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A role for adaptive developmental plasticity in learning and decision making

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A role for adaptive developmental plasticity in learning and decision making

By

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Professor Linda Wilbrecht, Chair
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Professor Helen Bateup

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Abstract

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Professor Linda Wilbrecht, Chair

The goal of my dissertation is to shed new light on how genetic variation and developmental experiences sculpt cognitive flexibility in young adulthood. My dissertation is intended to inform public health and understanding of human adversity by using mice as a model. However, this work may also contribute to a more established scientific understanding of how an organism's life experience can interact with development and have profound and persistent effects on expression of the neurobiological and behavioral phenotypes. This interaction between the environment and a developing organism has previously been studied in various fields under different names, as experience dependent plasticity in neuroscience, adaptive developmental plasticity (ADP) in biology, and life history theory in ecology. These three fields do not often interact because they tend to focus on different levels of analysis. Neuroscience tends to focus on the proximate or mechanistic level, while ultimate level questions about evolution are the domain of biology and ecology. By looking at neural systems and examining the effects of genotype and developmental experience, I attempt to forge links between the proximate and ultimate levels of understanding.

At the proximate level, I focus on the role of the striatal dopamine (DA) system in behaviors requiring cognitive flexibility or flexible updating. This critical executive function, responsible for adaptive learning and goal-directed behaviors, has been shown to rely heavily on the DA system. At the ultimate level, I discuss how genetic polymorphisms and phenotypic plasticity allow adaptation to different environmental conditions and how the application of ADP and life history theory may strengthen the interpretation of the changes in behavioral phenotypes and neural functions. Through a similar lens, cognitive flexibility may represent how sensitive an organism is to cues from the environment, with greater sensitivity associated with greater flexibility.

In Chapter 1, I first briefly introduce the framework of ADP by presenting different levels that ADP can act on as well as different models and hypotheses. I also review ideas of

life history theory and sensitive periods which interact with ADP and together affect and sculpt developmental trajectories of cognitive, behavioral, and neural functions. I then review the growing literature that demonstrates behavioral and neurobiological variables are sensitive to early life developmental experiences, with a special focus on cognitive function and the striatal DA system. Based on the ADP framework and the neurobiological literature, I develop a model of how experience may have profound effects on the development of striatal DA systems that support learning and decision making.

In Chapter 2, I present data from a mouse model of a common human genetic polymorphism in the brain derived neurotrophic factor (BDNF) gene, Val66Met. In these mice, we find that genotype affects cognitive flexibility in two separate tasks. Met/met mice (homozygous with the mutant allele) showed greater flexibility than the Val/Val controls. I discuss these findings in the context of literature that views this polymorphism as a plasticity allele instead of a risk allele. I also explore how the ADP framework explains why a genetic polymorphism that affects cognitive flexibility might be maintained in a population.

In Chapter 3 and 4, I focus on the impacts of developmental food abundance versus food scarcity on brain and behavior. Food abundance and scarcity are important environmental variables affecting organisms' survival and are relevant to public health. Food scarcity and unpredictability is known in public health as food insecurity. Currently, this is a growing public health challenge both nationally and globally. For this work, I developed a novel mouse model of food insecurity using a varying schedule of feeding for 20 days during development.

In Chapter 3, I examine the impacts of juvenile-adolescent (Postnatal Day (P)21-40) developmental feeding history on learning, cognitive flexibility, and decision-making in adulthood. I found that adult male mice with different developmental feeding histories (ad libitum or food insecurity treatment) during the juvenile-adolescent period P21-40 exhibited differences in cognitive flexibility, past reward integration, and sensitivity to reward uncertainty when tested after P60. These group effects were not found in females nor in males when the differences in feeding experience and testing were both shifted twenty days later, suggesting a sex difference and a sensitive window for the effects of treatment or testing. I also applied computational modeling to further characterize that behavioral differences in adult males with different P21-40 feeding histories. I found that differences in behavioral performance in the two tasks were due to differences in updating in response to negative outcomes, weighing of past unrewarded history, and sensitivity to different reward probabilities. While I did not see impacts of feeding experience on learning and cognitive flexibility in adult female mice, I did observe effects on adult weight gain in females.

In Chapter 4, I examine the impacts of developmental feeding history on neurobiological measures of DA neurons and DA release in the striatum in brain slices. I found that adult male mice with different developmental feeding histories showed differences in AMPAR/NMDAR-mediated excitatory postsynaptic currents ratios on mesolimbic DA neurons and differences in DA release in the nigrostriatal DA pathways *in vitro*. In both Chapter 3 and 4, I explore how we may use the ADP framework to explain our results as a predictive adaptive response to the developmental experience of food abundance or scarcity.

Together, my data demonstrate how genes and experience can impact cognitive flexibility and serve as an example of how we can use multiple levels of analyses to understand phenotypic variation. I hope to advance the field of adversity studies by using theoretical and mechanistic models and novel insights to explain how information from the environment can act on neural circuits and in turn alter expression of behavioral phenotypes. Furthermore, my data suggests that the juvenile adolescent period is a potentially significant time for interventions to impact core learning and decision making systems. This last point may have special relevance during the time of the COVID-19 pandemic, as the subsequent economic downturn increases food insecurity.

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Chapter 1

Early life experience and a role for adaptive developmental plasticity in learning and decision making

Introduction

There is great interest in understanding how life experience can interact with the development with life-long effects through biological mechanisms. These ideas have been addressed in parallel in the fields of neuroscience and biology as experience dependent plasticity (EDP) and adaptive developmental plasticity (ADP), respectively. The ADP framework was first developed by evolutionary biologists studied not only brains and behavior but also bodily phenotypes and it was applied to the study of a broad range of wild species (Bateson et al, 2014; Fawcett & Frankenhuis, 2015; Lea et al., 2017; Nettle & Bateson, 2015; E. Snell-Rood & C. Snell-Rood, 2020; Stearns, 1989).

In this dissertation, I try to bring the fields together to understand how the developing brain may set a thermostat for life-long patterns in learning, foraging, and decision making. I first introduce and briefly review ADP framework, ideas of life history strategies, and sensitive periods (a form of EDP). Then, I explore how early life experience can affect learning, cognitive flexibility, and decision making as well as how effects on the neural systems supporting these functions may be considered in the ADP framework. In Chapter 2, I investigate and discuss how a mouse model of a common human genetic polymorphism affects cognitive flexibility and examine my findings through an ADP lens. In Chapter 3 and 4, I use a mouse model to study impacts of different feeding and statistical input experiences aka *food ad libitum* versus *food insecurity* on behavior and neural systems, respectively, and discuss how an ADP framework may explain the behavioral and neural changes observed in the experiments.

Together, this dissertation offers an opportunity for me to work on ideas that connect the field of systems and behavioral neuroscience (with questions traditionally focusing more on proximate level) to the field of ADP and life history theory from ecology and evolutionary perspective (with questions usually addressed at ultimate level). Moreover, using mouse models allows me to better isolate specific variables of interest, compared to human studies. The data illustrate that the biological factors regulate learning, cognitive flexibility, and behavioral plasticity and that life experiences can affect the neural systems. Furthermore, my work in this dissertation provides information with public health and policy relevance, suggesting impacts of common human genetic

polymorphism and different feeding conditions, timepoints for potential intervention programs, and considerations to be made.

Genotype and phenotype

Different organisms have their own specific sets of characteristics to make them distinct from other organisms or other species. Describing the *genotypes* or *phenotypes* for certain characteristics is one of the ways to identify if there's specificity. *Genotype* is set of genes coded in the DNA sequence and usually held to be the same over organisms' lifetime (Taylor & Lewontin, 2017). Environmental factors, DNA replication or repairment mechanisms, and spontaneous errors may cause mutations in the DNA sequences and may result in different variants of genotypes. *Phenotype* is the physical or behavioral trials that organisms have, for example, body size, metabolic activity, movements, etc. It is observable and influenced by genotypes, gene expression, and often environmental effects on gene expression (Beldade et al., 2011; Fusco & Minelli, 2010; Lafuente & Beldade, 2019).

Adaptive developmental plasticity and phenotypic variance

Different genotypes and phenotypes may have different fitness values in different environments. The environment can vary and change over time. Information available during developmental periods that indicate a dramatic state or change in the environment or that have predictive power of the future state in the environment are likely to influence survival, reproduction, and overall fitness. Therefore, there may be selection pressure to absorb this kind of information and to incorporate it into decision points for phenotypic expression. The ability or capacity of organisms to respond to early life experience and changes in environmental information and circumstances during development with lasting alteration in phenotypic expression is termed as "adaptive developmental plasticity (ADP) " (Bateson et al, 2014; Fawcett & Frankenhuis, 2015; Lea et al., 2017; Nettle & Bateson, 2015; E. Snell-Rood & C. Snell-Rood, 2020; Stearns, 1989).

Several striking examples of ADP have been observed in wild species across various animal kingdoms. In a classic example, Daphnia of the same species can develop physical helmets and spines to protect themselves against their predator after they experience threat or detect kairomone cues in the environment (**Fig. 1A**) (Ruther et al., 2002; Weiss, 2019). If they do not detect this threat signal, then they develop a less costly but less protective phenotype.

Literature on adversity also shows effects of developmental experience on adult behaviors. Rodents that experienced prenatal stress, maternal stress, or isolation early in life exhibit hyperactivity and locomotor activities during adulthood (Brake et al., 2004; Del Arco et al., 2004; Fareri & Tottenham, 2016; Gue et al., 2004; Wang, Li, et al., 2015). In humans, childhood adversity is associated with higher risks of developing physical and/or psychosocial disorders (Davis et al., 2014; Green et al., 2010; Ke & Ford-Jones, 2015; McLaughlin et al., 2012). These studies are a few examples from various species showing that early life experience can sculpt the expression of different traits and tune the future behavioral patterns and psychophysiological responses. It is usually assumed that these alterations are deficits produced by stress, but less being discussed with ADP framework to see if there's adaptive benefits of the change in behavior, such as specialization and resilience (Ellis et al., 2017).

ADP can be discussed under two different timescales: 1) over generations where natural selection acts on individuals to select adaptive plasticity and eliminate non-adaptive or deleterious forms of plasticity 2) within a single generation, where evolved programs work (successfully or unsuccessfully) to adjust phenotypes to be expressed over that organisms' lifetime based on input from the developmental environment (Bateson et al., 2014; Fawcett & Frankenhuis, 2015; Frankenhuis & de Weerth, 2013; Nettle & Bateson, 2015; Snell-Rood, 2012).

ADP and phenotypic plasticity

Over these two timescales, the most obvious forms of ADP are those that result in different physical phenotypes expressed from a single genotype. This variation in physical phenotype may depend on inputs received by the organisms from the local environment (Forsman, 2015; Fusco & Minelli, 2010; Weiss, 2019). *Daphnia* and its emergence of physical helmets and spines is one of the illustrations of ADP observed at the single genotype to physical phenotype level. Another popular example is *Bicyclus anynana.* This is a butterfly species that alters the expression of eyespots on their forewings depending on rearing temperature during development (Beldade, et al., 2011; Lafuente & Beldade, 2019).

ADP on genetic polymorphisms

In addition to environmentally induced phenotypic variations and plasticity from a single genotype, natural selection can also select for or against the maintenance of different gene alleles, affecting the relative proportion of genetic polymorphisms in a population. These alleles may affect morphological or physiological characteristics of individuals including plasticity (Beldade et al., 2011; Forsman, 2015; Fusco & Minelli, 2010; Lafuente & Beldade, 2019; Lea et al., 2017). Comparing to phenotypic plasticity evoked

by environmental factors, there are relatively fewer studies focused genetic variation within the ADP framework. Yet, more evidence for adaptive traits arising from variations in genetic basis are accumulating (Lafuente & Beldade, 2019; Lea et al., 2017). For instance, the small and soft-bodied insect, aphids, especially male aphids, have genetically determined dimorphism with allelic variations controlling phenotypic expression in the wing. These can confer different fitness advantages for dispersal and reproduction as they affect how the insects fly and disperse (Braendel et al., 2006). Survival affects the frequency of this genetic polymorphism, or more specifically, the bi-allelic polymorphic site in the single nucleotide polymorphism (SNP), contributing to frequency of the physical phenotypes observed. Suzuki and Nijhout (2006) found that a single genetic mutation in *Manduca sexta* allowed it to increase sensitivity to low or high environmental heat stress by expressing different larval color and resulted in the evolution of different color phenotypes. On the contrary, a mutation in the receptor detecting pheromone resulted in that higher concentration of pheromone was required to affect the switch of mouth phenotypes in nematode *Pristionchus pacificus* (Bento et al., 2010). The variants from the SNP in turn potentially allows either a loss or gain of environmental sensitivity (Beldade et al., 2011; Lafuente & Beldade, 2019).

ADP can affect many systems including the brain and behavioral development

Genetic polymorphism and/or developmental differences in gene expression, of course may result in visible physical phenotypic differences. Less obvious changes in proteins and gene expression may also affect organs throughout the body. Previous work in both animal models, non-model organisms, and humans have demonstrated that early life experience in heterogenous environments can affect long-term patterns of gene expression controlling the immune system (Beldade, et al., 2011; Lea et al., 2017; Miller et al., 2009). Animal and human studies also illustrated that early life experience can affect neural and brain development, and through the brain affect behavioral plasticity (Dow-Edwards et al., 2019; Glasper & Neigh, 2019; Holtmaat & Svoboda, 2009; E. Snell-Rood & C. Snell-Rood, 2020; Sweatt, 2016). These effects on the brain have typically been studied as EDP but may reflect adaptive processes that have been described by ADP. Developmental behavioral plasticity may encompass learning and experience dependent changes in the neural systems (Snell-Rood, 2013). For instances, touch, sensory cues, and social interactions early in life can affect neural structural plasticity and metabolism in multiple brain regions such as visual and somatosensory systems (Fox & Wong., 2005; Lendvai et al., 2000; Seelke et al., 2016), and further affect their sensory processing functions and relevant social behaviors (McLaughlin et al., 2014; Opendak et al., 2017; E. Snell-Rood & C. Snell-Rood, 2020).

ADP models and hypotheses

ADP provides mechanisms that permit organisms to respond to environmental heterogeneity at different levels, from single genotype, genetic polymorphism, development of neural circuit, to behaviors as we discussed and reviewed in the previous sections. The plasticity or adaption does not always confer advantages in fitness; but, sometimes, the plasticity may appear to be deleterious (Lea et al., 2017; Nettle & Bateson, 2015).

Current models and hypotheses of ADP have proposed there are two general categories of ADP which differ in their value for short versus long term survival.

In the first broad category, organisms use the environmental information during early life to infer current conditions and inform their use of tradeoffs to protect development of critical functions. This form of ADP may increase fitness and chances for survival during early life but may reduce and compromise future fitness in adult phenotypes, functions, and behaviors (Lea et al., 2017; Nettle & Bateson, 2015; E. Snell-Rood & C. Snell-Rood, 2020). It is sometimes referred as “non-adaptive”, “constraint models”, “deficit models”, or “making the best of a bad lot”; and, future compromised phenotypes and behavior are often considered “maladaptive”, “nonoptimal”, “impaired,” or as “deficits” (Ellis et al., 2017; Frankenhuis & de Weerth, 2013; Lea et al., 2017; E. Snell-Rood & C. Snell-Rood, 2020).

The second broad category of ADP is more farsighted. In this form, environmental cues experienced and received early in life can be used to adjust phenotypic and behavioral developmental trajectories to maximize the fitness and adaptation to the predicted environments later in life (Bateson et al., 2014; Lea et al., 2017). This type of ADP is called a “predictive adaptive response (PAR)” (Bateson et al., 2014; E. Snell-Rood & C. Snell-Rood, 2020). A PAR therefore describes mechanisms that allow organisms to adaptively prepare for future environments and is mainly seen as the plasticity that leads to advantages and greater fitness for reproduction and survival from an evolutionary perspective (Bateson et al., 2014).

Literature on PAR ADP proposes two different hypotheses for how environmental or developmental input and phenotype outputs are related. The informational hypothesis posits that developmental experience provides information about the future environment and shapes phenotypic changes according to the predicted future adult environment. The somatic state-based hypothesis highlights effects of developmental input on developing individuals that specifically alters some somatic state variables such as body size, organ capacity, or DNA damage (Nettle & Bateson, 2015).

In fact, many instances of ADP may lie at the intersection of both general models, containing both adaptive and non-adaptive elements, and can be explained by one of

hypotheses under PAR with specific contexts. It is possible that environmental information early in life does not correctly predict the future environment, resulting in a mismatch and lower overall fitness between altered phenotypes and the environments (Bateson et al., 2014; Frankenhuis & de Weerth, 2013; Lea et al., 2017; Nettle & Bateson, 2015; E. Snell-Rood & C. Snell-Rood, 2020), which can be interpreted as "maladaptive" or "deficits". This is in contrast to the "matching" scenario – the increase of overall fitness is observed when the anticipated environment under ADP accurately matches the actual future environment.

To carefully interpret and understand how ADP provides mechanisms for organisms to respond to environmental changes early in life, researchers have proposed better ways to design the experiments to test ADP models and hypotheses. In short, organisms with two different early life experiences, for example, can be tested in two different conditions in the future timepoint or adulthood, one that matches and one that does not match the developmental environment (Bateson et al., 2014; Ellis et al., 2017; Lea et al., 2017; Nettle & Bateson, 2015). Organisms may show different ADP (observed in phenotypes) and then advantageous performance or fitness in one condition over the other in the match or mismatch condition.

In this dissertation, framework of ADP acting on genetic polymorphism, neural systems, and behavioral levels will be covered in Chapter 2-4. In Chapter 2, ADP over both organisms' lifetime and evolutionary timescales are discussed. In Chapter 3 and 4, an approach of the PAR model of ADP design with more informational hypothesis oriented, is used to discuss impacts of different early life experiences on behavioral and neurobiological phenotypic expressions later in life.

Life history theory, strategies, and life stages

ADP allows organisms to adaptively respond to changes in the environment during development. Life history theory has been discussed together with ADP. It highlights the *tradeoff* between different factors must be made in order to reach overall greater fitness. According to life history theory, tradeoffs made during development are shaped by natural selection to achieve greater fitness in terms of increasing chances of survival and reproduction. It emphasizes that when organisms are required to selectively allocate resources, energy, and time in face of different challenges in the environment, they may show specialized responses in environments characterized by scarcity, harshness, or unpredictability (Ellis et al., 2009; Roff, 2002; Stearns, 1992). These tradeoffs in turn sculpt the developmental trajectories and result in variations in behavioral strategies and adjustments in phenotypic expression. It then follows that growing up in a scarce, harsh, and unpredictable environment, organisms may enact more global life history strategies. For example, a fast life history strategy may involve being more aggressive, risky, and present oriented, not considering long-term

consequences, and prioritizing somatic growth and reproduction but with less investment in offspring care. In contrast, slower life history strategies may involve taking fewer risks and investing in more future orientated strategies. It is thought that this slower life history strategy will be adaptive when organisms grow up in a relatively more stable and resource abundant environment. It has been postulated that this is why more harsh environments in human society are associated with less self-regulation, earlier puberty and reproduction, and less investment in offspring care (Ellis et al., 2009; Ellis et al., 2017).

Variations in life history strategies, phenotypic expression, and behavioral plasticity are sensitive to environmental information itself and also the timing when the information is available. Information and development to be prioritized and emphasized are different at each life stage in which the same environmental information may be more or less valuable or important (Fawcett & Frankenhuis, 2015; Hochberg & Belsky, 2013). One of important stages for life history transition is the start of puberty (Ellison et al., 2012; Piekarski, Johnson, et al., 2017), where shifts in life history strategies or sensitivity for different information may be observed. Nutritional and food sources information may be more important during early life and during the peripubertal growth spurt because these periods relatively more energy needs to be allocated to somatic growth for basic survival, while breeding sources, nest sites available, and mating competition information are more important when organisms reach reproductive maturation (Ellis et al., 2009). In addition, at different stages of development, organisms focus on acquiring specific types of knowledge as well as cognitive skills that are important for current and future better survival and fitness. These knowledge and skills are then integrated, refined, and improved over time (Spear, 2000; Piekarski, Johnson, et al., 2017). Evidence from previous studies also suggests that neural circuits supporting these knowledge and cognitive skills are sensitive to different environmental information inputs and potentially life stage transitions (Piekarski, Johnson, et al., 2017). For instance, early-life touch and social interaction contribute to experience dependent development of the sensory processing systems (Fox & Wong., 2005; Lendvai et al., 2000; Seelke et al., 2016; E. Snell-Rood & C. Snell-Rood, 2020), while changes in associative neocortex around peripubertal period are associated with changes in flexible updating and executive functions observed between juvenile and adolescent periods (reviewed in Piekarski, Johnson, et al., 2017).

Together, ADP interacts with developmental stages to sculpt life trajectory. My dissertation aims to inform the information and mechanisms involved in sculpting learning and decision making in young adulthood.

Sensitive Periods

There may be specific life stages or periods that life experiences and environmental information have particularly strong impacts on EDP and ADP phenotypes (broadly defined). These may be called sensitive periods (Fawcett & Frankenhuis, 2015; Frankenhuis & Walasek, 2020; Knudsen, 2004). It is clear from decades of work on EDP that different neural circuits and functions have their specific windows of sensitivity to experience. In these periods, environmental inputs, such as visual and auditory inputs, can modify neural circuits and neural properties in fundamental ways by changing synaptic connectivity patterns, intrinsic excitability and firing rate, neurotransmitter availability, and receptors expression (Hensch 2005; Knudsen, 2004; Piekarski, Johnson, et al., 2017).

Sensitive periods may be regulated by different mechanisms and occur at different times in development. Puberty onset has been proposed to be a mechanism regulating a transition in sensitive periods for associative neocortex and cognitive flexibility (Laube et al., 2020; Piekarski, Johnson, et al., 2017). The juvenile and adolescent period may be a sensitive period for foraging related behavior like learning and decision making because the juvenile and peripubertal periods are first periods that organisms start to gain their own independence, leave the parental safety net, explore novel environments, and continue acquiring new knowledge and skills to support survival and development (Ellison et al., 2012; Piekarski, Johnson, et al., 2017; Spear, 2000).

Previous work from our lab shows a transition in cognitive flexibility in the juvenile-adolescent period. Specifically, we found that pre-pubertal juvenile mice (Postnatal (P) day 26) exhibited faster updating in associative learning and choice behavior – choosing the correct rewarded option, when the reward contingencies were updated and changed in the environment (Johnson et al., 2011). This flexible updating was slower after P40 (Piekarski, Johnson, et al., 2017), implying that juvenile-adolescent period is a period 1) when learning and decision making are in flux and 2) that mice were more sensitive to changes in environmental reward contingencies and statistical information when they were younger. Follow up work has also shown this change could be accelerated by acceleration of puberty (Piekarski, Boivin, et al. 2017).

Statistical variation and food insecurity

In the environment, the regular or irregular occurrence of reward, threat, or other variables can be integrated as a statistical pattern. This pattern can signal different factors that important for survival or basic needs such as weather conditions, numbers of predators, food availability, etc. Organisms are constantly sampling these environmental cues with various statistical information in order to get most updated vision of current environment to be used for anticipating future environment, adaptively

sculpting learning, and adjusting behavioral strategies. This may be especially true when organisms first leave the nest to explore the environment and gain individual independence (Ellis et al., 2009; Piekarski, Johnson, et al., 2017). Food availability is one of most critical and common statistical information that organisms sample from the environment each day as food provides energy and nutrition for survival and development. Different feeding or foraging experiences early in life, one with abundant food resource versus the other circumstance with food insecurity – scarcity and unpredictability of food resource and access (Cook and Frank, 2008; Coleman-Jensen et al., 2013), may result in different developmental trajectories in physical phenotypes, neural circuits, cognitive skills, and behavioral strategies. These different trajectories may be adaptively specialized in an experience- and context-dependent manner under life history strategy and ADP mechanisms.

The food-dependent statistical information is in particular critical for organisms in juvenile and adolescent periods as they start to explore novel environments and be responsible for individual basic needs and survival. Different experiences with fluctuating statistics of food resources may shape how organisms learn food reward contingencies, update resources values, and integrate past food resources and value history as well as sculpt the supporting neural systems differently to allow successfully search and pursuit of their targets and goals to reach greater overall fitness.

In addition, food insecurity, is a prevalent public health challenge present in human populations. Studies in human populations have found that food insecurity is associated with greater risk for substance use disorders, obesity, diabetes, poor health (Althoff et al., 2016; Davis et al., 2014; Ke & Ford-Jones, 2015; Laraia, 2013), and others (more extensive discussions of its impacts on humans are covered in Chapter 3). However, less attention has been paid to food insecurity as a factor affecting behavioral, cognitive, and brain development at neural circuits level as well as to impacts of different feeding experiences under the ADP framework.

Therefore, I aimed to particularly examine impacts of different feeding experiences –*ad libitum* versus *food insecurity* during juvenile-adolescent periods on these functions and neural systems and investigate if there is a developmental sensitive period for effects of feeding experiences in Chapter 3 and 4.

Goal-directed behavior, striatum, and dopamine system

Goal-directed behavior is characterized by flexibly choosing actions or options according to the reward feedback and outcome, so-called “action-outcome contingencies” in different situations depending on the goals that are currently pursuing (Yin et al., 2004; Zwosta et al., 2015). Being able to flexibly adjust the behavior – cognitive flexibility – is one of important executive functions and behaviors that

organisms have and perform in the face of different circumstances and changing information in the environment.

Dopamine (DA) activities and striatal circuits have been widely accepted that they play critical roles in reward, learning, flexibility, and goal-directed decision-making. They are essential for learning the associations between actions and rewards, updating the action values, and executing the selected actions and motor movements (Berke et al., 2018; Cox & Witten, 2019; Glimcher, 2011; Izquierdo et al., 2017; Klanker et al., 2013; Lee et al., 2015; Macpherson et al., 2014; Penner & Mizumori, 2012). DA system and activities contribute to these behaviors in many ways, including but not limited to signaling reward, values, and reward prediction errors, modulating synaptic plasticity in the relevant brain regions, and informing motivational levels (Hamid et al., 2016; Hong & Hikosaka, 2011; Ishikawa et al., 2013; Parker et al., 2016; Salamone & Correa, 2012; Schultz, 2016). For instance, empirical studies and computational models both suggest that changes in DA levels and/or DA D1 receptor (R) and D2R expressions on striatal spiny projection neurons (SPNs) can change the activity balance of striatal output pathways, which are integrated to mediate action selection and outcome evaluation (Collins & Frank, 2014; Shen et al., 2008). Specifically, neural activities of DA and SPNs in the dorsomedial striatum (DMS) integrate, represent, and update the value of available actions (Balleine et al., 2007; Kim et al., 2009; Nonomura et al., 2018; Tai et al., 2012). Optogenetically stimulating D1R-SPNs and D2R-SPNs in the DMS during the decision-making processes can bias organisms' choices in different directions (Tai et al., 2012). SPNs in the ventral striatum were found to modulate their activities according to the organisms' previous choices (Kim et al., 2007). DA systems and striatal circuits together work in concert to signal and represent many aspects and functions contributing to adaptive goal-directed behavior; and their activities and functions are found to be modulated by experiences.

Early life experience and cognitive functions

Early life exposure to conditions that are harsh or "adverse" have most often been studied from a public health perspective to understand what deficits they may produce. In human subjects and animal models, there is modest literature showing that developmental conditions associated with adversity can alter later cognitive functions, including reward processing, reinforcement learning, and decision making (Hanson et al., 2017; Novick et al., 2018; Tractenberg et al., 2016; Wang et al., 2020). For example, rodents with early life experience of less social interaction from either dams or siblings have demonstrated reduced ability to learn, flexibly update behavior, and choose correct actions in instrumental learning, reversal learning, and gambling-based decision tasks (Banqueri et al., 2017; Hinton et al., 2019; Kambali et al., 2019; Thomas et al., 2016; Wang et al., 2011; Yohn & Blendy, 2017; Zeeb et al., 2013). Similar findings with reduced cognitive functions have also been found in human populations that

experienced neglect or institutional rearing (Birn et al., 2017; Harms et al., 2018). In addition to alterations in cognitive functions, there is large literature showing that early life experiences with adversity can increase anxiety-like and depression-like behavior and alter social behavior (Banqueri et al., 2017; Cao et al., 2016; Chocyk et al., 2015; Grissom et al., 2012; Han et al., 2011; Kambali et al., 2019; Yohn & Blendy, 2017). However, some changes later in life may currently be considered as deficits while it may have had adaptive value during development.

It is less well known that early life adversity has also been shown in some studies to enhance learning and cognitive functions. Rodents with similar early life stress in interactions exhibited faster fear learning and enhanced retention of memory (Callaghan & Tottenham, 2016; Richardson et al., 2016; Zalosnik et al., 2014), faster decision making, enhanced reversal learning, and greater exploration of novel objects and environment (Chaby et al., 2015, 2016), increased reward seeking and better spatial learning (Kambali et al., 2019). Humans having high unpredictability in childhood also showed enhanced response in attention-shifting, procedural learning, present orientation, and work memory associated with rapid tracking and updating in contexts and environments primed with unpredictability or economic uncertainty and decline (Dang et al., 2016; Frankenhuis & de Weerth, 2013; Mani et al., 2013; Mittal et al., 2015; Young et al., 2018). These effects of adversity can be viewed as potential adaptations to the harsh and unpredictable environment (Mittal et al., 2015; Frankenhuis et al., 2016).

Early life experience and dopamine system

One place where work needs to be done is to connect how the environmental experience can signal to the developing brain and alter its phenotype. In my dissertation, I focus on how these signals may mechanistically be conveyed through the dopamine (DA) system.

There is rich literature from rodent models of adverse experience and different rearing environment early in life showing that life experience occurring within specific sensitive periods can alter developmental trajectories and activity, signaling, and functions of DA systems. For example, isolation rearing increases D2R expression in the nucleus accumbens (NAc) and medial prefrontal cortex (Han et al., 2012) and increases presynaptic midbrain DA transmission into the NAc in response to both rewarding and aversive stimuli (Fareri & Tottenham, 2016; Hall et al., 1998; Karkhanis et al., 2019; Powell et al., 2003; Watt et al., 2017). Maternal separation can lead to imbalance mRNA expression between D1R and D2R in both striatum and prelimbic cortex (Majcher-Maślanka et al., 2017), alter D1R and D2R level in NAc (Sasagawa et al., 2017; Zhu et al., 2010), and increase TH+ fiber density (Chocyk et al., 2015; Majcher-Maślanka et al., 2017). Additionally, animal studies with restraint stress identified that the same stress

experienced during adolescence and during adulthood had differential impacts on the ventral tegmental area (VTA) DA neuron population activity, with increased population activity 1-2 and 5-6 weeks post adolescent stress and decreased 1-2 weeks post adulthood stress (Gomes et al., 2019). Prolonged restraint stress starting after P14 can cause DA neuron loss in substantia nigra (Sugama et al., 2016).

Role of adaptive developmental plasticity in learning and decision-making[1]

Using the ADP framework, we propose that cues which indicate a harsh or adverse environment may have strong effects on the development of systems that support learning and decision making in the mammalian brain (**Fig. 1,** Lin et al., in press).

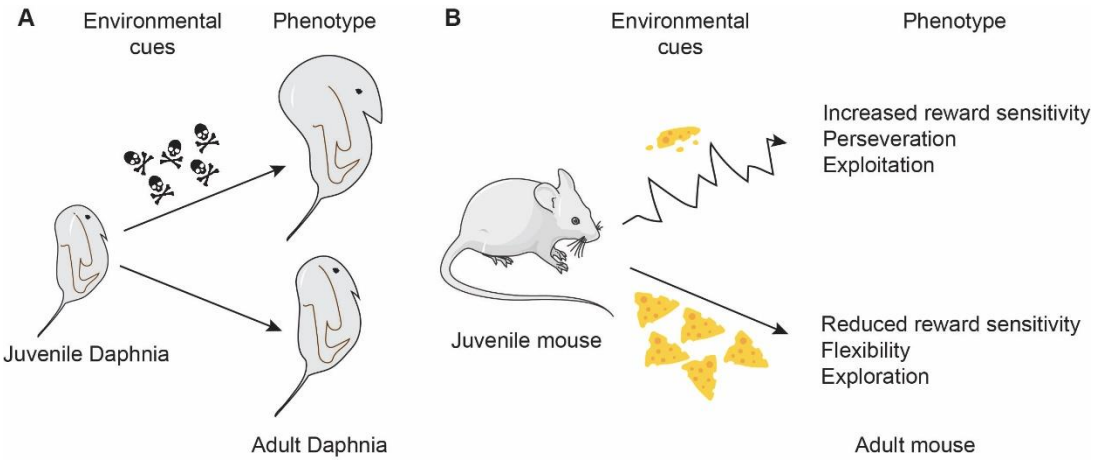


Figure 1. The adaptive developmental plasticity framework. Animals with a single genotype may develop different phenotypes based upon their experiences during development. **A**, The freshwater crustacean *Daphnia longicephala* develops a defensive helmet when chemical predator cues are present in the juvenile environment but does not invest in this armor if the cues are not detected (Weiss, 2019). **B**, Here, we propose that cues in the juvenile environment may alter phenotypic expression in behavioral domains related to reward processing, learning, and decision making. In this example, a food scarce versus a food rich environment (food represented by yellow "cheese" triangles) during development may lead to differences in reward sensitivity, cognitive flexibility, and explore/exploit balance.

[1] Some content in this chapter is adapted from a recently accepted manuscript.
Lin, W.C., Delevich, K., Wilbrecht L. (in press). A role for adaptive developmental plasticity in learning and decision making. *Current Opinion in Behavioral Sciences.*

We propose a three-step working model in which *cumulative differences in DA neuron activity in response to early life experience* may shift the developmental trajectory of downstream striatal and cortical circuits (**Fig. 2**).

1) The acute and long-lasting changes in DA release and function in response to fluctuations in feeding states, uncertainty, reward, and punishment during development may combine to drive cumulative downstream differences

DA neuron activity is known to be sensitive to feeding state, uncertainty in the environment, and shows phasic modulation in response to rewards, punishments, and prediction errors (Schultz, 2016; van der Plasse et al., 2015). The cumulative activity profile of the DA system is therefore predicted to differ in terms of amplitude, temporal patterning, and total activity in scarce vs. rich environments as well as volatile vs. stable environments. This environmental variation could be driven by food cues and foraging outcomes as well as social interactions or predation threats.

It is likely that environmental variables affect the brain throughout the lifespan. However, environmental impacts on DA system and downstream circuits may be more dramatic during the juvenile and adolescent period due to the greater plasticity in these circuits during development. DA system and signaling undergoes developmental refinement throughout juvenile, adolescence, and early adulthood (Matthews et al., 2013; McCutcheon et al., 2012; Sinclair et al., 2014; Wahlstrom et al, 2010). In studies of rodents, DA neurons show protracted outgrowth of axons during adolescence with innervation the prefrontal cortex continuing to grow until young adulthood (Hoops et al., 2018; Kalsbeek et al., 1988; Matthews et al., 2013; Naneix et al., 2012; Willing et al., 2017). Within this long period of development, there may be periods of punctuated change and possibly greater plasticity, but more research is needed to know when specific sensitive periods may occur. We do know for example, within the striatum the amount of DA available to be evoked by stimulation is low in the early juvenile period but increases with development (Lieberman et al., 2018; Matthews et al., 2013; Stamford, 1989), and that the increase from the early juvenile period to late juvenile period is critical for downstream targets (Lieberman et al., 2018, more on this below). DA axons from VTA that are present in the prefrontal cortex show greater activity dependent structural plasticity during adolescence compared to adulthood (Mastwal et al., 2014). Expression of DA receptors also peaks in DA target regions during the peripubertal period (Andersen et al., 2000; Brenhouse et al., 2008; Tarazi & Baldessarini, 2000; Teicher et al., 1995). In sum, experiments with higher temporal resolution of development suggest week-by-week changes are occurring throughout the juvenile and adolescent period. Greater temporal resolution will be needed to identify exactly when specific sensitive periods with specific mechanisms may occur (Piekarski, Johnson et al., 2017).

A large number of studies have found developmental experience with adversity can have effects on later DA neuron function, axonal anatomy and DA release in striatum measured in adulthood (reviewed in the previous section). Within this literature, some studies find harsh environments such as those involving maternal care disruption or social isolation are associated with facilitation of DA signals (via multiple measures) while others find DA signals are weakened. This variability may be driven by the timing, duration, and form of adversity. The ADP framework may help to clarify reasons for these different outcomes and provide an organizing framework for more comprehensive integration of the literature.

2) Dopaminergic neurotransmission can regulate the acute and long-term excitability of basal ganglia spiny projection neurons and cortical neurons

DA release and binding onto D1R or D2R can affect intracellular signaling cascades, including a major cascade involving protein kinase A (PKA). DA binding at D1Rs activates the cAMP-PKA cascades through excitatory G proteins while binding at D2Rs inhibits these same pathways through inhibitory G proteins. Changes in expression of D1Rs and D2Rs thus regulate SPN and cortical neuron responsiveness to changes in extracellular DA levels. An increase in DA will enhance excitability and connectivity (via long term potentiation of synapses) in SPNs and other neurons expressing D1Rs and reduce excitability and connectivity in SPNs and other neurons expressing D2Rs. These effects will be opposite in response to a dip in extracellular DA after a negative prediction error (Collins & Frank, 2014; Iino et al., 2020; Lahiri & Bevan, 2020; Shen et al., 2008; Yagishita et al., 2014).

