drosophila melanogaster* found that genes involved in
466 detoxification, antioxidant defence and protein protection tended to show increased
467 expression across experiments (Bono, 2021). However, suitable insect RNA-seq datasets

468 were available only for *D. melanogaster*, so the study could not determine whether these
469 responses extend to other insect lineages.

470 Comparable functional categories are repeatedly identified in vertebrate stress transcriptomes,
471 including genes involved in metabolism, oxidative stress, immune regulation and cellular
472 repair (Aluru and Vijayan, 2009; Claydon and Conway–Campbell, 2022; Flati et al., 2020;
473 Madaro et al., 2023). In vertebrates, these downstream programmes are preceded by a well-
474 characterised wave of IEG activation (Claydon and Conway–Campbell, 2022; Vlasov et al.,
475 2023), yet an equivalent canonical stress-associated IEG-programme has not been established
476 in insects. Nevertheless, homologous and lineage-specific IEGs, including *Hr38*, *kayak* (the
477 insect orthologue of *c-fos*), *stripe/egr*, and the honeybee genes *AmEgr* and *kakusei*, contribute
478 to neuronal activation, behavioural plasticity and the initiation of downstream transcriptional
479 responses (Sommerlandt et al., 2019; Ugajin et al., 2018, 2016). These findings suggest
480 potentially comparable roles for early transcriptional regulators, but do not yet establish that
481 insects and vertebrates share a canonical stress-associated IEG programme.

482 Taken together, these studies identify functional categories that recur in insect responses to
483 different challenges: neuropeptide and monoamine-related signalling, molecular chaperones,
484 antioxidant and detoxification processes, immune responses, and carbohydrate and lipid
485 metabolism (Girardot et al., 2004; Gong et al., 2025; McKinstry et al., 2017; Sørensen et al.,
486 2005). Across studies, different stressors recruit different combinations of these components,
487 producing both shared and stressor-specific transcriptional responses rather than a single
488 uniform signature (Girardot et al., 2004; Gong et al., 2025; Shen et al., 2023). These studies
489 identify shared molecular components, but understanding how neuroendocrine signals relate
490 to changes in gene expression requires attention to when and where each response is
491 measured.

Temporal dynamics and scaling challenges in insect transcriptomics

Vertebrate studies have identified staged waves of gene-expression change, with early transcriptional events followed by later changes in metabolic, immune and synaptic pathways. Comparable time-resolved datasets remain limited across insect taxa and stressors, making it difficult to connect rapid hormonal changes with subsequent gene-expression dynamics. Insect transcriptomic studies typically compare one or a few post-stressor time points with unstressed controls, capturing snapshots rather than the trajectory of response and recovery.

Physiological studies of heat-stressed *D. melanogaster* further illustrate why sampling time matters. Following a brief heat shock, body fat declined within 24 hours, and the reduction persisted for several days (Klepsatel et al., 2016). A transcriptomic sample taken immediately after exposure and one taken days later would therefore represent animals in different physiological states. Without repeated molecular and physiological measurements, it is difficult to determine how early gene-expression changes relate to later changes in energy reserves.

Resolving these dynamics requires pairing transcriptomic sampling with direct measurements of OA concentrations and functional measures of signalling activity. Expression of genes involved in octopaminergic signalling varies among tissues (Nässel and Winther, 2010; Nässel and Zandawala, 2020; Roeder, 2005). Whole-body transcriptomics averages expression across tissues and cell populations, potentially obscuring localised responses, a broader limitation highlighted in insect immunology (Merkling and Lambrechts, 2020). Single-cell and single-nucleus approaches offer finer resolution; for example, a recent atlas characterised distinct cell populations in the larval midgut and fat body of *S. frugiperda* (Sun et al., 2025). Some stressor-induced changes may also occur through post-transcriptional or

purely neurophysiological mechanisms that are not captured by transcriptomic approaches, while rapid OA surges may be missed by sparse temporal sampling.

Taken together, these molecular studies reinforce a broader point developed throughout this review: meaningful comparisons between insect and vertebrate stress responses require distinguishing conserved functional outcomes from lineage-specific mechanisms.

Transcriptomic approaches therefore provide an important bridge between neuroendocrine architecture and organismal stress responses, helping to trace how differences in signalling systems relate to downstream molecular changes.

