© 2024. Published by The Company of Biologists Ltd | Journal of Experimental Biology (2024) 227, jeb246215. doi:10.1242/jeb.246215

REVIEW

SPECIAL ISSUE

DEVELOPMENTAL PLASTICITY: FROM MECHANISMS TO EVOLUTIONARY PROCESSES

Experimental biology can inform our understanding of food insecurity

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ABSTRACT

Food insecurity is a major public health issue. Millions of households worldwide have intermittent and unpredictable access to food and this experience is associated with greater risk for a host of negative health outcomes. While food insecurity is a contemporary concern, we can understand its effects better if we acknowledge that there are ancient biological programs that evolved to respond to the experience of food scarcity and uncertainty, and they may be particularly sensitive to food insecurity during development. Support for this conjecture comes from common findings in several recent animal studies that have modeled insecurity by manipulating predictability of food access in various ways. Using different experimental paradigms in different species, these studies have shown that experience of insecure access to food can lead to changes in weight, motivation and cognition. Some of these studies account for changes in weight through changes in metabolism, while others observe increases in feeding and motivation to work for food. It has been proposed that weight gain is an adaptive response to the experience of food insecurity as 'insurance' in an uncertain future, while changes in motivation and cognition may reflect strategic adjustments in foraging behavior. Animal studies also offer the opportunity to make in-depth controlled studies of mechanisms and behavior. So far, there is evidence that the experience of food insecurity can impact metabolic efficiency, reproductive capacity and dopamine neuron synapses. Further work on behavior, the central and peripheral nervous system, the gut and liver, along with variation in age of exposure, will be needed to better understand the full body impacts of food insecurity at different stages of development.

KEY WORDS: Food insecurity, Uncertainty, Metabolism, Stress, Cognition, Adaptive

Introduction

Studies of developmental plasticity have the potential to inform one of the most important and complex issues faced by modern society: food insecurity. Food insecurity can roughly be defined as the lack of predictable access to nutritionally adequate food. The pattern of eating experienced by people facing food insecurity is characterized by greater temporal variability in food intake in the absence of chronic starvation. Food insecurity also commonly involves a lower quality or less diverse diet, characterized by lower intake of fiber and protein and higher intake of carbohydrates (Nettle and Bateson, 2019; Shinwell et al., 2021). Importantly, the experience of food insecurity, in terms of volatility, uncertainty and intermittent access, may have very different effects on development and plasticity when compared with sustained malnutrition and starvation. Currently, millions of children worldwide experience food insecurity (FAO et al., 2021), and the prevalence of food insecurity is predicted to worsen with international conflict, inflation, increasing wealth inequality and climate change. Given that there are limited resources to combat food insecurity, and the fact that well-intentioned government or charitable programs may not always realize their intended benefits, it is urgent to understand how and when food insecurity has its most severe impacts on human development.

A substantial body of epidemiological studies clearly demonstrate that food insecurity is linked to poor mental health, educational performance, metabolic health and cardiovascular health (Aurino et al., 2019, 2020; Burke, et al., 2016; Laraia, 2013; Liu and Eicher-Miller, 2021; Myers, 2020; Shankar et al., 2017). Notably, experience of food insecurity appears to promote obesity, which further negatively impacts health (Carvajal-Aldaz et al., 2022; Laraia, 2013). Developmental experience of food insecurity, from gestation through adolescence, may be especially detrimental because of effects on the developing body and brain (Argaw et al., 2023; Aurino et al., 2019, 2020; Dennison et al., 2019; Falconi et al., 2014; Ravelli, 1976).

Despite the large number of people affected and clear links to a wide-range of negative outcomes, research on the impacts of food insecurity on biological processes has not been well integrated across fields. In the biomedical sciences, we currently have little understanding of the pathways and mechanisms that link irregular, unpredictable food access to long-lasting risk of pathology and disease. Experimental studies in animals informed by a behavioral neuroscience, experimental biology and developmental plasticity perspective can help fill this gap.

Experimental biologists working across a wide variety of taxa have found that access to food plays a major regulatory role in developmental biology and life history. For example, it is well known that seasonal access to food sources has sculpted the timing of reproduction in many species. Also, year to year (or even day to day) food abundance may vary. To adjust for this variability, individual development may be guided by food-related information to enhance survival and reproduction in current environmental conditions (Davies et al., 2015; Selonen et al., 2016; Seward, et al., 2014; Sun et al., 2020; Zysling et al., 2009). For example, bulb mites that develop with scarce resources develop a scrambler phenotype that is smaller than the fighter phenotype that can be expressed when they have access to more resources (Smallegange et al., 2012; Stewart et al., 2018). Not all phenotypic differences are

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visible to the naked eye. For example, in fish, it has been shown that resource availability can also lead to changes in metabolic rate and the behavioral niche they occupy in their ecosystem (Auer et al., 2015, 2020). Thus, through changes in the body and brain, access to food can program phenotypic development through developmental plasticity mechanisms.

While these ideas are 'bread and butter' to those working in the tradition of experimental biology, they are not often enough used to inform neuroscience or the biomedical sciences applied to public health. Despite the fact that there have been extensive studies of acute food restriction and malnutrition, less attention has been paid to the possibly unique effects of volatile and unpredictable access to food that occurs with food insecurity. Because food insecurity disproportionately impacts vulnerable and marginalized groups in humans, it potentially serves to perpetuate social inequity and health disparities. The prevalence of food insecurity, in part, can rise and fall as a result of world events as well as social and economic policies (i.e. changes in inflation and changes in feeding program benefits; for example, the Supplemental Nutritional Assistance Program, SNAP, in the USA; Whiteman, et al., 2018). Deeper and more comprehensive understanding of both the short-term and lasting effects of food insecurity on behavior and biological systems can inform the design and management of food-related policy, ultimately to make people and nations healthier.

To this end, here we explore the growing literature on the experimental biology of food insecurity in birds and rodents and discuss how emerging studies from a range of animals and concepts from evolutionary biology may inform public health and medicine.

Food insecurity, weight gain and feeding

Studies of food insecurity and weight in birds

Experimental biologists working with songbirds have been pioneers in studying the impact of food access on brain and behavioral development. Over the past several decades, a series of experimental studies have manipulated developmental nutrition and observed effects on the oscine song system and song production (Nowicki, et al., 2002; Zann and Cash, 2008). From these studies emerged the 'nutritional stress hypothesis', which suggests that aspects of song (the specifics of which are still debated) can serve as an indicator of the quality of the rearing environment, which can inform sexual selection (Peters et al., 2014; Spencer and MacDougall-Shackleton, 2011).