In our working model, we propose that more subtle, developmental experience-driven differences in DA activity could tune/program D1R and D2R expression and intrinsic excitability lasting into adulthood. In development, DA release and signaling may have acute and long-term impacts on the excitability of D1R and D2R-expressing SPNs (Galiñanes et al., 2009; Kozorovitskiy et al., 2015; Lahiri & Bevan, 2020; Liberman et al., 2018) and DA receptor-expressing pyramidal neurons and interneurons of the prefrontal cortex (Seaman & Yang, 2004; Tseng & O'Donnell, 2007). Indeed, Lieberman et al. (2018) found that a developmental increase in DA in the striatum is necessary for maturation of the excitability of D1R-expressing SPNs of the dorsal striatum. This regulation of excitability was linked to changes in potassium channel currents in the D1R-expressing SPNs. In this same study, the authors showed that mutant mice which had lower levels of DA release in striatum during development showed blunted change in D1R-expressing SPN excitability (Liberman et al., 2018). A separate study by Lahiri & Bevan (2020) also showed that DA release in the striatum can augment excitability of D1R-expressing SPNs in a rapid and persistent manner.

There is considerable literature in laboratory rodents showing that rearing in different environments can affect striatal and prefrontal cortex DA receptor expression (Han et al., 2012; Karkhanis et al., 2019; Majcher-Maślanka et al., 2017; Sasagawa et al., 2017; Zhu et al., 2010). Differences in DA release and receptor expression are thought to sculpt learning and decision making in rodents, non-human primates, and human subjects. While many studies focus on DA signaling and learning in terms of reinforcement of behavior (Bamford et al., 2018; Steinberg et al., 2014), other studies have found relationships between DA receptors and aspects of decision making such as exploratory behavior and the explore-exploit tradeoff (Costa et al., 2014; Sasagawa et al., 2017).

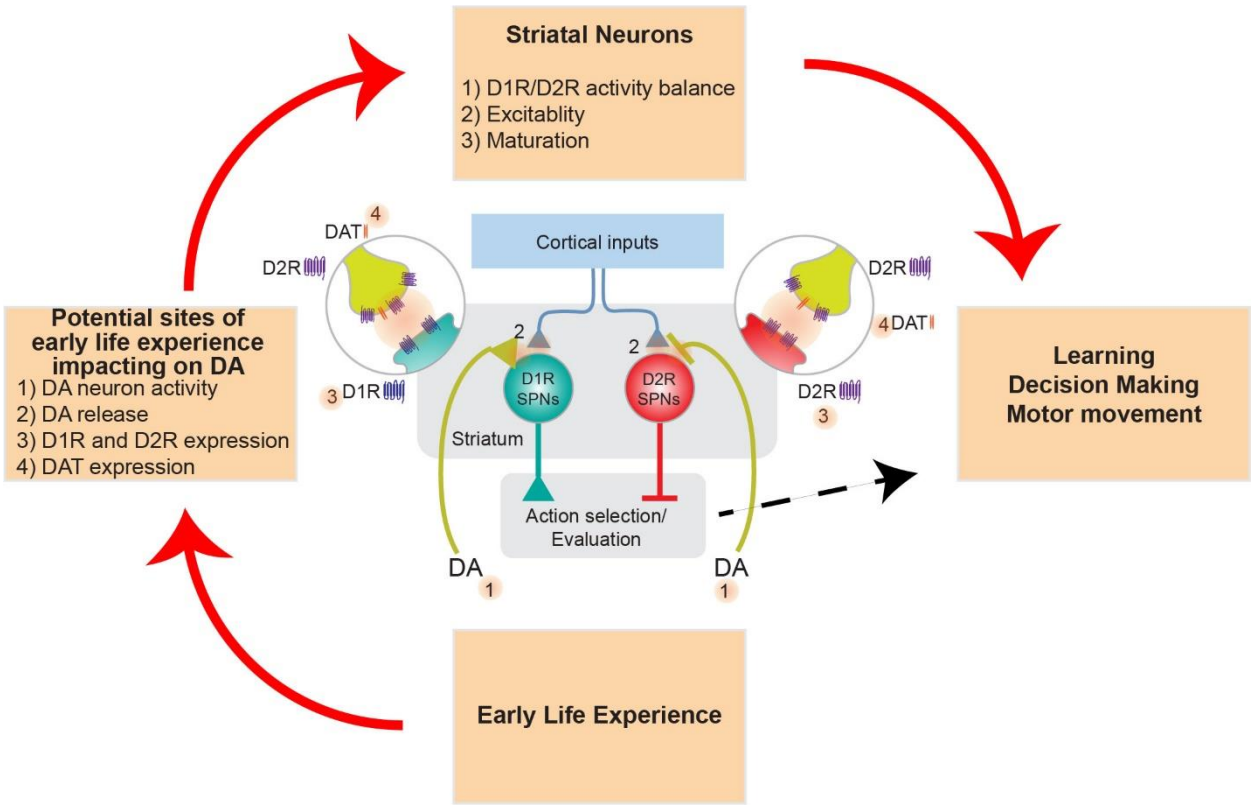


Figure 2. Working model in which differences in cumulative patterns of dopamine signaling during development leads to changes in cortico-striatal circuit function and behavior. Potential sites of adaptive developmental plasticity: 1) Changes in dopamine (DA) neuron activity and 2) release 3) D1R and D2R expression 4) DAT expression may occur in response to environmental cues and experience. This could have downstream effects on 1) cortical inputs weights and activity (D1R-SPN/D2R-SPN) 2) SPN intrinsic excitability 3) Maturation of SPNs. The sum of these changes can influence the weight of positive and negative outcomes, explore versus exploit behavior and other variables contributing to learning and decision making through changes in D1R SPN and D2R SPN output.

3) SPN excitability and history of activity will affect the weight or strength of cortical inputs

The excitability and activity of SPNs (sculpted by DA and DA receptor expression), may in turn influence the development of cortico-striatal inputs. This may be regulated by Hebbian and spike timing dependent plasticity (Shen et al., 2008) plus changes in intracellular signaling downstream of G protein coupled receptors (GPCRs) and activity dependent signals (Yagishita et al., 2014; Iino et al., 2020). Recent data suggest genetic mutations in SPNs that affect excitability also affect cortical input onto these specific SPNs and can enhance learning (Benthall et al., 2018). Manipulation of cortical inputs to the striatum has also been shown to alter decision making (Znamenskiy & Zador, 2013) and drug related compulsive behavior (Bock et al., 2013; Renteria et al., 2018).

In our working model, we suggest cumulative differences in experience may similarly affect cortical inputs to the striatum. Experiments in lab rodents support the basic premise that early experience can sculpt cortical inputs to the striatum. Cortical axons in the striatum continue to refine their synapses through development, and early life maternal care has been shown to affect the density of synapses made by frontal cortical axons in the dorsal striatum in adulthood (Thomas et al., 2020). Chronic stress during the juvenile period can also impact cortico-accumbal function (Dias-Ferreira et al., 2009; Watt et al., 2017). These same manipulations have also been shown to affect cognitive flexibility and addiction related behaviors such as alcohol consumption (Dias-Ferreira et al., 2009; Thomas et al., 2016). There is also a rich literature describing the effects of developmental adversity on reward processing (Lomanoswska et al., 2011; Ventural et al., 2013; Grissom et al., 2015; Watt et al., 2017; Novick et al., 2018), learning (Dia-Ferreira et al., 2009; Zhu et al., 2010; Thomas et al., 2016) and decision making (Lenow et al., 2017).

In sum, data from a broad literature suggest mechanisms by which accumulated experience affecting the DA system may have iterative downstream effects on the neurobiology of the striatum and its cortical inputs. We propose these effects, serving as a form of ADP, combine to alter how environmental stimuli engage learning and decision making processes in the brain.

Summary

The primary goal of this dissertation is using mouse models to understand how genetic and developmental experience can shape cognitive behavioral phenotypes and neural circuit function at both the proximate and ultimate level. At the proximate level, I examine how genes and developmental experience can affect behavior and neurobiology in adulthood. At the ultimate level, or evolutionary level, I discuss how

genetic polymorphisms and phenotypic plasticity may serve adaptation to different environments. In Chapter 2, I examine impacts of genetic polymorphism on BDNF on cognitive flexibility or flexible updating. I explore how we may use the ADP framework to explain why a genetic polymorphism that affects behavioral flexibility and sensitivity to environment might be maintained in a population over evolutionary timescales. In Chapter 3 and 4, I focus on investigating how developmental history of feeding experiences can affect learning, cognitive flexibility, and decision-making (Chapter 3) and the neurobiology of the DA systems (Chapter 4). In these chapters, I explore how we may use the ADP to explain how a change in behavioral phenotype driven by feeding experience may be a predictive adaptive response. Finally, in Chapter 5, I review the findings over all interpretation from ADP perspective, the public health and education relevance, and future directions for this line of work.

Chapter 2

A potentially adaptive role for the BDNF Val66Met polymorphism in flexible updating

Introduction

Adaptive developmental plasticity (ADP) works on different levels, from genetic expression to phenotypic expression levels, and from the properties of neural circuits to characteristics of behavioral patterns and performance (Fawcett & Frankenhuis, 2015; E. Snell-Rood & C. Snell-Rood, 2020; Stearns,1989). Differences in genetics, or genetic polymorphisms, may also titrate variations in phenotypic expressions through ADP mechanisms (Lafuente & Beldade, 2019; Lea et al., 2017) and may increase sensitivity to environmental stimuli and cues (Bento et al., 2010; Suzuki & Nijhout, 2006). The common human genetic polymorphism, brain derived neurotrophic factor gene (abbreviated *Bdnf* gene, or BDNF protein), may be one of genes that titrates how much experience can mediate the expression of phenotypic variants at the molecular, neural circuit, and behavioral level.

Human BDNF Val66Met polymorphism

A common BDNF variant in human is the single-nucleotide polymorphism (SNP) in which valine (Val) is substituted by methionine (Met) at codon 66 (defined as Val66Met) at the prodomain of the gene (Egan et al., 2003). The analogous human Val66Met SNP in a mouse model is at codon 68. The Met substitution at this codon confers disruptions in dendritic trafficking, differential protein distribution at local synapses, and decreased activity-dependent release of BDNF (Chen et al., 2004; Egan et al., 2003). The differences in activity-dependent release of BDNF resulting from the Val66Met SNP are thought to alter the developmental trajectory and time course of neural circuits (Bath & Lee, 2006; Jing et al., 2017; Pattwell et al., 2012; Vandenberg et al., 2015; Wang, Liu, et al., 2015).

The Val66Met SNP occurs in 20-50% of the human population, depending on the ethnicities, about 20-30% in Caucasian populations (Chen et al., 2006; Kowiański et al., 2018). It has been linked to increased risk for psychiatric disorders such as schizophrenia (Angelucci et al., 2005; Gratacos et al., 2007), depression and anxiety disorders (Angelucci et al., 2005; Chen et al., 2006; Joffe et al., 2009), post-traumatic stress disorders (Frielingsdorf et al., 2010), and eating and substance use disorders (Biskupska et al., 2013; Cheng et al., 2005; Duncan, 2012; Gratacòs et al., 2007; Greenwald et al., 2013).

Studies investigating the effects of the human BDNF Val66Met polymorphism in cognitive functions have come to an array of conclusions. Some studies indicate that Met carriers have cognitive and memory deficits, in inhibitory control (Enge et al., 2018), selective information processing (Miyajima et al., 2008; Schofield et al., 2009), learning and intelligence (Miyajima et al., 2008; Tsai et al., 2004;), fear conditioning, and hippocampal-dependent learning and memory (Bath & Lee, 2006; Egan et al., 2003). In contrast, others report that Met carriers have enhanced executive functions and conferred advantages to Val/Val carriers in response selection, inhibition, task switching, and tasks with interferences (Alfimova et al., 2012; Beste, Baune, et al., 2010; Beste, Kolev, et al., 2010; Erickson et al., 2008; Gajewski et al., 2011, 2012; Getzmann et al., 2013). However, a meta-analysis on studies of Val66Met SNP effects on visual processing skills, memory, cognitive ability, and executive function found no convergent evidence for associations between BDNF polymorphism and cognitive phenotypes (Mandelman & Grigorenko, 2012). These dramatic differences found in Val/Val versus Met carriers may be accounted by variations in developmental environments across different studies.

In medical contexts, genetic polymorphisms are often explored as “risk factors” that raise the risk of specific disorders or deficits. But in the context of evolutionary biology, it becomes imperative to question why polymorphisms are present and to ask what benefits come from polymorphisms that have been maintained in a population. It has been suggested that one benefit, potentially provided by some prevalent genetic polymorphisms, is a biological change which confers extra plasticity or sensitivity to the environment (Belsky et al., 2009). This can be examined by investigating differences in human carriers of different polymorphisms and by modeling these polymorphisms in mice.

For example, it has been shown that institutionalized children who carried a Met allele in codon 66 of the *Bdnf* gene fared worse in institutional setting and benefited most from interventions when they were compared to their Val/Val controls (Drury et al., 2012). This has been interpreted as evidence that this polymorphism and others previously associated with higher risk may instead be “plasticity alleles,” predicting higher responsiveness to both positive and negative adverse environments (Belsky et al., 2009; Drury et al., 2012; Gerritsen et al., 2012). A rodent study using a mouse model of Val66Met polymorphism also found that Met/Met mice displayed significantly augmented motor performance in motor functional recovery after stroke experience (Qin et al., 2014).

Based on these ideas, we set out to investigate if the BDNF polymorphism affects the sensitivity of mice to changes in the environmental cues within mouse’s lifetime by using mouse models of human BDNF Val66Met polymorphism. We examined effects of BDNF Val66Met on learning and cognitive functions in a battery of behavioral tests in two different mouse models of this SNP. It has been found that there are differences in

performance of a go/no-go learning task in humans carrying Val66Met polymorphism (Beste, Baune, et al., 2010; Enge et al., 2018), therefore we created a mouse go/no-go task and also added a reversal to test sensitivity to changes in contingency. A 4-choice foraging task was also used to test discrimination and reversal learning with an enhanced cognitive load and changes in environmental contingencies.

We found that mice with Met/Met alleles from a recently published BDNF Met knock in line (Warnault et al., 2016) had no significant differences in discrimination learning but showed significantly more efficient reversal learning in a go/no-go task and a 4-choice odor-based foraging task. This suggested they had greater flexibility and sensitivity in response to changes in environmental contingencies. These results are consistent with the hypothesis under the ADP framework that BDNF polymorphism with Met allele may confer greater sensitivity to the environment and provide adaptive plasticity mechanisms.

Methods

Animals and data collection

Two different mouse lines mimicking human BDNF Val66Met polymorphism were used in the experiments. The mouse line of BDNF Met allele knock in at codon 68, Val68Met mice, was generated by the Dorit Ron Lab (Warnault et al., 2016). The Val68Met in mice was found to be homologous to the human Val66Met mutation, where the target codon 68 is the appropriate valine (Val) location. The second mouse line used in the experiments were the Val66Met mice, in which the human BDNF methionine (Met) allele was selected and genetically engineered into the mouse genome at the BDNF codon 66 position (Chen et al., 2004; 2006). All mice were bred in the animal facility and were group housed on a 12h/12h reverse light-dark cycle (lights on at 10PM) in an environment enriched with bedding and toys. Adult males and females (postnatal day (P) 60-90) were used for these experiments with roughly equal sex proportions Animal procedures were approved by the Ernest Gallo Clinic and Research Center Institutional Animal Care and Use Committee and UC Berkeley Animal Care and Use Committee. Behavioral data was co-collected by Angela Vandenberg[2].

[2] Data included in this chapter was co-collected by Dr. Angela Vandenberg and published in Vandenberg, Lin, et al. (2018), I conducted data analysis and wrote the manuscript as co-first author. Here the writing is new and the data are presented and interpreted from a broader perspective that integrates with my larger thesis.

Go/No-go odor-based learning task

In this task (**Fig. 3A**), mice were water restricted for 2 days prior the behavioral training and kept water restricted throughout the training and testing. Mice were trained to nose-poke in a center port to initiate an odorant cue for either a 70% probability of "go" cue or 30% probability of "no-go" cue. In correct "go" trials, mice were required to nose-poke in an available peripheral port within 3 seconds to receive water reward. In correct "no-go" trials, mice were required to make no nose-poke response for 3 seconds and did not receive water reward. In incorrect "go" or "no-go" trials, mice received a 5-second time-out as punishment. There were three phases in this go/no-go task: a shaping phase (Phase 1) where the animals learned the task structures with odorants A ("go" cue) and B ("no-go" cue); a training phase (Phase 2) where new odorants C ("go" cue) and D ("no-go" cue) were introduced; and a reversal phase (Phase 3) where the reward contingency was reversed, odorant D becoming the "no-go" cue and odorant C the "go" cue. Mice were trained in each phase until they reached 80% correct.

4-choice odor-based foraging discrimination and reversal task

In our go/no-go task, there were two odorant cues simultaneously presented in each trial. In order to understand the effects of human Val66Met polymorphism on cognitive functions, we also tested a separate cohort of adult Val68Met mice in an odor-based foraging task (**Fig. 4A**). This 4-choice odor-based foraging task had two phases, discrimination and reversal phase, and four different odorant cues simultaneously presented in each phase, which allowed us to test these two types of learning with greater complexity and enhanced cognitive load.

The task was adapted from Kim and Ragozzino (2005) and has been used in several previous studies to test cognitive flexibility in both rats (Ragozzino & Rozman, 2007) and mice (Johnson & Wilbrecht, 2011; Thomas et al., 2016). A different reward modality was used in this task. Instead of water reward, we used Cheerio fragments as a food reinforcer. Adult mice were food restricted two days prior the training and kept food restricted throughout the training and testing, which was similar to the go/no-go training procedure. In the training phase, mice were habituated to the arena and learned to find out the Cheerio fragments buried in non-scented wood shavings in the pots by digging. Both discrimination and reversal learning were tested in the same testing day. In the discrimination phase, mice were required to discriminate among 4 different odorants (O1, O2, O3, O4) from the scented wood shavings in the 4 different pots and learn that only a single odorant (O1) was associated with a Cheerio reward. In this experiment, the mice were given a single 'sample' trial in which a pot with the rewarded odorant was placed in the center and allowed to retrieve the cheerio reward before the first trial of the discrimination phase (but not in the reversal phase). After this sample trial, the discrimination phase commenced. Mice had to reach the criterion of 8 out of 10

correct trials consecutively prior moving forward to the reversal phase. In the reversal phase, the previously rewarded odorant (O1) became unrewarded; and a previously used non-rewarded odorant (O2) became rewarded. A new odorant (O4') replaced the O4 in the task as a distractor with novelty in the learning environment. The same criterion rule was applied in the reversal phase. The scented pots were pseudo-randomized and shifted around 4 different quadrants of the testing arena.

Statistical analysis

Values are reported as mean (M) ± standard error of mean (SEM). Data were analyzed using two-tailed t-tests or ANOVAs with post-hoc analysis. GraphPad Prism 7 was used for statistical analysis.

Results

Go and No-go learning

Results from previous studies have suggested that human with Met allele substitution (Val/Met and Met/Met) made fewer false alarms and had better response inhibition in a go/no-go task when compared to homozygous Val/Val individuals (Beste, Baune, et al., 2010). To examine if we could observe the same behavioral phenotypes in a go/no-go task, we tested adult (P60-90) Val68Met knock-in mice from Warnault et al. (2016) on an automated odor discrimination go/no-go task (**Fig. 3A**).

We found that adult homozygous Val/Val and Met/Met littermates (P60-90) performed similarly in "go" performance (% of "go" trials correct) in all three phases of the task (**Fig. 3,** BDNF Val68Met line: Val/Val n = 10, Met/Met n = 10; **Fig. 3B,** Phase 1: genotype: $F(1,115) = 0.64$, $p = 0.42$, session: $F(6,115) = 4.51$, $p = 0.0004$, interaction: $F(6,115) = 0.70$, $p = 0.65$; **Fig. 3D,** Phase 2: genotype: $F(1,72) = 2.37$, $p = 0.13$, session: $F(3,72) = 9.99$, $p < 0.0001$, interaction: $F(3,72) = 0.049$, $p = 0.99$; **Fig. 3F,** Phase 3: genotype: $F(1,84) = 1.46$, $p = 0.23$; session: $F(5,84) = 8.06$, $p < 0.0001$, interaction: $F(5,84) = 0.57$, $p = 0.72$).

In "no-go" performance, adult homozygous Val/Val and Met/Met littermates (P60-90) showed similar performance (% of "no-go" trials correct) in the first two phases of the task, learning to avoid responding to the "no-go" cue with comparable accuracy (**Fig. 3C,** Phase 1: genotype: $F(1,115) = 0.96$, $p = 0.33$, session: $F(6,115) = 12.37$, $p < 0.0001$, interaction: $F(6,115) = 0.29$, $p = 0.94$; **Fig. 3E,** Phase 2: genotype: $F(1,72) = 0.31$, $p = 0.58$, session: $F(3,72) = 9.18$, $p < 0.0001$, interaction: $F(3,72) = 0.21$, $p = 0.89$).

However, in the reversal phase of the task Met/Met adult mice took fewer sessions to reach an 80% correct criterion than Val/Val adult mice did (**Fig. 3G**). Two-way analysis of variance (ANOVA) showed a significant main effect of genotype and session number on “no-go” performance (% “no-go” trials correct) (**Fig. 3G,** genotype: $F(1,84) = 4.03$, $p = 0.048$, session: $F(5,84) = 14.05$, $p < 0.0001$, interaction: $F(5,84) = 0.35$, $p = 0.88$). Our results showed that Val68Met mice with Met allele had a greater efficiency of learning in the reversal phase (phase 3) of the go/no-go task, especially in the trials with “no-go” cues.

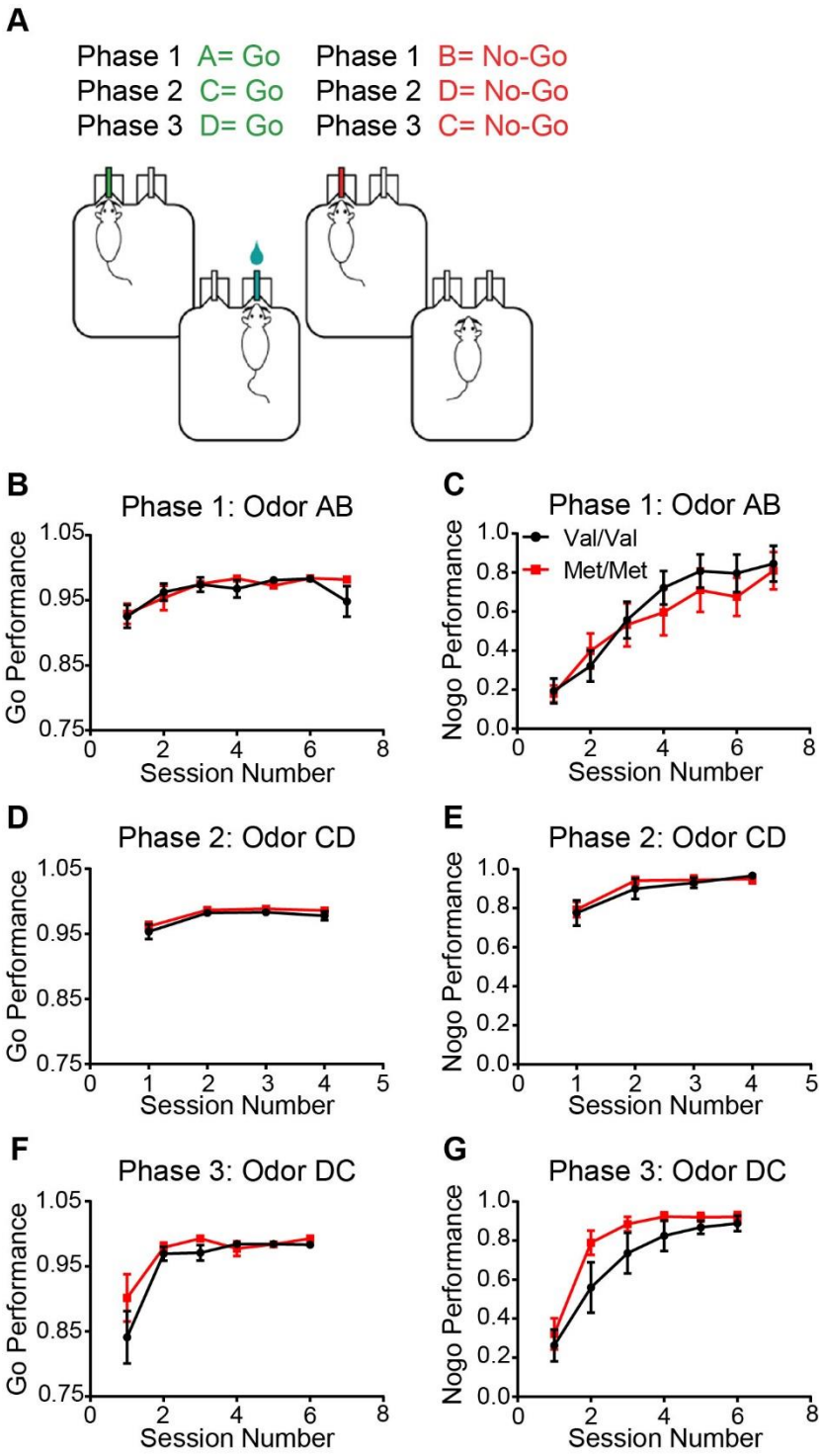


Figure 3. BDNF Met/Met mice learned a go/no-go task at rates comparable to Val/Val littermates, but showed faster acquisition of a reversal. **A**, Schematic of the go/no-go task. The task had three phases: In phase 1 (shaping) mice learned the task by responding to odorants A (go cue) and B (no-go cue); In phase 2 (training) new odorants C (go cue) and D (no-go cue) were introduced; In phase 3 (reversal), odorants C and D were reversed so that C became the "no-go" cue and D became the "go" cue. **B**, **C**, Val/Val (n=10) and Met/Met (n=10) mice learned the task at similar rates in go and no-go performance (% correct) during the initial shaping session (A=go cue, B=no-go cue). **D**, **E**, they also performed comparably during the training phase when novel odorants C (go) and D (no-go) were introduced. **F**, **G**, In phase 3, when go and no-go odors were reversed (DC), Val/Val and Met/Met mice differed in their no-go performance (% correct): A two-way ANOVA showed a significant main effect of genotype and session number (genotype: $F(1,84)=4.03$, $p=0.048$, session: $F(5,84)=14.05$, $p<0.0001$) but no significant interaction between the two ($F(5,84)=0.35$, $p=0.88$). Met/Met mice achieved >80% correct in session 3 while Val/Val mice reached >80% correct in session 4. Error bars represented SEM.

4-choice odor-based foraging discrimination and reversal learning

In addition to testing reversal learning or cognitive flexibility in the 2-choice go/no-go task, we also tested Val68Met mice in a foraging task with 4-choices (**Fig. 4A**) requiring that mice integrate and update more environmental cues prior to selecting a choice. We found that adult (P60-90) Val/Val and Met/Met mice took similar trials to reach the criterion in the discrimination phase (**Fig. 4B,** Val/Val n=10, Met/Met n=12, t(20) = 0.42, p = 0.68) with similar total numbers of error (**Fig. 4C,** t(20) = 0.13, p = 0.90). When the reward contingencies were changed, adult Val/Val and Met/Met mice took similar trials to reach 8 out of 10 trials correct (**Fig. 4D**). However, we found that Met/Met mice made significantly fewer perseverative errors back to the originally rewarded odor (O1) before their initial discovery of the new odorant (O2)-reward association (**Fig. 4E,** t(20) = 3.14, p = 0.005). There was no difference in regressive errors, another reversal error type, defined as errors back to the originally rewarded odor (O1) after the new reward contingency (O2) was found once, between groups (**Fig. 4F,** t(20) =1.18, p = 0.25).

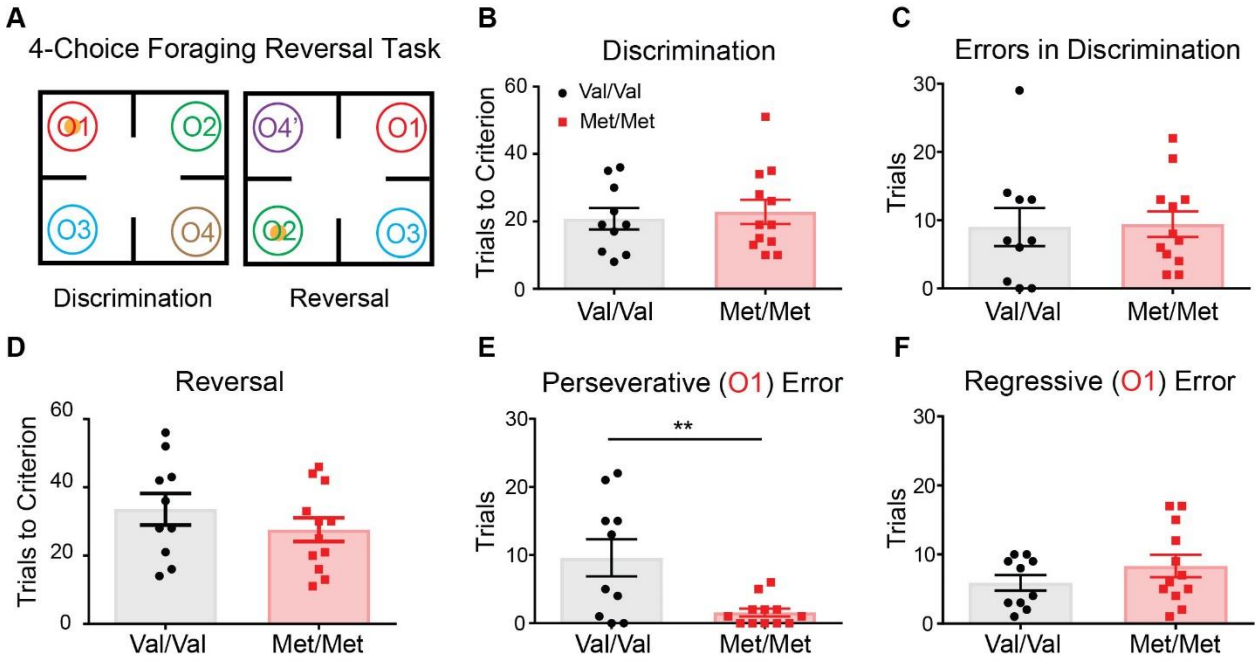


Figure 4. BDNF Val68Met Met/Met adult mice learned a 4-choice foraging task at rates comparable to their Val/Val littermates, but showed fewer perseverative errors in reversal learning. **A**, Schematic of the task. Four different odorants were introduced. In the discrimination phase, mice discriminated odorants to find a buried cheerio reward associated with O1. Pots were shifted after each trial. In the reversal phase, immediately after discrimination, a previously unrewarded odor (O2) predicted the reward and a novel odor (O4') was introduced. The criterion to complete was retrieving the reward correctly in 8 out of 10 consecutive trials. **B**, Met/Met (n=12) and Val/Val (n=10) mice took similar number of trials to complete the discrimination phase (p=0.68), and **C**, made a similar number of errors (t(20)=0.13, p=0.90). **D**, In the reversal phase, trials to criterion was comparable between groups (t(20)=1.1, p=0.30). **E**, Perseverative errors, made before 1 correct, were fewer in adult Met/Met mice compared to Val/Val mice (t(20)=3.14, p=0.005). **F**, Regressive errors, made after 1 correct, were similar between the two genotypes (t(20)=1.18, p=0.25). p**<0.01. Error bars represented SEM.

In addition to analyze trials to criterion and different types of errors in the 4-choice foraging task, we analyzed the latency to make a choice in each trial to see if BDNF Val66Met polymorphism affects response time in this task. We found that there was a main effect of trial type in the choice latency in the discrimination phase (**Fig. 5A,** Two-way ANOVA: genotype: $F(1,40) = 0.77$, $p = 0.39$, trial type: $F(1,40) = 4.27$, $p = 0.045$, interaction: $F(1,40) = 0.013$, $p = 0.91$) but were no significant differences in time spent making either a correct or incorrect choice between Val/Val and Met/Met genotypes in either the discrimination phase (**Fig. 5A,** correct choice latency (seconds, mean ± SEM): Val/Val = 44.68 ± 9.61, Met/Met = 36.12 ± 3.65; incorrect choice latency: Val/Val = 69.16 ± 19.34, Met/Met = 58.05 ± 9.26;) or the reversal phase (**Fig. 5B,** correct choice latency: Val/Val = 30.51 ± 4.87, Met/Met = 33.79 ± 6.66; incorrect choice latency: Val/Val = 45.35 ± 7.28, Met/Met = 40.78 ± 6.73; Two-way ANOVA: genotype: $F(1,40) = 0.0097$, $p = 0.92$, trial type: $F(1,40) = 2.78$, $p = 0.10$, interaction: $F(1,40) = 0.36$, $p = 0.55$).

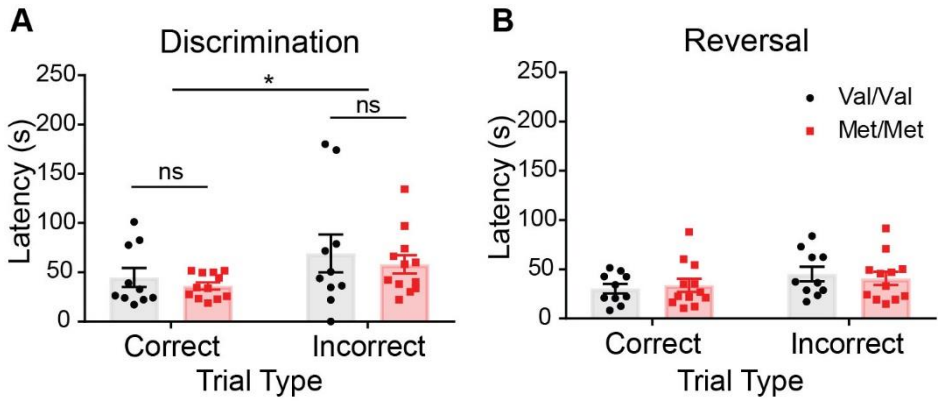


Figure 5. Adult Val/Val and Met/Met mice spent similar time making choice in the 4-choice foraging task. A,B, There were no significant differences in choice latency in correct and incorrect trials in the discrimination and in the reversal phase between the two groups (Val/Val n=10, Met/Met n =12). **A,** There was a main effect of trial type (p=0.0045) in the discrimination phase. *p<0.05. Error bars represented SEM.

Our results in this 4-choice foraging task showed that adult Val/Val and Met/Met mice from Val68Met line had similar performance in the initial acquisition of odorant-reward associations but in the reversal phase Met/Met mice made fewer perseverative errors.

BDNF Val66Met polymorphism in male vs female mice

Both adult male and female Val68Met mice (P60-90) were used in the go/no-go experiment and the 4-choice foraging task with roughly equal number of mice in each genotype. We found that male Val/Val mice had better “go” and “no-go” performance than female Val/Val mice in the initial acquisition of go/no-go task structure (Phase 1: shaping phase), but this sex difference was not observed in the Met/Met homozygous mice (**Fig. 6A,B,** Val/Val: n(M)=5, n(F)=5; Met/Met: n(M)=5, n(F)=5). We did not find other significant performance differences between male and female mice in each genotype within either second or third phases of the go/no-go task (**Fig. 6C-F**) or in the discrimination and reversal phase of the 4-choice foraging task (**Fig. 6G-I,**Val/Val: n(M)=5, n(F)=5; Met/Met: n(M)=4, n(F)= 8). These experiments were not powered to examine sex differences, so final conclusions are still difficult to draw from these data.