Comparing stress responses across taxa: system architecture and biological stressors

Having examined the mechanisms underlying insect and vertebrate stress responses, we now consider how these systems can be compared. We suggest that two complementary perspectives are particularly informative: the architecture of the stress response system itself, and the ecological stressors that have shaped its evolution, including developmental stage, mortality risk and social organisation. Together, these perspectives provide a framework for distinguishing conserved functional outcomes from lineage-specific regulatory mechanisms.

Stress-system architecture

Stress responses can be viewed as regulatory control systems whose organisation shapes how organisms maintain physiological stability during environmental challenges (Ramsay & Woods, 2014; Del Giudice *et al.*, 2018; Frank, 2019; Arias *et al.*, 2024). It has been proposed that stress occurs when a biological control system detects a failure to control a fitness-critical variable, which may be internal or external to the organism (Del Giudice *et al.*, 2018). This framework incorporates both reactive adjustments through feedback and anticipatory adjustments through feedforward regulation, providing a basis for comparing stress responses

across different regulatory architectures. Such systems must integrate information and regulate physiological processes across multiple tissues and timescales to maintain organismal function during disturbance (Kotas & Medzhitov, 2015). Their architecture may affect the timing of activation, the operation of feedback and the integration of information across these pathways.

In vertebrates, stress regulation occurs through hierarchical endocrine cascades, involving interacting neuromodulatory and endocrine systems in which signals pass through sequential regulatory layers before influencing target tissues (Herman et al., 2016). These cascades are accompanied by extensive feedback regulation and interactions with other physiological systems, including immune and metabolic pathways (Koolhaas et al., 2011; McEwen, 2007). Sequential signalling provides several points at which the magnitude and duration of a response can be regulated. From a control-systems perspective, these layers could support coordination and robustness, but their functional advantages and costs cannot be inferred from architecture alone (Frank, 2019).

In contrast, insect stress responses appear to operate through a more distributed regulatory organisation, in which neuromodulators, neurosecretory cells and peripheral neural circuits interact to coordinate physiological and behavioural responses. OA signalling plays a central role in this process, influencing behavioural arousal and metabolic mobilisation through both neural and hormonal routes (Adamo, 2017; Nässel and Zandawala, 2020). These pathways can produce local effects while also contributing to whole-body coordination through circulating signals and interactions with hormones such as AKH.

Differences in stress-system architecture are likely to influence how stress responses are coordinated across temporal and physiological scales. Vertebrate stress systems operate across multiple interacting timescales, with rapid neural responses mediated by the SAM axis

564 occurring within seconds, and slower endocrine signalling via the HPA system unfolding
565 over minutes to hours (McEwen, 2007; Sapolsky et al., 2000). This layered organisation may
566 allow vertebrates to coordinate immediate behavioural responses with longer-term
567 physiological adjustment while integrating information across neural, immune and metabolic
568 systems.

569 In insects, OA is stored in neuronal vesicles and can be released rapidly as a neuromodulator
570 (Sotnikova and Gainetdinov, 2009). Circulating OA also rises during behavioural challenges,
571 as observed in fighting crickets (*Gryllus bimaculatus*; Adamo et al., 1995), while
572 octopaminergic signalling influences locomotion, muscle performance and metabolic
573 organisation (Stevenson et al., 2005). While vertebrates also employ rapid catecholaminergic
574 and neuromodulatory signalling during an acute stress response, these signals are integrated
575 with slower systemic endocrine feedback. By comparison, insect stress regulation may
576 depend more strongly on flexible interactions among neuromodulators, neurosecretory cells
577 and peripheral tissues, although how these pathways are integrated across tissues and over
578 longer timescales remains less understood.

579 Similar functional outcomes in insects and vertebrates can arise from differently organised
580 regulatory systems, emphasising the importance of distinguishing functional convergence
581 from mechanistic equivalence when comparing stress responses across taxa. These
582 differences raise questions about how organisms balance responsiveness, robustness,
583 flexibility and the costs of regulation (Del Giudice et al., 2018; Frank, 2019). Both groups
584 coordinate rapid responses with longer-term physiological adjustments, although the
585 pathways involved differ.

Ecological context and the evolution of stress responses

While system architecture influences how stress responses are generated, ecological context helps explain why they have evolved differently across taxa. Different environments impose distinct selective pressures, shaping both the types of stressors organisms experience and the regulatory strategies that evolve to cope with them.

