lated lysine residues in histones through its affinity to diacetylated histone H4 (*11*).

By contrast, BD2 inhibition did not yield strong antiproliferative effects in cancer cell lines that are sensitive to BD1 inhibitors and did not displace BET proteins from chromatin. Thus, BD2 mediates interactions with nonhistone proteins, such as transcription factors. In support of this idea, BD2 inhibition altered gene expression signatures triggered by extracellular stimuli such as interferon-γ and phorbol-myristate, which activate specific transcription factors. The requirement of BD2 for induced gene expression was also evident in stimulated primary $CD4^+$ T cells, in which strong suppression of proinflammatory cytokine expression suggested applications of BD2-specific inhibitors in inflammatory disease. Indeed, selective BD2 inhibition showed efficacy in mouse models of arthritis and psoriasis, which are characterized by pathogenic inflammation. In addition, encouraging activity was also observed in mouse models of nonalcoholic fatty liver disease, in which GSK620 reduced deposition of fat in the liver (steatosis) and scarring of liver tissue (fibrosis).

Taken together, the development of BD1- and BD2-selective inhibitors will help to delineate the functions of these conserved proteins. The role of BD2 in induced transcription programs predestines BD2-selective inhibitors for treatment of inflammatory disease and fibrosis, potentially bypassing the rewiring of BET-protein interactions observed with pan-BET inhibitors (*12*). The effect of BD2 inhibition on hematopoiesis, a differentiation program that is also regulated by a myriad of transcription factors, remains to be investigated. In clinical studies, side effects of pan-BET inhibitors have been associated with defects in blood cell differentiation such as low platelet counts causing abnormal blood clotting. However, this new generation of domain-selective inhibitors will provide exciting research tools for studying transcriptional regulation by epigenetic readers. ■

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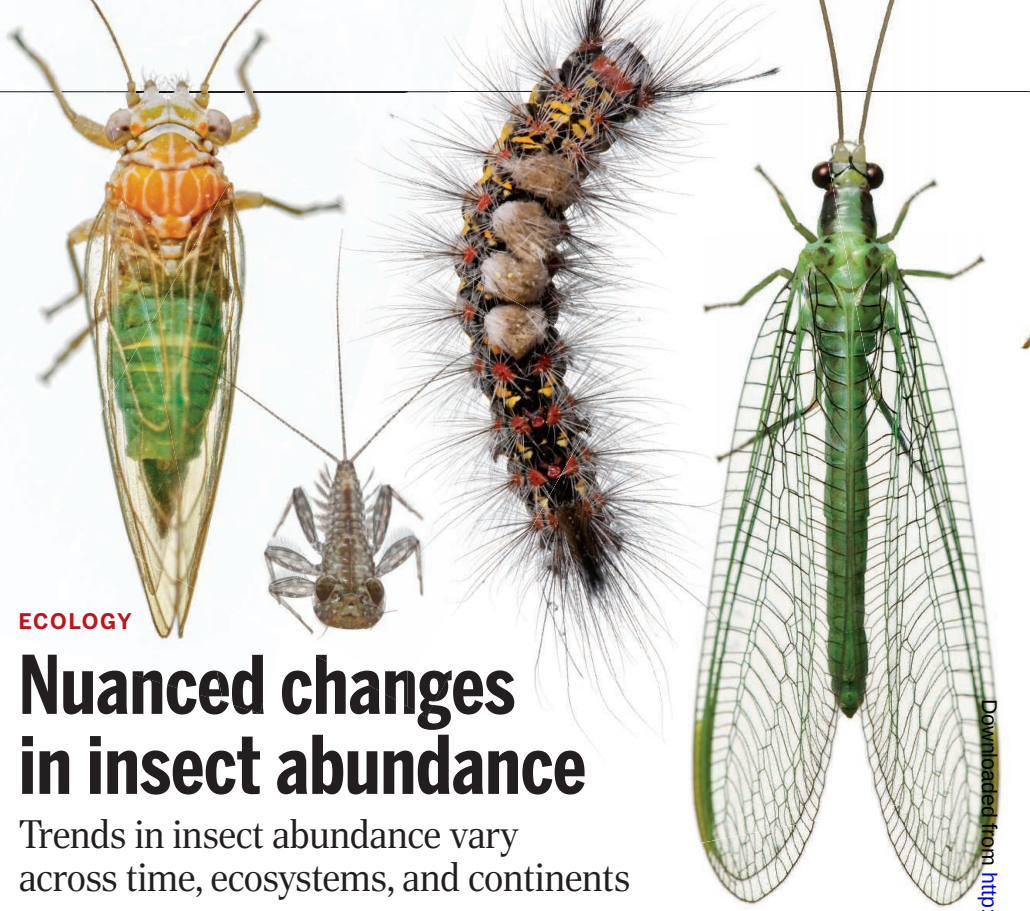