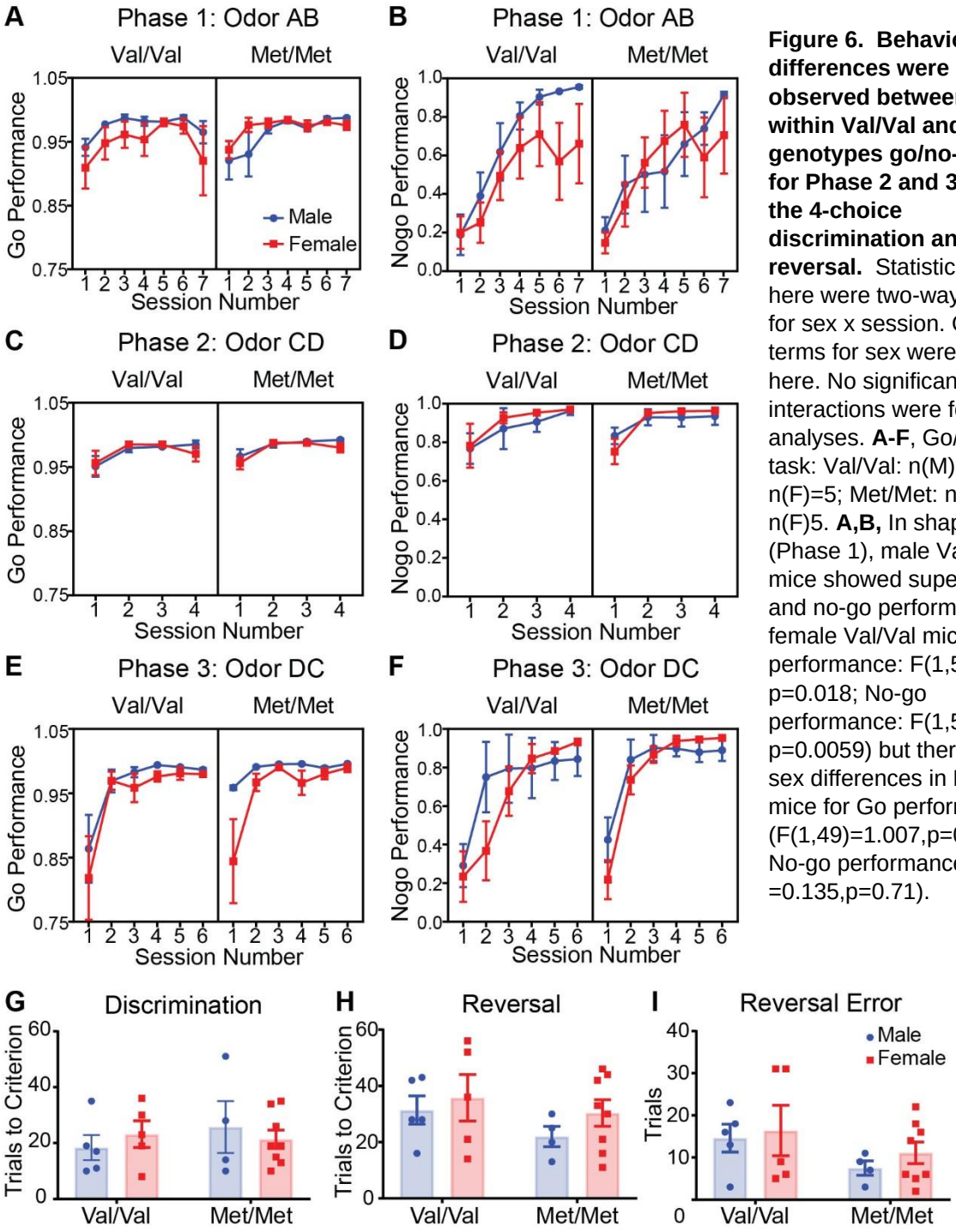


Figure 6. Behavioral differences were not observed between sexes within Val/Val and Met/Met genotypes go/no-go task for Phase 2 and 3 and in the 4-choice discrimination and reversal. Statistics reported here were two-way ANOVA for sex x session. Only terms for sex were reported here. No significant interactions were found in all analyses. **A-F**, Go/no-go task: Val/Val: n(M)=5, n(F)=5; Met/Met: n(M)=5, n(F)5. **A,B,** In shaping (Phase 1), male Val/Val mice showed superior go and no-go performance than female Val/Val mice (Go performance: $F(1,52)=5.934$, $p=0.018$; No-go performance: $F(1,52)=8.23$, $p=0.0059$) but there were no sex differences in Met/Met mice for Go performance ($F(1,49)=1.007$,$p=0.32$) or No-go performance ($F(1,49)=0.135$,$p=0.71$). **C-F,** In training (Phase 2) and reversal (Phase 3), there were no sex differences in both go and no-go performance in both Val/Val and Met/Met genotypes. (**C**, Val/Val: $F(1,32)=0.0005$, $p=0.98$; Met/Met: $F(1,32)= 1.46$, $p=0.24$; **D,** Val/Val: $F(1,32)=0.46$,$p=0.50$; Met/Met: $F(1,32)=0.00015$, $p=0.99$; **E,** Val/Val: $F(1,37)=1.50$,$p=0.23$; Met/Met: $F(1,35)=3.61$,$p=0.066$; **F**, Val/Val: $F(1,37)=0.47$,$p=0.50$ Met/Met: $F(1,35)=0.31$,$p=0.58$). **G-I**, Val68M did not have sex differences in the 4-choice discrimination and reversal learning in either genotype (Val/Val: n(M)=5, n(F)= 5; Met/Met: n(M)=4, n(F)=8; Trials to criterion in Discrimination: $F(1,18)=0.0017$, $p=0.97$; Trials to criterion in Reversal: $F(1,18)=1.16$, $p=0.30$; Reversal Error: $F(1,18)=0.51$,$p=0.49$). Error bars represented SEM.

An alternate mouse line of human BDNF Val66Met polymorphism

An alternate mouse line mimicking human BDNF Val66Met polymorphism was also available for experimentation which has a Met substitution for Val at codon 66 (Val66Met mice, Chen et al., 2004; Chen et al., 2006). We next obtained this line and tested it in the same 4-choice foraging task (**Fig. 7A**).

We did not find significantly different performance in learning across measures of trials to criterion and the numbers of errors in the discrimination and reversal phase in this alternate line of Val/Val and Met/Met Val66Met mice (**Fig. 7B,C**, Discrimination phase: trials to criterion: $t(21) = 1.14$, $p = 0.27$, errors in discrimination: $t(21) = 1.34$, $p = 0.19$; **Fig. 7D-F,** Reversal phase: trials to criterion: $t(21) = 0.22$, $p = 0.83$, perseverative errors: $U = 43.50$, $p = 0.17$, regressive error: $U = 51.50$, $p = 0.38$). We also found no difference between the WT Val/Val groups from the two lines (Discrimination phase: trials to criterion: $t(20) = 0.21$, $p = 0.83$, discrimination errors: $t(20) = 0.35$, $p = 0.73$; Reversal phase: trials to criterion: $t(20) = 0.02$, $p = 0.99$, perseverative errors: $U = 48$, $p = 0.44$; regressive errors: $U = 58$, $p = 0.91$; two-tailed unpaired t-tests were used when data was normally distributed. When data was not normally distributed found by a D'Agostino and Pearson omnibus test, a Mann-Whitney non-parametric test were used for comparison).

Previous studies had shown that there were different behavioral phenotypes in anxiety-like behavior in these two lines, with enhanced anxiety found in Val66Met mice (Chen et al., 2006) but not in Val68Met mice (Warnault et al., 2016). It is possible that greater anxiety-like behavior in the Val66Met mice (Chen et al., 2006) may interfere with flexibility in the 4-choice reversal.

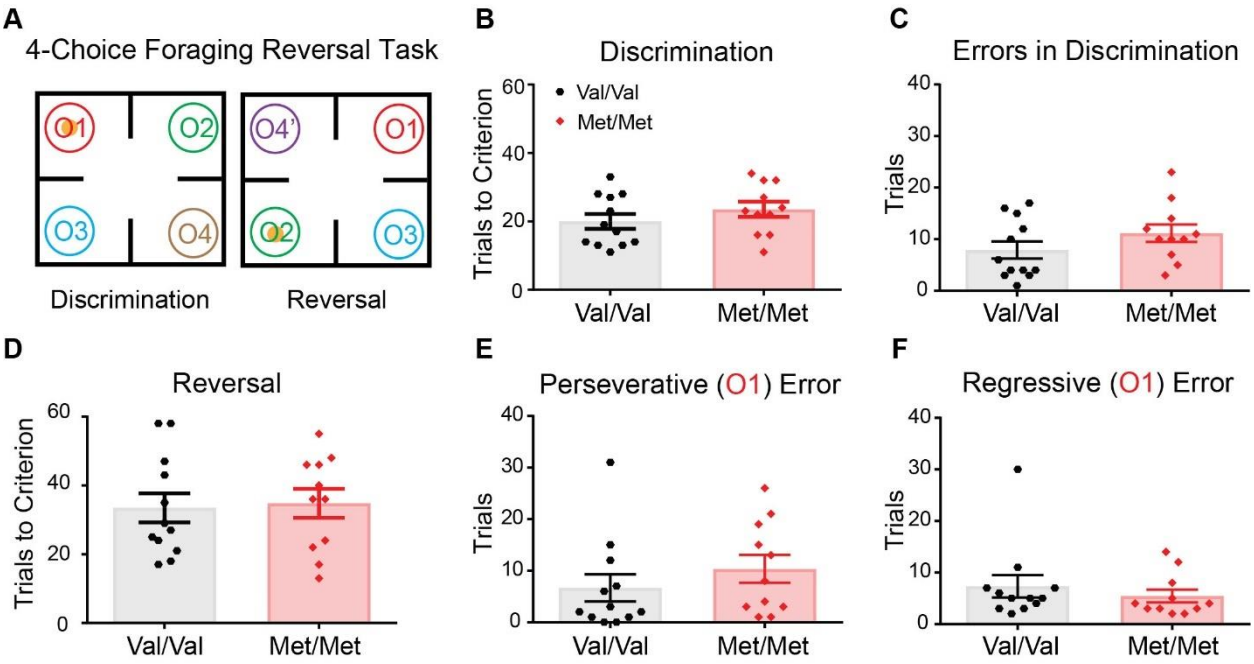


Figure 7. An alternate line of BDNF Val66Met mice (Chen et al., 2006) did not illustrate greater flexibility in reversal learning. A, Schematic of 4-choice foraging task. **B**, Met/Met (n=11) and Val/Val (n=12) mice took similar number of trials to reach criterion ($t(21)=1.14$, $p=0.27$), and **C**, made a similar number of errors ($t(21)=1.37$, $p=0.19$) in the discrimination phase. In the reversal phase, **D**, trials to criterion ($t(21)=0.22$, $p=0.83$), **E,** perseverative errors ($U=43.50$, $p=0.17$) and **F**, regressive errors ($U=51.50$, $p=0.38$) did not differ between the two genotypes.

Discussion

We found that BDNF Val68Met knock-in (Met/Met) mice showed similar performance to Val/Val WT littermates in the initial acquisition and learning (**Fig. 3B-E; Fig. 4B,C**). However, Met/Met mice were more flexible than Val/Val in updating their performance after a contingency reversal in a go/no-go task, taking fewer sessions to reach 80% correct performance in “no-go” trials (**Fig. 3G**). This might indicate they conferred an advantage in response selection with response inhibition when there were reversed reward contingencies and new information in the go/no-go task. It was consistent with the findings in human studies that human Met-allele carriers (Val/Met or Met/Met) performed better with fewer false alarms in a go/no-go task (Beste, Baune, et al., 2010). Val68Met Met/Met mice also displayed greater flexible updating in the reversal phase of the 4-choice odor-based foraging task, with fewer trials of perseverative error but not regressive error (**Fig. 4E,F**).

These data suggest that Met carriers are more flexible in reversal learning in two task contexts. This suggests they are more sensitive to changes in the environment. These data support the idea that a common genetic polymorphism such as Val66Met may

serve as a plasticity allele that modifies sensitivity to experience or the environment (Belsky et al., 2009; Qin et al., 2014). This differs from the risk hypothesis or deficit model interpretation that suggests a Val66Met polymorphism confers deficiencies in functions. The plasticity hypothesis may also explain why a SNP might be beneficial and therefore maintained by natural selection in the populations over time.

The concept of a plasticity allele is directly relevant to ADP in learning and decision making. Plasticity alleles and genetic polymorphisms might titrate a species responsiveness to the environment. By adjusting sensitivity to environmental signals, organisms could potentially hedge against the failure of phenotypes or behavioral strategies over time (Lafuente & Beldade, 2019; Lea et al., 2017).

Relevance to data on human cognition

Previous studies from human literature have found that elderly populations carrying Val/Met or Met/Met exhibited enhanced performance in task switching with reduced interference and distraction in an auditory distraction paradigm and Stroop task (Gajewski et al., 2011, 2012; Getzmann et al., 2013). Our enhanced performance in two reversal tasks are generally consistent with these data. Although our data does not fully replicate one human study that found Met carriers were better at No-go inhibitions than Val/Val subjects (Beste, Kolev, et al., 2010), our data does support the findings that Met genotypes can confer some cognitive benefits (Alfimova et al., 2012; Beste, Baune, et al., 2010; Erickson et al., 2008; Gajewski et al., 2011, 2012; Getzmann et al., 2013). Our acquisition and discrimination data in the two tasks, and in two lines of BDNF mutant mice (**Fig. 3,4,7**) do not support any general learning deficit in the Met/Met genotype.

Possible mechanisms

There are a number of mechanisms which may mediate the effect of the Val66Met polymorphism on learning and decision-making circuits. These different mechanisms could also possibly combine or independently affect different neural circuits supporting these cognitive functions (Izquierdo et al., 2017).

The neurotrophic factor, BDNF, is widely expressed in many brain regions and can activate multiple intracellular signaling pathways, both pre- and post-synaptically. BDNF together with one of its associated receptors, tropomyosin related kinase B (TrkB) receptors, form the signaling pathways that play a pivotal role in regulating development, structures, and functions of neural circuits as well as synaptic plasticity (Cohen-Cory et al., 2010; Kowiański et al., 2018; Lu et al., 2013; Park & Poo, 2013; Sasi et al., 2017). As a neurotrophic factor, BDNF was found to be necessary for initial

neural cell survival and differentiation of specific neuronal populations (Ahmed et al., 1995; Baydyuk & Xu, 2014; Park & Poo, 2013; Pinzón-Duarte et al., 2004; Shetty & Turner, 1998). It is also important in synaptogenesis and the growth of axons and dendrites in developing neural circuits (Alsian et al., 2001; Cohen-Cory et al.,2010; Lu et al., 2013; Park & Poo, 2013; Sanchez et al., 2006). In addition, BDNF also plays a critical role in refinement of activity-dependent synapses and synaptic plasticity of mature neural circuits, such as facilitation and maintenance of long-term potentiation (LTP) and regulation of long-term depression (LTD) with low frequency stimulation (Akaneya et al., 1997; Kowiański et al., 2018; Lu et al., 2013; Park & Poo, 2013; Sasi et al., 2017; Tanaka et al., 2008). BDNF is also thought to play a pivotal role in maturation of inhibitory circuits in the neocortex (Abidin et al., 2008; Huang et al., 1999).

Activity-dependent release of different variants of BDNF in dorsal prefrontal cortex, orbital frontal cortex, and anterior cingulate cortex can possibly be the underlying mechanism supporting the observed enhanced flexibility in reversal learning and potential better response inhibition (Bissonette et al., 2008; Johnson & Wilbrecht, 2011; Ragozzino & Rozman, 2007; Velanova et al., 2008). BDNF is also found to regulate development, maturation, and synaptic plasticity of striatal circuits (Baydyuk & Xu, 2014; Jia et al., 2010; Wang, Liu, et al., 2015), which is important for flexible updating, learning, and decision making (Cox & Witten, 2019; Lee et al., 2015). We speculate that higher levels of flexibility and exploratory behavior observed in juvenile mice in the same 4-choice foraging task (Johnson & Wilbrecht, 2011) may persist in the juvenile form in adult BDNF homozygous Met (Val68Met) mice due to lower activity-dependent release of BDNF. In future studies, it will be important to determine how circuit development is altered in BDNF Val68Met mice, particularly in cortical-striatal circuits known to support these cognitive functions.

Conclusion

In conclusion, our results support the idea that Met allele in human Val66Met polymorphism can confer some cognitive benefits and is possibly a “plasticity” allele (Belsky et al., 2009) potentially providing greater sensitivity to the context and environment through ADP mechanisms. This could manifest over the time scales of hours (in our experiment) or over years (for example in studies of institutionalized youth in Drury et al., (2012)). In the cumulative span of time, we posit the Met allele may enable higher sensitivity to both positive and negative environments.

Chapter 3

Different feeding experience during the juvenile-adolescent period affects cognitive flexibility and reward integration in adult male mice

Introduction

When encountering different experiences or statistics in the developmental environment (such as scarce or plentiful food), it is thought that organisms can respond with adaptive developmental plasticity (ADP). In ADP, information from the environment can trigger different developmental programs in order to enhance the likelihood of survival in specific types of environment (Nettle & Bateson, 2015; Stearns, 1989). It has been shown in many species that life experiences occurring during developmental time course (including neonatal, juvenile, and adolescent periods) may have profound impacts on body and brain development, including behavioral functions (Fawcett & Frankenuis, 2015; Frankenhuis & Walasek, 2020; Nettle & Bateson, 2014; E. Snell-Rood & C. Snell-Rood, 2020). Experience dependent plasticity may also be limited to specific developmental time periods or have different effects depending on their timing (Fawcett & Frankenhuis, 2015; Frankenhuis & Walasek, 2020). This is because neural circuits each have their own timeframe for development. The timeframe of these periods of plasticity, in turn, may limit the time when experience can alter the developmental trajectories of the neural circuits (Dow-Edwards et al., 2019; Glasper & Neigh, 2019; Hensch, 2005; Knudsen, 2004; Lin et al., in press; Piekarski, Johnson, et al., 2017).

Literature from human and rodents studies has shown that exposure to adverse experiences in early life (defined by a variety of factors) can alter sensitivity to reward, escalate responsivity to psychostimulants, enhance reward seeking, and increase vulnerability to develop substance use disorders (Duffy et al., 2018; Kambali et al., 2019; Novick et al., 2018; Valenti et al., 2011; Ventura et al., 2013). Further studies in rodent models have shown that experience of adversity (again defined by a variety of factors) can affect learning, memory and decision making (Banqueri et al., 2017; Birn et al., 2017; Hanson et al., 2017; Ricon et al., 2012; Wang et al., 2011; Zhu et al., 2010). Cognitive flexibility in particular has been found to be sensitive to developmental experiences. Rodent studies modeling maternal neglect in early life, social isolation, or restraint stress in juvenile adolescence period have found that these experiences can result in reduced cognitive flexibility and/or stronger habit formation (Amitai et al., 2014; Goodwill et al., 2018; Hurtubise & Howland, 2017; Thomas et al., 2016; ; Wang et al., 2011). These results illustrated that developmental experience can affect expression of specific functions. From an ADP perspective, it is possibly the effects of the developmental experience on these same functions would result in variations in the expression of phenotypes in a context-dependent manner. Adaptive phenotypic

alteration would be observed if the environment matches the predicted state under ADP.

Food insecurity is a growing issue with effects on human behavior that are not fully understood

We are interested in how the stability of access to food affects the development of learning and decision making in mammals. Food insecurity is a public health term defined as uncertain or limited access to sufficient, nutritionally adequate, and safe food (Coleman-Jensen et al., 2013; Cook & Frank, 2008). Food insecurity is a prevalent public health issue. Approximately, 14.5 million households with children in the United States and over 2 billion people worldwide currently experience food insecurity in their daily life (Coleman-Jensen et al., 2019; World Health Organization, 2019). Children from households with food insecurity were found more likely to have a variety of health and behavioral problems (Gundersen & Ziliak, 2014). Human studies have found that food insecurity is associated with greater risks of obesity and diabetes (Davis et al., 2014; Decker & Flynn, 2018; Franklin et al., 2012), poor health and adverse psychosocial outcomes (Althoff et al., 2016; Cook et al., 2008, 2013; Ke & Ford-Jones, 2015; Laraia, 2013), and learning, cognitive, and/or behavioral problems such as lower math scores, reading performance, and academic achievement, social skills, and self-control (Ashiabi 2005; Aurino et al., 2019; Belsky et al., 2010; Howard, 2011; Jackson et al., 2018; Jyoti et al., 2005; Ke & Ford-Jones, 2015; Raskind et al., 2019; Weigel & Armijos et al., 2018; Whitaker et al., 2006;).

Most of the human studies focused on the correlational and mediational effects of food insecurity early in life and childhood on health, psychosocial behavioral outcomes, academic learning, and overall school performance. There are fewer studies that examined effects of food insecurity on specific cognitive functions and/or neural functions. Aurino et al. (2019) found that chronic food insecurity or punctuated experiences of food insecurity at different stages of development up to age 12 had significant effects on tests of vocabulary, reading, and math. Dennison et al. (2019) found that food insecurity, but not other types of childhood adversity such as emotional deprivation and trauma, was associated with poor reward performance in terms of total reward earned. There are no specific studies of effects of food insecurity on direct measures of executive functions such as working memory, behavioral inhibition, and cognitive flexibility in humans, to our knowledge. Effects of food insecurity in human studies are often confounded with other factors such as poverty, parental mental health, substance misuse, abuse, education, etc. While researchers may try to control for these variables, it is hard to fully isolate food insecurity from other variables to test if early life experience of food insecurity, specifically, during childhood and adolescence, has direct causal effects on cognitive functions. Therefore, it is valuable to develop a mouse model of food insecurity in a controlled laboratory environment to understand its direct effects

on learning and an important executive function, cognitive flexibility, under different environmental contexts and its direct effects on neurobiology. We address the effects of food insecurity and feeding history on neurobiology in the next chapter (Chapter 4).

Effects of food insecurity on cognitive functions? Deficit vs. adaptive developmental plasticity?

We in particular focus on impacts of different developmental feeding experiences in our studies. Specifically, we ask if ad libitum and food insecurity feeding history with fluctuating statistical information during the juvenile-adolescent period have an impact on learning and cognitive flexibility during adulthood in two tasks that capture two different environmental contexts, stable and deterministic versus probabilistic environment. Cognitive flexibility or flexible updating is the ability to update and switch behavior flexibly between different strategies, idea sets, and tasks to execute goal-directed behaviors in response to dynamic demand and contingency changes in the environment, which depends on executive functions, appropriate feedback integration and utilization, and working memory capacity (Diamond, 2013; Gilbert & Burgess, 2008; Scott, 1962; Zelazo, 2015). Reversal learning is one of widely used cognitive flexibility paradigms (Izquierdo et al., 2017). Using reversal learning paradigm, we are able to examine the initial association learning between stimulus-outcome or response-outcome contingencies in the discrimination phase and examine cognitive flexibility and adaptive updating by changing the contingencies, which are the common themes that organisms encounter in environment. We also use an alternative choice switching task, in which we are able to examine how past reward history and reward integration in a probabilistic manner affect upcoming choices and switch behaviors, i.e. staying with previous choice or switching to the other choice. Application of computational modeling from Reinforcement Learning (RL) framework and logistic regression model allows us to investigate the latent variables or phenotypes that are not directly observable from behavioral data. RL models allow us to further understand reinforcement learning procedures, choice strategy, and value updating in response to both positive and negative feedback while logistic regression models can help extract how the past rewarded and unrewarded history contribute to switching and choice behaviors.

Here, we present a feeding manipulation to generate a mouse model of juvenile-adolescent food insecurity. This manipulation involved limiting access to food and delivering variable amounts of food daily in developing (P21-40) mice. Mice that experienced three variant of feeding manipulation were tested in the 4-choice odor based foraging discrimination and reversal task and a probabilistic switching task in adulthood at P60-70 and above P110, respectively. We then used standard behavioral and reinforcement learning models to examine learning, cognitive flexibility, reward integration and updating. In a separate cohort, to investigate if there is a decline in sensitivity with age to developmental experience of food insecurity, we also manipulated

feeding experience during P41-60 and tested mice at P80-90 to allow equivalent time for recovery from the experience.

We found that adult (P60-70) male mice with different juvenile-adolescent (P21-40) developmental feeding experiences exhibited significant group differences in cognitive flexibility and estimates of learning rates from a RL model in the 4-choice odor-based foraging discrimination and reversal task. Adult male mice with different juvenile-adolescent feeding experiences also showed different integration of past reward history and updating in a 2-alternative choice probabilistic switching task. In adult female mice with food insecurity versus ad libitum juvenile-adolescent developmental experience, no group differences in performance in these tasks were found, suggesting sex plays a major role in this effect. Finally, in adult (P80-90) male mice that experienced different feeding histories at later timepoint, P41-60, no group differences were found, suggesting that the developing brain may be more sensitive to feeding history during the juvenile/adolescent transition than in the adolescent/adult transition or that there is a sensitive period of testing.

Methods

Animals

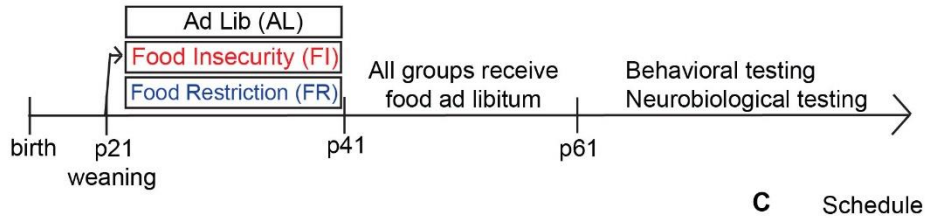
The wildtype C57BL/6 mice line (C57BL/6NJ) were originally obtained from Taconic Biosciences, Inc. and bred at the animal facility of University of California, Berkeley. We chose to use Taconic mice (C57BL/6NJ) because they do not have a mutation in the metabolism relevant nuclear-encoded, mitochondrial protein *Nnt* gene, unlike C57BL/6J mice from Jackson laboratory (Toye et al., 2005). Nicholson et al. (2010) found that the C57BL/6J mice with *Nnt* mutation had higher non-fasting level of glucose in plasma and more severe glucose intolerance compared to C57BL/6NJ. Mice were housed on a 12h/12h reverse light-dark cycle (lights off at 10 AM). Mice were weaned and individually housed at P21 and subject to the Food Insecurity Feeding Paradigm described in the following section (**Fig. 8**). Teklad Global 18% Protein Rodent Diet 2918 (Envigo) was used as the standard diet in all feeding experience experiments. All animals received nesting materials and water *ad libitum* in their home cages. Behavioral testing was conducted during dark cycle period. All procedures were approved by the UC Berkeley Animal Care and Use Committees.

Food insecurity, food restriction and ad libitum feeding paradigm[3]

Mice were weaned, individually housed, and assigned into 3 different groups at P21. Mice in Ad libitum (AL) group had free access to standard rodent chow from P21 to P40, while mice in the Food Restriction (FR) group and Food Insecurity (FI) group

experienced food restriction from P21 to P40 at level of 85% average weights of mice in the AL group for 20 days. Mice in the FI and FR groups had the same amount of food every two days during these 20 days with mice in the FI group receiving alternating day1-day2 ratios (100%-0%, 90%-10%, 80%-20%) and mice in the FR group receiving constant day1-day2 ratio (50%-50%)(**Fig. 8B**). All mice were weighed every two days from P21-P60 to track their weights and growth. Weights were used to determine the actual food amount given to mice in the FI and FR groups every two days. The baseline feeding amount for each day is shown (**Fig. 8C**). Together, mice in the FI group experienced uncertainty and unpredictability of food access each day while maintaining growth comparable to mice in the FR group over the 20-day food insecurity feeding paradigm period. At P41, all mice in the FR and FI groups began to receive food *ad libitum*, and thereafter feeding was matched among groups (**Fig. 8**). Nesting materials and water were always provided and freely available in their homecages. All behavioral experiments were performed after P60 (**Fig. 8A**).

A



B

Age(P)	21-22	23-24	25-26	27-28	29-30	31-32	33-34	35-36	37-38	39-40
AL	Free Access to Standard Rodent Diet									
FI (%)	100:0	80:20	90:10	100:0	80:20	90:10	100:0	80:20	90:10	100:0
FR (%)	50:50	50:50	50:50	50:50	50:50	50:50	50:50	50:50	50:50	50:50

C

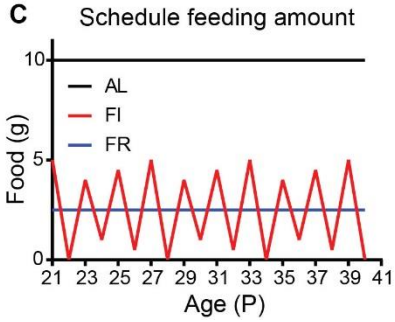


Figure 8. Food insecurity feeding paradigm and experimental timeline[3]. A, Single-housed mice were assigned to 3 different groups, Ad lib (AL), Food Restriction (FR), and Food Insecurity (FI) at P21. Adult mice after P60 were used in experiments for behavioral testing and neurobiological activities. **B,C,** FI and FR mice experienced a 20-day food restriction feeding paradigm from P21-40, controlling their weights to be 80-90% of AL mice. FI and FR mice received the same amount of the standard rodent diet every two days. FI mice received the food in alternating ratios while FR mice received the food constant ratio. The day 1: day 2 ratio is specified in the table **B**. **C**, The figure illustrated the baseline feeding amount for each group. Starting at P41, both FI and FR mice began to receive food *ad libitum*. AL mice always had free access to food. All groups of mice received water *ad libitum*.

[3] The feeding paradigm was developed with input from a Robert Wood Johnson Postdoctoral fellow, Dr. Ezequiel Galarce and his collaborator Dr. Mike McDannald.

4-choice odor-based foraging discrimination and reversal task

This task has been briefly described in the previous chapter (Chapter 2) and extensively described in the previously published work by our lab (Johnson & Wilbrecht, 2011; Thomas et al., 2016; Vandenberg et al., 2018).

In short, mice were mild food restricted for the first two days at 85% of average weight at *ad libitum* before the training. On Day 3, mice were habituated to the testing arena with four ceramic pots with a piece of cheerio reward (HoneyNut Cheerios, General Mills) for three 10-min sessions. The testing arena is a 12"x 12" x 9" square maze with four clear transparent acrylic walls partially dividing the arena into four quadrants (**Fig. 11A**). On Day 4, mice were trained and learned to dig in pots with gradually increased level of unscented Aspen wood shavings (Kaytee Products, Inc) to retrieve cheerio reward within 12 trials. In this shaping phase, only a single ceramic pot was used in each trial, with location pseudo randomly shuffled. Each quadrant was rewarded equally. Mice, in turn, were not trained to associate cheerio reward with location. On Day 5, the behavioral testing day, mice first went through the discrimination phase. Upon completion of the discrimination phase with a criterion 8 out of 10 consecutive trials correct, mice were immediately tested in the reversal phase. Mice had a 3-minute maximum to make a choice by digging in one of the four ceramic pots filled with specific scented wood shavings placed at the corners of 4 quadrants of the arena in each trial. Trial terminated earlier once a choice was made. One piece of cheerio was shamed baited and secured by a mesh screen at bottom of the ceramic pots to control the smell of cheerio. The location of the scented pots was pseudorandomized at the four quadrants in each trial. The same odorant would not appear at the same quadrants in two consecutive trials. In the discrimination phase, O1 was rewarded while O2, O3, and O4 were not rewarded. In the reversal phase, the previously unrewarded odor O2 became rewarded and O1 was no longer rewarded. We also replaced O4 with a novel odor (O4') to test if the novel odor in the environment interferes with reversal learning (**Fig. 11A**). Anise extract (McCormick), essential oils clove and litsea (San Francisco Massage Supply Co), and thyme (made from Thymol) were used as odorants O1, O2, O3, and O4, respectively. Essential oil eucalyptus (San Francisco Massage Supply Co) was used as the novel odorant in reversal phase (O4'). Choice made by digging, entries in each quadrant, and lapsing latency for each trial was recorded for further behavioral analysis.

Reinforcement learning modeling of the 4-choice odor-based foraging reversal task

To further examine the impacts of different juvenile-adolescent developmental feeding experiences on learning, updating, and decision making, we further analyzed the trial by trial data using reinforcement learning (RL) models (Sutton & Barto, 2018).

Computational models can help us understand the latent processes underlying behavioral performance.

Classic RL algorithms assume that subjects learn information in the environment by updating their value estimates of different cues and/or actions (options) incrementally through iterative trial-and-error processes (Rescorla & Wagner, 1972; Sutton & Barto, 2018). The RL models use prediction error (δ) to update the estimated expected value (Q) of each available option (i.e. the 4 different odorants in each phase of the 4-choice foraging task), where the prediction error (δ) is the difference between the current feedback value (λ) obtained from outcome and expected value ($Q(a)$).

In our RL models, the feedback value (λ) is set as 100 for rewarded choices and set as 0 for unrewarded choices. The value updating from the prediction error (δ) is scaled by a learning rate parameter (α), with $0 \leq \alpha \leq 1$ (**Eqn. 1**).

$$Q(a_t) = Q(a_{t-1}) + \alpha \times \delta(a_{t-1}),\ \delta(a_{t-1}) = \lambda - Q(a_{t-1}) \qquad \textbf{(Equation1)}$$

The action probability $P(a)$, or the relative probability of selecting each action, for each trial was calculated by transforming the expected action (option) value of action a, $Q(a)$, to relative probabilities using the softmax function (Daw, 2011). The inverse temperature parameters (β) in the function indicates the stochasticity of the actions and action selection policy, with $0 \leq \beta \leq 1$ (**Eqn. 2**).

$$P(a) = \frac{e^{Q(a)}}{e^{\beta \times Q(a)}} \qquad \textbf{(Equation 2)}$$

We fit the discrimination and learning behavioral data with several alternative classic RL models (**Table 1**), with the basic RL models (RL2) had 1 α parameter and 1 β parameter, assuming the agent had the same learning rate and action selection policy in both phases of the tasks. We also set up the RL models (RL3, RL4) with two separate learning rate parameters and inverse temperature, αdis and αrev, for discrimination and reversal phase, respectively, attempting to examine if the learned experience of the task structure in the discrimination phase changes the learning rate and selection strategy in the reversal phase. There were possible different reward prediction error mechanisms in response to rewarded and unrewarded outcomes. We also set up RL models (RL5) that accounted the learning rate for positive and negative prediction error, αpos and αneg, separately.

According to the error types analysis in the reversal phase, we also considered another alternative family of RL models, adding a single sticky parameter, st, in either both phases of the task or only the reversal phase (**Table 1**). The sticky parameter st was act on the level of transforming expected value $Q(a)$ to action probability $P(a)$, with $0 \leq st \leq 1$ (**Eqn. 3-4**). When sticky parameter st equals one, the estimated action value of

previously selected action being applied to the softmax function $W(a)$ is increased by a hundred-fold (**Eqn. 3**), suggesting agents will be more likely to choose the same previous action in current trial (**Eqn. 4**).

$$W = Q, W(a_{t-1}) = Q(a_{t-1}) + 100 \times st \quad \text{(Equation. 3)}$$

$$P(a) = \frac{e^{W(a)}}{e^{\beta \times W(a)}} \quad \text{(Equation. 4)}$$

The RL model with lowest Akaike Information Criterion (AIC) score was selected as the current working RL model, which is composed of 5 parameters, αdis, βdis, $\alpha revpos$, $\alpha revneg$, and βrev (RL5 model).

In our 4-choice foraging task, there were 5 total odorants as choices provided. Within the 5 odorants (O1, O2, O3, O4, O4'), mice had their subjective value assigned to each odorant as innate preferences at the beginning of the task. We calculated the percentage of choosing each odor in the first 4 trials in the discrimination phase for each mouse and used the averages of these percentages multiplied by 100 as the initial o values for each odorant option or associated action. Similar methods to identify the initial values were used and published (Johnson et al., 2016). The initial values were set to be Q(O1)=35.48, Q(O2)=12.86, Q(O3)=1.19, and Q(O4)=50.48. In the reversal phase, the initial values for O1, O2, O3 were the same as the values in the very last trial of the discrimination phase and the value for O4' was calculated by using the same method as described above (Q(O4')=0.7).

Table 1. Alternative Basic RL models

RL Model	Discrimination Phase	Reversal Phase
RL1 α1 β (RL2)	α, β	
RL2 α1 β (RL3)	$\alpha dis, \beta$	$\alpha rev, \beta$
RL2 α 2 β (RL4)	$\alpha dis, \beta dis$	$\alpha rev, \beta rev$
RL3 α 2 β (RL5)	$\alpha dis, \beta dis$	$\alpha revpos, \alpha revneg, \beta rev$

*__Table 1__ presented the family of basic RL models with the learning rate α and inverse temperature β parameters. Another family of RL models with sticky parameter st being tested had the same RL learning rate α and inverse temperature β parameters, but either adding a single st for both discrimination and reversal phase, or a single st in the reversal phase.

Shifting feeding manipulation to a later phase of development

Separate cohorts of male mice were used in this experiment. At P21, male mice were weaned and individually housed. Mice were provided with standard rodent diet *ad libitum* at P21-40. At P41, male mice were assigned into ad libitum (AL) or food insecurity (FI) group and subject to the Food Insecurity Feeding Paradigm described previously (**Fig. 8**) with time window shifted to P41-P60 for 20 days (**Fig. 9**). At P61, all mice were returned to food *ad libitum* for 20 days and tested in the 4-choice odor-based foraging reversal task at P80-90 (**Fig. 9**).

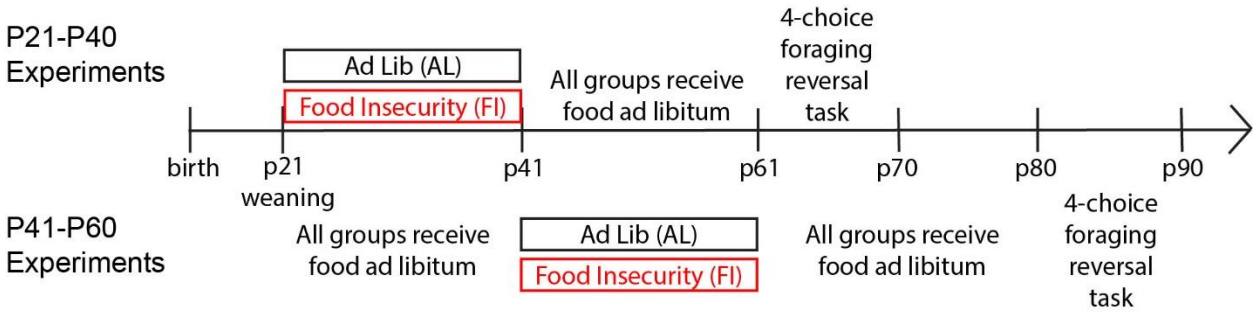


Figure 9. Food insecurity feeding paradigm and experimental timeline shifted 20 days later to test for a sensitive period. Separate cohorts of mice were weaned at P21, single housed, and provided with food *ad libitum* from P21-40. At P41, mice were assigned into ad libitum (AL) or food insecurity (FI) group and went through food insecurity feeding protocol for 20 days between P41 and P60 (**Fig. 8**). At P61, all mice were returned to food *ad libitum*. Mice were then tested in the 4-choice odor-based foraging reversal task at P80-90.