Some ecological stressors impose similar selective pressures on insects and vertebrates, whereas others impose different selective pressures because of lineage-specific physiology. Predation risk, for example, can affect survival and behaviour in both insects and vertebrates, even though the sensory and neuroendocrine pathways mediating their responses differ (Hawlena and Schmitz, 2010; Lima and Dill, 1990; Vinterstare et al., 2021). Likewise, pathogen exposure diverts energetic resources towards immune defence in both insects and vertebrates, often at the expense of reproduction, growth or other fitness-related processes (Adamo, 2012; Kurtz et al., 2025; Schmid-Hempel, 2005). Because pathogens reduce survival and condition across diverse taxa, selection has repeatedly favoured coordinated physiological and behavioural responses such as altered feeding or reduced activity, despite substantial differences in immune and neuroendocrine organisation (Adamo, 2012; Hart, 1988).

The frequency and duration of exposure also matter: repeated stressors may alter baseline physiological state as well as responses to individual challenges. In the cricket *Gryllus texensis*, repeated exposure to a mock predator increased baseline OA concentrations and changed feeding, weight gain and flight behaviour (Adamo and Baker, 2011). Chronic stressors can also alter baseline stress-hormone regulation in vertebrates, although the direction of change varies among studies and conditions (Dickens and Romero, 2013). These findings suggest that repeated challenges can reshape stress regulation in both groups, but do not establish whether a changed baseline reduces the cost of future responses.

Other environmental challenges may affect insects and vertebrates differently because of their distinct physiological and ecological contexts. Thermal stressors illustrate this distinction particularly well. Both taxa mount cellular responses to extreme temperatures, including the induction of heat-shock proteins and other protective pathways (Colinet et al., 2015; Feder and Hofmann, 1999). However, among vertebrates, endotherms can regulate body temperature internally within a range of environmental conditions, whereas the body temperatures of predominantly ectothermic insects are more directly influenced by their surroundings, despite behavioural thermoregulation. Environmental temperature can therefore have more direct effects on insect metabolism, locomotion and development (Angilletta Jr, 2009; Colinet et al., 2015). Together, these examples show that comparisons across taxa depend not only on the stressor itself, but also on the physiology and life history of the organisms experiencing it. Direct comparisons between insects and vertebrates therefore need to consider both shared ecological challenges and differences in how those challenges are experienced.

Early-life effects and developmental strategies

Developmental strategy provides one important route by which ecological context shapes stress responses, influencing when organisms are sensitive to stressors and how their effects persist throughout life. Stressors experienced during early development can have lasting consequences for physiology, behaviour and fitness. Many holometabolous insects undergo extensive tissue remodelling during metamorphosis, which may change how effects of larval stressor exposure carry over into adulthood; such effects can nevertheless persist (Callier and Nijhout, 2013; Truman and Riddiford, 2007). In vertebrates, early nutritional limitation and other early-life stressors have been associated with persistent changes in hormonal regulation, immune function, cognition and fitness (Chaby, 2016; Lupien et al., 2009; McEwen and Wingfield, 2010; Shonkoff et al., 2012). Long-lasting developmental effects are also well

636 documented in insects, but relatively few studies have examined them explicitly through the
637 lens of stress physiology (Westwick and Rittschof, 2021). Early experience can shape adult
638 insect behaviour and physiology, raising the question of how developmental mode influences
639 the persistence and regulation of these effects (Westwick and Rittschof, 2021).

640 The Adaptive Calibration Model proposes that information about the social and physical
641 environment acquired during development helps calibrate later stress responsivity, linking
642 stress regulation with behaviour and life-history variation (Del Giudice, Ellis & Shirtcliff,
643 2011). Developed primarily to explain human developmental variation, the model provides a
644 comparative question for insect research: does early experience alter the regulation of
645 subsequent stress responses, and under which later conditions are those changes beneficial?
646 Testing this possibility requires distinguishing changes in stress responsivity from broader
647 developmental effects on growth, condition or behaviour.

648 Insects exhibit two major developmental modes, holometaboly and hemimetaboly (Jindra,
649 2019), which differ markedly in the extent of morphological reorganisation during
650 development. These contrasting developmental strategies are likely to influence how
651 developmental experiences shape later phenotypes (English and Barreaux, 2020), and
652 consequently the timing, organisation and persistence of stress responses. In holometabolous
653 insects, the pupal stage may act as a partial “developmental reset” as tissues are remodelled
654 during metamorphosis (Callier and Nijhout, 2013; Truman and Riddiford, 2007).