More recently, researchers working with songbirds have begun to explicitly model food insecurity, in protocols that manipulate variability or predictability in the food supply independently from chronic restriction, and then measure the impact on feeding and body weight. These outcome metrics were chosen to test the role food insecurity may play in weight gain and obesity in modern day humans. It is appropriate to look at songbirds to learn about humans because there are potentially ancient and evolutionarily adaptive strategies that we have in common, that have only recently become maladaptive in modern humans with the advent of the modern food environment (Bateson and Pepper, 2023). Importantly, these studies have found that both early life and adult experience of food insecurity can impact weight and metabolism.

A series of studies from different labs using European starlings (*Sturnus vulgaris*) established a strong link between insecure access to food and weight gain (Table 1). Bauer et al. (2011) found that adult, wild-captured starlings housed in sheltered aviaries gained more weight than controls if they had food access removed for 4 h a day for 3 weeks. Andrews et al. (2015) showed that starlings that experienced higher early life competition for food in the nest (post-hatching day 2–12), a 'developmentally disadvantaged group', exhibited greater body weight and ate more after food deprivation in adulthood (10–13 months) than a 'developmentally advantaged' group of starlings. In a later study, Andrews et al. (2021) showed that juvenile starlings (4–5 months) that experienced unpredictable access to food for 5 h periods, 5 days a week for 19 weeks were heavier, had greater energy reserves compared with controls, but regrew their feathers more slowly, and had shorter telomeres than controls. Finally, Bateson et al. (2021) found that adult starlings provided limited and unpredictable daily access to food for 1–2 weeks gained weight, despite eating less. Exposure to this food insecurity protocol reduced energy density excreted in guano, suggesting that birds that experienced insecurity were quickly able to extract more calories from their food. This effect lasted weeks after food security was restored. Together, these studies illustrated that unreliable access to food affected weight gain or fat reserves during both developmental and adult periods, and these effects were sustained even when food security had been restored. As all the paradigms differed, it is not possible yet to say whether there was a sensitive period in development where effects were strongest, but importantly the data show that in development and in adulthood, a period of only ∼2 weeks exposure to food insecurity was sufficient to produce detectable differences.

While Bauer et al. (2011) considered lack of access to food a 'stressor', they found it did not increase the stress hormone corticosterone (CORT) in these birds in the manner induced by more anthropogenic stressors and in some cases insecure access to food reduced CORT levels compared with control conditions with *ad libitum* secure access.

Experimental studies such as these as well as studies in human subjects have led to 'the insurance hypothesis' posed by Nettle et al. (2017) (see also Higginson and McNamara, 2016, and a recent review by Bateson and Pepper, 2023). The insurance hypothesis states that experience of food insecurity alters feeding behavior and energy expenditure to adjust fat reserves as insurance against further food scarcity in the future. While additional body fat reduces the probability of starvation, it must come at a cost. The cost could arise from the reduced maneuverability of a larger body, or reduced investment in somatic maintenance and repair due to energy being diverted into fat stores. As noted above, Andrews et al. (2021) reported that food insecurity in starlings led to increased body fat, slower feather regrowth and shorter telomeres, supporting the latter hypothesis.

Studies of food insecurity, weight and feeding in rodents

Further experimental support for the insurance hypothesis comes from studies of food insecurity in rodents (Table 1). In both rats and mice, experience of insecure access to food has been found to enhance weight gain. Myers et al. (2022) fed two groups of adult female Sprague–Dawley rats the same amount of total daily food but with different predictability throughout the day. One group received unpredictable fractions of this total daily amount at different phases of the day (insecure group) while the other group always received a stable and therefore predictable fraction at each phase (secure group). Once the feeding manipulation was over, rats in the insecure group gained more weight than their secure controls when they had *ad libitum* access to high-fat, high-sugar food or even *ad libitum* chow. Using mice, Lin et al. (2022) modeled transient food insecurity in both males and females (C57Bl/6N) during juvenile/adolescent development. They compared three treatments: *ad libitum* access to food (AL), stable but restricted access to food (FR) and variable and restricted (insecure) access to food (FI) in