ECOLOGY

Nuanced changes in insect abundance

Trends in insect abundance vary across time, ecosystems, and continents

By **Maria Dornelas**[1] and **Gergana N. Daskalova**[2]

Drastic declines in insect biomass, abundance, and diversity reported in the literature have raised concerns among scientists and the public (*1*–*3*). If extrapolated across Earth, biomass losses of ~25% per decade (*1*) project a potential catastrophe developing unnoticed under our noses. The phrase "insect Armageddon" has captured the collective attention and shined a spotlight on one of the most numerous and diverse groups of organisms on the planet. Yet, insects are critically understudied. For example, the BioTIME database (*4*)—a compilation of biodiversity time series—contains records for 22% of known bird species but only 3% of arthropods (the phylum that includes insects and spiders). On page 417 of this issue, van Klink *et al.* conduct a thorough global assessment of insect abundance and biomass trends and paint a more nuanced picture than that predicted by extrapolations (*5*).

Given the critical environmental functions of insects, the consequences of their declines could propagate across ecosystems and affect the services they provide (for example, pollination of crops such as almonds, apples, and cherries). The prospect of widespread insect decline has prompted calls for rigorous scientific study and monitoring (*6*–*8*). The drivers of biodiversity changes are almost never simple, and their discovery requires context. Thus, simple extrapolation from a handful of locations is unlikely to reveal the layers of complexity that underpin real-world biodiversity change (*6*, *9*). To unpick insect-decline events, scientists must decipher whether site- and region-specific declines are representative of the state of insects around the world. This requires a systematic assessment of insect-abundance trends.

In what is the largest and most complete meta-analysis to date, van Klink *et al.* revealed substantial variation—surges and declines—in abundance and biomass trends. Similar to what is found across other taxa (*10*), the meta-analysis in the new study detected no net directional trend among 166 studies of 1676 geographical sites in 41 countries. Yet, van Klink *et al.* found that terrestrial insects declined in abundance by 9% per decade on average, whereas freshwater insects increased by 15%. The authors also noted variation across continents, with North America and some European regions emerging as hotspots of decline in insect abundance.

The findings of heterogeneity in insect abundance and biomass trends over time reinforce the need to consider spatial variation in biodiversity change (*11*). Other

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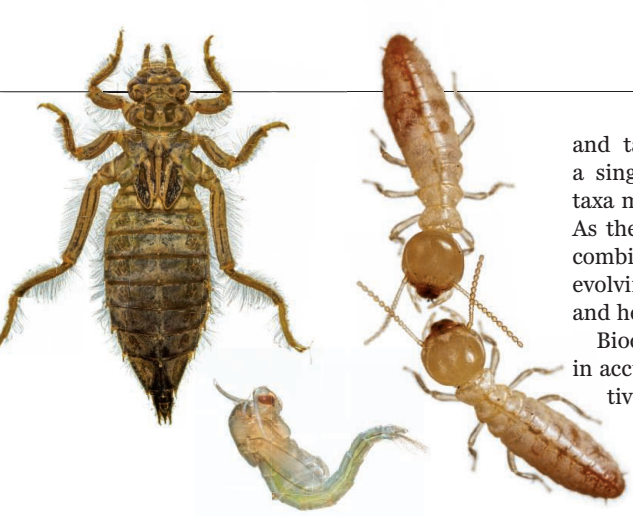

Insects are incredibly diverse, as are the trends of their abundance and biomass over time.

PHOTOS: DAVID LIITTSCHWAGER

studies with long-term monitoring have revealed additional layers of variation in patterns of invertebrate change. For example, occupancy (a metric of spatial abundance) of terrestrial insects in the United Kingdom has increased, whereas that of noninsect invertebrates has declined (*12*). Some trends vary across time, such as periods of increase in abundance of U.K. moths followed by periods of decline (*13*). The patterns that emerge across all insect-abundance studies to date are those of variation in trends across space, taxa, and time.