655 Nevertheless, early-life effects can persist across metamorphosis: larval starvation in the
656 holometabolous turnip sawfly (*Athalia rosae*) has been shown to affect later life-history
657 traits, as well as the development and feeding of offspring larvae (Paul et al., 2022). In
658 contrast, hemimetabolous development involves gradual maturation within a more continuous
659 body plan. Juveniles and adults often use similar microhabitats, though this varies among
660 groups (Pottier et al., 2026). This continuity may lead to greater influences of early-life

experience on later phenotypes. Additionally, it is likely that holometabolous insects are more likely to occupy non-overlapping ecological niches as larvae and adults than are hemimetabolous insects, potentially reducing the relevance of early-life effects.

More generally, theory predicts that sensitivity to environmental conditions can change across development as the information provided by those conditions and the scope for phenotypic adjustments change (Fawcett and Frankenhuis, 2015). In the hemimetabolous pea aphid (*Acyrtosiphon pisum*), embryonic exposure to elevated temperatures affected later development time, adult morphology and fecundity (Schaubroeck et al., 2026). The timing of development may also affect how reversible these changes are: changes made during a brief developmental window can be difficult to adjust if conditions change later (Hoffmann and Bridle, 2022). For comparisons between insects and vertebrates, the relevant questions are therefore when sensitivity to stressors is greatest, which traits remain plastic, and how early effects persist through subsequent development. Metamorphosis adds a distinctive dimension to these questions in holometabolous insects, but the evidence discussed here does not establish a general difference in persistence between developmental modes or between insects and vertebrates.

Developmental conditions can have lasting effects on behaviour, physiology and life-history traits. Across insect taxa, studies provide direct evidence that conditions experienced before adulthood can affect later development and adult traits. In the holometabolous fly *Drosophila ananassae*, larval diet altered adult resistance to heat, cold, starvation and desiccation, with different diets favouring resistance to different challenges (Sisodia and Singh, 2012). In the hemimetabolous damselfly *Ischnura elegans*, exposure to fish predator cues during the larval stage reduced survival to adult emergence and lengthened development time, although it did not affect mass at emergence (Sniegula et al., 2020). Together with the effects of larval starvation in the turnip sawfly described above (Paul et al., 2022), these studies show that

developmental experiences can carry over into later life across different insect groups. Whether such effects prepare individuals for predictable future conditions or reflect developmental constraints remains an active question (Fawcett and Frankenhuis, 2015; Monaghan, 2007; Taborsky et al., 2021). Further work is needed to establish how often these developmental effects involve lasting changes in stress regulation, rather than changes in traits such as body size or development time.

Persistent molecular effects of larval mitochondrial stress in *D. melanogaster*, discussed above, illustrate how developmental exposure can alter adult physiological regulation (Borch Jensen et al., 2017). However, whether such changes prepare insects for later challenges or instead reflect developmental constraints depends on the conditions that they subsequently encounter (Fawcett and Frankenhuis, 2015; Monaghan, 2007; Taborsky et al., 2021). These explanations need not be mutually exclusive: adaptive developmental adjustments may respond to changes in an organism's own condition and coexist with physiological damage or developmental costs.

Short generation times, experimental tractability and well-characterised life histories make insects particularly well suited for testing these ideas (English and Barreaux, 2020). The capacity to manipulate early-life environments at scale, and to track physiological and behavioural outcomes across development, positions insects as powerful models for uncovering how stress responses are regulated and programmed across the life course. This potential remains underused for comparing the mechanisms of developmental carry-over across insect taxa, particularly beyond a small number of model species. Broader work across developmental modes and ecological contexts could test when early-life conditions alter adult stress regulation, and whether those changes are beneficial under later conditions.

Developmental strategy is therefore one part of the ecological context needed to interpret stress responses across taxa.

Life-history strategy and mortality risk

Beyond developmental strategy, broader life-history characteristics may shape selection on stress response systems across taxa. Species differ in expected lifespan, exposure to extrinsic mortality and the predictability of environmental challenges. These differences may influence how stress responses are regulated and deployed (Adamo, 2017; Cinel et al., 2020; Frank, 2019). For example, insects encounter predation risk, fluctuating environmental conditions and food limitation, but the frequency and consequences of these challenges vary among species and are not unique to insects (Adamo, 2017; Angilletta Jr, 2009; Cinel et al., 2020; Schmid-Hempel, 2005). Comparing insects and vertebrates therefore requires attention to the ecological conditions and life histories of the species involved, as well as their taxonomic identity (Hawlena et al., 2011; Miyashita and Adamo, 2020).