2-Alternative choice probabilistic switching task

Adult mice were trained in this probabilistic switching task after P110 and previously have been trained and tested in the 4-choice odor-based foraging task at P60-70 (**Fig. 8,11**). In this 2-alternative choice switching task (**Fig. 19A**) that was previously developed and published by Tai et al. (2012), mice were trained to nose poke for a water reward with probabilistic nature and reward location periodically alternating at random interval. Mice were mildly water restricted 1-2 days prior the training sessions to motivate learning (**Fig. 19A**). During the training sessions, mice were placed in an operant chamber with 3 different ports on the same wall. To self-initiate the trial, mice needed to nose poke the center initiation port and made a decision by choosing the two peripheral ports, left (L) or right (R) port, for probabilistic reward water delivery. White LED light would be turned on at both peripheral ports when mice poked and held at the center initial port long enough, indicating two peripheral ports were ready for chosen. Water reward was only delivered at one peripheral port at a time. Infrared photodiode and phototransistor pairs (Island Motion) were used for detecting port entries and exits.

Water reward delivered by water valves (Neptune Research) was calibrated to be constant volume (2 µl) for rewarded choices.

In our version of the 2-alternative choice switching task, there were three training phases. In the first training phase, the correct choices were rewarded at 75% while the incorrect choices were always unrewarded (75% vs 0%). The side of rewarded port was switched every 15±8 rewarded trials, depending on total number of rewards collected in each block. The reward probabilities for the correct choice in second and third training phases were changed to 90% vs 0% and 65% vs 0%, respectively. Mice were trained at least 5 sessions in each phase.

Multivariate logistic regression in the 2-alternative choice probabilistic switching task

We employed the multivariate logistic regression model analysis used in the Tai et al. (2012) to analyze and compare our data obtained from this task. This logistic regression model (**Eqn. 5**) can be used to closely analyze the integration of past reward history, determine relative contribution of past rewarded and unrewarded outcomes trial by trial basis on next choice, and predict animal choice behavior.

$$\log\left(\frac{P_L(i)}{1-P_L(i)}\right) = \sum_{j=1}^{n} \beta_j^{Reward}\left(Y_L(i-j) - Y_R(i-j)\right) + \sum_{j=1}^{n} \beta_j^{NoReward}\left(N_L(i-j) - N_R(i-j)\right) + \beta_0$$

(**Equation. 5**)

$P_L(i)$ is the probability of choosing the L port. The variables Y_L or Y_R indicate if a water reward is received (1) or not (0) at the L or R port, respectively, while N_L or N_R indicate the absence of water reward (1 or 0) at either the selected L or R port, respectively. i indicates that the event happened in the i-th trial. The variable n represents the number of trials in the past that were included in the model (n=4). The regression coefficients β^{Reward} and $\beta^{NoReward}$ represent the contribution of past rewarded history and past unrewarded history, respectively, and β_0 represents the intrinsic bias of choosing L or R port of the animal.

Statistical analysis

Values are reported as mean (M) ± standard error of mean (SEM). Data were analyzed using two-tailed t-tests or ANOVAs with post-hoc analysis. GraphPad Prism 7 was used for statistical analysis. MATLAB 2016a was used for reinforcement learning model fitting and simulation and logistic regression modeling and analysis.

Results

Ad libitum (AL) vs Food insecurity (FI) growth curve comparison

To examine how differences in feeding history affected weight gain, we analyzed the growth curve in weights of mice from the AL, FR, and FI groups from P21 to 160.

Using two-way ANOVA between different developmental feeding experiences (referred as treatment in the experiments thereafter) and age, data from all mice (n(AL)=30, n(FI)=25, n(FR)=24), male only (n(AL)=16, n(FI)=12, n(FR)=11), and female only (n(AL)=14, n(FI)=13, n(FR)=13) all showed main effect of treatment, main effect of age, and significant interaction between treatment and age (**Fig. 10A,B,** all mice: treatment: $F(2, 2345)=9.479$, $p<0.0001$, age: $F(31,2345)=299.3$, $p<0.0001$, interaction: $F(62,2345)=2.671$, $p<0.0001$; **Fig. 10C,** male only: treatment: $F(2,1083)=9.877$, $p<0.0001$, age: $F(31,1083)=328$, $p<0.0001$, interaction: $F(62,1083)=2.808$, $p<0.0001$; **Fig. 10D**, female only: treatment: $F(2,1166)=47.05$, $p<0.0001$, age: $F(31,1166)=244.4$, $p<0.0001$, interaction: $F(62,1166)=3.642$, $p<0.0001$). Both male and female mice in the FR and FI groups significantly lighter during P30-41 when the mice were on average controlled at 80-90% of weights of the mice in the AL group (**Fig. 10A,B,** post-hoc Tukey: P35:AL vs FR: $p=0.017$; P37:AL vs FI: $p=0.017$, AL vs FR: $p=0.0007$; P39:AL vs FI: $p=0.0008$, AL vs FR: $p=0.0079$; P41:AL vs FI: $p=0.0002$, AL vs FR: $p<0.0001$). Interestingly, the mice in the FR and FI groups regained back to similar body weights compared to the mice in the AL group by P43, the first timepoint weight taken after all mice were returned to food *ad libitum* (**Fig. 10B,** post-hoc Tukey: P43:AL vs FI: $p=0.88$, AL vs FR: $p=0.37$, FI vs FR: $p=0.68$).

In adulthood after P100 (after all feeding group manipulations were discontinued and all mice were on ad libitum diet), mice from the FI group were significantly heavier than mice in the AL and FR groups (**Fig. 10A,** post-hoc Tukey: P100:AL vs FI: $p=0.015$; P110:AL vs FI: $p=0.0048$, FI vs FR: $p=0.020$; P120:AL vs FI: $p<0.0001$, FI vs FR: $p=0.021$; P130: AL vs FI: $p<0.0001$, FI vs FR: $p=0.017$; P140:AL vs FI: $p=0.027$; P150:AL vs FI: $p=0.0042$). This effect on adult weight was driven by group differences in female mice but not male mice (**Fig. 10C,D,** post-hoc Tukey: Male only: P140: FI vs FR: $p=0.011$; Female only: P90:AL vs FI: $p=0.0075$, FI vs FR: $p=0.01$; P100:AL vs FI: $p=0.0063$, FI vs FR: 0.035; P110:AL vs FI: $p<0.0001$, FI vs FR: $p=0.0016$; P120: AL vs FI: $p<0.0001$, FI vs FR: $p<0.0001$; P130: AL vs FI: $p<0.0001$, AL vs FR: $p=0.014$. FI vs FR: $p<0.0001$; P140:AL vs FI: $p<0.0001$, AL vs FR: $p=0.0065$, FI vs FR: $p=0.0009$; P150:AL vs FI: $p<0.0001$, AL vs FR: 0.020, FI vs FR: $p=0.0002$).

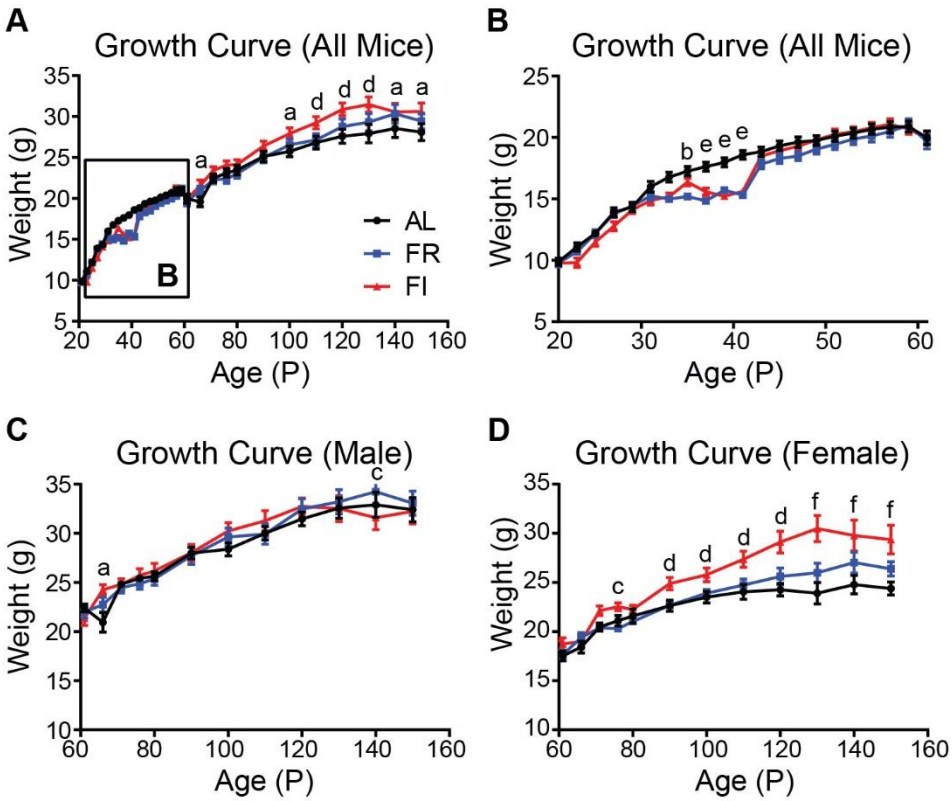


Figure 10. Differences in juvenile-adolescent (P21-40) feeding history affected weight gain in female mice in adulthood. A, Growth curve in weights for both male and female mice in the AL, FI, and FR groups. **B,** The same data as in A, focusing on P21-P60. **C**, Male data only from A. Male mice did not show significantly different weights in adulthood (after P60). **D**, Female data only from A. Female mice in the FI group significantly gained more weights after P90. Error bars represented SEM.

Statistics: Two-way ANOVA with post-hoc Tukey multiple comparison tests was used. post-hoc Tukey: a, $p<0.05$ in AL vs FI groups; b, $p<0.05$ in AL vs FR groups; c, $p<0.05$ in FI vs FR groups; d, $p<0.05$ in AL vs FI groups & FI vs FR groups; e, $p<0.05$ in AL vs FI groups & in AL vs FR groups; f, $p<0.05$ in AL vs FI groups, AL vs FR groups, & FI vs FR groups at each corresponding age. All mice: n(AL)=30, n(FI)=25, n(FR)=24; male only: n(AL)=16, n(FI)=12, n(FR)=11; female only: n(AL)=14, n(FI)=13, n(FR)=13.

In male mice, differences in feeding history during the juvenile-adolescent period (P21-40) affected reversal learning in adulthood (P60-70)

We next used a 4-choice odor-based foraging discrimination and reversal task (**Fig. 11A**), to test of multiple choice learning and cognitive flexibility or flexible updating (Johnson & Wilbrecht, 2011; Thomas et al., 2016; Vandenberg et al., 2018). We found that adult (P60-70) male mice in the ad lib (AL), food insecurity (FI), and food restriction (FR) groups took approximately the same numbers of trials to criterion (**Fig. 11B,** $F(2,30)=1.098$, $p=0.35$) and total numbers of errors (**Fig. 11C,** $F(2,30)=1.738$, $p=0.19$) in the discrimination phase, suggesting the groups showed similar capacity for multiple choice discrimination learning.

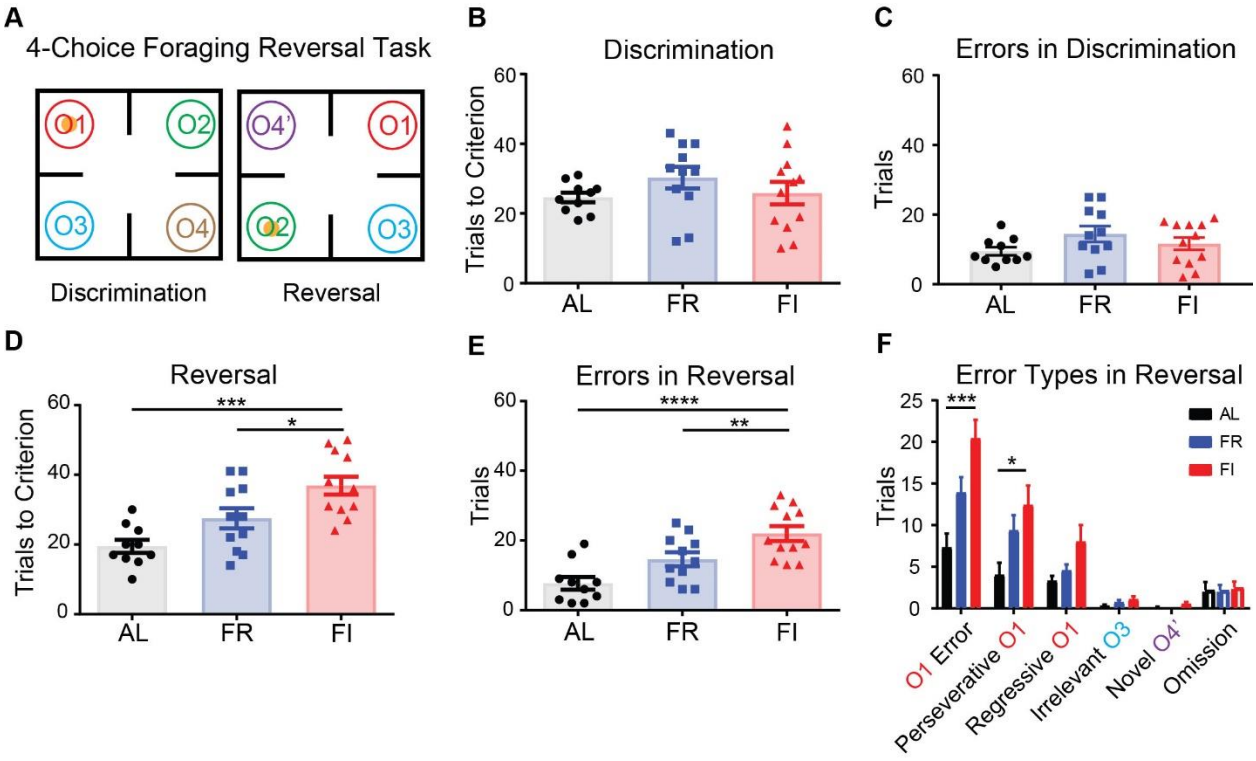


Figure 11. In male mice, differences in juvenile-adolescent feeding history affected cognitive flexibility in reversal learning in adulthood (P60-70). **A,** Schematic of the task. O1 was rewarded in the discrimination phase, which became unrewarded in reversal phase. Previously unrewarded O2 became rewarded in reversal phase. **B,C,** The performance was not different across three groups, AL, FI, and FR groups, in trials to criterion and total number of errors in the discrimination phase. **D,E,** Adult (P60-70) male mice in the FI group had significantly more trials to criterion and number of errors in the reversal phase. Mice in the FR group showed intermediate performance. **F,** When error types were compared, mice in the FI groups had significantly more reversal error (O1 Error), especially Perseverative O1 error. n(AL)=10, n(FI)=12, n(FR)=11 *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001. Error bars represented SEM.

In the reversal phase, we found clear group differences in males. Adult male mice with developmental history of food insecurity (FI), in the reversal phase of the task, showed less cognitive flexibility with significantly more trials to criterion (**Fig. 11D,** $F(2,30)=11.88$, $p=0.0002$) and total number of errors (**Fig. 11E,** $F(2,30)=12.5$, $p=0.0001$), compared to mice in the FR group and AL group. Using post-hoc Tukey multiple comparison, we found that performance of adult male mice in the FI group were significantly different from the AL group in both measures of total trials to criterion (AL vs FI: $p=0.0001$) and total number of errors (AL vs FI: $p<0.0001$). Notably, there were differential effects of feeding history on reversal learning between the FI and FR groups were observed in these two measures as well (**Fig. 11D,E,** post-hoc Tukey: total trials to criterion: FI vs FR: $p=0.031$; total number of errors: FI vs FR: $p=0.034$).

When the error types were closely examined and analyzed, adult male mice in the FI group were found to have significantly more reversal errors (O1 errors), which were defined as the error of selecting the previously rewarded odor (O1) (**Fig. 11F**, F(2,30)=10.72, p=0.0003; post-hoc Tukey: AL vs FI: p=0.0002). Specifically, they had greater perseverative error (Perseverative O1), a type of reversal error before making the first correct decision (**Fig. 11F**, F(2,30)=4.504, p=0.0195; post-hoc Tukey: AL vs FI: p=0.015). There was no difference found in regressive error (Regressive O1), a type of reversal error after making the first correct decision (F(2,30)=3.209, p=0.055), irrelevant error, a type of error choosing an unrewarded odorant (O3) in both discrimination and reversal phase (F(2,30)=1.992, p=0.15), novel error choosing O4' (F(2,30)=2.447, p=0.10), and omission (F(2,30)=0.05605, p=0.95)(**Fig. 11F**).

Juvenile-adolescent feeding history affected cognitive flexibility by altering learning rates used to update behavior in adult male mice

To better understand the mechanisms underlying differences in flexible updating in the reversal phase of the foraging task, we used reinforcement learning (RL) models to fit our data. In RL models, subjects can learn to update the action values associated with each option, compare the computed values, and select the best option from all available options in the context to adaptively change the behavior (Rescorla & Wagner, 1972; Sutton & Barto, 2018). We modeled trial by trial behavioral data from the 4-choice foraging decision task (**Fig. 11**) using multiple RL models (varying in parameter number) to find the best working model and extract latent variables driving the behavioral performance for each animal in the task.

By fitting multiple models, comparing the results, and using simulation to test if we can recover behavioral performance (Collins & Frank, 2012). We found our RL5 model with 5 parameters without sticky parameter st had the lowest AIC score and best simulation recovery of mouse behavioral data (**Table 1**). The 5 parameters included in this working model (RL5) are αdis, βdis, $\alpha revpos\ (a+)$, $\alpha revneg\ (a-)$, and βrev. In the discrimination phase of the 4-choice foraging task, there was no significant difference among the three groups in both the inverse temperature parameter βdis (**Fig. 12A**, F(2,30)=3.126, p=0.0585) and learning rate αdis (**Fig. 12B**, F(2,30)=0.2689, p=0.77). Interestingly, we observed that the FR group which experienced constant scarcity in terms of low amount of food during juvenile-adolescent period had on average smaller βdis (**Fig. 12A**, AL(n=10): 0.072±0.0147, FI(n=12): 0.078±0.0347, FR(n=11): 0.044±0.0050).

In the reversal phase, we found that feeding history affected learning rates, both $\alpha revpos\ (a+)$ and $\alpha revneg\ (a-)$, (**Fig. 12D,** F(2,30)=3.319, p=0.0499; **Fig. 12E**, F(2,30)=7.128, p=0.0029), especially, the $\alpha revneg\ (a-)$ in response to unrewarded outcomes, or negative prediction error in adulthood. Similar to the behavioral results

observed in trials to criterion (**Fig. 11D**) and total number of errors (**Fig. 11E**) in the reversal phase, $\alpha rev neg\ (a-)$ of adult male mice in the FI group (0.087±0.0228) was significantly different from those of adult male mice in the AL group (0.277±0.0550), with intermediate $\alpha rev neg\ (a-)$ values (0.144±0.0282) in the FR group (**Fig. 12E**, post-hoc Tukey: AL vs FI: p=0.0023, AL vs FR: p=0.041).

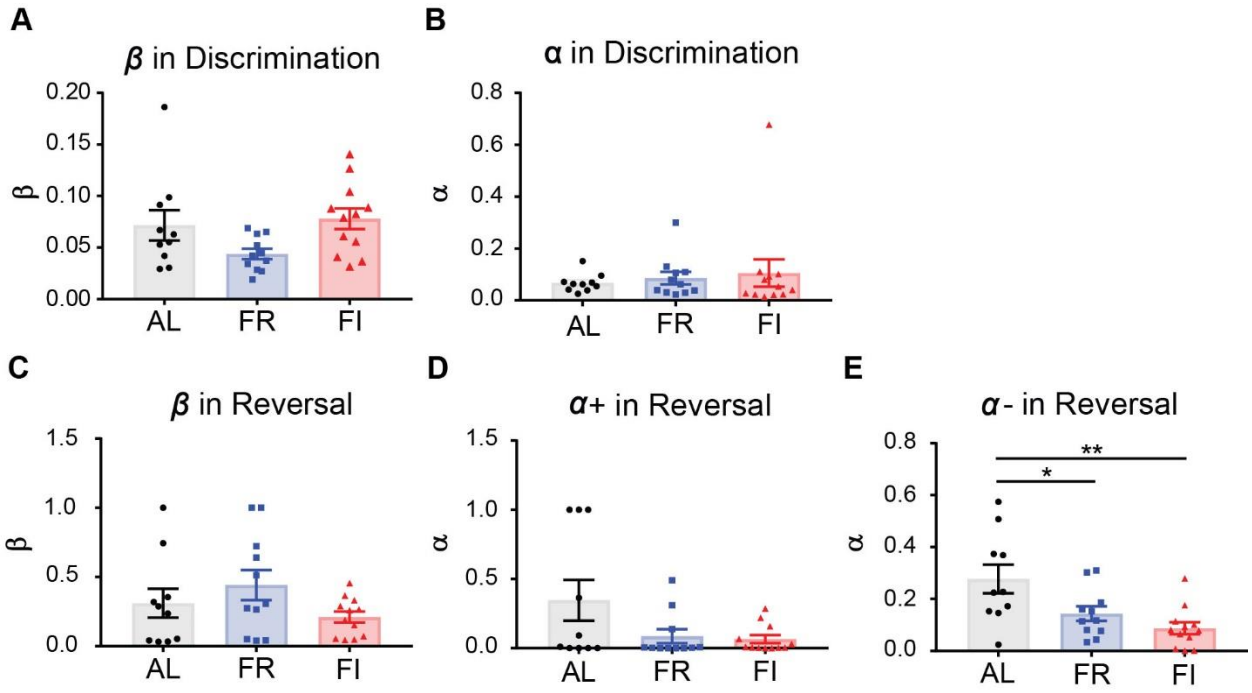


Figure 12. In male mice, differences in juvenile-adolescent feeding history affected the learning rate in response to negative feedback in reversal learning in adulthood (P60-70). A,C, Inverse temperatures in both phases βdis and βrev were similar across AL, FI, and FR groups. **B,** Learning rate αdis in discrimination were comparable. **D,E,** Learning rates, , $\alpha rev pos\ (a+)$ and $\alpha rev neg\ (a-)$ were significantly different among groups using 1-way ANOVA. Post-hoc Tukey's multiple comparison showed $\alpha rev neg\ (a-)$ was significantly smaller in adult (P60-70) male mice in the FI group. n(AL)=10, n(FI)=12, n(FR)=11; *p<0.05, **p<0.01. Error bars represented SEM.

When comparing the inverse temperature βrev across groups, we found that there was also no significant group difference (**Fig. 12C,** F(2,30)=1.861, p=0.17; AL: 0.310±0.1036, FI: 0.210±0.0401, FR: 0.441±0.1086). However, there was a significant difference in βdis and βrev between two phases of the task (**Fig. 12A,C,** t(64)=4.891, p<0.0001; βdis across groups: 0.065±0.0064, n=33; βrev across groups: 0.318±0.0513, n=33).

To validate if our working RL model (RL5 model) can capture the observed behavioral results, we simulated the obtained parameters 100 times with the same rules and task structures of our 4-choice foraging task. The behavioral differences observed in the actual experiments (**Fig. 11**) can be well recovered (**Fig. 13C,D**). The simulation of trials to criterion illustrated that numbers of trials were comparable among the AL, FI, and FR groups in the discrimination phase (**Fig. 13A,** $F(2,30)=2.233$, $p=0.1247$; $n(AL)=10$, $n(FI)=12$, $n(FR)=11$). In addition, this simulation revealed that there was a significantly difference in simulated trials to criterion in reversal phase with the FI group having the greatest number of trials (**Fig. 13B,** $F(2,30)=8.974$, $p=0.0009$). The similar pattern of behavioral observation among the three groups in the reversal phase, FI with greatest number, FR with intermediate number, and AL with smallest number of trials to criterion, was also captured in the recovery simulation (**Fig. 11B,** post-hoc Tukey: AL vs FI: $p=0.0007$, FI vs FR: $p=0.029$).

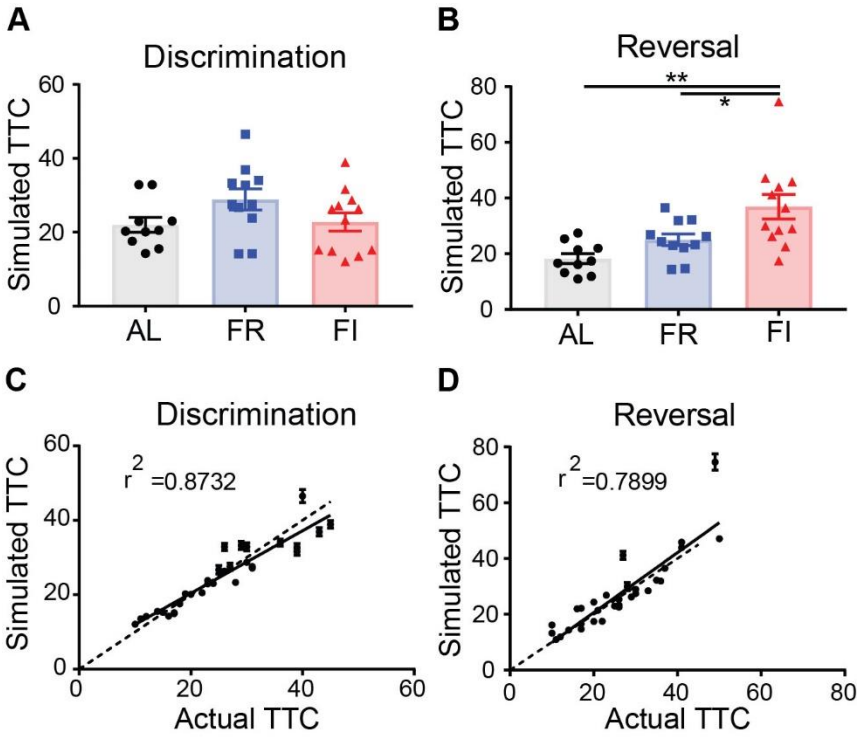


Figure 13. Simulation from the obtained parameters illustrated similar pattern of behavior in both phases of the 4-choice foraging decision task for adult male mice. A,B, The simulation showed that juvenile-adolescent history of food insecurity altered the cognitive flexibility in reversal learning with increased number of trials to criterion (TTC). **C,D,** The simulated TTC was recovered well compared to actual TTC in both phases. The simulated TTC presented for each subject was obtained from the average TTC of 100 simulation. Dotted line represented the unity line. A,B, $n(AL)=10$, $n(FI)=12$, $n(FR)=11$; C,D, $n=36$; $^*p<0.05$, $^{**}p<0.01$. Error bars represented SEM.

Differences in AL and FI group cognitive flexibility were replicable in a second cohort

In another separate cohort of animals, we observed the same results that adult (P60-70) male mice with juvenile-adolescent (P21-40) developmental *ad libitum* feeding experience (AL group) and food insecurity experience (FI group) showed significantly different performance in the reversal learning but no different performance in the initial discrimination and associative learning (**Fig. 14**).

The total trials to criterion and number of errors were comparable among AL, FI, and FR groups in adult male mice (**Fig. 14A,** F(2,17)=0.6583, p=0.53; **Fig. 14B,** F(2,17)=0.9883, p=0.39). In the reversal phase, adult male mice in the FI group took significantly more trials than mice in the AL groups to meet the criterion (**Fig. 14C,** F(2,17)=6.762, p=0.0069; post-hoc Tukey: AL vs FI: p=0.0071, AL vs FR: p=0.031) and significantly more reversal error (O1 Error)(**Fig. 14D,** F(2,17)=5.035, p=0.019; post-hoc Tukey: AL vs FI: p=0.027, AL vs FR: p=0.040).

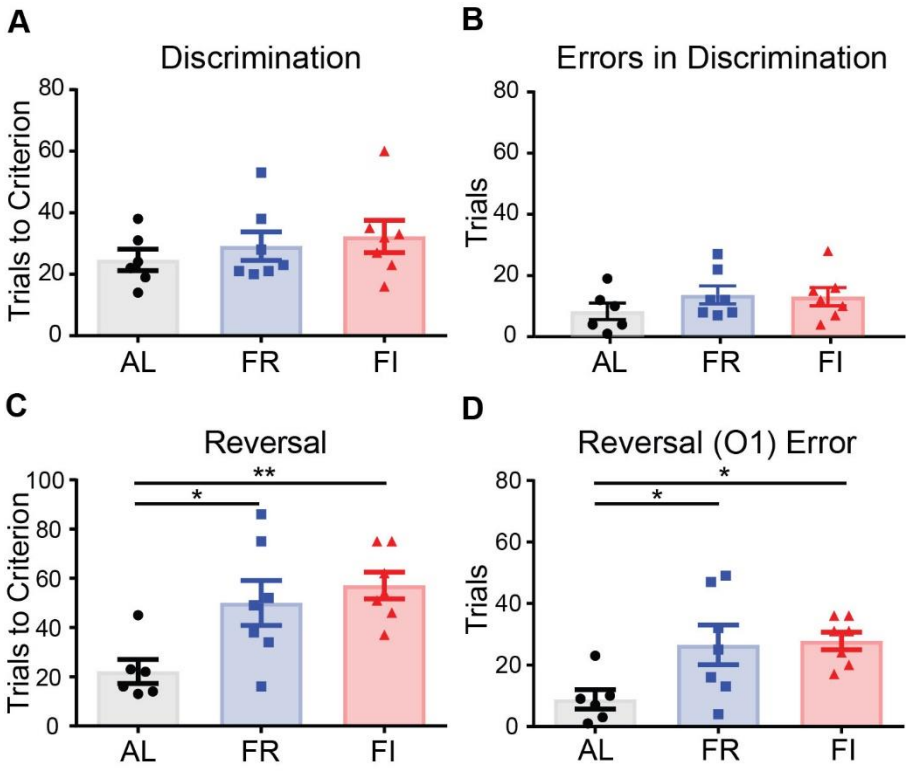


Figure 14. Effects of juvenile-adolescent feeding history on reversal learning were replicated in a second, separate cohort of adult (P60-70) male mice. A,B, There was no difference in performance in the discrimination phase among groups. **C,** Adult male mice from FI group took significantly more trials to reach criterion than AL group in reversal (F(2,17)=6.762, p=0.0069). **D**, In reversal phase, adult male mice from FI group and FR group chose O1 more often than mice from AL group (O1 Error) (F(2,17)=5.035, p=0.019). n(AL)=6, n(FI)=7, n(FR)=7, *p<0.05, **p<0.01. Error bars represented SEM.

In male mice, late developmental (P41-60) differences in feeding history did not create group differences in cognitive flexibility at P80-90.

To examine if the developmental timing of feeding history was critical to see group difference in cognitive flexibility performance, we next exposed male mice to either always ad libitum (AL) feeding experience or food insecurity (FI) experience from P41-60 (**Fig. 9**). These mice were then tested in the same 4-choice odor-based foraging reversal task at P80-90 (**Fig. 9,15A**), leaving this group, like the juvenile-adolescent P21-40 group, a full 20 days of ad lib feeding to recover from the experience of food insecurity. In this older cohort, mice in the AL (n=12) and FI (n=12) groups performed similarly in both discrimination and reversal phase (**Fig. 15**) In the discrimination phase, mice in the AL and FI groups had comparable numbers of trials to reach the criterion (**Fig. 15B,** t(22)=0.4233, p=0.68) and total numbers of error (**Fig. 15C,** t(22)=0.6598, p=0.52). In the reversal phase, adult (P80-90) male mice also performed similarly in total trials to criterion (**Fig. 15D,** t(22)=0.6164, p=0.54), total number of errors (**Fig. 15E,** t(22)=0.7696, p=0.45), reversal error (O1 error) (**Fig. 15F,** t(22)=0.7912, p=0.44), perseverative O1 error (t(22)=0.3232, p=0.75), regressive O1 error (t(22)=1.128, p=0.27), irrelevant O3 error (t(22)=1.599, p=0.12), novel O4' error (t(22)=0.3817, p=0.71), and omission (t(22)=0.2497, p=0.81).

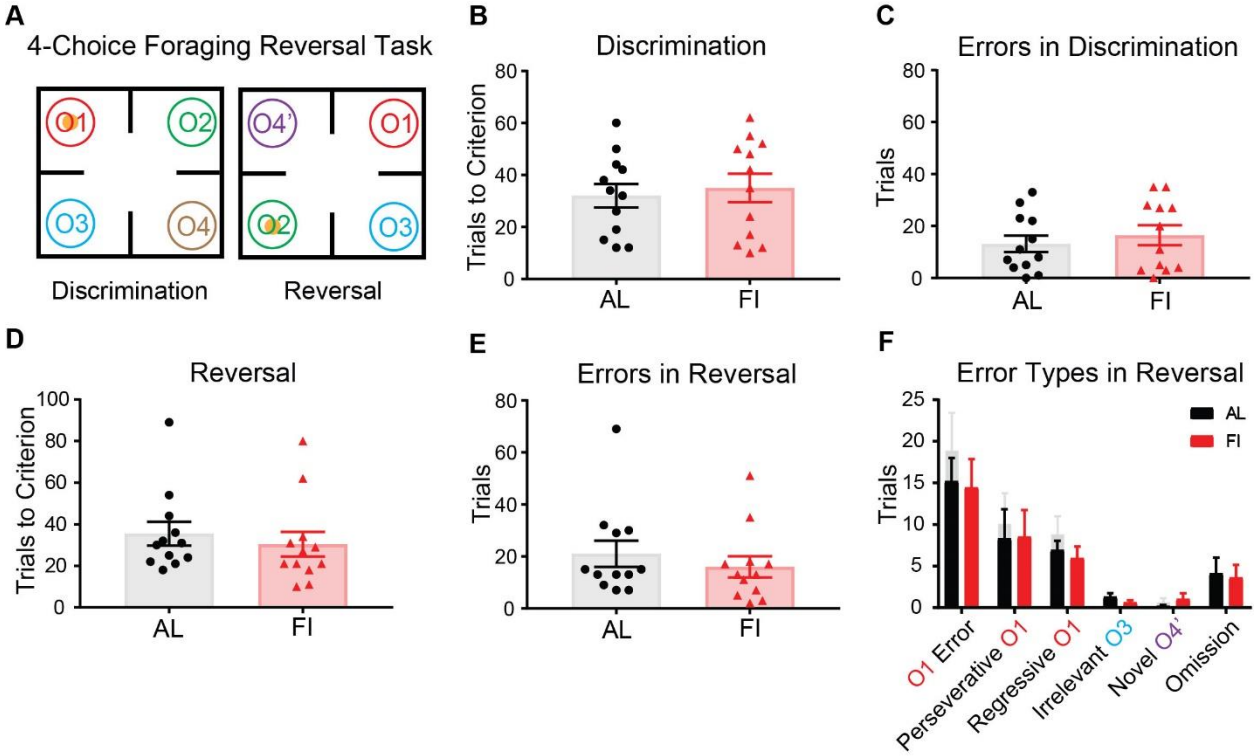


Figure 15. In male mice, late adolescent (P41-60) differences in feeding history did not affect reversal learning in adulthood (P80-90). A, Schematic of the task. **B,C,** Adult male mice in the AL and FI groups had similar trials to criterion and total numbers of errors in the discrimination. **D,E** The AL and FI groups did not differ in the trials to criterion and total numbers of errors in reversal phase. **F,** Two groups have similar errors in each error type. Gray bar indicated the average included the mouse with over 80 trials to criterion in **D.** n(AL)=12, n(FI)=12. Error bars represented SEM.

In female mice, differences in feeding history during the juvenile-adolescent period did not affect reversal learning in adulthood (P60-70)

Experience of food insecurity during childhood has been found to affect boys or girls differently in various measures (Jyoti et al., 2005; Franklin et al., 2012, Laraia, 2013). We therefore also examine the effects of AL, FR and FI feeding history (**Fig. 8**) on performance of female mice in the 4-choice odor-based foraging task at P60-70 (**Fig. 16A)**.

We found that unlike in males, in females, a difference in P21-40 feeding history did not affect their performance in discrimination and reversal learning in adulthood (**Fig. 16**). All three groups showed similar trials to criterion and number of errors in the discrimination (**Fig. 16B,** F(2,33)=0.2131, p=0.81; **Fig. 16C,** F(2,33)=0.4076, p=0.67; n(AL)=10, n(FI)=13, n(FR)=13). Performance in the reversal phase was also consistent across groups in terms of trials to criterion (**Fig. 16D,** F(2,33)=0.347, p=0.80), number of errors (**Fig. 16E,** F(2,33)=0.7401, p=0.50) and detailed error type analyses (**Fig. 16F**).

