Symposium

Neurobiology and Changing Ecosystems: Mechanisms Underlying Responses to Human-Generated Environmental Impacts

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Human generated environmental change profoundly affects organisms that reside across diverse ecosystems. Although nervous systems evolved to flexibly sense, respond, and adapt to environmental change, it is unclear whether the rapid rate of environmental change outpaces the adaptive capacity of complex nervous systems. Here, we explore neural systems mediating responses to, or impacted by, changing environments, such as those induced by global heating, sensory pollution, and changing habitation zones. We focus on rising temperature and accelerated changes in environments that impact sensory experience as examples of perturbations that directly or indirectly impact neural function, respectively. We also explore a mechanism involved in cross-species interactions that arises from changing habitation zones. We demonstrate that anthropogenic influences on neurons, circuits, and behaviors are widespread across taxa and require further scientific investigation to understand principles underlying neural resilience to accelerating environmental change.

Significance Statement

Neural systems evolved over hundreds of millions of years to allow organisms to sense and respond to their environments – to be receptive and responsive, yet flexible. Recent rapid, human-generated environmental changes are testing the limits of the adaptive capacity of neural systems. This presents an opportunity and an urgency to understand how neurobiological processes, including molecular, cellular, and circuit-level mechanisms, are vulnerable or resilient to changing environmental conditions. We showcase examples that range from molecular to circuit to behavioral levels of analysis across several model species, framing a broad neuroscientific approach to explore topics of neural adaptation, plasticity, and resilience. We believe this emerging scientific area is of great societal and scientific importance and will provide a unique opportunity to reexamine our understanding of neural adaptation and the mechanisms underlying neural resilience.

Introduction

The rapid pace of human-generated (anthropogenic) environmental change represents one of the most pressing challenges of our time, affecting ecosystems worldwide and posing significant threats to biodiversity and human well-being. While the impacts of environmental change on various species and ecosystems are becoming increasingly described (Tuomainen and Candolin, 2011; Candolin and Wong, 2012; Gunn et al., 2022), understanding its effects on

Received July 28, 2023; accepted Aug. 7, 2023. This work was funded in part by The Kavli Foundation. The authors declare no competing financial interests. Correspondence should be addressed to Angie Michaiel at amichaiel@kavlifoundation.org https://doi.org/10.1523/JNEUROSCI.1431-23.2023 Copyright © 2023 the authors the nervous system remains an understudied, yet complex field (Michaiel and Bernard, 2022). Focusing on the interaction between the environment and the cellular and circuit-based functions of the nervous system is vital for understanding an organism's capacity to flexibly perceive, respond, and adapt to its changing surroundings. What are the limits of neural adaptation in the face of rapid and accelerating change? What modulatory, homeostatic, or evolutionary mechanisms do nervous systems develop or leverage to enable successful survival of an organism? There are many open scientific questions, offering neurobiologists an exciting opportunity to reexamine and expand our knowledge on neural adaptation, plasticity, and resilience.

We define anthropogenic environmental change broadly as any environmental perturbation caused by human activity and urbanization, including exposure to chemical and sensory pollutants (e.g., artificial light and noise pollution), extreme weather events stemming from climate instability, temperature fluctuation and related changes in ocean acidity, as well as other environmental perturbations. These perturbations may have significant repercussions on population dynamics and animal behavior, and ultimately carry profound implications for the understanding of nervous system function. A growing body of research aims to understand how nervous systems respond and are potentially vulnerable or resilient to anthropogenic stressors. This research is motivated by the underlying concept that studying the response to such stressors will reveal novel insights into principles of neural flexibility, adaptation, and resilience (Michaiel and Bernard, 2022). Here, we delve deeper to review recent findings and present mechanistic insights of how nervous systems sense, compensate for, and are impacted by accelerated rates of change.

The examples we present span a broad spectrum of scientific and theoretical approaches, model systems, and types of environmental disturbances, all focused on the impact of human activities on neural function. By showcasing these compelling instances of anthropogenic influence on neural systems, we aim to highlight the accessibility of studying neural resilience and adaptation in response to novel anthropogenic stressors by using diverse experimental methods and conceptual frameworks. This underexplored research area holds vast potential for novel scientific investigations, groundbreaking discoveries, and long-lasting impact, with potential applications for society.