Life-history strategy may also influence the temporal dynamics of stress responses. Selection on stress regulation should depend on how responses affect survival and future reproduction, including the benefits of countering immediate threats and the costs of prolonged or repeated activation. Mortality risk, reproductive timing and expected lifespan therefore may shape investment in physiological maintenance and recovery (Adamo, 2017; Frank, 2019; Vitousek et al., 2019). However, because both short- and long-lived species may benefit from rapid defence, while the costs of prolonged activation depend on ecological and reproductive context, these considerations do not yield a simple prediction that shorter-lived species respond more rapidly, or that longer-lived species prioritise long-term maintenance over immediate defence. How these life-history factors shape stress response dynamics remains largely uncharacterised across taxa.

Social organisation

Finally, social organisation extends this ecological perspective by changing not only the stressors that individuals experience, but also how responses to those stressors are

coordinated within groups. Insects include some of the most socially complex organisms in the animal kingdom: eusocial lineages such as ants, termites, bees and wasps have evolved highly integrated societies characterised by cooperative brood care, reproductive division of labour and overlapping generations (Bourke, 2011; Hölldobler and Wilson, 1990). These societies provide opportunities to investigate how social interactions alter individuals' exposure to challenges and how responses to threats may be transmitted, buffered or amplified across a group (MacLeod et al., 2023). Division of labour and reproductive castes may further affect which individuals encounter a stressor and how its consequences are managed.

Stress buffering, in which the presence of conspecifics reduces an individual's physiological response to a stressor, has been widely documented in vertebrates (Kikusui et al., 2006).

Whether social interactions similarly buffer physiological stress responses in insects remains less well understood. What is clear is that eusocial insects can transmit information about threats rapidly: honeybees (*Apis mellifera*) use alarm pheromones during colony defence, while termites and ants use vibrational or chemical signals to coordinate responses (Hölldobler and Wilson, 1990; Leonhardt et al., 2016). Such communication can recruit nestmates and amplify a collective defensive response, even though its effect on an individual's stress physiology may differ. Colonies can also reduce exposure to some challenges through cooperative defence and social immunity (Straub et al., 2015).

In these contexts, responses to a stressor may be coordinated across many individuals, with consequences for both individual and colony survival. Eusocial organisation can also give colonies some capacity to tolerate the loss of workers while maintaining reproduction, described as “superorganism resilience” (Straub et al., 2015). Collective defence provides a different example of how colony members respond together: Japanese honeybees (*Apis cerana japonica*) surround invading hornets in a “heat ball” that helps kill the intruder

(Abrol, 2013; Ono et al., 1995). Collective hygienic behaviours can likewise limit pathogen spread within colonies, potentially reducing individuals' exposure to pathogen-related stressors (Spivak and Reuter, 2001). These examples show how social organisation can affect a colony's response to threats, although they do not by themselves establish that individual workers have a reduced physiological stress response.

Social interactions may shape the endocrine state of individual colony members. In honeybees (*Apis mellifera*), social and pheromonal cues are associated with changes in behaviour, reproduction and task allocation, involving pathways linked to JH, vitellogenin and biogenic amines including OA (Amdam and Page, 2010; Kocher and Grozinger, 2011). Social regulation begins during development: nutritional and social cues influence caste differentiation through hormonal pathways including JH (Hartfelder and Engels, 1998). These findings raise the possibility that social organisation affects not only exposure to challenges, but also the physiological state in which individuals encounter them.

Much of our mechanistic understanding of stress regulation comes from measuring responses in individuals, with less attention to how their social environment alters those responses (Koolhaas et al., 2011; McEwen, 2007; Taborsky et al., 2021). Yet social interactions can change an individual's exposure to stressors, transmit information about threats and potentially buffer or amplify responses. Recent work has highlighted how little we know about social effects on stress responses in invertebrates, including insects (MacLeod et al., 2023). In eusocial insects, social interactions also shape collective defence and the conditions experienced by different colony members. A key next step is to test how these colony-level processes affect individual stress physiology, and how individual responses in turn influence colony resilience. Such work would make eusocial insects particularly useful for comparing stress regulation across levels of biological organisation.