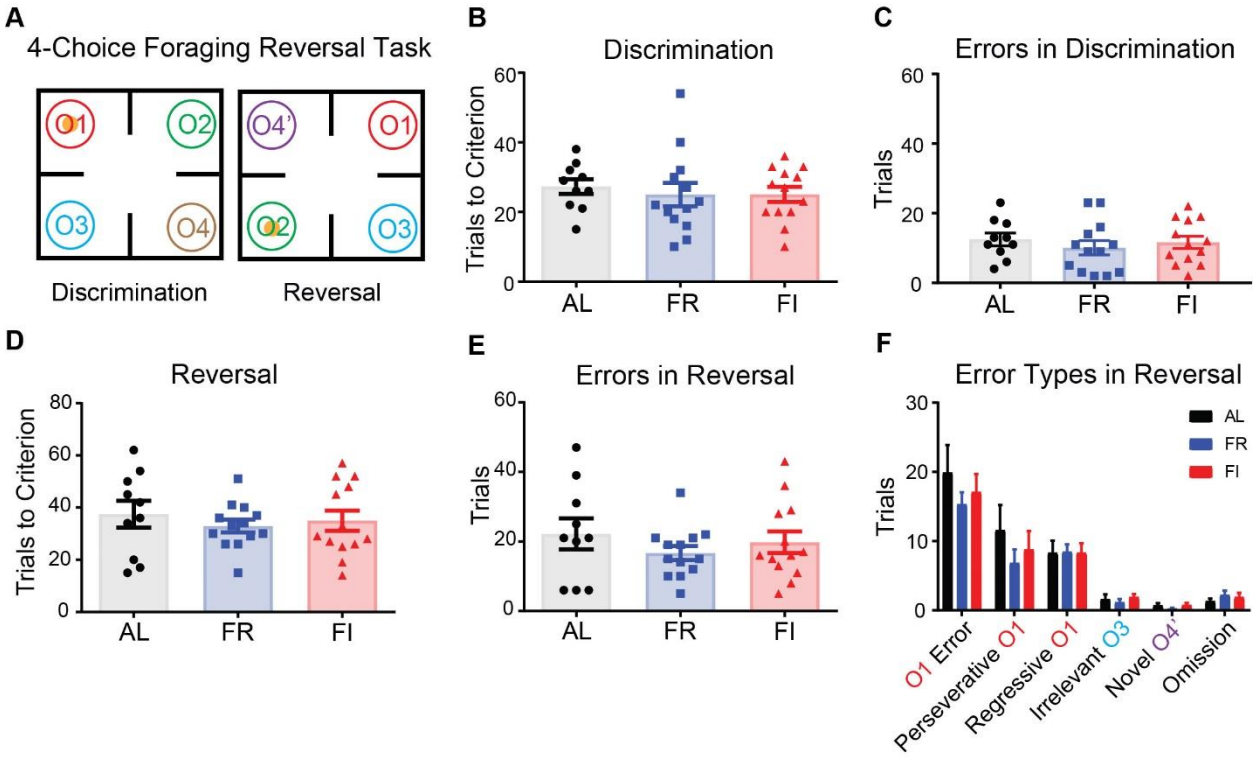


Figure 16. In female mice, differences in juvenile-adolescent feeding history did not affect cognitive flexibility in reversal learning in adulthood (P60-70). A, Schematic of the Task. **B,C,D,E,F** Performance were similar across AL, FI, and FR groups in both discrimination and reversal phase. n(AL)=10, n(FI)=13, n(FR)=13. One-way ANOVA showed that there was no significant difference *p<0.05 across the three groups. Error bars represented SEM.

In female mice, differences in feeding history during the juvenile-adolescent period did not affect reinforcement learning in adulthood (P60-70)

The similar performance observed in discrimination and reversal learning in adult female mice among the three groups (**Fig. 16**) could be possibly resulted from different combination of strategies and learning rates. We therefore also applied our working reinforcement learning model (RL5) to the female 4-choice foraging behavioral data (**Fig. 16**) to examine if there were differences in action selection strategy β and learning rates α.

We found that there was no difference in the obtained 5 parameters, αdis (F(2,33)=0.2918, p=0.75), βdis (F(2,33)=0.3224, p=0.73), $\alpha revpos$ $(a+)$ (F(2,33)=0.718, p=0.50), $\alpha revneg$ $(a-)$ (F(2,33)=0.5327, p=0.59), and βrev (F(2,33)=0.4047, p=0.67), in adult female mice across the 3 groups (**Fig. 17A-E**). The average inverse temperature across groups showed significantly difference between βdis (0.086±0.0265, n=36) and βrev (0.179±0.0379, n=36) with βrev is on average higher (t(70)=2, p=0.049) (**Fig. 17A,C**).

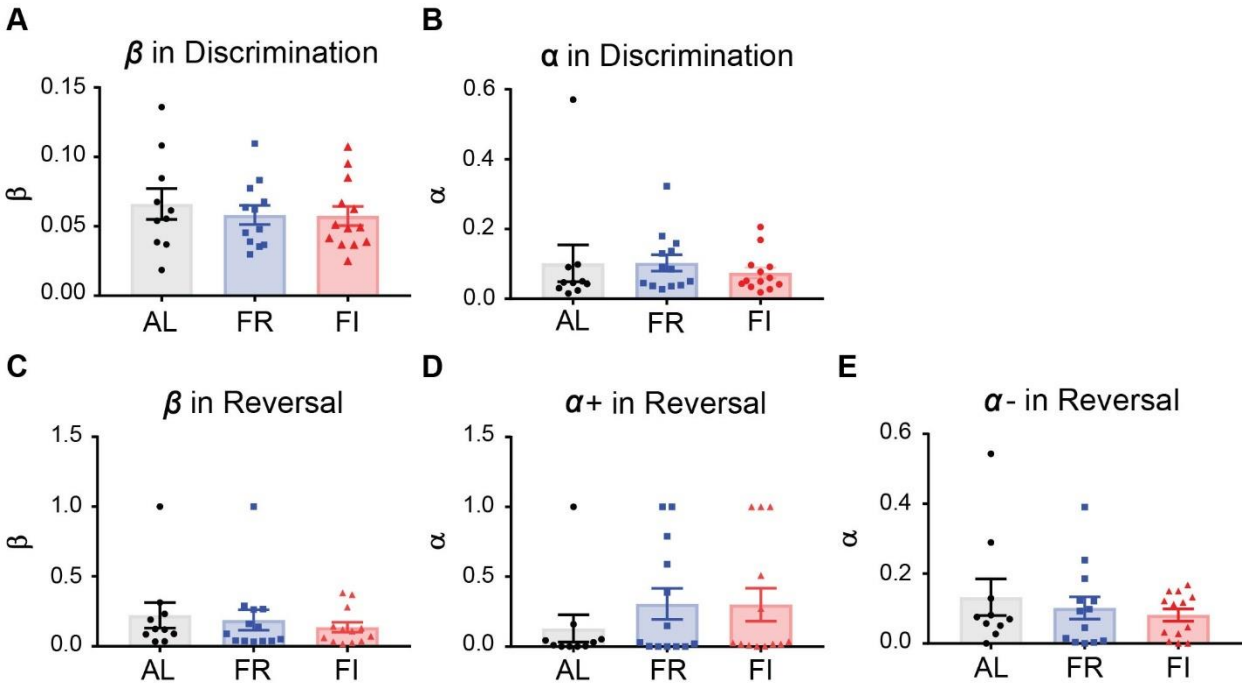


Figure 17. RL modeling suggests that there was no significant difference in learning rate and inverse temperature in reversal learning in adult female mice. A,C, The values of βdis and βrev are comparable across AL, FI, and FR groups in the discrimination phase and reversal phase, respectively. The average βrev across groups was significantly higher than average βdis across groups (t(70)=2, p=0.049). **B,D,E** Learning rates in discrimination and reversal phases were not significantly different among groups. n(AL)=10, n(FI)=13, n(FR)=13. Error bars represented SEM.

Simulation of trials to criterion using the obtained values of 5 parameters, αdis, βdis, $\alpha revpos\ (a+)$, $\alpha revneg\ (a-)$, and βrev 100 times illustrated that there was no difference across AL, FI, and FR groups in both discrimination (**Fig. 18A,** F(2,33) =0.6143, p=0.55) and reversal phase (**Fig. 18B,** F(2,33)=0.3502, p=0.71). The simulated results were consistent with actual adult female behavioral data presented in **Fig. 16**. Comparing the simulated trials to criterion and actual trials to criterion, the current reinforcement learning model with 5 parameters recovered the behavioral results well for each subject in both phases (**Fig. 18C,D**).

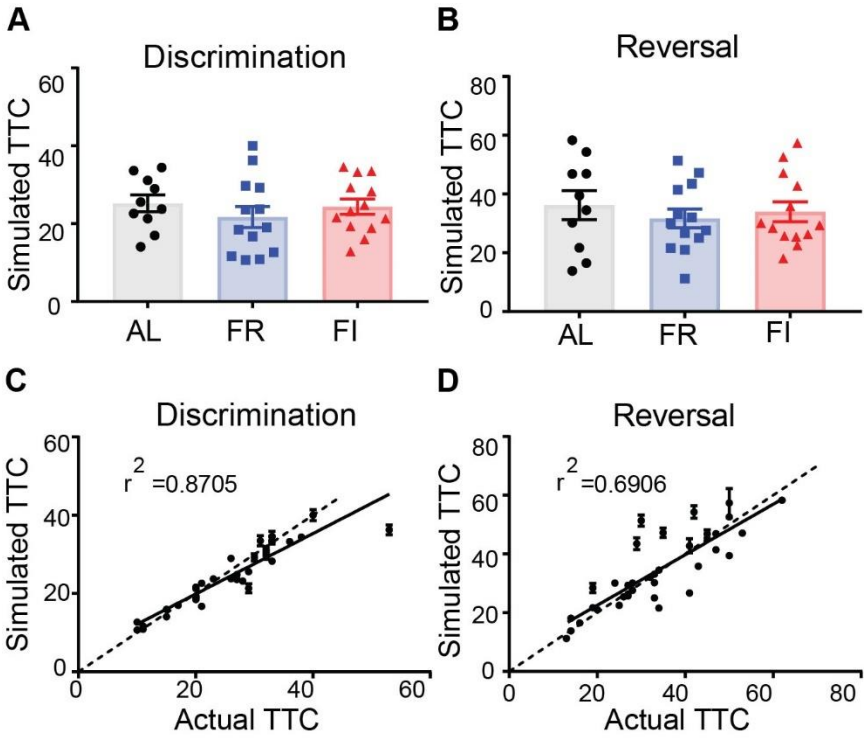


Figure 18. Simulation from the obtained parameters illustrated comparable performance in both phases of the 4-choice foraging reversal task in adult female mice A,B, There was no difference in trials to criterion among AL, FI, and FR groups in the discrimination and reversal phase. n(AL)=10, n(FI)=13, n(FR)=13. **C,D,** Simulated and actual trials to criterion were comparable in each phase (n=36).

In male mice, differences in feeding history during the juvenile-adolescent period affected sensitivity to probabilistic reward conditions or uncertainty in adulthood

Tai et al. (2012) have developed an alternative probabilistic switching task that is able to investigate learning, reward updating, and history integration in mice. The task delivers reward at probabilistic nature, which requires animals to integrate the past choice and reward history to make an optimal decision in the next trial. We found that juvenile-adolescent experience of food insecurity has impacts on cognitive flexibility in the reversal learning rewarded at deterministic nature (**Fig. 11,12,14**); therefore, we sought to investigate how this experience can affect the performance in the probabilistic environment.

Adult male mice in AL and FI groups were trained in three different phases of the 2-alternative choice probabilistic switching task, Phase 1 (75% vs 0%), Phase 2 (90% vs 0%), and Phase 3 (65% vs 0%) (**Fig. 19A,B**). Mice initiated the trial by poking at the center initiation port and chose either left (L) or right (R) peripheral port. For the L-port rewarded block, there was 75% of reward water delivery when mice made a correct decision at the L-port in the Phase 1. In this L-port rewarded block, there was always 0% of reward water delivery when mice made a choice at the R-port, and vice versa for R-port rewarded block (**Fig. 19A**). The block switching, i.e. L-port rewarded to R-port rewarded, was dependent on the number of rewards received in each block and occurs every 15±8 rewards.

We analyzed the number of trials for adult male mice took to exhibit the switching behavior when the action-outcome contingency changed. We found that mice (n(AL)=8, n(FI)=8) on average took similar number of trials between switching from L to R and R to L in all three phases, showing there was no side bias. We then combined the L to R and R to L trials to switch data together for further analysis. Adult male mice in the AL and FI groups did not differ significantly in the total number of trials they took on average to switch in Phase 1($t(14)=1.624$, $p=0.13$, AL:3.08±0.09, FI:2.71±0.21), Phase 2 ($t(14)=0.095$, $p=0.93$, AL:2.15±0.05, FI:2.133±0.18), and Phase 3 ($t(14)=1.083$, $p=0.30$, AL:3.00±0.08, FI:2.79±0.18) (**Fig. 19B**). However, when we examined the switching behavior more closely (trial by trial after a switch), it revealed that adult male mice with a history of FI switched faster than AL mice (**Fig. 19C**). **Fig. 19C** shows fraction of left (L-)choice relative to the switch trial (Phase 1 R-to-L switch data presented but both directions and all phases were analyzed). Adult male mice in the FI group showed faster switching than the AL group in Phase 1 (**Fig.19C,** Two-way ANOVA: treatment: $F(1,182)=10.73$, $p=0.0013$, trials relative to switch: $F(12,182)=547.3$, $p<0.0001$, interaction: $F(12,182)=2.851$, $p=0.0013$). Using post-hoc Sidak's multiple comparison, we found that adult male mice in the FI group reached the fraction of L-choice equaling 0.5 faster and that fraction of L-choice was significantly higher by second and third trials relative to R-to-L switch (2^{nd}: post-hoc Sidak's: $p<0.0001$; 3^{rd}: $p=0.019$). A similar behavioral difference between the adult male mice in the AL and FI group was observed in Phase 3 with 65% reward probability (post-hoc Sidak's: 2^{nd}: $p=0.011$; treatment: $F(1,182)=2.261$, $p=0.13$, trials relative to switch: $F(12,182)=362$, $p<0.0001$, interaction: $F(12,182)=1.725$, $p=0.065$) but not observed in Phase 2 with higher reward probability 90% (treatment: $F(1,182)=0.0145$, $p=0.90$, trials relative to switch: $F(12,182)=362.7$, $p<0.0001$, interaction: $F(12,182)=1.312$, $p=0.21$)(**Fig. 19C**).

We also looked at how many trials it took to switch *within each group* when the probability of reward was 75% vs. 90% vs. 65% (**Fig. 19B,** comparing phase 1,2,3 within group). Adult male mice in the AL and FI group both sped their switching (trials to switch) in Phase 2 with 90% reward probability compared to Phase 1 and 3 (One-way ANOVA, AL: $F(2,21)=44.85$, $p<0.0001$, post-hoc Tukey: Phase 1 vs 2: $p<0.0001$, Phase

2 vs 3: p<0.0001; FI: F(2,21)=3.717, p=0.042). This suggested both groups could detect the change in contingencies and reward probabilities and adjust switching time.

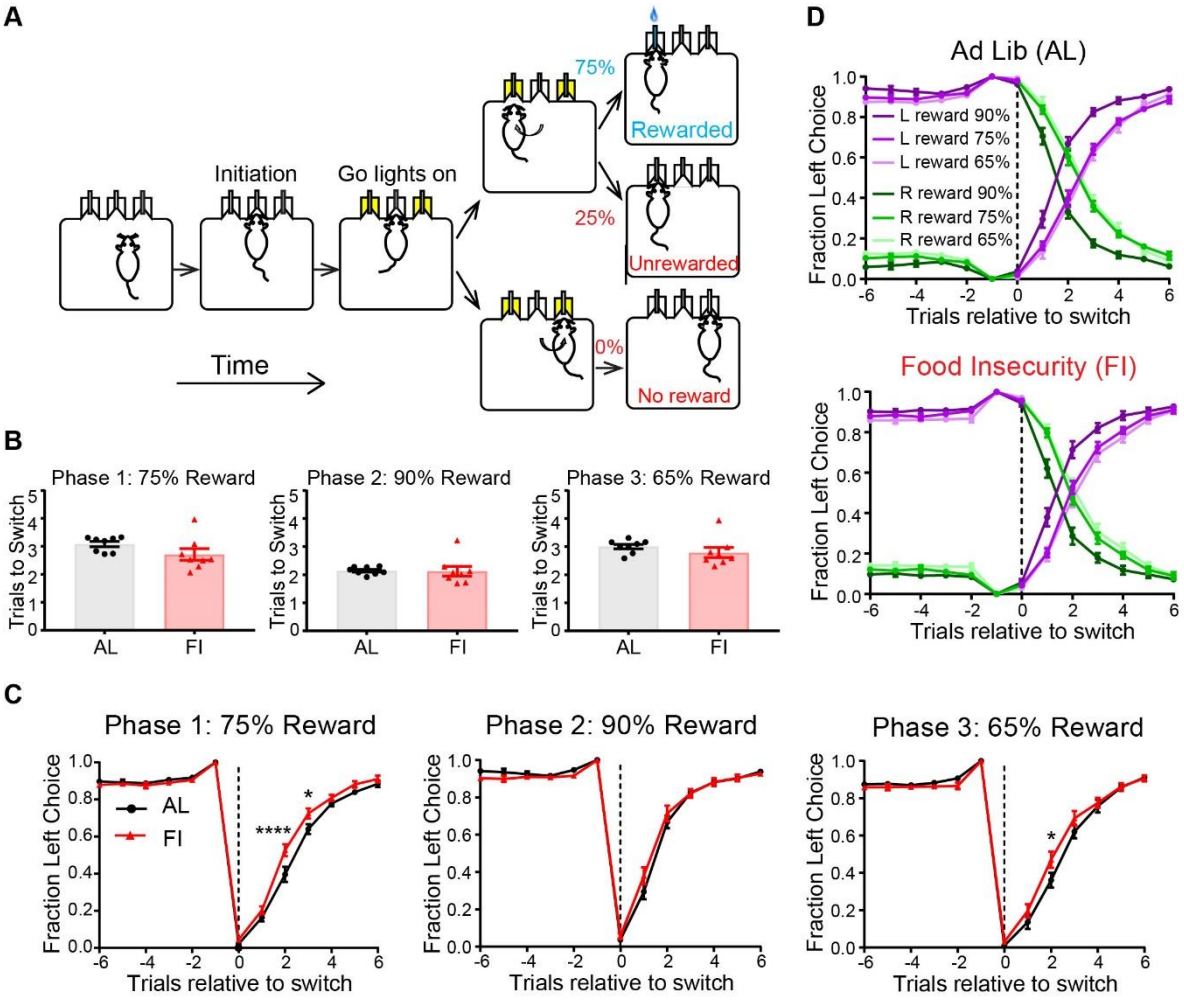


Figure 19. Differences in juvenile-adolescent feeding history affected cognitive flexibility in probabilistic reward conditions in adult male mice. **A,** Schematic of the 2-alternative choice probabilistic switching task. **B,** Adult male mice had similar average trials to switch between the AL and FI groups in each of the three training phases (Phase 1: 75%, Phase 2: 90%, and Phase 3: 65% reward probability). **C,** Adult male mice in the FI group reached 0.5 fraction of left choice faster after the right (R) to left (L) switch trial in Phase 1 and Phase 3, but not in phase 2, compared to the AL group. The L-rewarded trials were presented. **D,** Within both groups (AL & FI), mice reached 0.5 fraction of L-choice faster in Phase 3 with 90% reward probability. Adult male mice in the AL group illustrated comparable fraction of L-choice pattern in Phase 1 and Phase 3 while mice in the FI group reached 0.5 fraction of L-choice slower after R-to-L switch in Phase 3 with most uncertain conditions. Dotted line indicated the trial that either R-to-L trial or L-to-R trial happened.
n(AL)=8, n(FI)=8. *p<0.05, ****p<0.0001. Error bars represented SEM.

When comparing the behavior and fraction of L-choice aligned to switch events (**Fig. 19D**), we found that within the AL group, mouse fraction of L-choice patterns were similar between Phase 1 (75% reward) and Phase 3 (65% reward), but significantly different in Phase 2 (90% reward) (treatment: $F(2,273)=71.73$, $p<0.0001$, trials relative to switch: $F(12,273)=692.6$, $p<0.0001$, interaction: $F(24,273)=5.775$, $p<0.0001$; post-hoc Tukey: Phase 1 vs 2: $p<0.0001$, Phase 2 vs 3: $p<0.0001$). However, within the FI group, the fraction of L-choice patterns were different across three phases (treatment: $F(2,273)=41.83$, $p<0.0001$, trials relative to switch: $F(12,273)=526.3$, $p<0.0001$, interaction: $F(24,273)=3.344$, $p<0.0001$; post-hoc Tukey: Phase 1 vs 2: $p<0.0001$, Phase 1 vs 3: $p=0.025$, Phase 2 vs 3: $p<0.0001$).

In male mice, differences in feeding history during the juvenile-adolescent period affected integration of past reward history in adulthood

To more closely examined how mice used the past reward experience to guide the future behavior and choice selection upon periodical reversal changes in action-outcome contingencies, we applied similar analyses and the multivariate logistic regression model (**Eqn. 5**) (Tai et al., 2012) to analyze our data from the 2-alternative choice probabilistic switching task (**Fig. 19**).

We first analyzed the effects of past reward experience in the previous 3 trials on next choice and found that when all past 3 trials were unrewarded at either chosen L-port or R-port, mice exhibited a random choice behavior with probability of left choice, $P(L)$, about 0.5. As more reward evidence accumulated at the chosen L-port (i.e. with 3 rewarded trials in a row), mice were more likely to choose L-port in next upcoming trial with $P(L)$ approximately equal to 1(**Fig. 20A**). This analysis also revealed that qualitatively, the reward history 1 trial back has most strong effect on the choice probability and that rewarded experience had stronger influence than unrewarded experience.

To quantitatively comparing the effect of the past reward history, logistic model described in **Eqn. 5** was used to fit all mice ran in the task. From the model, the relative action values and choice probabilities for either L or R-port can be calculated. When the relative action value of choosing left was equal to 0, the choice probability $P(L)$ was roughly 0.5, where estimated action value was calculated from weighted sum of past rewarded event and past unrewarded event (**Eqn. 5**). As this action value increased, $P(L)$ was increased (**Fig. 20B**). The model was able to dynamically estimate and predict the choice probability and the actual choices from our behavioral data (**Fig. 20C**).

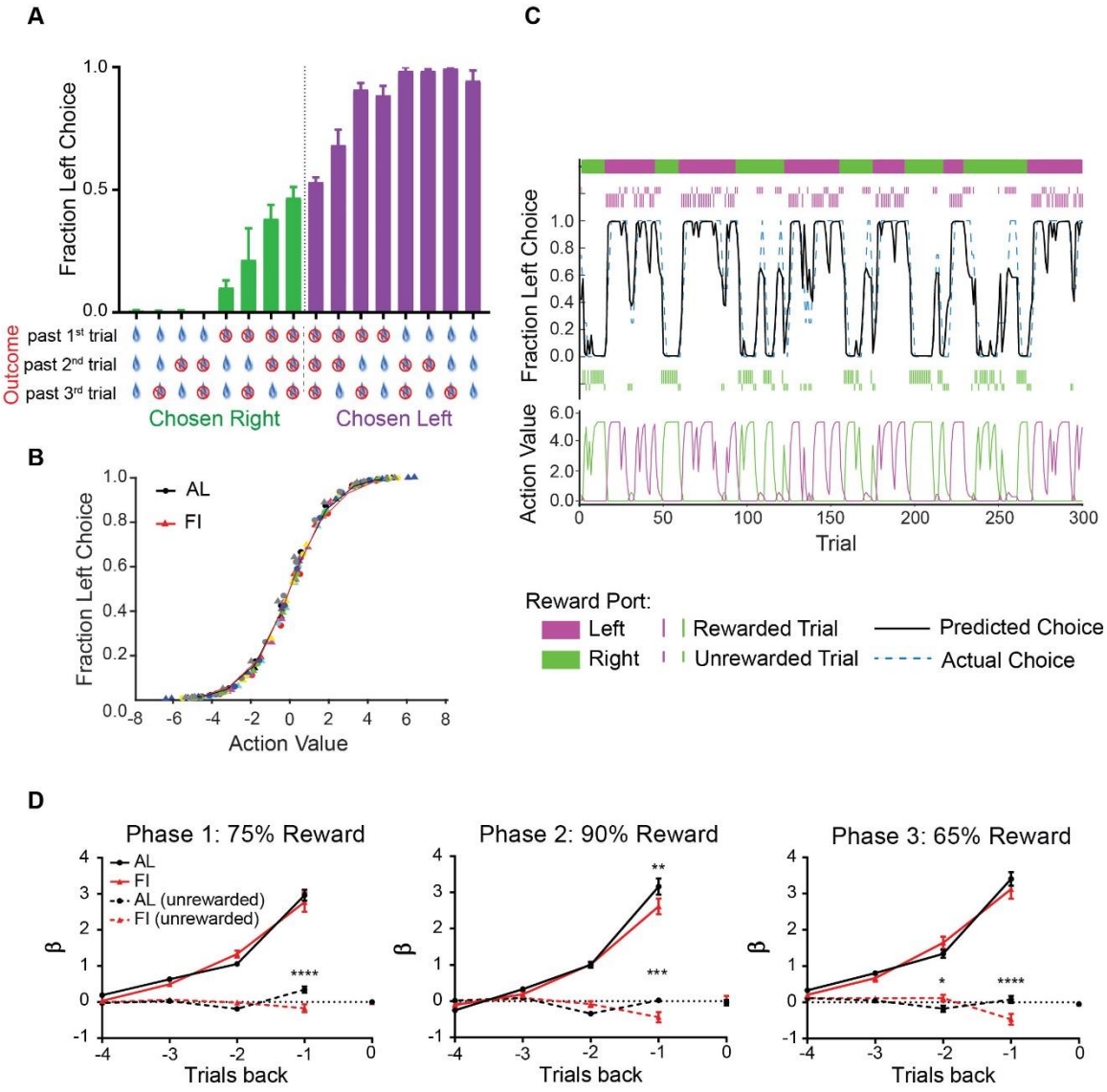


Figure 20. Differences in juvenile-adolescent feeding history affected integration of past reward history used to make an upcoming decision in adult male mice. **A,** Fraction of choosing left (L) port from one mouse (FI) for past 3-trial reward history to either L or right (R) port being chosen. **B,** The fraction of L choice and estimated action value by the logistic regression model (Eqn. 5). Each color represented a mouse. Different shapes indicated mice from different groups. Data from each subject were grouped into 10 bins for presentation. **C,** Example data for 300 trials from 1 mouse. Purple indicated the L-port rewarded block while green indicated the R-port rewarded block. Reward blocks were switched every 15±8 reward. Logistic regression model could predict the actual choice well. Black line indicated the predicted L-choice from the model. Dashed line showed the actual probability of L-choice from the average of running 4 trials. Long ticks represented rewarded trials. Short ticked represented unrewarded trials. **D,** Contributions of past rewarded history (solid line), unrewarded history (dotted line), and intrinsic bias in the past 4 trials to current choice derived from logistic regression. Positive regression coefficients β_j indicated mice were more likely to stay. Negative regression coefficients indicated mice were likely to switch. At least 5 training sessions were included in each phase for regression analysis. n(AL)=8, n(FI)=8. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Error bars represented SEM.

The regression coefficients for bias term β_0 were comparable between the AL and FI groups in all three phases and on average near 0 (**Fig. 20D,** Phase 1: t(14)=0.083, p=0.93, Phase 2: t(14)=0.8216, p=0.43, Phase 3: t(14)=0.1859, p=0.86). It suggested and supported the initial behavioral analysis that there was no intrinsic side bias.

In rewarded trials, the regression analysis showed that the positive regression coefficients β_j^{Reward} decreased with the numbers of trials in the past (past 1 to 3 trials, $\beta_1^{Reward} > \beta_2^{Reward} > \beta_3^{Reward}$) for both adult male mice in the AL and FI groups in all phases (**Fig. 20D**). Positive β_j^{Reward} values indicated that mice were more likely to stay with previously rewarded choice for the current upcoming trial. The modeling results from regression coefficients supported the qualitative observation we had. The past 1 trial rewarded trial history was most influential.

Comparing the β_j^{Reward} profiles between AL and FI groups (**Fig. 20D**), we found that there was no significant difference in Phase 1 (Two-way ANOVA: treatment: F(1,56)=0.3711, p=0.55, past trial: F(3,56)=194.2, p<0.0001, interaction: F(3,56)=1.6, p=0.20) and Phase 3 (treatment: F(1,56)=0.34, past trial: F(3,56)=166.6, p<0.0001, interaction: F(3,56)=1.532, p=0.22). In phase 2 with 90% reward probability, we found that β_1^{Reward} for adult male mice in the AL group was significantly higher than β_1^{Reward} for the FI group (post-hoc Sidak's: p=0.0093; treatment: F(1,56)=2.373, past trial: F(3,56)=247.5, p<0.0001, interaction: F(3,56)=3.074, p=0.035).

The obtained regression coefficients $\beta_j^{NoReward}$ were smaller than β_j^{Reward} , which indicated that mice weighed the past rewarded history more than past nonrewarded history to update and change their choice in the task. In unrewarded trials, adult male mice in AL group had a small but significantly positive regression coefficient for one trial back $\beta_1^{NoReward}$ in unrewarded trials in Phase 1 (**Fig. 20D,** post-hoc Sidak's: p<0.0001; treatment: F(1,56)=2.77, p=0.10, past trial: F(3,56)=3.544, p=0.020, interaction: F(3,56)=12.57, p<0.0001; also Mann-Whitney test: U=6, p=0.0047, median(AL)= -0.2187, median(FI)=0.3072). This was consistently observed in Phase 2 (post-hoc Sidak's: p=0.0004, treatment: F(1,56)=1.797, p=0.19, past trial: F(3,56)=6.983, p=0.0005, interaction: F(3,56)=7.321, p=0.0003) and Phase 3 (post-hoc Sidak's: p<0.0001, treatment: F(1,56)=0.73, p=0.40, past trial: F(3,56)=6.104, p=0.0011, interaction: F(3,56)=9.822, p<0.0001) with different reward probabilities.

In female mice, differences in feeding history during the juvenile-adolescent period did not affect integration of past reward history but did affect sensitivity to probabilistic reward conditions

We also ran the probabilistic switching task in female mice to test if juvenile-adolescent feeding history affected the behavioral processes taxed by this task.

In adult female mice, comparing AL and FI groups, we found that there was no difference in average number of trials to switch in Phase 1 (t(14)=0.2985, p=0.77), Phase 2 (t(14)=0.3609, p=072), and Phase 3 (t(14)=1.176, p=0.26) (**Fig. 21A**). When trial events were aligned to the R-to-L switch trial, fraction of L-choices from 6 trials back to 6 trials after the switch were compared. Again we found there was no difference in trials to switch between AL and FI female groups in all three phases (**Fig. 21B**, Phase 1: treatment: F(1,182)=0.2212, p=0.63, trials relative to switch: F(12,182)=516.9, p=<0.0001, interaction: F(12,182)=0.3156, p=0.99; Phase 2: treatment: F(1,182)=0.2323, p=0.63, trials relative to switch: F(12,182)=437.5, p<0.0001, interaction: F(12,182)=0.2767, p=0.99; Phase 3: treatment: F(1,182)=0.4907, p=0.48, trials relative to switch: F(12,182)=451.6, p<0.0001, interaction: F(12,182)=0.1949, p=0.99).

Within AL group females, mice switched faster in Phase 2 (90% probability), compared to Phase 1 (75% probability) and Phase 3 (65% probability)(**Fig. 21C,** fraction of L-choice plotted vs. trials relative to switch separated by phase; phase: F(2,273)=57.4, p<0.0001, trials relative to switch: F(12,273)=814.8, p<0.0001, interaction: F(24,273)=4.938, p<0.0001; post-hoc Tukey: phase 1 vs 2: p<0.0001, phase 2 vs 3: p<0.0001). FI group females exhibited differences in switching time all in three phases (**Fig. 21C,** fraction of L-choice plotted vs. trials relative to switch separated by phase; phase: F(2,293)=40.67, p<0.0001, trials relative to switch: F(12,273)=603.2, p<0.0001, interaction: F(24,273)=3.946, p<0.0001; post-hoc Tukey: Phase 1 vs 2: p<0.0001, Phase 1 vs 3: p=0.044, Phase 2 vs 3: p<0.0001).

We further examined the effects of trial by trial history on choice behavior using a logistic regression model, with beta coefficients for past rewarded and unrewarded trials and any side bias. We found that adult female mice in the AL and FI groups showed the similar weight of both rewarded and unrewarded trials in past history. Comparing the regression coefficients for past rewarded history β_j^{Reward}, adult female mice in the AL and FI groups had almost identical coefficient values for 1 trial back to 4 trials back in all phases (**Fig. 21E,** Phase 1: treatment: F(1,56)=0.0278, p=0.87, past trial: F(3,56)=281.7, p<0.0001, interaction: F(3,56)=0.1127, p=0.95; Phase 2: treatment: F(1,56)=0.0748, p=0.79, past trial: F(3,56)=348.3, p<0.0001, interaction: F(3,56)=0.3509, p=0.79; Phase 3: treatment: F(1,56)=1, p=0.32, past trial: F(3,56)=295.3, p<0.0001, interaction: F(3,56)=0.3727, p=0.77). They also had similar regression coefficients for past unrewarded trials $\beta_j^{NoReward}$ between groups in Phase 1

(**Fig. 12E,** treatment: F(1,56)=0.2203, p=0.64, past trial: F(3,56)=3.75, p=0.016, interaction: F(3,56)=0.2403, p=0.8679), Phase 2 (treatment: F(1,56)=0.6815, p=0.41, past trial: F(3,56)=13.96, p=<0.0001, interaction: F(3,56)=0.8745, p=0.46), and Phase 3 (treatment: F(1,56)=1.209, p=0.28, past trial: F(3,56)=8.9878, p<0.0001, interaction: F(3,56)=0.1989, p=0.90). Side bias suggested by the intrinsic bias term β_0 in both groups in all three phases was also minimal. (**Fig. 21E,** Phase 1: t(14)=0.0480, p=0.96), Phase 2: t(14)=0.2791, p=0.78, Phase 3: t(14)=0.3378, p=0.74).

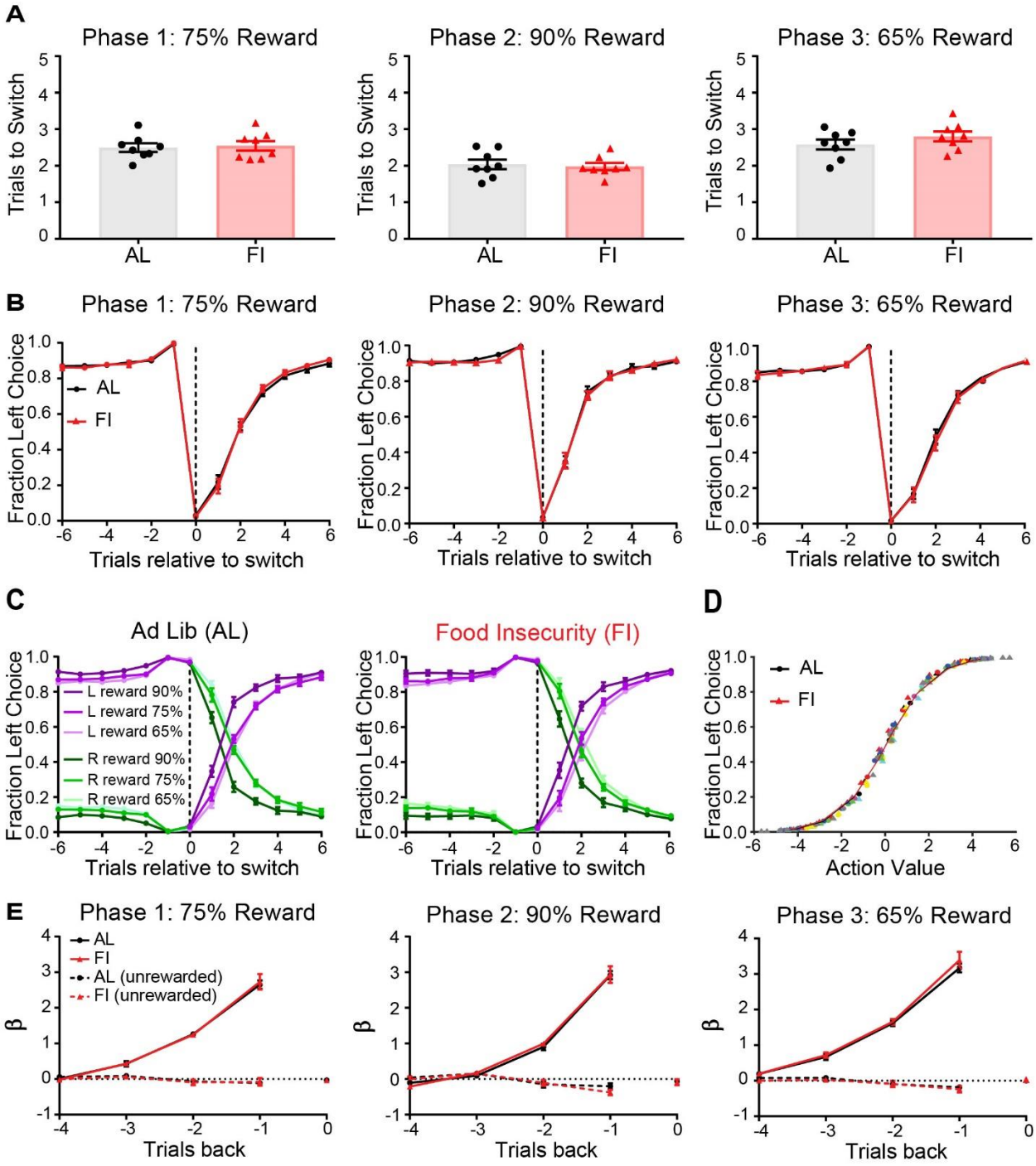


Figure 21. Adult female mice with different juvenile-adolescent feeding experiences showed similar performance in the 2-alternative choice probabilistic switching task. A, Adult female mice in the AL and FI groups did not differ in number of trials to switch in all phases. **B,** Trial events were aligned to right(R) to left(L) switch event. AL and FI groups did not differ in fraction of L-choice in all phases. **C,** Mice in AL group took fewer trials to fraction of L-choice over 0.5 in Phase 2 compared to Phase 1 and 3 that were similar. FI group exhibited different fraction of L-choice over trials relative to switch among Phase 1, 2, and 3. **D,** Both AL and FI groups centered around action value 0, fraction of L-choice 0.5. **E,** There was no difference in regression coefficients for side bias, rewarded history, and unrewarded history between groups in all three phases. n(AL)=8, n(FI)=8. Error bars represented SEM

Discussion

In this work, we generated a mouse model of developmental food insecurity to investigate impacts of juvenile-adolescent feeding history on adult learning and cognitive flexibility.