Table 1. Food insecurity studies in animal models

Feeding manipulation	Details of feeding diet	Species/strain	Sex	Age	Physiology, feeding, etc.	Cognitive/motivated behavior	Reference
Insecure disadvantaged: cross-fostered in the smallest nestling in the brood size hierarchy. Controls advantaged: cross-fostered in the largest nestling in the brood size hierarchy.	Food provided: mixture of domestic chick crumb supplemented with cat biscuits, dried insect food, live mealworms and fruit.	European starlings (*Sturnus vulgaris*)	M/F	Post-hatching day 2–12; testing in adults 10–13 months old	Weight ↑, food consumption ↑ following food deprivation, foraged rate ↑ on freely available food.	Time gathering information ↑ in contrafreeloading.	Andrews et al., 2015
Insecure: food removed for 5 h randomly during light cycle, 5 days a week (19 weeks). Controls: food available *ad lib.*	Food provided: mixture of dry cat food, chick crumb and insect mix.	European starlings (*Sturnus vulgaris*)	M/F	Juveniles	Weight ↑, fat scores ↑, feather regrowth ↓, erythrocyte telomere length ↓, food consumption ↔.		Andrews et al., 2021
Predictable: food removed for 4 h at 5 h after lights on. Unpredictable (insecure): food removed for 4 h alternating randomly between 1, 3, 5 or 7 h after lights on (20 days). Controls: baseline *ad lib.* feeding period (7 days).	Food provided: 18% protein diet.	European starlings (*Sturnus vulgaris*)	M/F	Not specified	Baseline and stress-induced CORT concentration (in non-molting birds) ↔, frequency of maintenance (beak wipe) ↑↓, feeding behavior ↑↓, heart rate ↑.		Bauer et al., 2011
Insecure: food removed for randomly chosen 12 out of 20 continuous 20 min periods (1 or 2 weeks); one cohort induced via an operant schedule with probability of 0.4, and 0.2 food availability (2 weeks). Controls: baseline *ad lib.* feeding period (1 week).	Food provided: nutritionally complete commercial poultry starter crumb.	European starlings (*Sturnus vulgaris*)	M/F	~4 or 6 years	Weight ↑, energetic efficiency ↑, food consumption ↓, energy density of guano ↓.		Bateson et al., 2021
Insecure: one of the 4 feeding times was omitted; 75% or 125% of the total amount of food delivered on different days (8 days, 26 days or 12 weeks). Controls (secure): constant amount of food at 4 feeding times each day (8 days, 26 days or 12 weeks).	Insecure: Chow: 75%: 1 omitted+3×3.8 g; 125%: 1 omitted+3×3×6.4 g HFHS: 75%: 1 omitted+3×2.8 g; 125%: 1+3×4.6 g Controls (secure): Chow: 4×3.8 g HFHS: 4×2.8 g Total food per 4 days: 206 kcal in both diets (see original paper).	Sprague–Dawley rats	F	Adult starting postnatal day (P)60–64.	Later palatable food consumption ↑, weight ↑.	Activity level ↑, progressive ratio breakpoints for sucrose ↑, memory in object recognition ↔.	Myers et al., 2022
Plenty–hard: *ad lib.* at each feeding, 36 min of begging per day, half of nest visits unfed. Lean–hard: 73% of *ad lib.* at each feeding, 36 min of begging per day, half of nest visits unfed. Plenty–easy: *ad lib.* at each feeding, 18 min of begging per day, all nest visits fed. Lean–easy: 73% of *ad lib.* at each feeding, 18 min of begging per day, all nest visits fed.	Cat biscuit, domestic chick crumb, fruit.	European starlings (*Sturnus vulgaris)*	M/F	Wild-caught nestling, feeding manipulation day 6–15 then feeding comparable.	Hard versus easy: hard lighter than easy in adulthood. Plenty versus lean: no effect on weight in adulthood.	Hard versus easy: hard ↑ motivation and negative contrast effects after loss. Plenty versus lean: lean decreased positive contrast effect after gain.	Neville et al., 2017
Restriction (FR): constant restricted amount (50:50% day1:day2 ratio of baseline per 2 days) delivered at the same time each day (20 days). Insecure (FI): variable amount (100:0%, 90:10%, 80:20% day1:day2 ratio of baseline per 2 days) delivered at the same time each day (20 days). Controls (AL): always *ad lib.*	Food provided: 18% protein rodent diet, 3.1 kcal g^{-1} (see original paper).	C57Bl/6N mice (from Taconic Biosciences)	M/F	P21–40; testing in adults over P60.	Weight in FI adult females ↑, weight in adult males ↔, later palatable food consumption ↔.	FI adult males' flexibility in odor-cue reversal learning ↓, flexibility in 2ABT (with 75% and 65%, not 90% reward probability) ↑, FR males showed intermediate performance in odor-cue reversal learning, flexibility in adult females ↔.	Lin et al., 2022
Insecure: variable amounts (50%, 75%, 125%, 150% of baseline) of food 4 days a week (4 weeks). Controls: always *ad lib.*	Food provided: 18% protein rodent diet, 3.1 kcal g^{-1}	CD-1 mice (from Charles River)	F	18 months	Food consumption during manipulation ↓, later high-fat food consumption ↑.	Active escaping behaviors in the forced swim test ↑, exploratory behavior in the elevated plus maze and light dark box ↔, memory in object recognition ↓.	Estacio et al., 2021

Arrows represent effects of feeding manipulation on physiological/feeding or cognitive/motivated behaviors compared with controls (↑: increased, ↓: decreased, ↑↓: altered, increased/decreased, ↔: no change). 2ABT, two arm bandit task (see text).

Journal of Experimental Biology (2024) 227, jeb246215. doi:10.1242/jeb.246215

development from postnatal day (P)21 to P40. They then measured weight gain from P40 into adulthood P150, a period when all groups were matched with *ad libitum* access to chow. They found that in female mice, treatment affected weight gain trajectories such that the FI treatment group became significantly heavier than the AL group, with the FR group intermediate in their adulthood. Male weight gain was not affected by AL, FI or FR treatment. Estacio et al. (2021) also studied effects of food insecurity on weight in adult female mice, but found no effect of insecure access to food on weight. This difference with Lin et al.'s (2022) study of mice could be explained by feeding paradigm differences, age of exposure or differences between strains of mice. Estacio et al. (2021) focused on aging mice, and therefore used 18 month old female mice in the CD-1 line and exposed them to a variable percentage of *ad libitum* consumed food on a 4 day schedule (50%, 75%, 125%, 150%) that was intermittent with full *ad libitum* access to food for 4 weeks. An always *ad libitum* feeding group was used as a control. With this paradigm, weight was comparable in the control secure versus insecure group.

Based on work in starlings, it is of interest to know whether weight gain in rodents that experienced food insecurity was the product of changes in eating or metabolism. Myers et al. (2022) and Estacio et al. (2021) found that experience of insecurity enhanced consumption of palatable foods in rodents. Myers et al. (2022) also reported that during the time of the ongoing manipulation, the insecure rats showed hyperactivity and greater motivation to work for palatable food in a progressive ratio test. Importantly, Myers et al. (2022) noted that the predictability of access to a high-fat/high-sugar diet influenced the performance of the animals on this motivation task over time. Rats with consistent, reliable access to a highly palatable fat/sugar diet eventually exhibited a predictable decline in motivation, as if 'junk food' had become less rewarding, while rats maintained on the same diet on an insecure access schedule maintained an elevated state of motivation for palatable foods. Together, these observations in adult mice and rats have implications for understanding how food insecurity interacts with motivational factors in food choice, both quantity and quality of diet (e.g. Keenan, et al., 2021; Leung et al., 2014).

Interestingly, Lin et al. (2022) found that there were few-to-no effects of developmental experience of food insecurity on palatable food consumption in adult male or female mice despite differences in weight in treatment groups in females. Future work on metabolic measures in rodents in both development and adulthood, during and after food insecurity will help inform questions of mechanism underlying weight gain after food insecurity. Cross-comparison of paradigms, strains and species will also be needed to help isolate critical variables leading to weight and/or feeding changes.