Future directions and outlook

The following priorities emerge from the mechanistic and ecological themes reviewed above. They identify questions that insect systems are well suited to address and, where possible, predictions that can be tested.

At the molecular level, a major frontier lies in resolving the temporal and spatial organisation of insect stress responses. Early time-series work in *D. melanogaster* has identified distinct temporal patterns of gene expression during recovery from heat stress (Sørensen et al., 2005), but comparable datasets across other stressors and insect taxa remain limited. Studies that sample only one or a few post-stressor time points, or focus on particular components, such as heat-shock proteins (Zhang et al., 2014), cannot fully resolve how early signals relate to later transcriptional changes. More detailed time-series transcriptomics could distinguish immediate responses from longer-term adjustments, while single-cell, single-nucleus and spatial approaches could reveal which tissues and cell types contribute to each phase (Li et al., 2022). CRISPR-based methods now enable targeted gene disruption and tagging in *D. melanogaster* and, increasingly, other insects including *G. bimaculatus* (Matsuoka et al., 2025; Zirin et al., 2022). CRISPR-mediated fluorescent tagging has shown that food and sleep deprivation alter the organisation of presynaptic structures in *Drosophila* mushroom-body neurons through a local mechanism involving OA, Oct β 2R and cyclic AMP signalling (Wu et al., 2025). Automated tracking can also measure changes in behaviour from video recordings (Pereira et al., 2022). Combining automated behavioural tracking with fluorescent tagging and direct chemical measurements could test how octopaminergic signalling relates to transcriptional and behavioural changes over time. Together, these approaches could reveal how insect stress responses unfold across time and tissues, and whether those patterns resemble those described in vertebrates.

809 A further priority is to understand how the organisation of stress-regulatory systems
810 influences the timing, coordination and flexibility of responses across taxa. Network and
811 control-theoretic models could compare the distributed insect systems discussed above with
812 more hierarchical vertebrate systems, asking how each responds when challenges are
813 frequent, unpredictable or prolonged (Cohen et al., 2012; Frank, 2019). By representing
814 feedback, anticipatory responses and interactions among regulatory components, such models
815 could generate predictions about response speed, recovery and the ability to maintain
816 physiological stability (Del Giudice et al., 2018; Frank, 2019). These predictions could then
817 guide empirical tests of how alternative regulatory architectures perform under different
818 challenge regimes.

819 Studies of wild populations and experimental evolution provide complementary ways to test
820 how ecological conditions shape stress responses. Comparisons among populations
821 experiencing different frequencies or predictability of stressors could reveal whether baseline
822 stress-system activity, response magnitude or recovery differ. Experimental evolution could
823 then test whether such differences arise when stressor regimes are manipulated across
824 generations. Recent evolutionary models predict that environmental predictability and
825 constraints on response dynamics can shape how stress responses evolve (Taborsky et al.,
826 2021). More broadly, models of gene regulatory networks show how the mechanisms
827 underlying plasticity can affect evolutionary outcomes (van Gestel and Weissing, 2016).
828 Many insects, with their short generation times, are highly amenable to large-scale selection
829 experiments and thus offer powerful systems for examining how stress responses evolve
830 under chronic disturbance, repeated stress exposure or altered temporal structure of
831 environmental risk. Together, these approaches could test whether different ecological
832 regimes favour distinct balances between responsiveness, robustness and plasticity.

833 Another priority is the systematic investigation of repeated exposure to stressors in wild
834 insect populations, moving beyond the single, acute challenges that dominate current
835 research. Insects routinely encounter recurring challenges such as predation risk,
836 environmental disturbance and social conflict. Understanding how responses change across
837 successive exposures represents a major gap in insect stress biology. Such context-dependent
838 changes remain poorly characterised in natural settings, partly because successive encounters
839 are difficult to measure in the wild. One promising approach is to expose free-living
840 individuals to repeated, standardised, ecologically relevant disturbance cues and measure how
841 behavioural or physiological responses change across exposures. In wild field crickets
842 (*Gryllus campestris*), repeated predator-like vibrations did not produce uniform habituation:
843 some aspects of antipredator behaviour showed modest sensitisation, while responses also
844 varied substantially among individuals (Gilford et al., 2026b). Other field experiments show
845 that cricket escape behaviour varies with predator-cue intensity and thermal conditions (Li et
846 al., 2026). Tracking both behaviour and physiology across repeated exposures could reveal
847 whether these behavioural changes are accompanied by changes in stress regulation.