In our experiments, we found that in male mice with experience of food insecurity (P21-40) did not affect adult weight **(Fig. 10)** or simple discrimination learning (**Fig. 11,14**) but did have significant impacts on cognitive flexibility in a foraging task (**Fig. 11,14**) and integration of reward history in a probabilistic switching task (**Fig. 19,20**). Effects on cognitive flexibility in the foraging task were replicated in a second cohort (**Fig. 14**). In female mice, experience of food insecurity (P21-40) significantly affected adult weight (**Fig. 10**) but did not have significant impacts on cognitive flexibility and integration of reward history in adulthood (**Fig. 16,21**). Finally, in an experiment that altered experience of food insecurity to a later age P41-60 and testing to P80-90, we did not see phenotype differences between treatment groups at testing age (**Fig. 15**). It may suggest that there may be a sensitive period for effects of feeding or testing on behavior.

Effects of food insecurity on weight

In human subjects, previous studies have found that developmental and adult food insecurity is associated with increased weight gains and greater risks of developing obesity and that this phenomenon is more pronounced and more consistent in females (Davis et al., 2014; Dinour et al., 2007; Franklin et al., 2012). Comparing the weight trajectories from all three groups of mice in the food insecurity feeding paradigm (**Fig. 8**), we observed greater weight gains in mice in the female but not male FI group during adulthood (**Fig. 10**). These basic data suggest our rodent model may replicate aspects of human food insecurity on weight. Future work will be needed to investigate the biological mechanisms resulting in increased of body weight later in life. Our results are consistent with the somatic state-based hypothesis from the Predictive Adaptive Response (PAR) model of ADP that developing individuals specifically alter somatic state variable such as body weight in response to the developmental input in the environment (Nettle & Bateson, 2015). From an evolutionary life history perspective, it is also consistent with the idea that increased body weight after a history of food insecurity or other harsh circumstances may serve somatic preparedness for reproduction, especially for females (Ellis et al., 2009; Hochberg & Belsky, 2013; Roff, 2002).

Feeding history effects on human cognition

Our data are also consistent with literature on human development suggesting that food insecurity can affect cognition. Experience of food insecurity has been associated with negative impacts on academic performance and mental health (Aurino et al 2019; Belachew et al., 2011; Jyoti et al., 2005; Raskind et al., 2019; Winicki & Jemison, 2003). Studies that specifically isolate food insecurity and the cognitive domain however are rarer. Aurino et al. (2019) found that chronic food insecurity through development as well as acute early, and more punctuated episodes of food insecurity in the later juvenile period impaired academic performance at age 12. Dennison et al. (2019) also found that people with childhood adversity also had altered reward processing and responses in a monetary incentive delay task. By controlling for multiple factors, they determined that these differences were mediated by the experience of food insecurity, but not by other forms of adversity such as neglect and abuse.

More general studies from early life adversity in humans have also shown that experience of early life adversity can result in reduced cognitive flexibility (Amitai et al., 2014; Goodwill et al., 2018; Harms et al., 2018; Hurtubise & Howland, 2017; Wang et al., 2011). Our mouse model offers a chance to manipulate feeding alone and control other factors that are confounded with food insecurity in human subjects. Lab mice are also highly inbred and so they offer the chance to control for nearly identical genetic factors at the outset of the study and allow us to examine how multiple cognitive phenotypes may emerge from a single genotype in an experience- and context-dependent manner (Nettle & Bateson, 2015; Lin et al., in press). This approximates the incredibly rare situation in human society when it is possible to investigate identical twins that were reared in different environments.

Beyond the basic observation that feeding history in mice matched for genetic strain, dam, and housing but differed in cognitive flexibility, what more can we glean from our data? For this, we turned to finer grained analysis and computational modeling to examine how the different feeding groups behaved differently in our two tasks. These analyses can inform mechanisms and also highlight both potential strengths and weaknesses generated by experience of food insecurity when the testing environment is matched or mismatched to experienced and predicted environments. There is of course no guarantee that identical results will be present in human subjects, but these data may inspire future human subject work.

In male mice, impacts of juvenile-adolescent feeding experiences on cognitive flexibility likely emerge due to differences in sensitivity to negative outcomes, reward probability, and past reward integration

Using reinforcement learning (RL) modeling analyses, we were able to more closely investigate the trial by trial behavior to examine how learning from rewarded and unrewarded outcomes contributed to task performance. We found that juvenile-adolescent feeding history did not affect the learning rate αdis in the discrimination phase as predicted by similar behavioral performance (**Fig. 11B,C**; **Fig. 12B**). Yet, they had significant differences in learning rates, both positive learning rate $\alpha revpos\ (a+)$ and negative learning rate $\alpha revneg\ (a-)$ in the reversal phase (**Fig. 12D,E**). Especially, adult male mice had significantly smaller learning rate $\alpha revneg\ (a-)$ in response to negative outcomes (**Fig. 12E**), which suggests that more perseverative errors (choosing O1 in reversal) in the foraging task (**Fig. 11F**) resulted from a smaller negative learning rate (**Fig. 12E**).

We also observed that there was a significant decrease in the fit inverse temperature parameters between the discrimination and reversal phases ($\beta dis, \beta rev$) (**Fig. 12A,C; Fig. 17A,C**). With higher inverse temperature, the probabilities of choosing a rewarding action saturate approaching 1 (Averbeck & Costa, 2017), suggesting same actions are more likely to be repeated and more exploitative. Thus, the average higher inverse temperature β observed in the reversal phase suggests that adult mice (both AL and FI) employed more exploitative action selection strategy after they learned the task structure during the discrimination phase. This finding is consistent with Johnson et al. (2016), in which mice were found to have use more exploitative strategies in reversal phase of this same foraging task.

In addition to the differences we found in the deterministic 4-choice odor-based foraging reversal task, we also found the adult male mice with different juvenile-adolescent (P21-40) feeding experiences showed different sensitivity to probabilistic reward conditions and integration of past reward history in the probabilistic switching task (**Fig. 19,20**). In this switching task, we again found that developmental feeding history affects cognitive flexibility in males. In these more uncertain and probabilistic task conditions, however, effects were in a different direction.

First, when comparing across different reward probability conditions (Phase 1 to Phase 3), we found that both male and female mice in the FI groups showed greater sensitivity to shifts in probability in the three phases of the task compared to AL groups (**Fig. 19D** males and **Fig. 21C** females).

Next, when comparing behavior in different phases between groups, we found that adult male mice in the FI group switched faster than AL mice in the Phase 1 (75%) and Phase 3 (65%) reward contingencies but not in the Phase 2 (90%) reward contingency

(**Fig. 19C**). These data suggest that mice in the AL and FI group behaved differently under more uncertain conditions. With logistic regression analysis, we found that there were significantly different regression coefficients β_j^{Reward} and $\beta_j^{NoReward}$ for 1 trial back between male groups (**Fig. 20D**). Adult male mice in the FI group had smaller positive β_1^{Reward} than AL in Phase 2, suggesting the contribution of one-trial-back rewarded experience to current choice was smaller and that the mice in the FI group have less tendency to stay with the previous choice when reward was more certain compared to mice in the AL group. We also observed that adult male mice in the AL group had a significantly small but positive $\beta_1^{NoReward}$ in Phase 1 and Phase 3 whereas mice in the FI group had negative $\beta_1^{NoReward}$ in these two phases. These data illustrate how under more uncertain conditions (75 and 65% reward probability), adult male mice in the FI and AL group are weighing and integrating past unrewarded trials differently. This suggests a different strategy for choice behavior is used in the two groups with different developmental history.

Why are male and FI and AL mice showing opposing difference in the two tasks?

In the 4-choice foraging reversal task, adult male mice with juvenile-adolescent experience of food insecurity showed less flexibility when there are changes in reward contingencies, driven by reduced learning rate, especially learning rate in response to negative outcome in reversal phase (**Fig. 11,12**). However, in the probabilistic switching task in phases with lower probability of reward, adult male with juvenile-adolescent experience of food insecurity were more sensitive to phase to phase contingency shifts (**Fig 19,20**) and faster to switch after receiving unrewarded and negative outcomes (**Fig. 19,20**). These results both illustrate that effects of juvenile-adolescent (P21-40) feeding history may at first seem in conflict. They may be, however, explained by the differences in the environmental stimuli and context received in the two tasks as well as different phenotypic adaptation via ADP mechanisms.

The two tasks differ in that one is rewarded by food and the other by water. One takes only 1 session and often less than 100 trials (after 1 day of shaping) while the other has 1 week of pre-training, multiple sessions are used to record data for each phase, and each session has hundreds of trials. Finally, and perhaps most importantly, the two tasks differ in uncertainty, which is known to affect the dopamine system. The odor based foraging task has 4 choices but the rewarded odor is rewarded 100% of the time at deterministic reward nature. The probabilistic switching task has three phases with 75%, 90% and 65% reward contingencies.

Our initial idea was that learning and cognitive flexibility would differ between the two feeding history groups but have similar effects across tasks. However, the contrast in the data (even with many of the same mice tested in the two tasks), suggests the different tasks elicit different strategies from the two groups of mice. These data

support the idea that behavioral strategies used in response to the environment themselves are developmentally plastic and can vary as function of experiences earlier in life (Stamps, 2016). This builds on the ADP framework from the evolutionary literature suggesting in genetically identical mice there are multiple possible phenotypes that are selected based on developmental experiences (Bateson et al., 2014; Fawcett & Frankenhuis, 2015; Nettle & Bateson, 2015; Rago et al., 2019). It then adds a layer, which is also emerging in cognitive neuroscience, that elements like learning rate are not intrinsic features of a subject alone, but an emergent property of the subject's phenotype, developmental stage, and the subject's best assessment of the most optimal strategy in the particular task environment (Nussenbaum & Hartley, 2019).
If we want to examine whether mice in the AL or FI group are more efficient, it may be helpful to consider the idea of "match vs mismatch." It has been suggested that when the developmentally predicted and actual environment are not the same, there will be mismatch in individual's programmed behavioral strategies (Bateson et al., 2014; Frankenhuis & de Weerth, 2013; Lea et al., 2017; Nettle & Bateson, 2015; E. Snell-Rood & C. Snell-Rood, 2020). Using the "match vs mismatch" hypothesis as a guide, we might assume the mice growing up with ad libitum experience during the juvenile-adolescent period will be tuned to 'succeed' and "adaptive" in a deterministic environment while mice with insecure feeding experience are tuned to 'succeed' and "adaptive" in a more uncertain or probabilistic environment. This may explain why the AL group males showed greater flexibility in the deterministic foraging task and the FI group males showed greater flexibility in the probabilistic switching task. It does not however explain why these changes were largely absent in females and why performance differences were limited to aspects of flexibility but not learning. More tests in different task conditions and studies focus on variables might lead to sex difference will be required to determine if and why different cognitive and behavioral phenotypes resulted from different feeding experience is only observed in the males.

The possibility of a sensitive period for the impacts of developmental experience of food insecurity

A final consideration we can address with our data is the timing of food insecurity. We performed one experiment in males which shifted the timing of the feeding manipulation to a later time in development P41-60 (**Fig. 9,15**). When we shifted the timeframe of food insecurity feeding paradigm to P41-60 and tested mice in the foraging task at P80-90, we found there was no difference in performance across all behavioral measures in the discrimination and reversal phase (**Fig. 15**). These data suggest that the impacts of past feeding history on cognitive function wane with age. This could be due to sensitive period for exposure or testing. We favor the hypothesis that P21-40 is a sensitive period for cognitive development. Other studies have identified this period in mice as more sensitive to experience than later periods in development (Makinodan et al., 2012; Murray & Chen, 2019; Yohn & Blendy, 2017). Other studies also found that the

interacting neural circuits and brain areas supporting reversal learning, such as dorsomedial prefrontal cortex, striatum, cortical-striatal circuits, and dopamine systems are still undergoing refinement and have protracted development in this juvenile adolescent period (Boivin et al., 2018; Delevich et al., 2020; Johnson et al., 2016; Klanker et al., 2013; Krajeski et al., 2019; Mastwal et al., 2014; Matthews et al., 2013; Naneix et al. 2012; Pattwell et al., 2016). Feeding experience may particularly modulate these systems more heavily during P21-40 period due to greater neurobiological plasticity at this time (Chapter 1; Lin et al., in press; Murray & Chen, 2019). In next chapter (Chapter 4), we will focus on the impacts of juvenile-adolescent feeding history on neurobiology.

Studies of feeding manipulations in rodents have focused on addiction and hippocampus-dependent learning and memory but not cognitive functions and not examined at later stages of development

There is a large existing literature that strongly supports the idea that food and feeding manipulations in rodents can strongly impact brain and behavior. However, there is a gap in understanding feeding effects on the juvenile and adolescent development. In adult rodents, there are multiple animal studies in rodents focusing on investigating the effects of acute or chronic food restriction on learning and behavioral changes as well as the neuroadaptations in dopaminergic activities in several brain areas. Acute food restriction has been found to enhance fear conditioning (Riddle et al., 2013), promote relapse to drug seeking (Maric et al., 2011; Reiner et al., 2019; Shalev et al., 2000) and alter dopamine neuron activity and dopamine release (Branch et al., 2013; Roseberry 2015). Chronic food restriction has been found to decrease memory in spatial and novel object recognition tests (Carlini et al., 2008; Fu et al., 2017), enhance later binge eating (Car, 2011; Davis & Carter, 2009), and augment the effect of drug abuse such as greater dopaminergic response, increased chances of relapse, and increased drug conditioned place preference (Carr, 2007, 2011; D'Cunha et al., 2013; Sevak et al., 2008; Zheng et al., 2012).

Previous studies in rats show that learning about food availability during adulthood under different satiation state (i.e. hunger or sated) with uncertainty makes rats have different food consumption patterns and the responsivity to the cues signaling the presentation and delivery of the food reward (Galarce & Holland 2009). The cue previously signaling interruption of meals or food scarcity was found to potential later food consumption (Galarce & Holland, 2009). Other studies found that irregular feeding schedules were more likely to elicit binge eating in adult rats (Corwin et al., 2011) and that intermittent eating schedules could alter feeding, metabolism, mood regulations, and anxiety related behaviors (Murphy & Mercer, 2014).

Literature studying impacts of high-fat or high-sugar diet has accumulating evidence that high-fat/high-sugar feeding experience occurred early in life, especially adolescence period, had more profound effects on later hippocampus-dependent functions (Del Olmo & Gayo, 2018; Del Rio et al., 2016; Khazen et al., 2019; first systematic reviewed by Murry & Chen, 2019). Murry and Chen (2019) reported that majority of study, 7 out 8 studies, showed the high-fat diet exposure starting from adolescence was associated with diet-induced memory performance.

However, these studies illustrated that different feeding experiences can result in different phenotypes mainly in metabolism, hippocampal-dependent learning and memory, vulnerability and drug seeking behavior. How history of juvenile adolescent feeding experience, especially instability of food resources, affects adult behavior in flexible updating and reward integration that contribute to many goal-directed behaviors has not been examined. This is an important question given the increasing prevalence of food insecurity in the USA and worldwide, particularly in 2020. Our data added an important piece to the literature studying different feeding experiences and early life adversity when food insecurity is considered as a form of adversity.

Conclusion and public health relevance

Our results suggest that experience of food insecurity during juvenile-adolescent period, which is parallel to human childhood and peripubertal period, has impacts on cognitive flexibility, reward integration, and updating in adult male mice. These data are consistent with associations in human subjects between food insecurity and negative mental health, substance abuse, and academic outcomes and may explain some of the pathways that lead to these negative outcomes. However, our data also suggest there are behavioral strengths that can also emerge from an experience of food insecurity in specific contexts. Our study in mouse models in which we can isolate feeding as a variable should inform public health decision making. Our data suggest that feeding history in the juvenile-adolescent period can significantly impact adult weight and behavioral functions. These data suggest prioritization of school feeding programs should be sought not only to ameliorate hunger itself, but also to ameliorate obesity and support adult cognitive function.

Chapter 4

Different feeding experience during the juvenile-adolescent period alters VTA dopaminergic neurons and striatal dopamine release

Introduction

Developmental experience of food insecurity is associated with multiple negative physical and mental health outcomes, including obesity, substance use disorders, and reduced academic performance (Althoff et al., 2016; Aurino et al., 2019; Franklin et al., 2012; Ke & Ford-Jones, 2015). From an evolutionary perspective, experience of scarcity in the food supply is likely to a common problem faced by wild organisms. Therefore, adaptations may have evolved to adjust the brain and behavior in response to this food uncertainty and scarcity experience (Bateson et al., 2014; Fawett & Frankenhuis, 2015; Lin et al., in press). Here, we describe experiments investigating how differences in juvenile-adolescent feeding experience affect the mesolimbic and nigrostriatal dopamine (DA) systems which support learning, reward integration and flexible updating.

The mesolimbic DA system comprises neurons that project from the ventral tegmental area (VTA) to the ventral striatum including the nucleus accumbens of the striatum (NAc). The nigrostriatal DA system comprises neurons that project from the substantia nigra pars compacta to the dorsal striatum. We initially focused on the mesolimbic DA system because mesolimbic DA neurons are known to play a role in reward prediction errors, cue-associative and reinforcement learning, reward seeking and motivated behaviors, and decision-making (Hamid et al., 2016; Salamone & Correa, 2012; Saunders et al., 2018; Schultz, 2016; Watabe-Uchida et al,. 2017). As a target of mesolimbic DA projections, the NAc core was found to be important for cue-associative learning (Ambroggi et al., 2011; Floresco et al., 2008; Lex & Hauber, 2010) and signaling the receipti of an unexpected and/or expected food reward (Brown et al., 2011; Biesdorf et al., 2015). Prediction errors are thought to be signaled by increases and decreases in DA neuron firing in response to outcomes that are better or less than expected (Schultz, 2016; Schultz et al., 1997; Steinberg et al., 2013; Watabe-Uchida et al., 2017).

We hypothesized that differences in the function of mesolimbic DA neurons that project to the NAc may be responsible for differences in learning from negative outcomes and differences in reward integration in AL and FI males discussed in the previous chapter (Chapter 3). We also hypothesized that DA neurons that support learning, cognitive flexibility and reward integration may be particularly susceptible to changes in feeding experience and in particular food insecurity because they are known to both modulate

their firing rate in response to feeding/satiety state (Branch et al., 2013; van den Plasse et al., 2015) and to respond to uncertainty in the environment (de Lafuente & Romo, 2011; Fiorillo et al., 2003; Tennyson et al., 2018).

In addition, the DA system shows protracted development and changes into adolescence or early adulthood (Matthews et al., 2013; McCutcheon et al., 2012; Sinclair et al., 2014; Wahlstrom et al, 2010). For instance, DA neurons alter their firing rate in an inverted-U-shaped manner, with the firing rate peaking shortly after P40 (McCutcheon et al., 2012). DA receptor expression peaks during the transition from the juvenile to adolescent period (P28-42), around the time of puberty onset, and varies by brain regions depending on specific subtypes of receptor (Wahlstrom et al., 2010). Striatal DA release and total level of striatal DA increases during the juvenile period (Lieberman et al., 2018; Matthews et al., 2013; Stamford, 1989). These developmental neurobiological changes overlap with the juvenile-adolescent period in which we manipulated feeding history. Therefore, we hypothesized that juvenile-adolescent feeding history may interact with the protracted development of the DA system, thereby sculpting its development and exerting effects on its adult function (See the working model in Chapter 1).

Here, we focused on investigating the impacts of different juvenile-adolescent (P21-40) developmental feeding experiences on DA systems in adult (P61-70) male mice. We first examined the properties and plasticity of the DA projections from the VTA to NAc core. We then examined DA release in the NAc core and expanding the sampling subregions over ventral and dorsal striatum, which are together thought to play a pivotal role in learning, action selection, and decision making (Burton et al., 2015; Cox & Witten et al., 2019; Hong & Hikosaka, 2011; Kim et al., 2007, 2009; Macpherson et al., 2014; Shin et al., 2018)

We found that different developmental feeding experiences – ad libitum (AL) or food insecurity (FI) – affect neuroplasticity of NAc-core projecting VTA DA neurons in terms of ratio of AMPA/NMDA receptor (R)-mediated excitatory postsynaptic currents (EPSCs). In addition, we found that *in* vitro electrically evoked DA release in the dorsolateral striatum (DLS) and the ratio of 4-pulse over single pulse (4p/1p) stimulation evoked DA release in dorsomedial striatum (DMS) differed between developmental feeding experiences. Together, our results suggest that different feeding experiences during juvenile-adolescent development period can affect the function of the adult mesolimbic and nigrostriatal DA systems that are thought to support learning, cognitive flexibility, and decision making. We discuss how this may inform issues in public health but also consider the possibility that these changes reflect an adaptive plasticity to abundance and scarcity in the developmental environment.

Methods

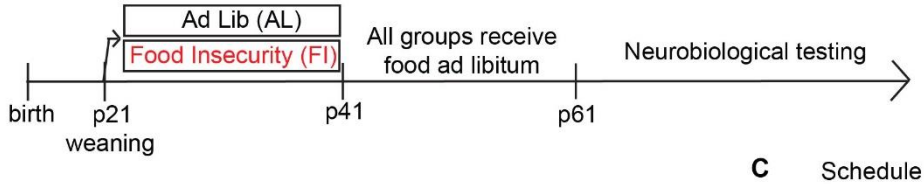
Animals

The wildtype C57BL/6 mice line were originally obtained from Taconic Biosciences, Inc. and bred at the animal facility of University of California, Berkeley. We chose to use Taconic mice (C57BL/6NJ) because they do not have a mutation in the metabolism relevant nuclear-encoded mitochondrial protein *Nnt* gene, unlike C57BL/6J mice from Jackson Laboratory (Toye et al., 2005). Nicholson et al. (2010) found that the C57BL/6J mice with *Nnt* mutation had higher non-fasting level of glucose in plasma and more severe glucose intolerance compared to C57BL/6NJ. Mice were housed on a 12h/12h reverse light-dark cycle (lights off at 10 AM). Mice were weaned and individually housed at P21 and then treated with always ad lib feeding or a food insecurity paradigm for 20 days, described in the following section (**Fig. 22**). Teklad Global 18% Protein Rodent Diet 2918 (Envigo) was used as the standard diet. All animals received nesting materials and water *ad libitum* in their home cages. Brains were all harvested during the animals' dark phase period. All procedures were approved by the UC Berkeley Animal Care and Use Committees.

Food insecurity versus Ad libitum feeding paradigm

Male mice were weaned, individually housed, and assigned into 2 different groups at P21. Mice in Ad libitum (AL) group had free access to standard rodent chow from P21 to P40, while mice in the Food Insecurity (FI) group experienced food restriction from P21 to P40 at level of 85% average weights of mice in the AL group for 20 days. Mice in the FI group had the same baseline amount of food every two days during these 20 days with alternating day1-day2 ratios (100%-0%, 90%-10%, 80%-20%) (**Fig. 22B**). All mice were weighed every two days from P21-P60 to track their weights and growth. Weights were used to determine the actual food amount given to mice in the FI group every two days. The baseline feeding amount for each day is shown (**Fig. 22C**). Together, mice in the FI group experienced uncertainty and unpredictability of food access each day while maintaining on average 85% weights in the AL group over the 20-day food insecurity feeding paradigm period. At P41, all mice in the FI group began to receive food *ad libitum* as mice in the AL group (**Fig. 22**), and thereafter experiences were matched between groups. Nesting materials and water were always provided and freely available in their homecages. All neurobiological experiments were performed after P60 (**Fig. 22A**).

A



B

Age(P)	21-22	23-24	25-26	27-28	29-30	31-32	33-34	35-36	37-38	39-40
AL	Free Access to Standard Rodent Diet									
FI (%)	100:0	80:20	90:10	100:0	80:20	90:10	100:0	80:20	90:10	100:0

C

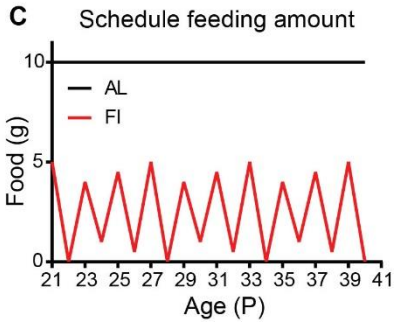


Figure 22. Food insecurity feeding paradigm and neurobiological experimental timeline. A, Single-housed mice were assigned to 2 different groups, Ad lib (AL) and Food Insecurity (FI) at P21. Adult mice after P60 were used in experiments for neurobiological activities. **B,C,** FI mice experienced a 20-day food restriction feeding paradigm from P21-40, controlling their weights to be 80-90% of AL mice. FI mice received the same baseline amount of the standard rodent diet every two days in alternating ratios. The day 1: day 2 ratio is specified in the table. **B**,**C**, The figure shown in the baseline feeding amount for each group. Starting at P41, FI mice returned to food *ad libitum*. AL mice always had free access to food. All groups of mice received water *ad libitum*.

Retrograde labeling of DA neurons and electrophysiology[4]

Male mice in AL and FI groups were unilaterally injected with red retrobeads (100 nl; LumaFluor Inc.) into NAc core (bregma +1.1 mm, lateral 1.4 mm, ventral -4.4 mm from skull) 2 days before electrophysiology experiments at P61-70 (**Fig. 23A**).
Mice were deeply anaesthetized with pentobarbital (200 mg/kg i.p.; Vortech). After intracardial perfusion with ice-cold artificial cerebrospinal fluid (ACSF), 200 µm coronal midbrain slices were prepared. ACSF solutions contained in mM: 2.5 glucose, 50 sucrose, 125 NaCl, 2.5 KCl, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 0.1 $CaCl_2$, and 4.9 $MgCl_2$, and oxygenated with 95% O_2/ 5% CO_2. After 90 minutes of recovery, slices were transferred to a recording chamber and perfused continuously with oxygenated ACSF containing in mM: 11 glucose, 125 NaCl, 2.5 KCl, 25 $NaHCO_3$,1.25 NaH_2PO_4, 1.3 $MgCl_2$, and 2.5 $CaCl_2$. Patch pipettes (3.8-4.4 MΩ) were pulled from borosilicate glass (G150TF-4; Warner Instruments) and filled with internal solution containing in mM: 117 $CsCH_3SO_3$, 20 HEPES, 0.4 EGTA, 2.8 NaCl, 5 TEA, 4 MgATP, 0.3 NaGTP, 5 QX314, and 0.1 Spermine, pH7.3 (270-285 mOsm). D-AP5 (50 µM) was applied to block NMDA receptors.

[4] Data collected using electrophysiology was facilitated by a collaboration with Christine Liu in the Stephan Lammel's Lab at UC Berkeley. I prepared the mice and Christine Liu performed the whole cell patch recordings.

Electrophysiological recordings were made at ~ 30-32^{o} C using a MultiClamp700B amplifier and acquired using a Digidata 1440A/1550 digitizer, sampled at 10kHz, and filtered at 2 kHz. All data acquisition was performed using pCLAMP software (Molecular Devices). Labeled DA neurons were identified by retrobead labeling. A concentric bipolar stimulating electrode was placed 100-300 µm lateral to the recording electrode, controlled by an ISO-Flex stimulus isolator (A.M.P.I) (**Fig. 23A**). AMPAR/NMDAR ratio at +40 mV was calculated from values obtained from average of excitatory postsynaptic currents (EPSCs) before and after application of D-AP5, where NMDAR EPSCs were calculated by the subtraction of average EPSC with D-AP5 from average EPSC without D-AP5 (Lammel et al., 2011). Rectification index (RI) was calculated by plotting average EPSCs at -70, -50, 0, +20, and +40 mV and taking the ratio of the slopes between currents (I) at different potentials (V) by the formula shown below (**Eqn. 6**)(Adesnik & Nicoll, 2007; Panicker et al., 2008).

$$RI = \left\{\frac{I_{+40} - I_0}{I_0 - I_{-70}}\right\} \times \frac{7}{4} \qquad \textbf{(Equation 6)}$$

Fast scan cyclic voltammetry (FSCV) and electrical stimulation[5]

DA release was monitored using FSCV in acute coronal slices containing striatum (Threlfell et al., 2012; Kosillo et al., 2019). Separate cohort of male mice in AL and FI groups at P61-70 were anesthetized with isoflurane and decapitated. Following decapitation, the brain was removed. Coronal slices with 275 µm thickness were cut on a vibratome (Leica VT1000S) in ice-cold high Mg^{2+} ACSF containing in mM: 85 NaCl, 25 $NaHCO_3$, 2.5 KCl, 1.25 NaH_2PO_4, 0.5 $CaCl_2$, 7 $MgCl_2$, 10 glucose, 65 sucrose, oxygenated with 95% O_2/5% CO_2. Slices between +1.5 mm and +0.5 mm from bregma containing dorsal striatum (DS) and nucleus accumbens (NAc) were used for experimentation (Paxinos & Franklin, 2008). Slices were then placed in ACSF containing in mM: 130 NaCl, 25 $NaHCO_3$, 2.5 KCl, 1.25 NaH_2PO_4, 2 $CaCl_2$, 2 $MgCl_2$, 10 glucose at room temperature during 1 hour recovery and at 32^{o} C in recording chamber. Striatal dopamine (DA) release following electrical stimulation with a bipolar concentric stimulating electrode (2 ms, 600 µA) was monitored with fast cyclic voltammetry (FCV) at carbon-fiber microelectrodes (CFMs) using Millar voltammeter (Julian Millar, Barts, and the London School of Medicine and Dentistry). CFMs were fabricated from epoxy-free carbon fiber 7-8 µm in diameter (Goodfellow Cambridge Ltd) enclosed in glass capillary and cut to final tip length of 50 – 100 µm. Electrical stimulation was controlled by a Master-8 pulse simulator or Isoflex stimulus isolator (A.M.P.I.) that was delivered out of phase with voltammetric scans. A triangular waveform was applied to CFMs scanning from -0.7V to +1.3V and back, against Ag/AgCl reference electrode at a rate of 800 V/s.

[5] Data collected using FSCV was facilitated by a collaboration with Dr. Polina Kosillo in the lab of Helen Bateup at UC Berkeley. I prepared the mice and Dr. Kosillo performed the recordings.

CFMs were approximately 100 µm away from the stimulating electrode. Evoked DA transients were sampled at 8 Hz, and data were acquired to 50 kHz using AxoScope 10.2 (Molecular Devices). Recorded FCV signals were identified as DA by comparing oxidation (+0.6V) and reduction (-0.2V) potential peaks from experimental voltammograms with currents recorded during calibration with 2 µM DA dissolved in experimental media ACSF.

Electrical stimulation was delivered in the following sequence: single pulse, pulse train of 4 pulses at 100 Hz, and single pulse. Each pulse or pulse train was delivered 2.5 minutes apart. Slices from different treatment slices were recorded with the same CFMs for every treatment pair. There were two release events per recording site per slice for single-pulse data, while 4-pulse data consisted of one release event per recording site per slice. Sampling subregions (**Fig. 24A**) included dorsomedial striatum (DMS), dorsocentral striatum (DCS), dorsolateral striatum (DLS), central striatum (CS), ventrolateral striatum (VLS), ventromedial striatum (VMS), and nucleus accumbens core (NAc). Two recording sites within the NAc core were averaged together for analysis. FSCV data were first processed using the AxoScope 10.2 software and analyzed using excel and GraphPad Prism. Peak-evoked DA release levels were compared.

Statistical analysis

Values are reported as mean (M) ± standard error of mean (SEM). Data were analyzed using two-tailed t-tests or ANOVAs with post-hoc analysis. GraphPad Prism 7 was used for statistical analysis.

Results

Differences in feeding history during the juvenile-adolescent period (P21-40) affected AMPAR/NMDAR mediated EPSCs ratio onto mesolimbic VTA DA neurons

To understand if differences in feeding during the juvenile-adolescent period affect activities of DA neurons that may contribute to differences observed in behaviors in adulthood (P61-70) (**Fig. 11,12,19,20**), we first investigated the neuroplasticity of DA neurons in the midbrain slices of adult (P60-70) male mice from AL and FI groups. We unilaterally injected retrobeads into NAc core and measured the EPSCs in response to electrical stimulation (**Fig. 23A,B**). We then calculated the ratio of AMPAR-mediated EPSCs to NMDAR-mediated EPSCs at +40 mV, which is a common property of synaptic plasticity (Kauer & Malenka, 2007).

The electrically evoked EPSCs revealed that the AMPAR/NMDAR ratio from the FI group (0.335±0.045, n=10) was significantly smaller compared to the ratio from the AL

group (0.523±0.051, n=11) (**Fig. 23C,** t(19)=2.721, p=0.014). There was a lower but not significantly different average AMPAR-mediated EPSCs from the FI group compared to the values from AL group (**Fig. 23D,** AL: 142.7±37.22 pA, FI: 77.96±15.81 pA; t(19)=1.545, p=0.14), while the average NMDAR-mediated EPSCs from both groups were similar (Fig. 23E, AL: 251.6±47.77 pA, FI: 252.9±48.56 pA; t(19)=0.019, p=0.99). We also examined the current (I)-voltage (V) relationship (**Fig. 23F**) and calculated the rectification index (**Eqn. 6**) to see if there was difference in the composition of AMPA receptors, especially the presence of GluR2-lacking AMPA receptors (Liu & Cull-Candy, 2002; Panicker et al., 2007). The rectification index was not significantly different between the two groups (**Fig. 23G,** AL: 2.12±0.42, n=9, FI: 1.64±0.27, n=9; t(16)=0.9775, p=0.34). We also did not find a significant difference in the paired-pulse ratios in 50-ms interval (AL: 1.14±0.12, n=10, FI:1.11±0.18, n=8), 100-ms interval (AL:1.10±0.08, n=11, FI:0.95±0.09, n=9), and 200-ms interval (AL: 0.93±0.04, n=10, FI: 0.89±0.08, n=8) between the two groups (**Fig. 23H,I**: treatment: F(1,50)=0.7816, p=0.38, paired pulse interval: F(2,50)=2.184, p=0.12, interaction: F(2,50)=0.2118, p=0.81).

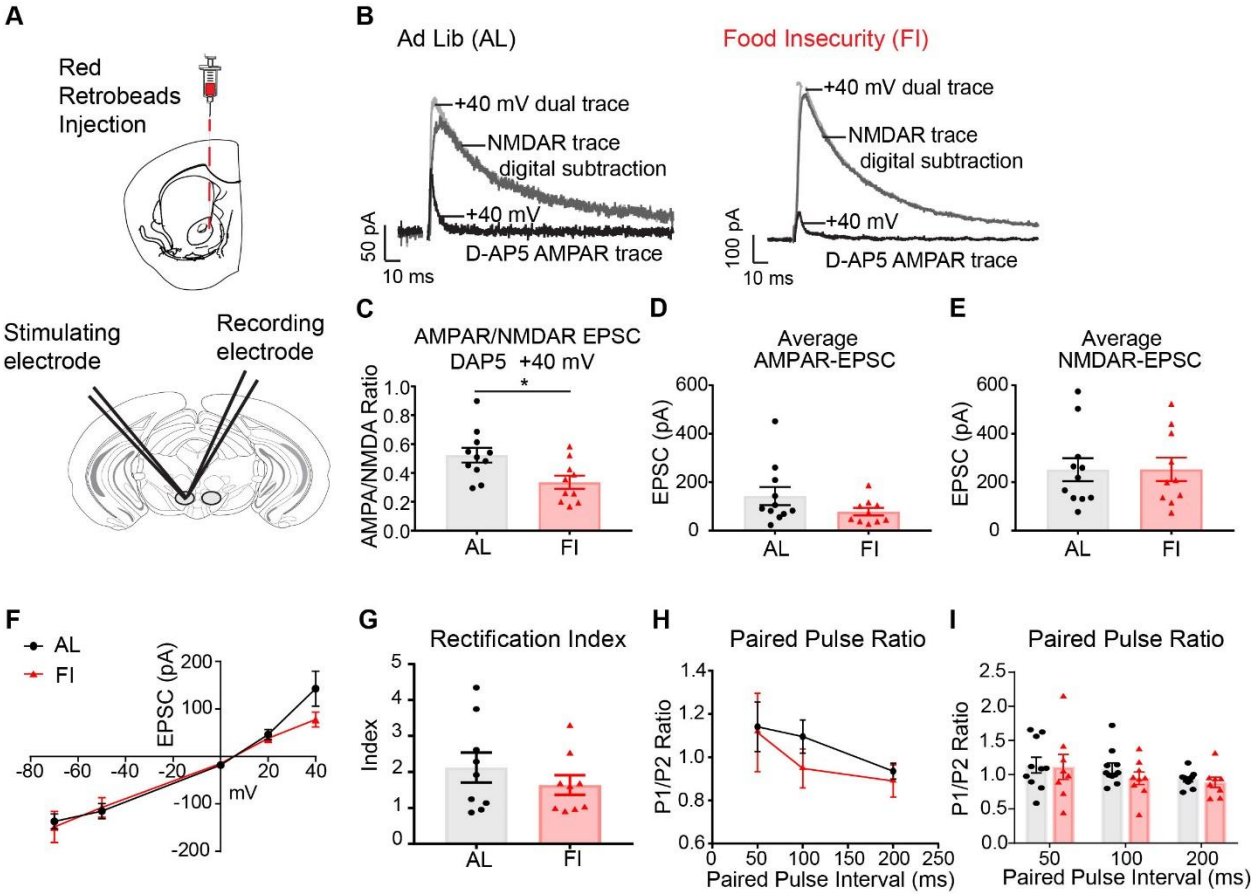


Figure 23. In adult male mice, differences in juvenile-adolescent feeding history affected AMPAR/NMDAR-mediated EPSCs in mesolimbic DA neurons. A, Retrobeads were injected in NAc and electrophysiological recording at VTA in midbrain slices. Electrical evoked EPSCs were recorded. **B,** Example EPSC traces with before and after application of D-AP5 and calculation of NMDAR-mediated EPSC were presented. Scale bars were presented. **C-E,** Electrically evoked ratios of AMPAR/NMDAR mediated EPSC were on average smaller in the slices obtained from adult (P61-70) male mice with juvenile-adolescent food insecurity feeding history. n(AL)=11, n(FI)=10. **F,G,** AMPAR-EPSC I-V relationship curve. Rectification Index was calculated using **Eqn. 6**. There was no significantly different rectification index between the AL(n=9) and FI (n=9) groups. **H,I,** Paired-pulse ratios were similar between groups in 50-ms interval (n(AL)=10, n(FI)=8), 100-ms interval (n(AL)=11, n(FI)=9), and 200-ms interval (n(AL)=10, n(FI)=9). *p<0.05. Error bars represented SEM.