The drivers of change in insect biodiversity around the world remain to be fully ascertained. Because of their short life spans and quick population dynamics, insect abundances are naturally highly variable, which presents a challenge for quantifying long-term trends (*8*). Species exposure to global change, as well as their sensitivity and resilience, likely all interact to drive ongoing biodiversity changes.

Across the sites represented in the new study, declining trends seemed to be associated with land-use intensification, with no signals of climatic influences. Increasing trends, namely in the freshwater realm, coincided with the establishment of stricter water policies, demonstrating that appropriate legislation can bring positive biodiversity outcomes. Yet, the world is a complex mosaic of threats (*14*). As scientists tackle the challenge of disentangling drivers of various insect-biodiversity trends (*8*), they will be better poised to predict the consequences for ecosystem function and services, such as pollination, decomposition of organic matter, and pest control (*15*).

The variation in insect trends has several broader implications. Variation adds to the doubts that biodiversity change can be represented by a single trend. Thus, it is wise for scientists to heed this lesson as they debate biodiversity targets. To understand the complexities of biodiversity change, ecologists require data on realm-, region- and taxa-specific trends. Inferences from a single global scenario or one indicator taxa must be treated with extreme caution. As these smaller studies accumulate, their combined results should contribute to the evolving patchwork of biodiversity changes and help to elucidate the various drivers.

Biodiversity monitoring should increase in accuracy as it becomes more representative of the biosphere itself. Therefore, in addition to advancing our knowledge of insect biology and behavior, scientists must approximate stratified random sampling of biodiversity across space and taxa, as insects are not the only understudied group of organisms. Researchers should also widen their focus on drivers of individual global changes to incorporate the complex interactions among different types of environmental shifts (*14*), natural species' variability over time, and species' sensitivity and resilience in the Anthropocene (*8*). Advances in our knowledge about ongoing biodiversity changes and ability to predict future ones will require the incorporation of layers of nuance in patterns of change and drivers of that change.

The temptation to draw overly simple and sensational conclusions is understandable, because it captures the attention of the public and can potentially catalyze much needed action in policy development and research arenas. However, fear-based messages often backfire. This strategy has the grave risk of undermining trust in science and can lead to denialism, fatigue, and apathy. Embracing nuance allows us to balance accurate reporting of worrying losses with hopeful examples of wins. Hope is a more powerful engine of change than fear. ■

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SIGNALING

Calcium as a biased cofactor

Crystal structure of an anti-obesity drug target reveals an important calcium-binding site

By **Madhu Chaturvedi** *and* **Arun K. Shukla**

The α-melanocyte–stimulating hormone (α-MSH) is a neuropeptide that is secreted by the cells in the intermediate lobe of the pituitary gland in the brain. In humans, α-MSH plays a pivotal role in the regulation of feeding behavior, energy homeostasis, and sexual activity, in addition to its primary function of regulating melanogenesis, the process of hair and skin pigmentation (*1*). α-MSH activates four of the five melanocortin receptors [melanocortin-1 receptor (MC1R), MC3R, MC4R, and MC5R but not MC2R] (*1*). Of these, MC4R is of peculiar interest as a drug target because mutations in this receptor are associated with different forms of obesity in humans (*2*). On page 428 of this issue, Yu *et al.* (*3*) present a crystal structure of human MC4R in complex with a peptide antagonist, SHU9119. This reveals a calcium-binding site on MC4R, and Ca^{2+} is found to be an important modulator of MC4R activation, which could potentially facilitate therapeutic development.

High-resolution structural analysis of heterotrimeric GTP-binding protein (G protein)–coupled receptors (GPCRs)—such as MC4R, the largest class of cell-surface receptors in the human body—has seen unprecedented progress in the past decade owing to numerous methodological and technological advances (*4*). As a result, understanding of these receptors has reached a new level with structural insights into their activation, signaling, and regulation, providing previously lacking frameworks for drug discovery (*5*, *6*). MC4R is expressed on neurons in the hypothalamus and brainstem. It is a prototypical, rhodopsin-like class A GPCR and primarily couples to the Gαs subfamily of heterotrimeric G proteins upon agonist activation (*7*). Gain-of-function mutations in MC4R appear to impart a protective ef-

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