Food insecurity, affective behavior, learning and cognition

In humans, experience of food insecurity is associated with greater risk for mental illness, substance abuse and worse performance in school (Aurino et al., 2019, 2020; Laraia, 2013; Turner et al., 2022). It is hard to control for the multitude of variables that can contribute to these issues in humans, and causality is not simple to infer, as psychopathology and substance abuse may further perpetuate food insecurity. Therefore, animal models can help us evaluate the importance and the direct causal impact of food and feeding programs on emotional and cognitive health. The effects of food insecurity in affective and cognitive behavior may also be best understood in light of evolutionary biology. For example, access to nutrition or signals about food scarcity and uncertainty may have guided organisms to express brain and behavioral phenotypes that enhance survival in scarce or uncertain environments (Lin et al., 2020). These phenotypes could alter the need for calories (i.e. through body size or activity level), strategies for foraging (i.e. through effects on learning and decision making), or reproduction (which we address in the next section).

Studies of affective and addiction related behavior

In laboratory rodent studies, researchers have developed methods to study anxiety- and depression-like behaviors (often related to escape behaviors in assays sensitive to pharmacology with utility in humans). Estacio et al. (2021) used two of these methods, elevated plus maze and light dark box, in aged female CD-1 mice, and found no effects of food insecurity on these metrics. Neville at al. (2017) found that starlings raised with a low food amount and high effort in early life showed both an enhanced negative contrast effect following a reduction in reward value (more 'disappointment') and a reduced positive contrast effect following an increase in reward value (a lack of 'elation') characteristic of depression. Related to reward, there are rodent tasks/tests that are relevant to addiction, such as compulsive drug seeking and taking, but again there have not to our knowledge been published accounts of studies that included drugs with abuse potential in rodents that specifically experienced food insecurity. As noted above, Myers et al. (2022) found that adult rats that experienced insecure access to food showed higher progressive ratio break points than secure rats when working to gain access to palatable food. They were also hyperactive. These findings together with Neville et al. (2017) suggest that insecure access to food impacts motivational systems. Future studies of food insecurity investigating anxiety, and depression-like and addiction-related behavior as well as more ethologically inspired motivated behaviors will be of great interest.

Studies of cognitive function

In starlings, experience of food insecurity did not impact multiple tests of cognition (Nettle et al., 2015). However, in rodent studies, experience of food insecurity has been shown to have lasting impacts on cognitive function, but not all studies reveal deficits. Indeed, some changes may reflect strengths that may support different strategies for foraging, a putative predictive adaptive response to food insecurity (Lin et al., 2022). Estacio et al. (2021) found that food insecurity negatively impacted novel object memory in aged female mice. In contrast, Myers et al. (2022) found no significant impact of insecure access to food on novel object memory in younger adult female rats; however, that study also described it as a relatively simple task with low cognitive load, and recommended further study with more cognitively demanding tasks.

Lin et al. (2022) used tests of cognitive function that focused on learning and flexibility in decision making in mice. They found that prior developmental experience of FI, FR or AL treatment had no impact on odor cue discrimination learning in either adult male or female mice in an operant 'digging task' motivated by food rewards. However, when they measured reversal learning in the same odor cue task in males, the insecure FI group showed significantly less flexible reversal than the secure AL group. In females, prior feeding treatment had no significant effect on reversal performance. These data suggest experience of food insecurity can have lasting negative impacts on cognitive flexibility (4 weeks after food insecurity is over), but only in male mice. These experimental findings from developing mice could help inform our understanding of effects of food security on children's cognitive function. They are consistent with studies that show that even transient experience of food insecurity in middle childhood and adolescence can impact

children's academic performance, numeracy, short-term memory and self-regulation (Aurino et al., 2019, 2020).

However, we should be careful to not jump to the conclusion that experience of food insecurity is always either detrimental or neutral to cognition. In another test of flexibility in decision making, Lin et al. (2022) measured switching behavior in a value-guided two arm bandit choice task (2ABT) motivated by water rewards. In this task, the probability of getting a reward when choosing the correct side was probabilistic. In phase 1, the probability was 75%, and this was shifted to 90% for phase 2, and then back down to 65% for phase 3 over a series of daily sessions. In this switching task, Lin et al. (2022) found flexibility differed between secure and insecure groups but in the opposite direction, as seen in the odor cue reversal task. In the 2ABT, adult males with FI treatment were now significantly more flexible than AL males. Again, females showed no effect of treatment on performance. Deeper analysis of this behavior revealed that males with insecure feeding history only performed better than males with secure feeding history when there was 75% or 65% but not 90% uncertainty in the task (phases with different reward probability). Lin et al. (2022) postulated that a more uncertain environment gates flexibility in mice with a history of food insecurity and that this might represent a 'predictive adaptive response' (PAR). This idea was supported by work in human subjects that found acute priming for uncertainty enhanced flexibility in human subjects who had experienced more uncertain environments in their past (Mittal et al., 2015). In this way, flexibility may be gated such that it emerges in environments that 'match' the more uncertain developmental environment. By this same logic, organisms that are adapted for uncertainty may face a 'mismatch' between their environment and their phenotypic strategy if the environment becomes more stable when they are developmentally mature and no longer plastic.

Placing food insecurity in the broader context of nutrition, adversity and life history

More work will be needed to examine how food insecurity in animals fits into the broader context of theory and data that examines human and animal undernutrition, experience of adversity, and life history. These established traditions and ideas are all relevant to studies of food insecurity, but the food insecurity data, so far, do not yet fit easily into the frameworks as they have been established.

For example, it is easy to see there may be connections between food insecurity and the insurance hypothesis discussed above and the 'thrifty phenotype' hypothesis (Hales and Barker, 1992, 2001), but there are important differences. The thrifty phenotype hypothesis proposes that early life undernutrition causes metabolic shifts that lead to subsequent type II diabetes. While food insecurity and undernutrition both include food scarcity, there are likely to be important mechanistic differences between the effects of early food insecurity and those described in the thrifty phenotype model. First, the thrifty phenotype hypothesis was concerned chiefly with prenatal undernutrition, whereas animal models of food insecurity reveal effects when introduced to hatchling birds (Andrews, et al., 2015), juvenile/adolescent animals (Andrews, et al., 2021; Lin et al., 2022), and adult (Myers, et al., 2022) and aged rodents (Estacio et al., 2021). However, no animal studies have yet tested across infant, juvenile and adult food insecurity within the same paradigm, and considerable future work will be necessary to identify developmental sensitive periods for specific physiological and behavioral effects of insecurity. Second, the thrifty phenotype effect describes nutritional inadequacy, whereas insecurity is characterized by an unpredictable, volatile pattern of food availability across time, and may not necessarily be accompanied by chronic undernutrition. In fact, the vast majority of children under 4 years old in food insecure households in the US are not stunted or underweight (Drennen et al., 2019), and total daily energy of food insecure children matches that of food secure children, despite inherent day-to-day variability (Jun et al., 2021). Further, the thrifty phenotype model chiefly focused on alterations in glucose homeostasis, especially insulin secretion and insulin resistance. Food insecurity may also act on energy homeostasis directly but, additionally appears to have a number of effects on CNS circuits mediating reward processing, motivation and cognition (as detailed in the preceding paragraphs). Thus, food insecurity may be best understood not as a response to inadequate nutrition but more broadly as a response to an uncertain or stressful environment. Making this distinction more clearly may help us to design studies which can isolate critical overlapping versus separate mechanisms.