Differences in feeding history during the juvenile-adolescent period affected evoked DA release in the dorsal striatum nigrostriatal system

In addition to examine neuroplasticity and basal properties of VTA DA neurons, we also investigated DA release across the NAc core and striatum, including total 7 subregions (**Fig. 24A**). We found that single-pulse electrically evoked peak DA concentration $[DA]_o$ in the DLS was significantly lower from the FI group (in μM: 0.71±0.08) compared to the AL group (1.05±0.09)(**Fig. 24B,** t(19)=4.307, p=0.0004, paired two-tailed t-test). Single-pulse evoked peak DA concentrations between the AL and FI group were similar in DMS (t(19)=0.6852, p=0.50), DCS(t(18)=0.5364, p=0.60), CS(t(19)=1.272, p=0.22), VLS(t(16)=1.358, p=0.19), VMS(t(19)=0.7658, p=0.45), and NAc core (p=0.21, two-tailed Wilcoxon matched-pairs signed rank task). Using one-way ANOVA analysis with post-hoc tests (Tukey's and Dunnett's multiple comparison tests) within each group, we found that single-pulse evoked peak $[DA]_o$ was highest in VLS compared to all other 6 sampled regions in both AL ($F(6,142)=11.72$, $p<0.0001$) and FI group ($F(6,142)=6.495$, $p<0.0001$). We found that 4-pulse 100Hz evoked peak $[DA]_o$ was significantly lower in the DLS of the FI group (in μM: 1.35±0.19) compared to the AL group (1.81±0.26, t(9)=2.432, p=0.038), but not in other regions (**Fig. 24C**). We further calculated and compared the ratio of peak DA release between 4-pulse 100Hz train and single pulse stimulation. The 4p/1p ratio was significantly higher in the DMS from the AL (n= 5 mice) group than from the FI (n=5 mice) group (**Fig. 24D,** AL: 1.68±0.10, FI:1.38±0.02, t(4)=2.814, p=0.04, paired two-tailed t-test), suggesting that the release probability of DA upon first stimulus event may be higher in the DMS of the FI group or the total storage pool of DA content available for release may be greater in the DMS of the AL group .

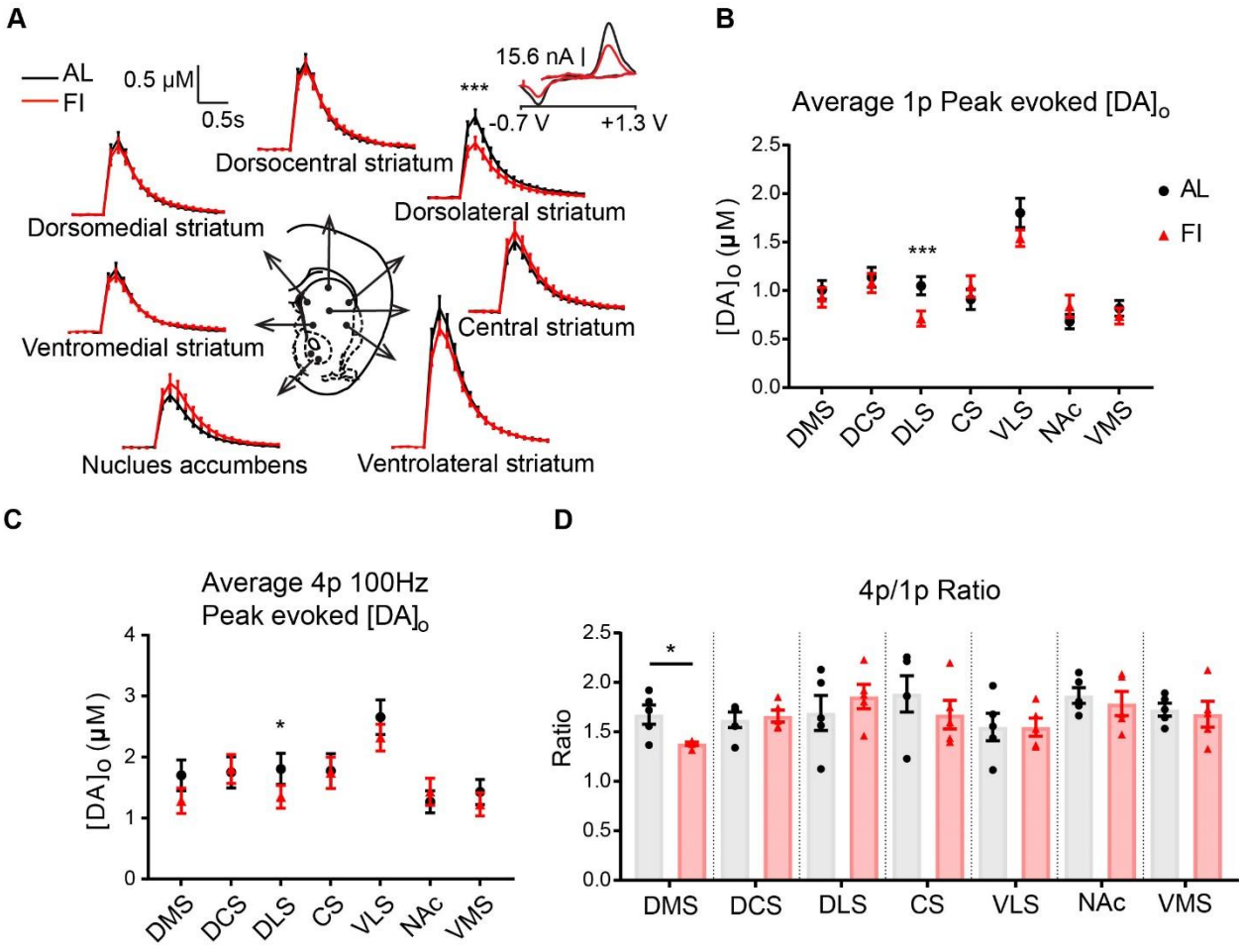


Figure 24. In adult male mice, differences in juvenile-adolescent feeding history affected evoked striatal dopamine release in the dorsolateral striatum. A, Peak DA release $[DA]_o$ verse time evoked from 7 different subregions of striatum by a single pulse electrical stimulus. Traces were an average of 17-32 transients per site from 5 mice per treatment group. Inset, the typical cyclic voltammograms show characteristic DA waveforms. **B,** Peak $[DA]_o$ by a single pulse stimulation per subregion. N= 17-32 transients per site from 5 mice per treatment group. Evoked peak $[DA]_o$ was significantly lower in the DLS from the FI group. **C,** Peak $[DA]_o$ by a 4-pulse train 100Hz stimulation per subregion. N= 9-16 transients per site from 5 mice per treatment group. Peak $[DA]_o$ was significantly lower in the DLS from the FI group. **D,** Ratio of peak $[DA]_o$ evoked by a 4-pulse train to single-pulse stimulation per subregion. N= 5 mice per treatment group. The 4p/1p ratio was significantly lower in the DMS in the FI group, compared to AL group. Detailed single-pulse and 4-pulse peak $[DA]_o$ per region per animal see **Fig. 25**. Paired two-tailed t-tested used for DA release

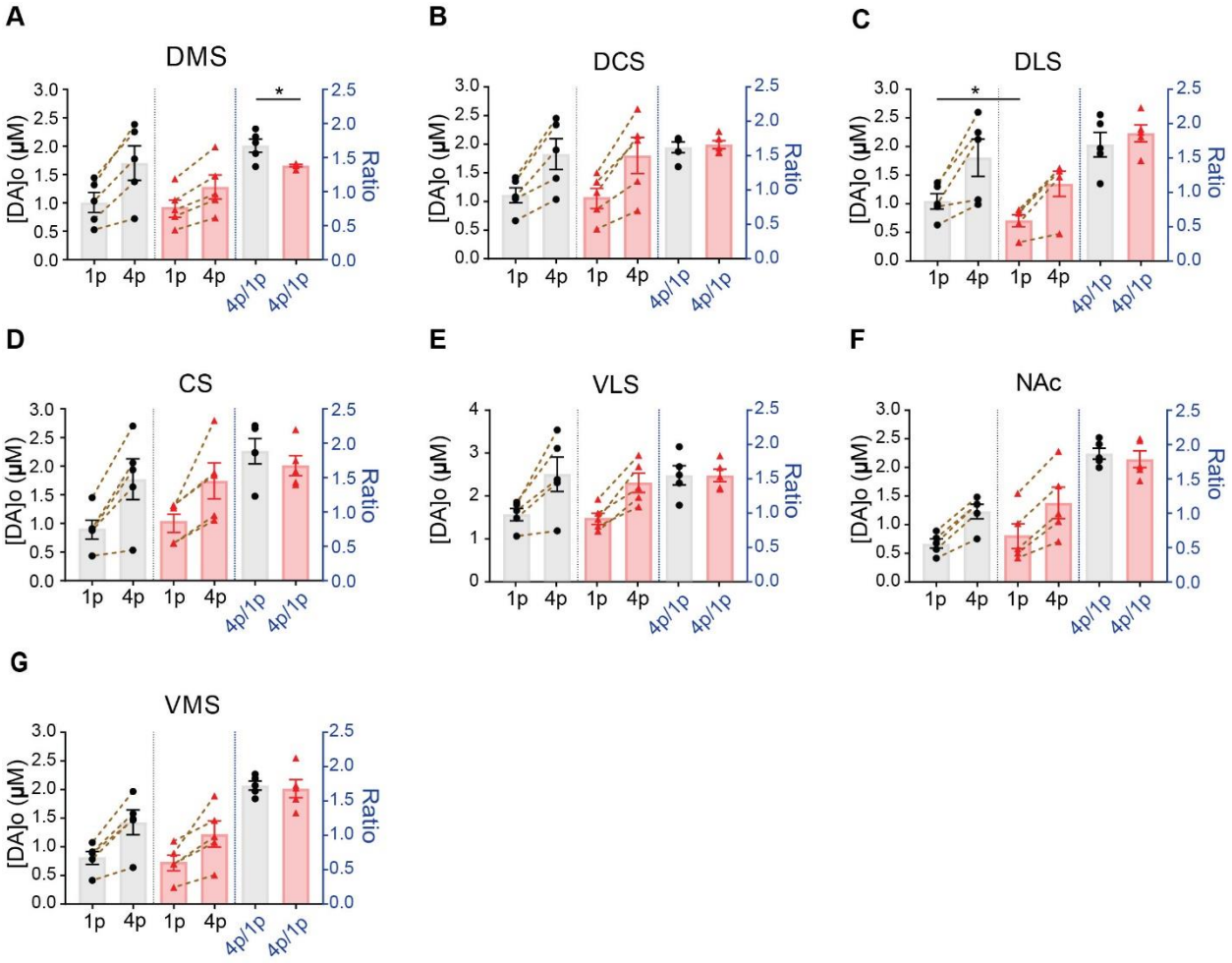


Figure 25. Different juvenile-adolescent feeding experiences affected striatal dopamine release differentially in adult male mice. A-G, Electrically evoked DA release was significantly different in DLS, while 4p/1p evoked DA release ratio was significantly different in DMS. FSCV 2-5 transient DA release signals were averaged for each data point. Each data point represented one animal. The 1p and 4p data for the same animal were connected with dotted lines. Electrical stimulation was delivered in the following sequence: single pulse, pulse train of 4 pulses at 100 Hz, and single pulse. The evoked DA release data from 1p and 4p stimulation were plotted against the left y-axis. The 4p/1p ratio data were plotted against the right y-axis. Paired two-tailed t-test were used for analysis. *p<0.05, Error bars represented SEM.

Discussion

The adaptive developmental plasticity (ADP) framework posits that organisms can express different phenotypes and behavioral patterns through modulations of neural circuits in response to environmental challenges to confer greater advantages and survival chances. We found that different juvenile-adolescent feeding experiences did affect the neurobiological properties of the mesolimbic and nigrostriatal DA system. We initially focused on the mesolimbic system because these neurons are known to play a role in reinforcement and reward prediction errors and may be responsible for different cognitive and behavioral phenotypes found in the adult male mice in the AL and FI groups described in Chapter 3. We found that VTA DA neurons that project to the NAc had smaller AMPAR/NMDAR-mediated EPSCs ratios in the FI conditions, suggesting that inputs onto these VTA DA neurons in the mice from the AL and FI groups were different. We next investigated evoked DA release in the striatum to test if regulation of DA release at the presynaptic level was also altered. There we found only a trend level difference in the two feeding history groups in the NAc region. However, we also uncovered a difference in evoked DA release in the DLS. These data illustrate that juvenile adolescent feeding experience can significantly influence the neurobiology of multiple regions of the DA system in adulthood.

Interactions between feeding experiences and developmental trajectory of neuroplasticity of DA neurons

Many studies have implicated VTA DA neuron firing in signaling reward prediction error (Glimcher, 2011; Schultz, 2016; Schultz et al., 1997) and reward probability and uncertainty in reinforcement learning (Fiorillo et al., 2003). Studies have found that VTA DA neurons encode subjective perceived reward and uncertainty associated with reward probabilities in a probabilistic environment (de Lafuente & Romo, 2011; Tennyson et al., 2018) but also uncertainty about threat and fear (Jo et al., 2018). Experience of food insecurity with fluctuating natural food reward probabilities and uncertainty may affect the inputs and synaptic plasticity into VTA DA neurons that encode these properties.

To understand how different developmental (P21-40) feeding experiences between ad libitum (AL) and food insecurity (FI) feeding on DA neurotransmission, we performed electrophysiological recording with electrical stimulation in slices containing VTA from adult (P60-70) male mice. We measured AMPAR/NMDAR-mediated EPSCs ratio in NAc-core projecting VTA DA neurons and found that it was significantly smaller in the brain slices of adult male mice with P21-40 FI experience that did not undergo behavioral training (**Fig. 23C**), suggesting there was a difference in VTA DA neuron synaptic plasticity with different feeding experiences. We also found there was no difference in average NMDAR-mediated EPSCs and rectification index (**Fig. 23E-G**)

which indicated there was no difference in calcium-permeable GluA2 lacking AMPAR (Liu & Cull-Candy, 2002; Panicker et al., 2007), but found that there was on average smaller but not significant AMPAR-mediated EPSCs in the brain slices of adult male mice with P21-40 FI experience (**Fig. 23D**). These data are consistent with another study that found that adult rats had smaller AMPAR-mediated EPSCs at -70 mV after food restriction for three to four weeks, compared to Ad lib animals (Pan et al., 2011). However, Pan et al. (2011) also found approximately 50 percentage decrease in NMDAR-mediated and/or AMPAR-mediated EPSCs at +40 mV in the rats immediately following chronic food restriction. In development studies, it has been shown that AMPAR-mediated EPSCs increase in amplitude between adolescence and adulthood in rats, with lower frequencies and amplitude during adolescence (McCutcheon et al., 2012). Our study adds to these data by showing that feeding related differences in glutamatergic function in VTA DA neurons can persist after a 20-day recovery from the feeding treatment. Further work would need to be done to test if this is the case when the manipulation is performed in adulthood. Behavioral data in Chapter 3 suggest effects of the manipulation may wane with age.

Our results together with these findings suggest that the observed changes in synaptic plasticity in terms of AMPAR/NMDAR ratio onto VTA DA neurons may result from the interaction of effects of feeding experiences and developmental changes in DA systems. It is possible that, on average, there was lower expression of GluA2-containing AMPAR but similar composition of GluA2 lacking AMPAR expression on VTA DA neurons in adult male mice with FI feeding experience, resulting in smaller AMPAR/NMDAR ratio but consistent rectification index. Or alternatively, male mice with P21-40 FI experience may not exhibit a typical developmental increase in AMPAR-mediated EPSC amplitude, maintaining lower AMPAR-mediated EPSC into adulthood. Further studies would be needed to test these possibilities.

Different feeding experiences affect DA release in the striatum

Food and feeding experience in adult animals have also been found to affect DA release at axonal terminals in both ventral and dorsal striatum (Avena et al., 2008, 2013; Bassareo & Di Chiara, 1999; Brown et al., 2011; Pothos et al., 1995). Therefore, we also prepared slices of the striatum to investigate effects of feeding experience on DA release at this site. To measure DA release at the terminals, we performed fast-scan cyclic voltammetry (FSCV) and examined the electrically evoked DA release across ventral and dorsal striatum, with total 7 striatal regions (**Fig. 24A**).

Our initial focus was on the NAc region, where we saw a trend toward greater DA release in the FI group compared to AL, but this was not statistically significant. In this brain slice preparation, we were fortunately able to sample other regions of the striatum and found that changes in evoked dopamine release occurred in other locations. We

found that there were group differences in DA release in the DLS, with FI mice showing lower DA release than AL mice both at 4p and 1p stimulation rates. We also found that there was a smaller ratio of 4-pulse 100Hz train over single pulse (4p/1p) evoked peak $[DA]_o$ in the DMS from the FI group, compared to the AL group (**Fig. 24D**). Differences in the 4p/1p $[DA]_o$ ratio in DMS could possibly result from different release probabilities of DA upon first event or total amount of DA content ready for release. However, we did not observe significant differences in 1p evoked $[DA]_o$ nor 4p 100Hz evoked $[DA]_o$ in the DMS (**Fig. 24B,C; Fig. 25A**). These results suggest that the observation of smaller 4p/1p $[DA]_o$ in DMS may result from a combination of both mechanisms.

Based on our behavioral results (Chapter 3), we predicted we would find significant differences in evoked DA in the NAc, but instead we found that FI treatment reduced DA in the DLS. Lack of a difference in the NAc may be consistent with other studies showing no effect of scarcity or restricted feeding on DA release in the NAc (Pothos et al., 1995; Stuber et al., 2002). Studies focusing on the diet-induced-obesity (DIO) or drug abuse also show decreased or blunted striatal DA response in treatment groups (Burke & Small, 2016; Geiger et al., 2009) which may be relevant to our DLS finding. It is also consistent with a previous study founding that DA release in DLS is more sensitive to different feeding experiences compared to DMS (Fritz et al., 2018). Each striatal region is thought to contribute to learning, action selection and flexible updating in different ways. Our data suggest effects on the DA system are not focal to a specific circuit.

In both treatment groups (AL and FI), we found that 1p evoked $[DA]_o$ was significantly higher in the VLS compared to other sampling subregions (**Fig. 24B; Fig. 25E**). This finding is inconsistent with previous studies that have demonstrated that there is a gradient from ventral to dorsal striatum in DA release with more of evoked DA release in dorsal striatum (Calipari et al., 2012; Cragg et al., 2002). These data may reflect only a strain difference, or they potentially reflect an effect of individual housing that is present in all our groups. Studies have showed that levels of DA in the ventral striatum are modulated by experience of stress (Abercrombie et al., 1989; Anstrom et al., 2009; Valenti et al., 2011). A recent study specifically examining DA release in VMS and VLS found that stress experience selectively augmented the reward-evoked DA release in VLS but not in VMS (Stelly et al., 2020).

Experience-dependent modulation of DA system may contribute to differential learning, cognitive flexibility, and integration through adaptive developmental mechanisms

Together, we found that different juvenile-adolescent (P21-40) developmental food insecurity (FI) feeding experiences modulated the DA system differentially and that the effects were long-lasting enough to be observable in adulthood (**Fig. 23-25**). Adult (P60-70) male mice with P21-40 FI experience were found to have reduced AMPAR/NMDAR-

mediated EPSC ratio in VTA DA neurons and electrically evoked DA release in dorsal striatum (**Fig. 23,24**), and in a separate cohort of mice, adult (P60-70) male mice with P21-40 FI experience exhibited less cognitive flexibility and reward integration (Chapter 3, **Fig. 11,12,19,20**). These neurobiological and behavioral data together suggest that differences in cognitive flexibility, learning rates, and reward integration observed in male AL and FI mice at P60-70 may result at least in part from altered glutamatergic regulation of VTA DA neurons and alterations in nigrostriatal DA release.

These data are consistent with results from previous studies. Alteration or disruption in DA system is commonly associated with changes or deficits found in associative learning, reversal learning and cognitive flexibility, and decision making (Borwick et al., 2020; Breitenstein et al., 2006; Clarke et al., 2013; Dajani et al., 2015; Kjær et al., 2018; Klanker et al., 2013; Rogers, 2011). VTA DA neuron activity and dorsal striatal activity and signaling have been implicated in cognitive flexibility or reversal learning, and diminished VTA DA neural activity and/or striatal DA can reduce performance and cognitive flexibility (Adamantidis et al., 2011; Cools et al., 2009; Darvas et al., 2014; Klanker et al., 2017; Parker et al., 2016; Sala-Bayo et al., 2020; Verharen et al., 2018). Specifically, our findings also consistent with the results from two other labs using the same 4-choice odor-based foraging reversal task. Luo et al. (2016) showed that mice lacking TGF-B signaling in DA neurons with altered balance of excitatory and inhibitory input onto DA neurons and phasic firing pattern also exhibited flexible updating and learning deficits. Also, Kosillo et al. (2019) found that the DA-Tsc1 KO mice with a phenotype of average 60% reduction in evoked DA release in dorsal striatum also had significantly more total errors in reversal phase in the same task.

We also found that a difference in peaked DA release was selectively observed in DLS whereas a difference in 4p/1p peaked DA release ratio was selectively observed in DMS (**Fig. 24,25**). Decreased DA level in DLS has been linked to delayed learning tasks involving food rewards, operant tasks, and reduced motivation (Darvas & Palmiter, 2009, 2011). DMS has been found to play an essential role in goal-directed behavior (Balleine et al., 2007; Gremel & Costa, 2013). The observed differences in DA release were associated with the slower behavioral adjustment and flexible updating in the 4-choice foraging reversal task (**Fig. 11,12**). The value encoding of food reward is gradually propagated from the ventral striatum to the DMS and then DLS. The propagation of value coding from DMS to DLS is believed to mediate the transition from goal-directed to habitual behavior (Balleine et al., 2009; Graybiel & Grafton, 2015; Lipton et al. 2019; Torres et al., 2016; Yin & Knowlton, 2006). Inactivation of DMS or activation of DLS were found to render mice less sensitive to devaluation or adjustment to reward uncertainty, consistent with less goal-directed and more habitual-like behavior (Torres et al., 2016; Yin et al., 2004). Neural activity and DA signals in the DLS therefore are thought to be more associated with habitual behavior and less sensitive to reward uncertainty and outcome. Although we did not directly test whether differences in juvenile-adolescent feeding experience in tasks testing habitual behaviors using

established devaluation procedures (Dias-Ferreira et al., 2009; Gremel & Costa, 2013), we did observe that adult male mice with P21-40 AL feeding experience which was associated with higher *in vitro* evoked DA release in DLS exhibited more habitual-like behavior, staying with the previous choice after negative feedback and exhibiting lower sensitivity to reward probability across phases in a probabilistic switching task (**Fig. 19,20**).

Limitations of the study and future directions

In our studies, we found that there were effects of different developmental feeding experiences both on neurobiological DA systems and cognitive and behavioral functions, and that the differences in neurobiology can be associated with different behavioral phenotypes observed. However, in current studies, we did not examine DA system dynamics during the time of learning, flexible updating, and making decisions. Further studies with *in vivo* measurement of DA neuron activity or DA release dynamics can help disentangle how DA system activity gives rise to the behavioral phenotypes we observed in response to developmental feeding experiences. In addition, we only examined DA neural plasticity and DA release in the slices from adult male mice that had significant differences in behavioral performance, but we did not make recordings from adult female mice. We therefore are not able to make conclusions on effects of feeding history on neurobiology of DA system in adult female mice. Future studies in females are required to know if changes in neurobiology were sex-specific and to test if these changes might be present in absence of cognitive effects.

Chapter 5

Conclusions and Future Directions

A role for adaptive developmental plasticity in learning and decision making

Adaptive developmental plasticity (ADP) allows organisms to adjust phenotypic expression in response to environmental stimuli at the genetic, neural circuit, and behavioral level in order to confer greater fitness advantages in an organisms' lifetime or across many generations. In my dissertation, I adapted the ADP framework to consider differences in behavior and neurobiology in mouse models.

In the first chapter showing experimental work, Chapter 2, I showed that in a mouse model of the Val66Met polymorphism in the BDNF gene, mice with Met/Met allele showed greater flexibility in reversal learning than Val/Val controls in two tasks: an odor-based go/no-go task and a 4-choice foraging discrimination and reversal task. Although this result may seem surprising and inconsistent with certain themes in past literature, it is interpretable using the ADP framework. In the literature, the single nucleotide polymorphism (SNP) in Val66Met has often been labeled a "risk allele" as it has been associated with enhanced risk for eating, substance abuse, and psychiatric disorders as well as learning deficits (Angelucci et al., 2005; Gratacòs et al., 2007). In mice, this SNP has been associated with anxiety (Chen et al., 2006). Yet, there have also been studies that find evidence of cognitive enhancement in human Met carriers (Alfimova et al., 2012; Beste, Baune, et al., 2010; Erickson et al., 2008; Gajewski et al., 2011, 2012; Getzmann et al., 2013).

Observation of paradoxical effects of the Met allele have led some to propose that this polymorphism and others may be "plasticity alleles" that confer extra sensitivity to the environment (or extra ADP), magnifying sensitivity and changes in response to both positive or negative influences (Drury et al., 2012). This idea can explain why this SNP is maintained in populations over generations under natural selection pressure. On a much shorter timescale, it is also consistent with Met/Met mice showing hypersensitivity to a change in task contingencies.

There are several limitations to the work presented in Chapter 2. First, it is difficult to bridge the time scales of an individual's single day in young adulthood to understand behavior and fitness over generations. Second, we did not examine how the SNP and BDNF protein directly affects the development and functions of neural circuits implicated in reversal learning. Previous work in the mice suggests that viral expression of BDNF in prefrontal cortical neurons can rescue some of its phenotypes implicating prefrontal cortical neurons and possibly their downstream striatal connections in behavioral differences (Warnault et al., 2016). It is plausible that this region and circuit is also implicated in cognitive flexibility as well.

In Chapter 3 and 4, I took a different approach to probe ADP by using genetically identical mice and varying the juvenile adolescent environment to investigate if divergent experiences affect adult phenotypes. The different juvenile-adolescent feeding experiences consisted of ad libitum food, the standard method for animal facility feeding and a mouse model of food insecurity, which I developed with input from a Robert Wood Johnson Postdoctoral fellow, Dr. Ezequiel Galarce. All mice were housed in isolated conditions.

In Chapter 3, I used two tasks and computational modeling to show how these different developmental experiences altered adult male behavioral phenotypes. In short, the two treatment groups diverged in their cognitive flexibility in adulthood due to differences in response to negative outcomes and differences in reward integration over time. Interestingly, in the deterministic task (100% reward contingencies), male mice with a juvenile adolescent history of food insecurity were less flexible than mice with a history of ad libitum feeding. Findings were the opposite in the probabilistic task. This suggests that the experience of food insecurity or food abundance in development does not just create a “deficit” compared to “normal” feeding. Instead, these data can be interpreted using an ADP framework suggesting different potentially adaptive developmental programs have been executed in the two groups to cause them to use different strategies in different kinds of environments in adulthood.

In Chapter 4, I examined neurobiological systems, with a focus on the dopaminergic (DA) system. In Chapter 1, I outlined why the DA system was a likely target for developmental experience of scarcity or unpredictability to affect learning and decision making. In our model of ADP in the developing brain, we hypothesized that suggested scarcity and prediction error affect DA release which could in turn have effects on the development of striatal neurons and their glutamatergic inputs (**Fig. 2**, Lin et al., in press). These changes, subsequently, could drive alterations in learning, flexible updating, and reward integration. Indeed, in Chapter 4, we found that DA neurons were significantly different in the young adults from the two treatment groups. Glutamatergic inputs to the mesolimbic dopamine neurons in the VTA were significantly different in the AMPAR/NMDAR-mediated EPSCs ratio suggesting different plasticity or control over the firing of these neurons. Also, evoked DA release in the dorsal striatum was different between groups. Both changes could possibly contribute to different responses to outcomes or integration of rewards. We suspect that differences between the two groups will include additional underlying variations that culminate in the observed phenotypes. Future studies are needed to investigate other impacts, such as DA receptor expression and effects on SPN excitability and connectivity in order to isolate what changes contribute to what aspects of phenotype differences.

In Chapter 3, preliminary data showed that development feeding experience has significant impact during the juvenile-adolescent period (P21-40). We did not see effects of developmental feeding experience on behavior when we moved the feeding

manipulation timing to the late adolescence (P41-60) and behavioral testing to after P80. This suggests that there is a sensitive window for either feeding experience or testing. A recent meta-analysis concluded that other experiences, such as exposure to high fat foods, results in prominent learning and memory performance difference during development and adolescence but not in adulthood (Murry & Chen, 2019).

My studies also revealed sex differences in response to developmental differences in feeding history. We found the effects of our P21-P40 feeding treatments on adult cognitive flexibility were limited to males. Secondly, adult female mice that experienced food insecurity P21-40 showed increased body weight after P90 when mice had abundant and unlimited access to food resources, but males did not. While we did find adult male mice exhibited different DA neurobiology, we did not measure DA neurobiology in female mice. Further studies will be required to understand the sex-specific mechanisms of these different phenotypes.

Evidence for the Match and Mismatch hypothesis

My data may also inform questions that emerge from life history theory. The predictive ADP framework together with life history theory suggests that the effects of scarcity or harshness may not always produce deficits, but instead adaptive changes. In this framework, a phenotype is thought to be more likely to be adaptive if the information is predictive and the environment remains the same (i.e. matches the developmental environment). If the environment does not stay the same, then there may be a "mismatch" between the predictive adaptive response an organism has executed and the adult environment. My behavioral data from Chapter 3 may be in line with these ideas. I found that adult male mice that experienced food insecurity were more flexible in a more probabilistic environment, whereas mice that always experienced stable food supply were more flexible in a deterministic environment. Though the two tasks were not perfectly balanced on other variables, this is suggestive support for the "match vs mismatch" hypothesis.

Another limitation of the study is our inability to know what would be more optimal and therefore more adaptive in the wild for mice. For instance, exposure to harsh and unpredictable experiences, skills may be manifested for the conditions following similar harshness and unpredictability in order to achieve greater fitness. These enhanced skills, such as cognitive functions and behavior may be considered as resilience to stress (Ellis et al., 2017). Studies of early life experience with adversity usually focus on prevailing "deficit models." Our work may suggest that there are alternative ways and experimental designs to consider and investigate impacts of early life experience with adversity.

Food insecurity as a prevalent public health challenge

Food insecurity has been considered as a form of adversity and public health challenge that is increasingly prevalent in the United States and worldwide (Coleman-Jensen et al., 2019; World Health Organization, 2019). This challenge is thought to be exacerbated by the COVID-19 pandemic of 2020. Human studies have found associations between food insecurity and obesity, diabetes, enhanced risk for psychosocial development and psychiatric issues (Althoff et al., 2016; Cook et al., 2008, 2013; Davis et al., 2014; Decker & Flynn, 2018; Franklin et al., 2012; Ke & Ford-Jones, 2015; Laraia, 2013). Work within schools, specifically, has shown detrimental effects of childhood and early adolescent food insecurity on grades and academic performance (Aurino et al., 2019; Jyoti et al., 2005; Winicki et al., 2003). My dissertation using mouse models confirms that feeding history, especially during the juvenile-adolescent period, can have long-term effects, significantly impacting adult weight, cognitive functions, and behaviors later in life. These human and animal model data together are highly consistent and suggest that the juvenile-adolescent period might be a critical timeframe to invest in food access and feeding programs. Benefits of such an intervention should be seen and considered from physical healthcare outcomes (i.e. cost of obesity and diabetes) to cognitive health and academic outcomes.