Alteration in neural function during heat stress in the zebrafish

Heat spells become more frequent and severe as anthropogenic climate change progresses. Brain function relies on temperaturesensitive biochemical processes and therefore operates best within a species-specific thermal range. Understanding the neural mechanisms that confer resilience to heat stress is urgent, especially for ectotherms (e.g., zebrafish) that hold body temperatures similar to the environment. Under heat stress, ectotherms reach a critical thermal limit (CT_{max}), which is a temperature where movement becomes disorganized, equilibrium is disturbed, and the animal is unable to escape the adverse conditions (Becker and Genoway, 1979; Lutterschmidt and Hutchison, 1997; Morgan et al., 2018).

When neural circuits are exposed to high temperatures beyond the animal physiological range, important functional alterations occur, such as loss of rhythmic activity (Marder et al., 2015), spreading depolarization (Jørgensen et al., 2019), and seizures (Dube et al., 2000; Shinnar and Glauser, 2002; Hunt et al., 2012). Therefore, heat-induced dysfunction in neural circuits controlling locomotion and balance might underlie the behavioral alterations observed at CT_{max}. Yet, very few studies have investigated how heat-induced neural dysfunctions relate to the animal's thermal tolerance, in part because of technical limitations hindering the simultaneous measurement of brain activity and behavior in freely moving animals. In this study (Andreassen et al., 2022), we addressed this technical challenge by using transparent larval zebrafish expressing a genetically encoded calcium indicator in neurons, to characterize the sequence of behavioral and neural events occurring during a heat ramp.

To establish the behavioral alterations caused by heat exposure, the movement of 5-d-old larval zebrafish was recorded while increasing the water temperature from 28°C at a rate of 0.3°C/min. Episodes of spiral swimming and loss of equilibrium were significantly more prevalent in heat-exposed fish than in fish held at 28°C. Toward the end of the assay, the heat-exposed larva became unresponsive to repeated gentle pokes to the trunk, which we used as the criterion for CT_{max} . Interestingly, CT_{max} occurred at similar temperatures when measured at different life stages (larvae, juvenile, and adults), indicating that heat resilience remains stable during development.

To gain access to brain activity during the heat ramp, calcium events were recorded in the brain locomotor center of restrained larval fish under an epifluorescence microscope. Several changes in neural activity occurred along with increasing temperature: the frequency of Ca^{2+} events in the medulla first increased, before a strong decrease in neural activity below control levels, followed by a large depolarization that spread throughout the brain. To link the timing of the behavioral and neural events, both CT_{max} and brain activity were then measured as the larva was swimming during the heat ramp. CT_{max} occurred before the onset of the brain-wide depolarization, during the period of suppressed neural activity.

Insufficient oxygen supply to tissues at high temperatures has been suggested to set the limit for upper thermal tolerance in several species (Jutfelt et al., 2018). To determine whether heat resilience is modulated by oxygen availability, the larvae were exposed to different oxygen levels in the water. Results indicated that downward and upward manipulations of oxygen levels produced bidirectional changes in CT_{max} and neural activity, with decreased thermal tolerance and earlier onset of brain depolarization in hypoxic conditions, and increased thermal tolerance and later onset of brain depolarization in hyperoxic conditions.

Together, this work sheds light on the sequence of behavioral and neural dysfunctions occurring as the temperature increases toward the animal's thermal limit. It revealed that neural activity is suppressed before the thermal limit is reached and demonstrates that oxygen levels contribute to setting the limit for heat resilience in the zebrafish larvae. Understanding the role of oxygen availability in thermal tolerance can aid in predicting and managing the impacts of climate change on animal populations, particularly in aquatic environments where oxygen levels may fluctuate.

Exploring the physiological basis of parent-embryo communication of high environmental temperature in zebra finches

The environmental effects of anthropogenic activity challenge the fitness of animals and the functionality of their neural systems, requiring adaptive capabilities for survival. In the example above, we explored how an anthropogenic stressor (rising temperature) directly affects neurophysiology and has a downstream impact on motor behavior. The following example instead describes a behavioral adaptation in response to rising temperature (i.e., vocal heat calls in zebra finches) that may have indirect, downstream consequences on adaptive neurophysiological processes, specifically during embryonic development. While this work has not yet identified a neural mechanism underlying the adaptive behavior presented here, it poses an interesting set of questions in neurobiology and changing ecosystems research: how is environmental information transferred from parent to offspring, and how is this information detected and used to develop adaptive neural or behavioral processes in offspring?