Another relevant framework coming from public health is the Adverse Childhood Experience (ACE) framework. The ACE framework is focused on the negative impacts of developmental adversity. Originally described by Felitti et al. (1998), the ACE framework proposes that early experiences of abuse, neglect and household dysfunction alter neuroendocrine development in ways that impact cognition, emotions and decision making, in turn increasing the propensity to engage in health-damaging behaviors. The ensuing ACE literature has clearly documented robust relationships in human development between the number and degree of certain adverse events in early life and subsequent psychopathology and poor health outcomes in adulthood (for reviews, see Hughes et al., 2017; Nelson et al., 2020). Though correlational, these findings are tacitly interpreted as support for a causal model with chronic activation of the HPA axis as the linchpin in altered brain development, eventually resulting in permanently dysregulated neurobehavioral responses to future stressors, promoting weight gain and other factors linked to poor health.

Neither food insecurity nor poor nutritional status was included in the original operationalization of ACEs (Felitti et al., 1998) and the measures most commonly used in the descriptive and epidemiological research on ACEs either do not include food insecurity (such as the ACE Module of the Behavioral Risk Factors Surveillance Survey; Swedo et al., 2023) or do not differentiate insufficient food from other forms of physical neglect (e.g. ACE-10; Dube et al., 2001; Finkelhor et al., 2013). Adding questions about food insecurity and other forms of adversity in addition to the original set of ACE variables has been shown to increase predictive power for some health behaviors (e.g. Mersky et al., 2017) but the causal implications are unclear. As food insecurity is more likely to be present in households affected by more severe levels of dysfunction (Jackson et al., 2019), and people who experience a wider range of major stressors are more likely to also be food insecure (Temple, 2018), the putative causal relationships between childhood insecurity, stress and health in adulthood are far from straightforward.

Like food scarcity and ACE accumulation, food insecurity may also program life history trajectory. Cues about uncertain access to food early in life may be a warning signal for risks of future starvation or even for greater extremes of resource depletion and hazardous environment that threaten survival. One popular idea is that these signals should then promote animals to enact fast life history strategies, such as early maturation, accelerated reproduction and less parenting of offspring (Ellis et al., 2009; Giudice et al., 2015).

Studies in humans found that an unpredictable environment between 0 and 5 years (but not 6–16 years) was a stronger predictor of sexual and risky behavior at age 23, putatively a faster life history strategy (Simpson et al., 2012). Research using another form of insecure and unpredictable environment in attachment early in life found that insecure infants began and completed their pubertal development earlier and had a younger age of menarche compared with secure infants (Belsky et al., 2010).

However, links between unpredictability specifically in terms of access to food and accelerated life history are not clear. It is true that greater weight gain after food insecurity may mechanistically lead to earlier puberty, which could support earlier reproduction (Chehab et al., 1997). However, it is possible that, if food resources are too low, animals may not be able to invest in reproduction and delays may be observed. Experimental studies in birds and rodents have found that different levels of food availability can have varied effects on reproductive success and parameters such as body mass, gonad/testis size, puberty onset, etc. (briefly summarized in Prabhat et al., 2023). In zebra finches, time-restricted feeding was found to increase total latency to build new nests and latency of first egg laying, and to reduce the clutch size and reproductive hormones (testosterone in males, estradiol in females) in plasma compared with *ad libitum* feeding controls (Prabhat et al., 2023). Similarly, adult male *Melozone aberti* that experienced food restriction for 2 or 4 weeks showed reduced plasma testosterone and luteinizing hormone levels (Davies et al., 2015) that would presumably depress reproduction.

It is also possible that a fast life history strategy may not be adaptive for all species when facing food insecurity or other forms of adversity (Rakesh et al., 2023). Sex differences too may lead to different selective pressures. Therefore, it is difficult to predict *a priori* how developmental food insecurity might impact life history in specific contexts. Given these questions, future studies of developmental food insecurity in animals would benefit from inclusion of metrics of puberty, tests of reproductive competence and frameworks of life history.

Possible mechanisms by which food insecurity may impact the brain and body

Experimental studies in animals are also valuable because they enable high resolution study of mechanisms. Studies of the brain and body in birds and rodents have begun to illuminate how and when food insecurity can impact the body and brain at the cellular level (Fig. 1).

Weight gain and accumulated fat send signals that inform and program developing neural systems

It is known that in mammals, the complex process of neural development of the metabolic system occurs perinatally and postnatally, is dependent on nutrient availability, and sets the tone for how an animal will behave and function in later life (McCance, 1962). Body nutrient availability is communicated to the brain by the circulating fat hormone leptin, while nutrient paucity is communicated by the gut-secreted hormone ghrelin. Leptin is secreted proportionally to fat amount, and leptin circulating during the first weeks postnatally is essential for the formation and programming of the primary metabolic circuitry of the hypothalamus (Ahima et al., 1998; Bouret and Simerly, 2006). This hypothalamic circuitry is formed during postnatal day (P)4–16, making this a critical period in the development of the neuroendocrine system. After P28, the primary role of leptin is to signal nutrient abundance, which it does through its access to hypothalamic and brainstem neurons. These regions have leaky blood–brain barriers and contain populations of neurons known to be involved in metabolic homeostasis that can impact body weight and reproductive status.