848 Related questions concern how chronic, sublethal challenges, including pesticide and
849 pathogen exposure, affect insect behaviour and physiology. Pesticides are recognised as
850 major contributors to insect declines (Sánchez-Bayo and Wyckhuys, 2019; Wagner et al.,
851 2021), and field-realistic sublethal exposure can affect behaviour, cognition and fitness
852 without causing immediate mortality (Siviter et al., 2021; Siviter and Muth, 2020). Effects
853 need not always increase with exposure: a systematic review of insect hormesis studies
854 identified cases in which mild stressors were associated with increased reproduction or stress
855 tolerance and changes in heat-shock, antioxidant or detoxification responses (Rix and Cutler,
856 2022). Thus, the absence of mortality does not imply the absence of an effect, while sublethal
857 effects need not be detrimental under every condition. We know less about how low-level

exposure alters stress responsiveness and decision-making in the wild, particularly when insects face other challenges. In wild field crickets (*G. campestris*), a single residue-level exposure to a diamide insecticide did not consistently alter antipredator behaviour following simulated predator attacks. Re-emergence latency nevertheless increased from the first to the second testing day in both treated and control crickets, suggesting that this behaviour may change with recent experience independent of pesticide exposure (Gilford et al., 2026a). A priority now is to test whether repeated or chronic sublethal exposure selectively affects particular physiological systems or behavioural traits, and whether those effects depend on ecological context. Combining realistic exposure regimes with behavioural and physiological measures could inform conservation, agriculture and insect welfare.

Finally, growing evidence highlights the social environment as an influence on stress responses (MacLeod et al., 2023), yet its effects remain underexplored in insects, particularly outside of a small number of eusocial species. Experiments across solitary and social insects, alongside individual-based and state-dependent models, could test how social interactions change exposure to stressors, individual physiological responses and collective outcomes. Insects offer opportunities to link social environment, behaviour and physiology, and to test how social structure interacts with stress regulation across evolutionary scales. Together, these approaches could reveal when social groups buffer or amplify their members' responses to challenges, and how the consequences for individuals relate to the resilience of the group or colony.

Conclusion

Stress responses enable organisms to cope with environmental challenges through coordinated changes in behaviour, physiology and gene expression. Insects and vertebrates

882 share ecological functions, including detecting challenges, mobilising energy, altering
883 behaviour, regulating immune and metabolic activity, and activating cellular protection and
884 recovery. Some signalling components and downstream molecular programmes also recur
885 across taxa, but the organisation of the neural and endocrine systems that produce these
886 responses differs. Cross-taxon comparisons are therefore most informative when they
887 distinguish shared ecological functions from their underlying mechanisms, including the
888 hormones involved, feedback relationships and the timing and tissue specificity of a response.
889 These mechanistic differences may shape the timing, flexibility and costs of stress regulation;
890 theoretical and control-system models offer a way to develop testable predictions about those
891 consequences.

892 Generalisation among insects requires similar care. Studies of *Drosophila*, honeybees, locusts
893 and other species have identified conserved genes with similar functions across taxa,
894 alongside signalling molecules and cellular responses shared across species. However, the
895 relationships among these components and their contributions to stress responses may vary
896 with species, stressor, developmental stage, life history and social organisation. Findings
897 from well-studied species provide valuable starting points, rather than a single model of the
898 “insect stress response”. Comparative experiments across insect groups can establish which
899 regulatory relationships are shared, which vary, and how those differences relate to the
900 challenges each species encounters.

901 Resolving these questions matters both for comparative biology and for the use of insects as
902 experimental and applied study systems. Interpreting results from models such as *Drosophila*
903 depends on understanding which findings extend beyond the species or conditions in which
904 they were obtained. In agriculture, a clearer account of how insects respond to heat, resource
905 limitation, pathogens and pesticides can improve predictions about the impact on pest species
906 and pollinators. Combining behavioural and physiological measurements with direct assays

of signalling molecules, molecular time series and experimental manipulation will connect the components of stress responses to their consequences for organisms. Insect diversity can then help explain not only how stress regulation works, but how it evolves under different ecological demands.

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