Zebra finches have been shown to produce "heat calls" when exposed to environments with raised temperatures (Mariette and Buchanan, 2016). Interestingly, a series of studies suggest that these whistle-like, ~ 8 kHz heat calls act as an acoustic signal in zebra finch parent–embryo communication. Specifically, the acoustic exposure to heat calls during embryonic development has been demonstrated to affect the postnatal development of the exposed offspring, priming them to live in hot environments (Mariette and Buchanan, 2016; Mariette et al., 2018; Udino et al., 2021). Whether these heat calls are communicative signals or merely a side product of thermal panting is being debated (McDiarmid et al., 2018; Mariette and Buchanan, 2019; Pessato et al., 2020, 2022).

The idea that the developing zebra finch auditory system can detect these heat calls is in conflict with the notion that the development of hearing sensitivity in zebra finches occurs mostly postembryonically (Amin et al., 2007) as in many other altricial species. To explore the unknown physiological basis of heat call sensing, we have quantified the 2-to-25 d post-hatch development of the zebra finch auditory system by recording air conduction- and head vibration-induced auditory brainstem responses (ABRs). ABRs can be recorded with electrodes placed on the subject's head and are routinely used, for example, in newborn hearing screening programs. Our results indicate that earliest air conduction-ABRs can be recorded with intense broadband clicks (20 μ s, 95 dB sound pressure level) at ~4-6 d post-hatch. The sensitivity for click and 0.25-to-6 kHz tone burst stimuli mature over the 3 first weeks from hatching with the sensitivity to 8 kHz tone bursts remaining very limited throughout this time period. Head vibrations induce vestibular-like responses at high stimulus intensities but fail to induce prominent ABR-like responses, suggesting that heat call detection is not based on bone conduction hearing.

To understand how heat calls are produced, we have tested whether directing airflow through the respiratory tract is sufficient to produce heat calls. Indeed, air flow at ranges expected to occur during thermal panting readily generates $\sim 8 \text{ kHz}$, soft whistles in *ex vivo* preparations and appear to be generated in the larynx. By modeling the acoustic environment within eggs that are further covered by the incubating parent, we find that these soft sounds are greatly attenuated before arriving to the embryo. In summary, our results demonstrate that the early hearing function of developing zebra finches may support lowfrequency acoustic communication, but it is unlikely that it supports high-frequency parent–embryo acoustic communication. Future work will continue to investigate how such sensory signals arising from behavioral adaptations to anthropogenic change are detected and integrated during neural development.

These studies are an important step toward identifying the sensory modality mediating heat call detection in embryonic zebra finches and determining whether there are mechanisms of avian acoustic communication that enable anthropogenically changing environmental temperatures to directly impact embryonic development.

Effects of light at night on Drosophila sleep/wake cycles

In addition to temperature, light pollution stands out as one of the primary threats to ecosystems, and it exerts significant adverse effects on both animal and plant physiology (Falcón et al., 2020; Jägerbrand and Spoelstra, 2023). Artificial light at night (ALAN) has the potential to disrupt migratory patterns (Parlin et al., 2022), competitive interactions (Bennie et al., 2015), predator-prey relationships (Ditmer et al., 2021), circadian timekeeping (Dominoni et al., 2016), represents a threat to pollination (Knop et al., 2017), and has profound effects on nocturnal insect species (Owens and Lewis, 2018). Millions of years of evolution have shaped phenomena, such as spatial orientation, while ALANinduced changes have been operating only during the past few decades.

The natural daily cycles of bright days and dark nights orchestrate physiologic, metabolic, and behavioral rhythms, and disturbances to these patterns directly impact ecological dynamics. Circadian clocks, present in nearly all organisms, evolved as a mechanism to maintain internal temporal order and anticipate predictable daily environmental changes (DeCoursey et al., 2000; Herzog, 2007; Golombek and Rosenstein, 2010). Disruption of these rhythms by modern environmental conditions has significant impacts on health (Roenneberg and Merrow, 2016; Logan and McClung, 2019). The Drosophila timekeeping system, comparable to the mammalian suprachiasmatic nuclei is called the Circadian Clock Neuron Network. This network comprises a group of \sim 150 neurons that display synchronous oscillation in the abundance of the clock genes *period* (*per*) and *timeless* (*tim*). The Circadian Clock Neuron Network can be subdivided into distinct neuronal populations based on gene expression, anatomy, location in the brain, and connectivity patterns (Helfrich-Förster, 2005, 2007a,b; Shafer et al., 2006, 2022; Ma et al., 2021). The small ventral lateral neurons (s-LN_vs) release the key circadian neuropeptide Pigment Dispersing Factor), and release of Pigment Dispersing Factor from the s-LN_vs, which takes place in the dorsal protocerebrum where the dorsal clock neurons are located, is required for endogenous circadian timekeeping (Renn et al., 1999; Park et al., 2000). The Drosophila circadian clock also serves as a seasonal timer, and the relation between the morning and evening peaks of activity is key for adapting activity patterns to summer and winter days with their distinct photoperiods (Stoleru et al., 2007).