The hypothalamic arcuate nucleus (ARC) (Fig. 1) contains two melanocortinergic populations of cells that respond to leptin in opposite ways: (1) those that produce pro-opiomelanocortin (POMC)-derived alpha melanocyte stimulating hormone (αMSH), a melanocortin receptor agonist that leads to reduced food intake and increased energy expenditure in response to leptin activation; and (2) those that produce the melanocortin antagonist Agouti-related protein (AgRP), which drive hyperphagia and anabolic metabolism, but are inhibited by circulating leptin. These structures begin to develop in fetal life, mature postnatally, and are impacted by metabolic and sex hormones (Ahima et al., 1998; Sheng et al., 2021). These metabolic neuronal circuits are not functional until 2 weeks postnatally and, within the hypothalamus, are not fully formed until 4 weeks (Bouret et al., 2004). Disruption of these circuits is associated with obesity and metabolic disease in animal models. Rodent pups raised with reduced nutrition have a decreased density of feeding neuron fibers in the hypothalamus and decreased inhibitory tone, leading to elevated food intake and body weight later in life (De Solis et al., 2016). Humans and animals that lack leptin or its receptor are obese (Zhang et al., 1994). In animals congenitally lacking leptin, exogenous leptin given prior to P28 rescues the metabolic phenotype and the density of hypothalamic metabolic projections (Kamitakahara et al., 2018). This supports the idea that the development and plasticity of the melanocortinergic circuitry in response to leptin may be responsible for appropriate homeostatic function.

These hypothalamic systems are also impacted by the ‘hunger’ hormone, ghrelin, which is secreted by the stomach in the setting of low nutrient availability. Like leptin, ghrelin levels are altered by neonatal nutritional states; overabundance of nutrients in early postnatal life leads to lower levels of ghrelin (Collden et al., 2014). Unlike leptin, ghrelin is not necessary for metabolic circuit development (Sun et al., 2003), but it does participate in driving adaptive outcomes. Blockade of ghrelin action in early post-natal life leads to overgrowth of the AgRP and POMC neuronal projections to the paraventricular hypothalamus, and is associated with elevated food intake, hyperglycemia and increased fat mass in adult mice (Steculorum et al., 2015). Thus, in early post-natal life, ghrelin acts opposite to leptin to inhibit growth of metabolic circuitry. Receptors for ghrelin are found on the melanocortinergic neurons in the ARC as early as P6, and in adulthood the response pattern is similarly opposite to that of leptin. In states of hunger, ghrelin, through binding the ghrelin receptor, leads to activation of AgRP neurons and motivated food-anticipatory behavior (Blum et al., 2009; Mani et al., 2017; Verhagen et al., 2011). The modulating effect of ghrelin on POMC neurons is less well understood (Chen et al., 2017; Schaeffer et al., 2013), and probably unrelated to leptin.

In addition to ghrelin and leptin, other metabolic hormones which are involved in nutrient use and storage are likely to be important in driving the coordinated response to food insecurity. For example, in humans who experience food insecurity, the intestine-derived hormone glucagon like peptide 1 (GLP-1) is reduced, and people show a preference toward carbohydrate metabolism for energy production (Booker et al., 2022). These dynamics will be important to interrogate in animal models, and are likely to be relevant to understanding the physiological impact of food insecurity over time.

Journal of Experimental Biology (2024) 227, jeb246215. doi:10.1242/jeb.246215

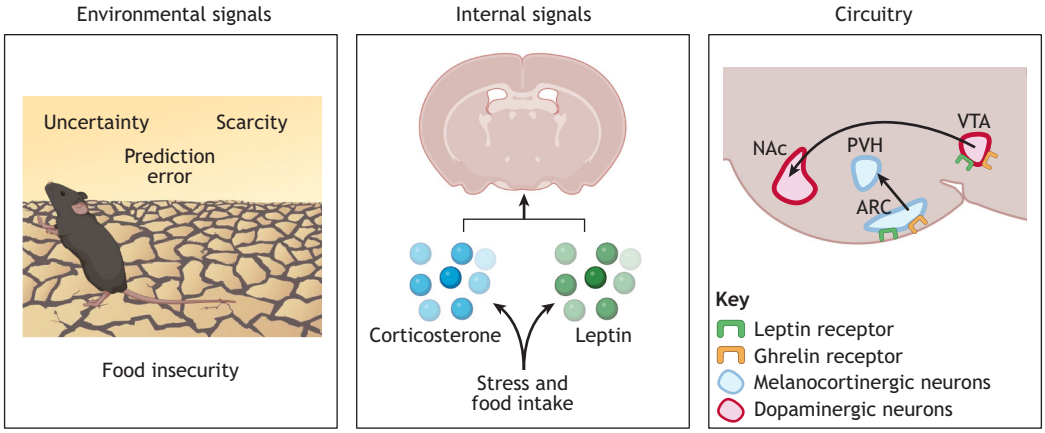

Fig. 1. Mechanisms by which experience of food insecurity impacts the brain. Environmental signals: an animal (once independent from parental care) can detect scarcity and uncertainty in the feeding environment by monitoring its foraging success. We posit that prediction errors in the dopamine system are likely to be larger and more frequent in animals experiencing food insecurity than in their more securely fed conspecifics (Lin et al., 2020). For younger animals (not shown) parental care quantity and quality may also reflect external conditions. Internal signals: the brain also receives input about stressors from corticosterone released from the adrenal glands and body condition through leptin signaling from adipose tissue. These signals may contribute to programming homeostatic systems in the brain which may be particularly sensitive to these changes during development. Circuitry: zooming in on the ventral portion of the brain, which has access to the circulating hormones, shows circuits that are implicated in the behavior and physiological outcomes of food insecurity. These include the ventral tegmental area (VTA) dopamine neurons, which send projections to the ventral striatum nucleus accumbens (NAc), and the hypothalamic arcuate nucleus (ARC) melanocortin neurons, which project to the paraventricular nucleus (PVH). The schematic diagram shows that leptin and ghrelin receptors are present in these systems, and studies of food insecurity and food scarcity have shown dysfunctional signals within them. These hypothalamus circuits may be particularly sensitive to food-related signals during gestation and the perinatal period, and striatal-dopamine circuits may be sensitive during the late juvenile/early adolescent period. By changing how these neurons function, experience of food insecurity can impact metabolic homeostasis and a wide range of behaviors. Figure made using BioRender.