As is the case in other species, the presence of light at night affects circadian behavior in Drosophila. Under standard entrainment conditions (light-dark, 12 h of bright 500 lux light and 12 h of darkness), Drosophila has a bimodal activity in which flies are most active when lights are turned on (morning peak of activity) and lights are turned off (evening peak of activity). When WT flies were exposed to dim white light at night (comparable to moonlight light levels, 0.01 lux), flies show a 1 h morning activity peak advance and a 3 h evening peak delay relative to flies under light-dark (Bachleitner et al., 2007). This study, focused solely on males, also showed that the presence of light at night modifies the cycling of circadian clock proteins within specific subsets of clock neurons. For flies exposed to moonlight, the phase of clock protein oscillations was advanced in the s-LN_vs, which are known as the "morning cells" (responsible for the morning activity peak) and delayed in the LNds, which are known as the "evening cells" (responsible for the evening activity peak of activity). Overall clock protein levels were also significantly lower under dim white light conditions (Bachleitner et al., 2007). Studies using nocturnal light intensities that mimic urban light pollution (>1 lux) have shown that ALAN affects mating, fecundity, and survival (McLay et al., 2017), and cause a reduction in reactive oxygen species (McLay et al., 2018). In addition, on LAN exposure, flies appear to be more vulnerable to metabolic stress (Kim et al., 2023).

Our work shows that ALAN has profound effects on *Drosophila* sleep/wake cycles, with substantially higher impact in males compared with females (M.P. Fernandez, unpublished observations). Specifically, males exhibit a more pronounced increase in nocturnal activity, a marked delay in their clock-controlled evening peak of activity, and greater levels of sleep deprivation. Furthermore, mutations in the clock gene *period (per)*, a key component of the negative feedback loop in the molecular oscillator, enhance the behavioral response to ALAN, particularly in males. Surprisingly, mutations in the clock gene *cycle (cyc)* do not affect the response to ALAN, as *cyc* mutants exhibit similar behavior under ALAN exposure compared with standard entrainment conditions. Importantly, a CRISPR-Cas9 mediated *per* KO specifically in clock neurons

replicates the phenotypes observed in the *per* null mutant, indicating that the effects are because of *per* expression in clock neurons rather than other cell types, such as glia or photoreceptors.

Together, our work leveraging *Drosophila* molecular tools has identified a genetic target within a specific neuronal cell type that is vulnerable to ALAN. Studying the effects of light at night in model systems, such as *Drosophila*, will contribute to expanding our knowledge of the impact of light pollution on biological rhythms and has implications for a wide range of organisms living in illuminated environments in diverse ecosystems.

Neurobiology of seasonal migration of monarch butterflies in changing environments

Long-distance animal migration, which is widespread in nature, is another example of adaptive response to natural changes in the environment. Often driven by the changing seasons, animal migration allows organisms to anticipate the arrival of inhospitable conditions and escape following precise routes and navigational strategies to locate shelter, food sources, breeding, or overwintering grounds (Mouritsen, 2018; Merlin and Liedvogel, 2019; Merlin et al., 2020). By disturbing the environment and accelerating climate change, human activities in the Anthropocene are posing a serious threat to animal migrations (Burt et al., 2023). Whether these migrations could be lost, completely change destination, or persist in the face of man-made environmental changes is unknown. Exploring the sensitivity and/or resilience of the nervous system to rapid anthropogenic environmental changes may provide scientists with a framework on which to make realistic predictions and deploy risk mitigation strategies for vulnerable migratory species.

One focal migratory species of interest for such studies is the Eastern North American migratory monarch butterfly; the Eastern North migratory monarch population has been on a steady decline for decades, and the environmental cues used by monarchs to orient and navigate have been identified (Reppert et al., 2016). Every fall, monarchs anticipate the arrival of unfavorable winter conditions in their North American breeding grounds by migrating southward in a state of reproductive dormancy (i.e., diapause) to their overwintering sites in Mexico. In the spring, after breaking diapause and reproducing at the overwintering sites, the same individuals switch their flight orientation northward to remigrate to the southern states of the United States. At least two successive generations of reproductively active monarchs progressively move northward to complete the multigenerational migratory cycle, which starts anew the following fall when summer butterflies receive environmental cues that trigger their migratory physiology and behavior.

Both fall migrants and spring remigrants use a bidirectional sun compass to adjust their flight in the correct direction (Perez et al., 1997; Mouritsen and Frost, 2002; Froy et al., 2003; Merlin et al., 2009; Guerra and Reppert, 2013). This navigational mechanism relies on the circadian clock, an endogenous timekeeping machinery that keeps track of the \sim 24 h day and is reset everyday by natural light, to compensate for the positional change of the sun in the sky throughout the day (Mouritsen and Frost, 2002; Froy et al., 2003; Merlin et al., 2009). While the neural substrate for sun compass information integration has been identified in the central complex of the brain (Heinze and Reppert, 2011), the primary timing information for time compensation is most likely provided by circadian clocks located in the monarch antennae (Guerra et al., 2012; Merlin et al., 2009). Anthropogenic nighttime light pollution that monarchs may experience at stopover sites during their migratory journey may disrupt the functioning

of these clocks, thus compromising the ability of monarchs to orient in the proper direction (Parlin et al., 2022). Studies in the wild assessing both clock function and migratory orientation of monarchs exposed to artificial light at night of various intensities would help determine the degree to which environmental light pollution impacts monarch migration.

The environmental signal responsible for the reversal in seasonal flight orientation between fall migrants and spring remigrants has been identified as a prolonged exposure to cold temperatures (Guerra and Reppert, 2013). Three weeks of exposure to cycling temperature of 11°C/4°C in 12 h light/12 h dark conditions that simulate the coldness conditions experienced by monarchs at the overwintering sites are sufficient to flip southward orientation of fall migrants northward. We do not know, however, the temperature threshold at which this behavior could be lost, hampering the successful completion of the monarch migratory cycle, or whether the nervous system controlling this behavior could adapt to increasing temperatures driven by global climate change. Identifying the yet unknown molecular and cellular mechanisms that govern this cold-induced seasonal flight orientation reversal will be a necessary step to ultimately be able to assess the impact of increasing temperatures on the neurobiology of monarch migration. A promising avenue of investigation will be to examine whether cold-induced reprogramming of flight orientation is paralleled by a reprogramming of gene expression in the monarch brain.

This study highlights how anthropogenic changes can significantly influence the migratory patterns of butterflies, suggesting that such alterations in the environment dynamically affect the timing and location of animal behaviors by influencing environmental cues.

Exploring the impact of interspecies interactions on mosquito mating

With increasing anthropogenic activity, species habitation zones are changing, leading to novel interactions and, in some cases, cross-species competition for resources within shared ecological niches. As predicted environmental changes continue, the likelihood of novel cross-species interactions will continue to increase, posing significant threats to ecosystem dynamics. The mechanism below explores how neural processes shape interspecies competitive interactions that may arise from changing habitation zones, specifically through sensory processing pathways involved in mating decisions.

Anthropogenic climate change, human movement, habitation, and land use patterns impact mosquitoes' geographical ranges, their invasion potential, and which other species they encounter (Lounibos, 2002). Aedes aegypti and Aedes albopictus, two highly invasive species that are vectors of chikungunya, dengue, and Zika are now globally distributed beyond their native ranges via human transport and range expansion (Hawley et al., 1987; Kraemer et al., 2015; Battaglia et al., 2016). Ae. albopictus invasions are generally more recent compared with Ae. aegypti, and this species has largely displaced Ae. aegypti in many regions (Nasci et al., 1989; O'Meara et al., 1995; Zhou et al., 2022). These species are reproductively incompatible but share a similar ecological niche (Legros et al., 2009). Here, we focus on mating behaviors because these are evolutionarily labile depending on cohabitation history, and mating interference between newly encountered species may drive changes in the nervous system to ensure that species barriers are robust (Bargielowski et al., 2013; Burford Reiskind et al., 2018).