Impacts of food insecurity on the HPA axis are not clear-cut

Another mechanism by which food insecurity may impact physiological and neural function is through the hypothalamic-pituitary–adrenal (HPA) axis. One might equate food insecurity with stress and therefore expect that it would lead to elevated CORT levels, as is promoted by the ACE framework. In humans, there is some limited evidence that early life experience of food insecurity is linked to contemporaneously elevated glucocorticoids (Ling et al., 2019; Tarullo et al., 2020). However, another study (Distel et al., 2019) found elevated cortisol only in higher body mass index (BMI) food insecure children, suggesting insecurity does not act alone to affect metabolism or behavior, but instead works in conjunction with other events that elevate cortisol. In animals, there is conflicting evidence to date that supports this link. Chickadees exposed to limited and unpredictable food showed elevated CORT compared with *ad libitum* fed controls (Pravosudov et al., 2001). However, a study of starlings that experienced insecure access to food did not detect significant increases in CORT (at baseline or in response to a stressor) compared with more securely fed starlings (Bauer et al., 2011). This was in contrast to elevated levels seen in starlings that had been exposed to other more classic, threatening stressors (Bauer et al., 2011). In rodents, specific studies of food insecurity and CORT have not been done to our knowledge, but we can look to studies of nutrient content and scarcity. Protein restriction (Martins, et al., 2023) and reduced maternal nutrition (Vieau et al., 2007) in rat dams have been found to program the HPA axis in offspring but in opposite directions. Further study will therefore be needed to test whether food insecurity in development or adulthood has significant impacts on the HPA axis, and whether it is at all similar to the outcomes of changes in nutrient content or amount, which is different from food insecurity. It is possible that the HPA axis or neuroendocrine axis may cause aberrant metabolic circuitry and physiological change through indirect effects on metabolic circuits. Stress-related food intake change is mediated by ghrelin (Chuang et al., 2011), potentially through an interaction between ghrelin and the HPA axis (Spencer et al., 2012, 2015). In early life, these hormone interactions may impact the development of melanocortin neurons as well. In an experiment using the limited bedding and nesting paradigm of early life stress, which impacts maternal caretaking (Molet et al., 2014), AgRP projection density in the pups was found to be decreased within the paraventricular nucleus (Yam et al., 2017).

The elements of scarcity and unpredictability present in food insecurity may each represent a different form of ‘stress’ from more commonly studied stressors. In studies of adversity in child development, newer dimensional models of adversity consistently find that scarcity (i.e. deprivation) has different effects on children from the experience of threat (McLaughlin et al., 2021; Rakesh et al., 2023). Threat in these studies of adversity is more consistent with classic ‘stressors’ used in animal research, such as predator odor or shock, which activate the HPA axis. One take-home message from these large-scale studies is that threat, scarcity and uncertainty may get ‘under the skin’ via different mechanisms and therefore may have different effects. In the human data, it is unfeasible to fully separate the effects of early insecurity from other sources of adversity, so here in particular the experimental control over the timing of exposure and types of stressors in animal models may be especially useful (see Nettle et al., 2017). Animal work would enable researchers to test whether background conditions of food insecurity also act to amplify or exacerbate the effects of other early life stressors.

Dopamine neurons as a route by which food insecurity may directly impact the brain

A large body of neuroscience studies have revealed that the dopamine system can detect surprising events, such as unpredicted food or unexpected omission of food, and send signals that relay these surprises to much of the brain. These are called reward

prediction errors (Schultz, 1997; Watabe-Uchida et al., 2017). Interestingly, dopamine neurons that signal prediction errors change their activity patterns and/or firing properties under different reward probabilities, suggesting they also encode uncertainty (Starkweather et al., 2017). In human studies, experience of food insecurity is associated with overvaluation of immediate reward relative to delayed reward (Crandall et al., 2022; Epstein et al., 2014), indicating possible dopamine system involvement across species.

Dopamine neurons are, in addition, sensitive to food scarcity: they change their activity patterns and/or firing properties under sated versus hungry conditions (Branch et al., 2013; van der Plasse et al., 2015). Furthermore, dopamine neurons express ghrelin receptors, leptin receptors, melanocortin receptors, and other receptors which are sensitive to nutritional state (Abizaid et al., 2006; Abizaid, 2009; Cornejo et al., 2020; Fulton et al., 2006; Hommel et al., 2006; Kleinridders and Pothos, 2019; Lippert et al., 2014; Yoon and Baik, 2015). Studies showed that application of ghrelin stimulates dopamine release in the nucleus accumbens and dorsal striatum, and increases both ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) dopamine neural activity (Andrews et al., 2009; Jerlhag et al., 2007), while leptin inhibits VTA dopamine neural activity in brain slices (Xu et al., 2017). Ghrelin or leptin *in vivo* decreased the baseline firing rate of VTA dopamine neurons (Hommel, et al., 2006; van der Plasse, et al., 2015), whereas ghrelin but not leptin affected the VTA dopamine neuron burst firing under food restriction conditions (van der Plasse et al., 2015). Similarly, αMSH and γMSH, peptides produced by POMC neurons, can affect the activity of VTA dopamine neurons, especially promoting firing of VTA dopamine neurons that express melanocortin-3 receptors (MC3Rs) (Pandit, et al., 2016; West et al., 2019). In addition, αMSH administration in VTA is found to enhance dopamine release in the nucleus accumbens and this increase is blunted with pretreatment of a melanocortin-4 receptor (MC4R) antagonist in the VTA (Lindblom et al., 2001).

In sum, external environmental factors and a host of metabolic hormones and peptides that respond to internal nutrient availability and modulate energy metabolism have the capacity to influence dopamine neural activity and release. Also, we know that developmental manipulation of dopamine levels has downstream impacts on the striatum, its excitability and connectivity (Lieberman et al., 2018; Benthall et al., 2018). Based on these facts, several groups have proposed that dopamine is a major hub for the impacts of food insecurity or uncertainty in foraging more generally (Fig. 1) (Anselme and Güntürkün, 2019; Lin et al., 2020). We hypothesize that experience of scarcity and unpredictability in the food supply (food insecurity) should have direct effects on brain development via (1) cumulative impacts on the activity of the dopamine system and (2) plastic changes in downstream striatal neurons and their inputs (Lin et al., 2020, 2022). In our working model, we envisage that dopamine neurons may integrate and broadcast information about the surprising arrival or omission of food, the state of the stomach, body condition and fat stores, and that plasticity in the system should be programmed by these inputs to establish the appropriate phenotype (Lin et al., 2020). Dopamine and striatal neurons are known to play a critical role in motivation, feeding, learning and decision making (Anselme and Güntürkün, 2019; Lin et al., 2020). Therefore, changes in dopamine neurons and subsequent plastic changes in circuits downstream of dopamine release could have lasting impacts on feeding and other motivated behavior, as well as learning and cognitive function.

Experimental studies in mice have confirmed that developmental experience of secure versus insecure food delivery can alter the adult function of dopamine neurons at the synaptic level. Lin et al. (2022) found that in male mice with FI versus AL experience in development, the glutamate synapses onto VTA dopamine neurons were significantly different later in adulthood. They found that the AMPA:NMDA ratio was lower in FI mice than in AL mice, which will affect how the neurons filter input to drive firing and regulate plasticity in their inputs. Moving out to dopamine neuron terminals to examine synapses that release dopamine in the striatum, Lin et al. (2022) also found that SNpc dopamine neurons showed lower evoked dopamine release in male mice with a developmental history of food insecurity than in those with a secure history. Together, these data show that differential developmental feeding history has a lasting impact on dopamine neuron synapses, even 20 days after the feeding differences have ended. These differences are likely to impact functional dopamine levels in the awake behaving brain and may be responsible for differences in feeding, learning and decision making seen in adulthood (Lin et al., 2020, 2022).

Evidence implicating differences in dopamine-rich reward centers also comes from human subjects. College students with experience of food insecurity show increases in functional connectivity between the salience network and cortical regions in brain imaging studies (Guerithault et al., 2022). Imaging studies of youths that experience food insecurity have also shown changes in reward processing (Dennison et al., 2019).

Further mechanisms and interactions between mechanisms

The possible mechanisms we have listed here are not exhaustive. Future work could implicate other systems such as other modulatory neurotransmitters, the liver (Tapper et al., 2023), the gut microbiome (Coley and Hsiao, 2021) and/or immune system function (Gowda et al., 2012). We may also need to examine social interactions as a possible indirect mechanism. For example, when parents are stressed by nutritional stress or other factors, they may alter their care patterns. In rodents, limited nesting and bedding (Rice et al., 2008) and maternal separation (Thomas et al., 2020) have both been shown to alter patterns of care and behaviors such as licking and grooming in rats and mice. Changes in care, potentially through changes in feeding, social cues and also tactile stimulation can alter the development of the offspring nervous system, including areas such as the hypothalamus, frontal cortices, amygdala and striatum, and also adult behavior (Melo et al., 2006; Walker et al., 2017; Yam et al., 2017). As food insecurity is a complex stressor, it is likely that adrenal, gonadal, gut, liver, immune, sensory and brain systems are involved and produce complex feedback to each other. Given this complexity, we may need to use organized team science from multiple fields to understand food insecurity in animals. To translate between animals and human biology, hopefully there can be more dialogue between experimental biology and medical, epidemiological and public health scientists who focus on humans.

Conclusions

In conclusion, controlled studies in animals and evolutionary biology perspectives can inform our understanding of food insecurity in developing, mature and even aged organisms. While work explicitly modeling patterns of food scarcity and volatility in food insecurity is only nascent, work to date suggests that experience of food insecurity has powerful effects on weight and feeding behavior as well as motivation and cognition. These effects

may best be understood through the lens of developmental plasticity as adaptive responses to scarcity and uncertainty. This means that prevention of food insecurity is particularly important during pregnancy, childhood and adolescent development when the brain and body are most strongly programmed by the environment.

Because food insecurity presents an unstable stressor with complex inputs, it has complex and widespread effects on the brain and body. So far, controlled experimental studies with animals have revealed that experience of food insecurity can impact multiple neural systems and energy homeostasis. A series of studies of lab animals exposed to insecure feeding conditions found changes in weight, feeding and motivated behavior, changes in metabolic metrics and changes in the synapses of dopamine neurons. When comparisons can be drawn between the studies, they suggest that differences in the age of exposure, sex, strain and species may influence the outcome of these studies, but many commonalities hold across them all. Future studies will need to systematically vary the duration, timing and chronicity of food insecurity in order to better understand developmental plasticity and the timing of possible sensitive periods in the systems affected by food insecurity. Team science will also be needed to understand interactions between mechanisms.

As the research stands now, it is clear that food insecurity does have significant and lasting impacts on the body and brain across species and that efforts to mitigate food insecurity in people, especially children and adolescents, are warranted to prevent long-term negative outcomes. In adults, food insecurity has been linked to adverse outcomes such as obesity, type II diabetes, hypertension, depression and anxiety (Abdurahman et al., 2019; Arenas et al., 2019; Weaver and Fasel, 2018). In children and adolescents, food insecurity has been linked to lower educational achievement, cognitive deficits, impaired growth and development, depression and other poor mental health measures (Burke et al., 2016; Shankar et al., 2017). A variety of data suggest that early development (0–5 years in humans) may be an important period for intervention in people because of the extensive brain and body growth at that time, but later epochs of development such as adolescence have been found to be critical periods for experience as well (Falconi et al., 2014). Different intervention strategies may be needed to address food insecurity in different age groups.

Lastly, research in animals shows that the unpredictability or uncertainty inherent in food insecurity may be as influential as scarcity, with separate or at least additive effects on development. The combination of food insecurity and exposure to high-fat, high-sugar diets or poor quality diets may also amplify effects. From these data, we conclude that interventions that provide daily access to feeding programs or benefits plus higher quality food may significantly reduce the negative impacts of food insecurity. Further research can help by defining sensitive periods when prevention is most important and by defining the mechanisms through which experience of food insecurity leads to pathology, which may provide targets for biological intervention.

Acknowledgements
We thank Ezequiel Galarce, Len Epstein, Dana Small, Carrie Ferrario, Chris Newgard, Ana Arruda and the participants of the JEB 100th Anniversary Symposium on developmental plasticity for discussion.

Competing interests
The authors declare no competing or financial interests.

Funding
Funding was received from the National Institutes of Health R21 AA025172 (to L.W.). Deposited in PMC for release after 12 months.

Special Issue
This article is part of the Special Issue ‘Developmental plasticity: from mechanisms to evolutionary processes’, guest edited by Patricia A. Wright and Kathleen M. Gilmour. See related articles at https://journals.biologists.com/jeb/issue/227/Suppl_1

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