Both species use acoustic cues to guide mating, which occurs in flight (Roth, 1948; Hartberg, 1971; Gubler and Bhattacharya, 1972; Cator et al., 2009). Male accessory gland (MAG) factors are transferred to the female during mating to suppress her lifetime receptivity to subsequent suitors (Craig, 1967; Gwadz et al., 1971). Ae. albopictus males can reproductively interfere with females of multiple species, including Ae. aegypti, by copulating with them and suppressing their receptivity to subsequently encountered conspecifics, effectively sterilizing these females (Ribeiro and Spielman, 1986; Tripet et al., 2011; Giatropoulos et al., 2015). The penalty for erroneous mating is severe for females because they generally mate once, while males can mate multiply (Craig, 1967). After cohabitation with Ae. albopictus, Ae. aegypti females can develop resistance to interspecific mating, which could be implemented through neural changes that alter responses to potential mates or post-mating receptivity (Bargielowski et al., 2013, 2015; Bargielowski and Lounibos, 2014, 2016; Burford Reiskind et al., 2018).

Neural control of mating behavior and female post-mating receptivity is well established. Drosophila melanogaster males transfer sex peptide to females, which activates its receptor in female internal sensory neurons, resulting in reluctance to remate (Liu and Kubli, 2003; Peng et al., 2005; Yapici et al., 2008; Häsemeyer et al., 2009; Yang et al., 2009; Feng et al., 2014). Injection of MAG homogenate into Aedes females suppresses lifetime remating, independent of sperm transfer (Fuchs et al., 1969; Helinski et al., 2012). MAG homogenate contains hundreds of peptides and proteins, and recent work identified a specific MAG-derived peptide/female receptor pair in Aedes that regulates short-term remating suppression and showed that in vitro peptide/receptor interactions align with observed reproductive interference (Sirot et al., 2011; Tripet et al., 2011; Helinski et al., 2012; Boes et al., 2014; Duvall et al., 2017). More research is needed to identify the complete suite of male-derived signals required for inducing lifetime changes, their cognate receptors in females, the neural circuits that mediate post-mating changes, and the mechanism(s) by which these changes are maintained. Most mating attempts are unsuccessful, and identifying cues used to evaluate potential mates and how responses to potential mates are affected by interactions with other species will provide insight into sensory pathways involved in mating (Aldersley and Cator, 2019; Cramer et al., 2023).

Reproductive interference is an ecological process with consequences for patterns of coexistence between *Aedes* mosquitoes and impacts pathogen transmission (Paton and Bonsall, 2019). Importantly, anthropogenic changes have the potential to remap habitation and mating zones, thus changing the likelihood of interspecies encounters and mating incidents. These studies are revealing the precise mechanisms by which mosquito fertility is impacted by interspecies mating.

Tracking the effects of temperature perturbations in neuronal models: a data-driven approach

Many climate science approaches rely on generating predictive models to infer how environmental temperature change may impact a particular system of study (e.g., predicting local precipitation based on future temperature scenarios). A major challenge in extending this concept to predict neuronal circuit resilience to temperature change lies in creating a model that can comprehensively link biophysics with neuronal spiking activity. To address this gap, these investigators created methodology to rapidly track changes in biophysical parameters in a spiking neural circuit by combining both model-based and data-based approaches. The increasing amplitude of regional temperature variations caused by climate change adversely affects life on the planet in many different ways. In particular, many cold-blooded animals (that lack the homeostatic temperature regulation mechanisms of birds and mammals) are faced with the challenge of coping with large bodily temperature variations over the course of short periods of time (Marder and Rue, 2021). The neural systems in these animals are particularly sensitive to such temperature variations, since the biophysical properties of neuronal cells are temperature-dependent. Although the behavior and function of neural systems can present robustness and adaptation to temperature perturbations, it is not clear whether these features, evolved over the course of millions of years, can deal with the unprecedented environmental perturbations of modern climate change.

To pursue a mechanistic understanding of robustness and homeostasis in neural circuits that are subject to large time-varying temperature perturbations, consider the stomatogastric ganglion circuit of the crab *Cancer borealis*, which displays a triphasic bursting activity pattern with individual membrane voltage shapes and relative phases that have been observed to be remarkably temperature-robust (Ratliff et al., 2021). Previous studies suggest that robustness is achieved through compensatory mechanisms involving both intrinsic and synaptic currents with counterbalancing temperature dependencies (Tang et al., 2010; O'Leary and Marder, 2016). However, the exact details of this mechanism, and why it is so reliable despite variability between individual stomatogastric ganglion circuits, remain unresolved questions.

Traditionally, such studies have relied on both model-based and data-based approaches. In model-based approaches, the parameters of a conductance-based model are estimated from current-clamp data, and the model becomes the object of study. This approach provides a detailed interpretable model that spikes, but it comes with a high computational cost and with uncertainty over the model choice (Almog and Korngreen, 2016). In data-based approaches, a neuron's current–voltage (I-V) curves, obtained with voltage clamp, are used to infer neuronal properties. This approach provides a rough but faithful description of a neuron's behavior, but it comes with the costs associated with a voltage-clamp experiment. When dealing with rapidly varying biophysical perturbations, both approaches may prove inadequate, as they only provide a snapshot of a neuron's behavior at a given moment in time.

In this work, we present a novel method to capture the behavior of a neuron that leverages the advantages of model-based and I-V curve-based approaches, and that in addition allows one to track changes in biophysical properties in real-time, during an experiment. The method builds on a flexible data-driven model of neuronal excitability that can be regarded as a specific class of recurrent artificial neural network (Burghi et al., 2020). We show how this data-driven model can be made more or less constrained, depending on the desired level of interpretability and on the particular neuronal property under scrutiny. Using a version of the model with few constraints, we show that it rapidly recovers the I-V curves of a neuron from current-clamp data while being able to reproduce the neuron's spiking dynamics in a simulation environment. By adding biophysical constraints, we show that the model can be made more conductance-based-like (hence more interpretable), and that it has the potential to recover the time courses of specific conductances in real-time. Finally, we show that our method can track changes in the I-V curves and the dynamics of a neuron during an experiment in which the temperature of the environment is increased monotonically over

the timescale of minutes. We argue that this method has profound implications for the study of neuronal behavior under temperature variations, and that this will provide us with new insights into the ability of some species to withstand the challenges of climate change.

Discussion

Environmental changes because of human activity have reached an acceleration point; however, neuroscience research investigating how organisms respond to such rapid change has not kept pace. This emerging theme within neurobiology is essential for a basic understanding of systems that may inform environmental, economic, and societal questions and needs. As exemplified in this review, anthropogenic environmental changes have profound effects on neural function, operating at molecular, cellular, and circuit levels across diverse taxa, environments, and timescales. In turn, these changes impact behaviors and may disrupt entire ecosystem dynamics (Michaiel and Bernard, 2022). Despite its broad significance, the study of neural resilience in the face of environmental perturbations remains relatively unexplored. Our symposium highlights emerging research at this frontier.

Biochemical processes are generally extremely temperaturesensitive and tend to have a narrow range of operating temperatures, as demonstrated in the zebrafish example above. A variety of adaptive mechanisms exist to enable animals to change their behavior in response to temperature fluctuations outside of their normal physiological range, such as zebra finch heat calls. We are only now learning the extent to which small fluctuations in temperature can have wide-ranging effects. Modeling approaches can shed some light on the temperature dependencies of biophysical processes, such as neuronal excitability, which in turn affect behavior and have implications for organismal resilience.

While sensory inputs themselves do not have as direct an impact on biophysical processes as temperature, they can have profound effects on neural and behavioral processes because they provide information on environmental conditions. Behavioral changes can lead animals to explore new environments or to become displaced from their habitation zones, thus encountering environmental changes that can affect fundamental biochemical processes - creating a closed loop of impacts. For example, the circadian clock circuit is impacted by sensory inputs, yet it drives many biochemical processes involved in sleep and metabolism. As another example, changes in butterfly migration from light pollution may lead them to encounter new environments that may or may not be favorable to their physiological needs. Similarly, neural systems may develop novel adaptive mechanisms to maintain fitness in new habitation zones, as demonstrated by the reproductive interference in Aedes species.

There is considerable opportunity going forward to investigate mechanisms that confer neural resilience in the face of rapid anthropogenic environmental change. By understanding how neural systems respond and adapt to environmental challenges, new avenues for scientific inquiry can emerge, leading to novel discoveries and scientific impact. This essential field of research holds vast potential to advance our understanding of adaptive neural mechanisms, uncover evolutionary adaptations, and inform strategies for mitigating or adapting to the negative consequences of anthropogenic environmental changes.

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