References

Abercrombie, E. D., Keefe, K. A., DiFrischia, D. S., & Zigmond, M. J. (1989). Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *Journal of Neurochemistry, 52*(5), 1655–1658. https://doi.org/10.1111/j.1471-4159.1989.tb09224.x

Abidin, I., Eysel, U. T., Lessmann, V., & Mittmann, T. (2008). Impaired GABAergic inhibition in the visual cortex of brain-derived neurotrophic factor heterozygous knockout mice. *The Journal of Physiology, 586*(7), 1885–1901. https://doi.org/10.1113/jphysiol.2007.148627

Adamantidis, A. R., Tsai, H. C., Boutrel, B., Zhang, F., Stuber, G. D., Budygin, E. A., Touriño, C., Bonci, A., Deisseroth, K., & de Lecea, L. (2011). Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. *The Journal of Neuroscience, 31*(30), 10829–10835. https://doi.org/10.1523/JNEUROSCI.2246-11.2011

Ahmed, S., Reynolds, B. A., & Weiss, S. (1995). BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors. *The Journal of Neuroscience, 15*(8), 5765–5778. https://doi.org/10.1523/JNEUROSCI.15-08-05765.1995

Akaneya, Y., Tsumoto, T., Kinoshita, S., & Hatanaka, H. (1997). Brain-derived neurotrophic factor enhances long-term potentiation in rat visual cortex. *The Journal of Neuroscience, 17*(17), 6707–6716. https://doi.org/10.1523/JNEUROSCI.17-17-06707.1997

Alfimova, M. V., Korovaitseva, G. I., Lezheiko, T. V., & Golimbet, V. E. (2012). Effect of BDNF Val66Met polymorphism on normal variability of executive functions. *Bulletin of Experimental Biology and Medicine, 152*(5), 606–609. https://doi.org/10.1007/s10517-012-1587-x

Alsina, B., Vu, T., & Cohen-Cory, S. (2001). Visualizing synapse formation in arborizing optic axons in vivo: dynamics and modulation by BDNF. *Nature Neuroscience, 4*(11), 1093–1101. https://doi.org/10.1038/nn735

Althoff, R. R., Ametti, M., & Bertmann, F. (2016). The role of food insecurity in developmental psychopathology. *Preventive Medicine, 92*, 106–109. https://doi.org/10.1016/j.ypmed.2016.08.012

Ambroggi, F., Ghazizadeh, A., Nicola, S. M., & Fields, H. L. (2011). Roles of nucleus accumbens core and shell in incentive-cue responding and behavioral inhibition. *The Journal of Neuroscience, 31*(18), 6820–6830. https://doi.org/10.1523/JNEUROSCI.6491-10.2011

Amitai, N., Young, J. W., Higa, K., Sharp, R. F., Geyer, M. A., & Powell, S. B. (2014). Isolation rearing effects on probabilistic learning and cognitive flexibility in rats. *Cognitive, Affective & Behavioral Neuroscience, 14*(1), 388–406. https://doi.org/10.3758/s13415-013-0204-4

Andersen, S. L., Thompson, A. T., Rutstein, M., Hostetter, J. C., & Teicher, M. H. (2000). Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. *Synapse, 37*(2), 167–169. https://doi.org/10.1002/1098-2396(200008)37:2<167::AID-SYN11>3.0.CO;2-B

Angelucci, F., Brenè, S., & Mathé, A. A. (2005). BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry, 10*(4), 345–352. https://doi.org/10.1038/sj.mp.4001637

Anstrom, K. K., Miczek, K. A., & Budygin, E. A. (2009). Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience, 161*(1), 3–12. https://doi.org/10.1016/j.neuroscience.2009.03.023

Ashiabi, G. (2005). Household food insecurity and children's school engagement. *Journal of Children and Poverty, 11*(1), 3–17. https://doi.org/10.1080/10796120420000333027

Aurino, E., Fledderjohann, J., & Vellakkal, S. (2019). Inequalities in adolescent learning: Does the timing and persistence of food insecurity at home matter? *Economics of Education Review, 70*, 94–108. https://doi.org/10.1016/j.econedurev.2019.03.003

Avena, N. M., Rada, P., & Hoebel, B. G. (2008). Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience, 156*(4), 865–871. https://doi.org/10.1016/j.neuroscience.2008.08.017

Avena, N. M., Murray, S., & Gold, M. S. (2013). Comparing the effects of food restriction and overeating on brain reward systems. *Experimental Gerontology, 48*(10), 1062–1067. https://doi.org/10.1016/j.exger.2013.03.006

Averbeck, B. B., & Costa, V. D. (2017). Motivational neural circuits underlying reinforcement learning. *Nature Neuroscience, 20*(4), 505–512. https://doi.org/10.1038/nn.4506

Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience, 27*(31), 8161–8165. https://doi.org/10.1523/JNEUROSCI.1554-07.2007

Balleine, B. W., Liljeholm, M., & Ostlund, S. B. (2009). The integrative function of the basal ganglia in instrumental conditioning. *Behavioural Brain Research, 199*(1), 43–52. https://doi.org/10.1016/j.bbr.2008.10.034

Banqueri, M., Méndez, M., & Arias, J. L. (2017). Behavioral effects in adolescence and early adulthood in two length models of maternal separation in male rats. *Behavioural Brain Research, 324*, 77–86. https://doi.org/10.1016/j.bbr.2017.02.006

Bamford, N. S., Wightman, R. M., & Sulzer, D. (2018). Dopamine's effects on corticostriatal synapses during reward-based behaviors. *Neuron, 97*(3), 494–510. https://doi.org/10.1016/j.neuron.2018.01.006

Bassareo, V., & Di Chiara, G. (1999). Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *The European Journal of Neuroscience, 11*(12), 4389–4397. https://doi.org/10.1046/j.1460-9568.1999.00843.x

Bateson, P., Gluckman, P., & Hanson, M.A. (2014). The biology of developmental plasticity and the Predictive Adaptive Response hypothesis. *The Journal of Physiology, 592*(11), 2357-68.https://doi.org/10.1113/jphysiol.2014.271460

Bath, K. G., & Lee, F. S. (2006). Variant BDNF (Val66Met) impact on brain structure and function. *Cognitive, Affective & Behavioral Neuroscience, 6*(1), 79–85. https://doi.org/10.3758/cabn.6.1.79

Baydyuk, M., & Xu, B. (2014). BDNF signaling and survival of striatal neurons. *Frontiers in Cellular Neuroscience, 8*, 254. https://doi.org/10.3389/fncel.2014.00254

Belachew, T., Hadley, C., Lindstrom, D., Gebremariam, A., Lachat, C., & Kolsteren, P. (2011). Food insecurity, school absenteeism and educational attainment of adolescents in Jimma Zone Southwest Ethiopia: A longitudinal study. *Nutrition Journal, 10*, 29. https://doi.org/10.1186/1475-2891-10-29

Beldade, P., Mateus, A. R., & Keller, R. A. (2011). Evolution and molecular mechanisms of adaptive developmental plasticity. *Molecular Ecology, 20*(7), 1347–1363. https://doi.org/10.1111/j.1365-294X.2011.05016.x

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes?. *Molecular Psychiatry, 14*(8), 746–754. https://doi.org/10.1038/mp.2009.44

Belsky, D. W., Moffitt, T. E., Arseneault, L., Melchior, M., & Caspi, A. (2010). Context and sequelae of food insecurity in children's development. *American Journal of Epidemiology, 172*(7), 809–818. https://doi.org/10.1093/aje/kwq201

Bento, G., Ogawa, A., & Sommer, R. J. (2010). Co-option of the hormone-signalling module dafachronic acid-DAF-12 in nematode evolution. *Nature, 466*(7305), 494–497. https://doi.org/10.1038/nature09164

Berke J. D. (2018). What does dopamine mean?. *Nature Neuroscience, 21*(6), 787–793. https://doi.org/10.1038/s41593-018-0152-y

Beste, C., Baune, B. T., Domschke, K., Falkenstein, M., & Konrad, C. (2010). Paradoxical association of the brain-derived-neurotrophic-factor val66met genotype with response inhibition. *Neuroscience, 166*(1), 178–184. https://doi.org/10.1016/j.neuroscience.2009.12.022

Beste, C., Kolev, V., Yordanova, J., Domschke, K., Falkenstein, M., Baune, B. T., & Konrad, C. (2010). The role of the BDNF Val66Met polymorphism for the synchronization of error-specific neural networks. *The Journal of Neuroscience, 30*(32), 10727–10733. https://doi.org/10.1523/JNEUROSCI.2493-10.2010

Biesdorf, C., Wang, A. L., Topic, B., Petri, D., Milani, H., Huston, J. P., & de Souza Silva, M. A. (2015). Dopamine in the nucleus accumbens core, but not shell, increases during signaled food reward and decreases during delayed extinction. *Neurobiology of Learning and Memory, 123*, 125–139. https://doi.org/10.1016/j.nlm.2015.06.002

Birn, R. M., Roeber, B. J., & Pollak, S. D. (2017). Early childhood stress exposure, reward pathways, and adult decision making. *Proceedings of the National Academy of Sciences of the United States of America, 114*(51), 13549–13554. https://doi.org/10.1073/pnas.1708791114

Biskupska, J., Borowiak, K. S., Karlin-Grazewicz, K., Janus, T., Waloszczyk, P., Potocka-Banas, B., Machoy-Mokrzynska, A., Ossowski, A., & Ciechanowicz, A. (2013). Estimation of BDNF gene polymorphism and predisposition to dependence development for selected psychoactive compounds: genetic aspects of addiction with the selected drugs, amphetamine, tetrahydrocannabinol and opiates. *Human & Experimental Toxicology, 32*(3), 236–240. https://doi.org/10.1177/0960327112459203

Bissonette, G. B., Martins, G. J., Franz, T. M., Harper, E. S., Schoenbaum, G., & Powell, E. M. (2008). Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. *The Journal of Neuroscience, 28*(44), 11124–11130. https://doi.org/10.1523/JNEUROSCI.2820-08.2008

Boivin, J. R., Piekarski, D. J., Thomas, A. W., & Wilbrecht, L. (2018). Adolescent pruning and stabilization of dendritic spines on cortical layer 5 pyramidal neurons do not depend on gonadal hormones. *Developmental Cognitive Neuroscience, 30*, 100–107. https://doi.org/10.1016/j.dcn.2018.01.007

Borwick, C., Lal, R., Lim, L. W., Stagg, C. J., & Aquili, L. (2020). Dopamine depletion effects on cognitive flexibility as modulated by tDCS of the dlPFC. *Brain Stimulation, 13*(1), 105–108. https://doi.org/10.1016/j.brs.2019.08.016

Burke, M. V., & Small, D. M. (2016). Effects of the modern food environment on striatal function, cognition and regulation of ingestive behavior. *Current Opinion in Behavioral Sciences, 9*, 97–105. https://doi.org/10.1016/j.cobeha.2016.02.036

Burton, A. C., Nakamura, K., & Roesch, M. R. (2015). From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. *Neurobiology of Learning and Memory, 117*, 51–59. https://doi.org/10.1016/j.nlm.2014.05.003

Braendle, C., Davis, G. K., Brisson, J. A., & Stern, D. L. (2006). Wing dimorphism in aphids. *Heredity, 97*(3), 192–199. https://doi.org/10.1038/sj.hdy.6800863

Brake, W. G., Zhang, T. Y., Diorio, J., Meaney, M. J., & Gratton, A. (2004). Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. *The European Journal of Neuroscience, 19*(7), 1863–1874. https://doi.org/10.1111/j.1460-9568.2004.03286.x

Branch, S. Y., Goertz, R. B., Sharpe, A. L., Pierce, J., Roy, S., Ko, D., Paladini, C. A., & Beckstead, M. J. (2013). Food restriction increases glutamate receptor-mediated burst firing of dopamine neurons. *The Journal of Neuroscience, 33*(34), 13861–13872. https://doi.org/10.1523/JNEUROSCI.5099-12.2013

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology, 31*(11), 2552–2564. https://doi.org/10.1038/sj.npp.1301167

Brenhouse, H. C., Sonntag, K. C., & Andersen, S. L. (2008). Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. *The Journal of Neuroscience*, *28*(10), 2375–2382. https://doi.org/10.1523/JNEUROSCI.5064-07.2008

Brown, H. D., McCutcheon, J. E., Cone, J. J., Ragozzino, M. E., & Roitman, M. F. (2011). Primary food reward and reward-predictive stimuli evoke different patterns of phasic dopamine signaling throughout the striatum. *The European Journal of Neuroscience, 34*(12), 1997–2006. https://doi.org/10.1111/j.1460-9568.2011.07914.x

Calipari, E. S., Huggins, K. N., Mathews, T. A., & Jones, S. R. (2012). Conserved dorsal-ventral gradient of dopamine release and uptake rate in mice, rats and rhesus macaques. *Neurochemistry International, 61*(7), 986–991. https://doi.org/10.1016/j.neuint.2012.07.008

Callaghan, B. L., & Tottenham, N. (2016). The stress acceleration hypothesis: Effects of early-life adversity on emotion circuits and behavior*. Current Opinion in Behavioral Sciences, 7*, 76–81. https://doi.org/10.1016/j.cobeha.2015.11.018

Cao, B., Wang, J., Zhang, X., Yang, X., Poon, D. C.-H., Jelfs, B., Chan, R. H. M., Wu, J. C.-Y., & Li, Y. (2016). Impairment of decision making and disruption of synchrony between basolateral amygdala and anterior cingulate cortex in the maternally separated rat. *Neurobiology of Learning and Memory, 136*, 74–85. https://doi.org/10.1016/j.nlm.2016.09.015

Carlini, V. P., Martini, A. C., Schiöth, H. B., Ruiz, R. D., Fiol de Cuneo, M., & de Barioglio, S. R. (2008). Decreased memory for novel object recognition in chronically food-restricted mice is reversed by acute ghrelin administration. *Neuroscience, 153*(4), 929–934. https://doi.org/10.1016/j.neuroscience.2008.03.015

Carr K. D. (2007). Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. *Physiology & Behavior, 91*(5), 459–472. https://doi.org/10.1016/j.physbeh.2006.09.021

Carr K. D. (2011). Food scarcity, neuroadaptations, and the pathogenic potential of dieting in an unnatural ecology: binge eating and drug abuse. *Physiology & Behavior, 104*(1), 162–167. https://doi.org/10.1016/j.physbeh.2011.04.023

Chaby, L. E., Cavigelli, S. A., Hirrlinger, A. M., Lim, J., Warg, K. M., & Braithwaite, V. A. (2015). Chronic stress during adolescence impairs and improves learning and memory in adulthood. *Frontiers in Behavioral Neuroscience, 9*, 327. https://doi.org/10.3389/fnbeh.2015.00327

Chaby, L. E., Sheriff, M. J., Cavigelli, S. A., Hirrlinger, A. M., Lim, J., & Braithwaite, V. A. (2016). Stress during adolescence shapes performance in adulthood: Context-dependent effects on foraging and vigilance. *Ethology*, *122*(4), 284-297. doi:10.1111/eth.12463

Chen, Z. Y., Jing, D., Bath, K. G., Ieraci, A., Khan, T., Siao, C. J., Herrera, D. G., Toth, M., Yang, C., McEwen, B. S., Hempstead, B. L., & Lee, F. S. (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science, 314*(5796), 140–143. https://doi.org/10.1126/science.1129663

Chen, Z. Y., Patel, P. D., Sant, G., Meng, C. X., Teng, K. K., Hempstead, B. L., & Lee, F. S. (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *The Journal of Neuroscience, 24*(18), 4401–4411. https://doi.org/10.1523/JNEUROSCI.0348-04.2004

Cheng, C. Y., Hong, C. J., Yu, Y. W., Chen, T. J., Wu, H. C., & Tsai, S. J. (2005). Brain-derived neurotrophic factor (Val66Met) genetic polymorphism is associated with substance abuse in males. *Brain Research. Molecular Brain Research, 140*(1-2), 86–90. https://doi.org/10.1016/j.molbrainres.2005.07.008

Chocyk, A., Majcher-Maślanka, I., Przyborowska, A., Maćkowiak, M., & Wędzony, K. (2015). Early-life stress increases the survival of midbrain neurons during postnatal development and enhances reward-related and anxiolytic-like behaviors in a sex-dependent fashion. *International Journal of Developmental Neuroscience, 44*, 33–47. https://doi.org/10.1016/j.ijdevneu.2015.05.002

Clarke, H. F., Hill, G. J., Robbins, T. W., & Roberts, A. C. (2011). Dopamine, but not serotonin, regulates reversal learning in the marmoset caudate nucleus. *The Journal of Neuroscience, 31*(11), 4290–4297. https://doi.org/10.1523/JNEUROSCI.5066-10.2011

Cohen-Cory, S., Kidane, A. H., Shirkey, N. J., & Marshak, S. (2010). Brain-derived neurotrophic factor and the development of structural neuronal connectivity. *Developmental Neurobiology, 70*(5), 271–288. https://doi.org/10.1002/dneu.20774

Coleman-Jensen, A., Nord M., & Singh A. (2013). Household food security in the United States in 2012. *Economy Research Report, ERR-155*. U.S. Washington, D.C.: U.S. Dept. of Agriculture, Economic Research Service.

Coleman-Jensen, A., Rabbitt., M.P., Gregory, C.A., Singh, A. (2019). Household food insecurity in the United States in 2018. *Economy Research Report, ERR-270,* 47. U.S. Washington, D.C.: U.S. Dept. of Agriculture, Economic Research Service.

Collins, A. G., & Frank, M. J. (2012). How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational, and neurogenetic analysis. *The European Journal of Neuroscience, 35*(7), 1024–1035. https://doi.org/10.1111/j.1460-9568.2011.07980.x

Collins, A. G., & Frank, M. J. (2014). Opponent actor learning (OpAL): Modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. *Psychological Review, 121*(3), 337–366. https://doi.org/10.1037/a0037015

Cook, J. T., Black, M., Chilton, M., Cutts, D., Ettinger de Cuba, S., Heeren, T. C., Rose-Jacobs, R., Sandel, M., Casey, P. H., Coleman, S., Weiss, I., & Frank, D. A. (2013). Are food insecurity's health impacts underestimated in the U.S. population? Marginal food security also predicts adverse health outcomes in young U.S. children and mothers. *Advances in Nutrition, 4*(1), 51–61. https://doi.org/10.3945/an.112.003228

Cook, J. T., & Frank, D. A. (2008). Food security, poverty, and human development in the United States. *Annals of the New York Academy of Sciences, 1136*, 193–209. https://doi.org/10.1196/annals.1425.001

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *The Journal of Neuroscience, 29*(5), 1538–1543. https://doi.org/10.1523/JNEUROSCI.4467-08.2009

Corwin, R. L., Avena, N. M., & Boggiano, M. M. (2011). Feeding and reward: perspectives from three rat models of binge eating. *Physiology & Behavior, 104*(1), 87–97. https://doi.org/10.1016/j.physbeh.2011.04.041

Costa, V. D., Tran, V. L., Turchi, J., & Averbeck, B. B. (2014). Dopamine modulates novelty seeking behavior during decision making. *Behavioral Neuroscience, 128*(5), 556–566. https://doi.org/10.1037/a0037128

Cox, J., & Witten, I. B. (2019). Striatal circuits for reward learning and decision-making. *Nature Reviews. Neuroscience, 20*(8), 482–494. https://doi.org/10.1038/s41583-019-0189-2

Cragg, S. J., Hille, C. J., & Greenfield, S. A. (2002). Functional domains in dorsal striatum of the nonhuman primate are defined by the dynamic behavior of dopamine. *The Journal of Neuroscience, 22*(13), 5705–5712. https://doi.org/10.1523/JNEUROSCI.22-13-05705.2002

Dajani, D. R., & Uddin, L. Q. (2015). Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends in Neurosciences, 38*(9), 571–578. https://doi.org/10.1016/j.tins.2015.07.003

Dang, J., Xiao, S., Zhang, T., Liu, Y., Jiang, B., & Mao, L. (2016). When the poor excel: Poverty facilitates procedural learning. *Scandinavian Journal of Psychology, 57*(4), 288–291. https://doi.org/10.1111/sjop.12292

Darvas, M., Henschen, C. W., & Palmiter, R. D. (2014). Contributions of signaling by dopamine neurons in dorsal striatum to cognitive behaviors corresponding to those observed in Parkinson's disease. *Neurobiology of Disease, 65*, 112–123. https://doi.org/10.1016/j.nbd.2014.01.017

Darvas, M., & Palmiter, R. D. (2009). Restriction of dopamine signaling to the dorsolateral striatum is sufficient for many cognitive behaviors. *Proceedings of the National Academy of Sciences of the United States of America, 106*(34), 14664–14669. https://doi.org/10.1073/pnas.0907299106

Darvas, M., & Palmiter, R. D. (2011). Contributions of striatal dopamine signaling to the modulation of cognitive flexibility. *Biological Psychiatry, 69*(7), 704–707. https://doi.org/10.1016/j.biopsych.2010.09.033

Davis, C., & Carter, J. C. (2009). Compulsive overeating as an addiction disorder. A review of theory and evidence. *Appetite, 53*(1), 1–8. https://doi.org/10.1016/j.appet.2009.05.018

Davis, C. R., Dearing, E., Usher, N., Trifiletti, S., Zaichenko, L., Ollen, E., Brinkoetter, M. T., Crowell-Doom, C., Joung, K., Park, K. H., Mantzoros, C. S., & Crowell, J. A. (2014). Detailed assessments of childhood adversity enhance prediction of central obesity independent of gender, race, adult psychosocial risk and health behaviors. *Metabolism: Clinical and Experimental, 63*(2), 199–206. https://doi.org/10.1016/j.metabol.2013.08.013

D'Cunha, T. M., Sedki, F., Macri, J., Casola, C., & Shalev, U. (2013). The effects of chronic food restriction on cue-induced heroin seeking in abstinent male rats. *Psychopharmacology, 225*(1), 241–250. https://doi.org/10.1007/s00213-012-2810-1

de Lafuente, V., & Romo, R. (2011). Dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proceedings of the National Academy of Sciences of the United States of America, 108*(49), 19767–19771. https://doi.org/10.1073/pnas.1117636108

Decker, D., & Flynn, M. (2018). Food insecurity and chronic disease: Addressing food access as a healthcare issue. *Rhode Island Medical Journal, 101*(4), 28–30.

Del Arco, A., Zhu, S., Terasmaa, A., Mohammed, A. H., & Fuxe, K. (2004). Hyperactivity to novelty induced by social isolation is not correlated with changes in D2 receptor function and binding in striatum. *Psychopharmacology, 171*(2), 148–155. https://doi.org/10.1007/s00213-003-1578-8

Del Olmo, N., & Ruiz-Gayo, M. (2018). Influence of High-Fat Diets Consumed During the Juvenile Period on Hippocampal Morphology and Function. *Frontiers in Cellular Neuroscience, 12*, 439. https://doi.org/10.3389/fncel.2018.00439

Del Rio, D., Morales, L., Ruiz-Gayo, M., & Del Olmo, N. (2016). Effect of high-fat diets on mood and learning performance in adolescent mice. *Behavioural Brain Research, 311*, 167–172. https://doi.org/10.1016/j.bbr.2016.04.052

Delevich, K., Okada, N. J., Rahane, A., Zhang, Z., Hall, C. D., & Wilbrecht, L. (2020). Sex and pubertal status influence dendritic spine density on frontal corticostriatal projection neurons in mice. *Cerebral Cortex, 30*(6), 3543–3557. https://doi.org/10.1093/cercor/bhz325

Dennison, M. J., Rosen, M. L., Sambrook, K. A., Jenness, J. L., Sheridan, M. A., & McLaughlin, K. A. (2019). Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: A developmental pathway to depression. *Child Development, 90*(1), e96–e113. https://doi.org/10.1111/cdev.13011

Diamond A. (2013). Executive functions. *Annual Review of Psychology, 64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dias-Ferreira, E., Sousa, J. C., Melo, I., Morgado, P., Mesquita, A. R., Cerqueira, J. J., Costa, R. M., & Sousa, N. (2009). Chronic stress causes frontostriatal reorganization and affects decision-making. *Science, 325*(5940), 621–625. https://doi.org/10.1126/science.1171203

Dinour, L. M., Bergen, D., & Yeh, M. C. (2007). The food insecurity-obesity paradox: a review of the literature and the role food stamps may play. *Journal of the American Dietetic Association, 107*(11), 1952–1961. https://doi.org/10.1016/j.jada.2007.08.006

Dow-Edwards, D., MacMaster, F. P., Peterson, B. S., Niesink, R., Andersen, S., & Braams, B. R. (2019). Experience during adolescence shapes brain development: From synapses and networks to normal and pathological behavior. *Neurotoxicology and Teratology, 76*, 106834. https://doi.org/10.1016/j.ntt.2019.106834

Drury, S. S., Gleason, M. M., Theall, K. P., Smyke, A. T., Nelson, C. A., Fox, N. A., & Zeanah, C. H. (2012). Genetic sensitivity to the caregiving context: the influence of 5httlpr and BDNF val66met on indiscriminate social behavior. *Physiology & Behavior, 106*(5), 728–735. https://doi.org/10.1016/j.physbeh.2011.11.014

Duffy, K. A., McLaughlin, K. A., & Green, P. A. (2018). Early life adversity and health-risk behaviors: proposed psychological and neural mechanisms. *Annals of the New York Academy of Sciences, 1428*(1), 151–169. https://doi.org/10.1111/nyas.13928

Duncan J. R. (2012). Current perspectives on the neurobiology of drug addiction: a focus on genetics and factors regulating gene expression. *ISRN Neurology, 2012*, 972607. https://doi.org/10.5402/2012/972607

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*(2), 257–269. https://doi.org/10.1016/s0092-8674(03)00035-7

Ellis, B. J., Bianchi, J., Griskevicius, V., & Frankenhuis, W. E. (2017). Beyond risk and protective factors: an adaptation-based Approach to Resilience. *Perspectives on Psychological Science, 12*(4), 561–587. https://doi.org/10.1177/1745691617693054

Ellis, B. J., Figueredo, A. J., Brumbach, B. H., & Schlomer, G. L. (2009). Fundamental dimensions of environmental risk: The impact of harsh versus unpredictable environments on the evolution and development of life history strategies. *Human Nature, 20*(2), 204–268. https://doi.org/10.1007/s12110-009-9063-7

Ellison, P. T., Reiches, M. W., Shattuck-Faegre, H., Breakey, A., Konecna, M., Urlacher, S., & Wobber, V. (2012). Puberty as a life history transition. *Annals of Human Biology, 39*(5), 352–360. https://doi.org/10.3109/03014460.2012.693199

Enge, S., Fleischhauer, M., Gärtner, A., Reif, A., Lesch, K. P., Kliegel, M., & Strobel, A. (2016). Brain-derived neurotrophic factor (Val66Met) and serotonin transporter (5-HTTLPR) polymorphisms modulate plasticity in inhibitory control performance over time but independent of inhibitory control training. *Frontiers in Human Neuroscience, 10*, 370. https://doi.org/10.3389/fnhum.2016.00370

Erickson, K. I., Kim, J. S., Suever, B. L., Voss, M. W., Francis, B. M., & Kramer, A. F. (2008). Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. *Frontiers in Human Neuroscience, 2*, 11. https://doi.org/10.3389/neuro.09.011.2008

Fareri, D. S., & Tottenham, N. (2016). Effects of early life stress on amygdala and striatal development. *Developmental Cognitive Neuroscience, 19*, 233–247. https://doi.org/10.1016/j.dcn.2016.04.005

Fawcett, T. W., & Frankenhuis, W. E. (2015). Adaptive explanations for sensitive windows in development. *Frontiers in Zoology*, *12 Suppl 1*(Suppl 1), S3. https://doi.org/10.1186/1742-9994-12-S1-S3

Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science, 299*(5614), 1898–1902. https://doi.org/10.1126/science.1077349

Floresco, S. B., McLaughlin, R. J., & Haluk, D. M. (2008). Opposing roles for the nucleus accumbens core and shell in cue-induced reinstatement of food-seeking behavior. *Neuroscience, 154*(3), 877–884. https://doi.org/10.1016/j.neuroscience.2008.04.004

Forsman, A. (2015). Rethinking phenotypic plasticity and its consequences for individuals, populations and species. *Heredity, 115*(4), 276–284. https://doi.org/10.1038/hdy.2014.92

Fox, K., & Wong, R. O. (2005). A comparison of experience-dependent plasticity in the visual and somatosensory systems. *Neuron, 48*(3), 465–477. https://doi.org/10.1016/j.neuron.2005.10.013

Frankenhuis, W. E., & de Weerth, C. (2013). Does early-life exposure to stress shape or impair cognition? *Current Directions in Psychological Science, 22*(5), 407–412. https://doi.org/10.1177/0963721413484324

Frankenhuis, W. E., Panchanathan, K., & Nettle, D. (2016). Cognition in harsh and unpredictable environments. *Current Opinion in Psychology, 7*, 76–80. https://doi.org/10.1016/j.copsyc.2015.08.011

Frankenhuis, W. E., & Walasek, N. (2020). Modeling the evolution of sensitive periods. *Developmental Cognitive Neuroscience, 41*, 100715. https://doi.org/10.1016/j.dcn.2019.100715

Franklin, B., Jones, A., Love, D., Puckett, S., Macklin, J., & White-Means, S. (2012). Exploring mediators of food insecurity and obesity: a review of recent literature. *Journal of Community Health, 37*(1), 253–264. https://doi.org/10.1007/s10900-011-9420-4

Frielingsdorf, H., Bath, K. G., Soliman, F., Difede, J., Casey, B. J., & Lee, F. S. (2010). Variant brain-derived neurotrophic factor Val66Met endophenotypes: implications for posttraumatic stress disorder. *Annals of the New York Academy of Sciences, 1208*, 150–157. https://doi.org/10.1111/j.1749-6632.2010.05722.x

Fritz, B. M., Muñoz, B., Yin, F., Bauchle, C., & Atwood, B. K. (2018). A high-fat, high-sugar 'Western' diet alters dorsal striatal glutamate, opioid, and dopamine transmission in mice. *Neuroscience, 372*, 1–15. https://doi.org/10.1016/j.neuroscience.2017.12.036

Fu, Y., Chen, Y., Li, L., Wang, Y., Kong, X., & Wang, J. (2017). Food restriction affects Y-maze spatial recognition memory in developing mice. *International Journal of Developmental Neuroscience, 60*, 8–15. https://doi.org/10.1016/j.ijdevneu.2017.03.010

Fusco, G., & Minelli, A. (2010). Phenotypic plasticity in development and evolution: Facts and concepts. *Philosophical Transactions of the Royal Society B: Biological Sciences, 365*(1540), 547–556. https://doi.org/10.1098/rstb.2009.0267

Gajewski, P. D., Hengstler, J. G., Golka, K., Falkenstein, M., & Beste, C. (2011). The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly. *Neurobiology of Aging, 32*(12), 2327.e7–2327.e2.327E19. https://doi.org/10.1016/j.neurobiolaging.2011.06.010

Gajewski, P. D., Hengstler, J. G., Golka, K., Falkenstein, M., & Beste, C. (2012). The Met-genotype of the BDNF Val66Met polymorphism is associated with reduced Stroop interference in elderly. *Neuropsychologia, 50*(14), 3554–3563. https://doi.org/10.1016/j.neuropsychologia.2012.09.042

Galiñanes, G. L., Taravini, I. R., & Murer, M. G. (2009). Dopamine-dependent periadolescent maturation of corticostriatal functional connectivity in mouse. *The Journal of Neuroscience, 29*(8), 2496–2509. https://doi.org/10.1523/JNEUROSCI.4421-08.2009

Galarce, E. M., & Holland, P. C. (2009). Effects of cues associated with meal interruption on feeding behavior. *Appetite, 52*(3), 693–702. https://doi.org/10.1016/j.appet.2009.03.009

Geiger, B. M., Haburcak, M., Avena, N. M., Moyer, M. C., Hoebel, B. G., & Pothos, E. N. (2009). Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. *Neuroscience, 159*(4), 1193–1199. https://doi.org/10.1016/j.neuroscience.2009.02.007

Gerritsen, L., Tendolkar, I., Franke, B., Vasquez, A. A., Kooijman, S., Buitelaar, J., Fernández, G., & Rijpkema, M. (2012). BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. *Molecular Psychiatry, 17*(6), 597–603. https://doi.org/10.1038/mp.2011.51

Getzmann, S., Gajewski, P. D., Hengstler, J. G., Falkenstein, M., & Beste, C. (2013). BDNF Val66Met polymorphism and goal-directed behavior in healthy elderly - evidence from auditory distraction. *NeuroImage, 64*, 290–298. https://doi.org/10.1016/j.neuroimage.2012.08.079

Gilbert, S. J., & Burgess, P. W. (2008). Executive function. *Current Biology, 18*(3), R110–R114. https://doi.org/10.1016/j.cub.2007.12.014

Glasper, E. R., & Neigh, G. N. (2019). Editorial: Experience-dependent neuroplasticity across the lifespan: From risk to resilience. *Frontiers in Behavioral Neuroscience, 12*, 335. https://doi.org/10.3389/fnbeh.2018.00335

Glimcher P. W. (2011). Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 108 Suppl 3*(Suppl 3), 15647–15654. https://doi.org/10.1073/pnas.1014269108

Gomes, F. V., Zhu, X., & Grace, A. A. (2019). The pathophysiological impact of stress on the dopamine system is dependent on the state of the critical period of vulnerability. *Molecular Psychiatry*, 10.1038/s41380-019-0514-1. Advance online publication. https://doi.org/10.1038/s41380-019-0514-1

Goodwill, H. L., Manzano-Nieves, G., LaChance, P., Teramoto, S., Lin, S., Lopez, C., Stevenson, R. J., Theyel, B. B., Moore, C. I., Connors, B. W., & Bath, K. G. (2018). Early life stress drives sex-selective impairment in reversal learning by affecting parvalbumin interneurons in orbitofrontal cortex of mice. *Cell Reports, 25*(9), 2299–2307.e4. https://doi.org/10.1016/j.celrep.2018.11.010

Gratacòs, M., González, J. R., Mercader, J. M., de Cid, R., Urretavizcaya, M., & Estivill, X. (2007). Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biological Psychiatry, 61*(7), 911–922. https://doi.org/10.1016/j.biopsych.2006.08.025

Graybiel, A. M., & Grafton, S. T. (2015). The striatum: where skills and habits meet. *Cold Spring Harbor Perspectives in Biology, 7*(8), a021691. https://doi.org/10.1101/cshperspect.a021691

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Archives of General Psychiatry, 67*(2), 113–123. https://doi.org/10.1001/archgenpsychiatry.2009.186

Greenwald, M. K., Steinmiller, C. L., Sliwerska, E., Lundahl, L., & Burmeister, M. (2013). BDNF Val(66)Met genotype is associated with drug-seeking phenotypes in heroin-dependent individuals: a pilot study. *Addiction Biology, 18*(5), 836–845. https://doi.org/10.1111/j.1369-1600.2011.00431.x

Gremel, C. M., & Costa, R. M. (2013). Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions*. Nature Communications, 4*, 2264. https://doi.org/10.1038/ncomms3264

Grissom, E. M., Hawley, W. R., Bromley-Dulfano, S. S., Marino, S. E., Stathopoulos, N. G., & Dohanich, G. P. (2012). Learning strategy is influenced by trait anxiety and early rearing conditions in prepubertal male, but not prepubertal female rats. *Neurobiology of Learning and Memory, 98*(2), 174–181. https://doi.org/10.1016/j.nlm.2012.06.001

Gué, M., Bravard, A., Meunier, J., Veyrier, R., Gaillet, S., Recasens, M., & Maurice, T. (2004). Sex differences in learning deficits induced by prenatal stress in juvenile rats. *Behavioural Brain Research, 150*(1-2), 149–157. https://doi.org/10.1016/S0166-4328(03)00250-X

Gundersen, C., & Ziliak, J. P. (2014). Childhood Food Insecurity in the U.S.: Trends, Causes, and Policy Options. *The Future of Children, 24*(2), 1–19. https://doi.org/10.1353/foc.2014.0007

Hall, F. S., Wilkinson, L. S., Humby, T., Inglis, W., Kendall, D. A., Marsden, C. A., & Robbins, T. W. (1998). Isolation rearing in rats: Pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacology, Biochemistry, and Behavior, 59*(4), 859–872. https://doi.org/10.1016/s0091-3057(97)00510-8

Hamid, A. A., Pettibone, J. R., Mabrouk, O. S., Hetrick, V. L., Schmidt, R., Vander Weele, C. M., Kennedy, R. T., Aragona, B. J., & Berke, J. D. (2016). Mesolimbic dopamine signals the value of work. *Nature Neuroscience, 19*(1), 117–126. https://doi.org/10.1038/nn.4173

Han, X., Li, N., Xue, X., Shao, F., & Wang, W. (2012). Early social isolation disrupts latent inhibition and increases dopamine D2 receptor expression in the medial prefrontal cortex and nucleus accumbens of adult rats. *Brain Research, 1447*, 38–43. https://doi.org/10.1016/j.brainres.2012.01.058

Han, X., Wang, W., Shao, F., & Li, N. (2011). Isolation rearing alters social behaviors and monoamine neurotransmission in the medial prefrontal cortex and nucleus accumbens of adult rats. *Brain Research, 1385*, 175–181. https://doi.org/10.1016/j.brainres.2011.02.035

Hanson, J. L., van den Bos, W., Roeber, B. J., Rudolph, K. D., Davidson, R. J., & Pollak, S. D. (2017). Early adversity and learning: Implications for typical and atypical behavioral development. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 58*(7), 770–778. https://doi.org/10.1111/jcpp.12694

Harms, M. B., Shannon Bowen, K. E., Hanson, J. L., & Pollak, S. D. (2018). Instrumental learning and cognitive flexibility processes are impaired in children exposed to early life stress. *Developmental Science, 2*1(4), e12596. https://doi.org/10.1111/desc.12596

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews. Neuroscience, 6*(11), 877–888. https://doi.org/10.1038/nrn1787

Hinton, E. A., Li, D. C., Allen, A. G., & Gourley, S. L. (2019). Social isolation in adolescence disrupts cortical development and goal-dependent decision-making in adulthood, despite social reintegration. *eNeuro, 6*(5), ENEURO.0318-19.2019. https://doi.org/10.1523/ENEURO.0318-19.2019

Hochberg, Z., & Belsky, J. (2013). Evo-devo of human adolescence: Beyond disease models of early puberty. *BMC Medicine, 11*, 113. https://doi.org/10.1186/1741-7015-11-113

Holtmaat, A., & Svoboda, K. (2009). Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature Reviews. Neuroscience, 10*(9), 647–658. https://doi.org/10.1038/nrn2699

Hong, S., & Hikosaka, O. (2011). Dopamine-mediated learning and switching in cortico-striatal circuit explain behavioral changes in reinforcement learning. *Frontiers in Behavioral Neuroscience, 5*, 15. https://doi.org/10.3389/fnbeh.2011.00015

Hoops, D., Reynolds, L. M., Restrepo-Lozano, J. M., & Flores, C. (2018). Dopamine development in the mouse orbital prefrontal cortex is protracted and sensitive to amphetamine in adolescence. *eNeuro, 5*(1), ENEURO.0372-17.2017. https://doi.org/10.1523/ENEURO.0372-17.2017

Howard, L. L. (2011). Does food insecurity at home affect non-cognitive performance at school? A longitudinal analysis of elementary student classroom behavior. *Economics of Education Review, 30*(1), 157–176. https://doi.org/10.1016/j.econedurev.2010.08.003

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M. F., Maffei, L., & Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell, 98*(6), 739–755. https://doi.org/10.1016/s0092-8674(00)81509-3

Hurtubise, J. L., & Howland, J. G. (2017). Effects of stress on behavioral flexibility in rodents. *Neuroscience, 345*, 176–192. https://doi.org/10.1016/j.neuroscience.2016.04.007

Khazen, T., Hatoum, O. A., Ferreira, G., & Maroun, M. (2019). Acute exposure to a high-fat diet in juvenile male rats disrupts hippocampal-dependent memory and plasticity through glucocorticoids. *Scientific Reports, 9*(1), 12270. https://doi.org/10.1038/s41598-019-48800-2

Ishikawa, M., Otaka, M., Huang, Y. H., Neumann, P. A., Winters, B. D., Grace, A. A., Schlüter, O. M., & Dong, Y. (2013). Dopamine triggers heterosynaptic plasticity. *The Journal of Neuroscience, 33*(16), 6759–6765. https://doi.org/10.1523/JNEUROSCI.4694-12.2013

Iino, Y., Sawada, T., Yamaguchi, K., Tajiri, M., Ishii, S., Kasai, H., & Yagishita, S. (2020). Dopamine D2 receptors in discrimination learning and spine enlargement. *Nature, 579*(7800), 555–560. https://doi.org/10.1038/s41586-020-2115-1

Izquierdo, A., Brigman, J. L., Radke, A. K., Rudebeck, P. H., & Holmes, A. (2017). The neural basis of reversal learning: An updated perspective. *Neuroscience, 345*, 12–26. https://doi.org/10.1016/j.neuroscience.2016.03.021

Jackson, D. B., Newsome, J., Vaughn, M. G., & Johnson, K. R. (2018). Considering the role of food insecurity in low self-control and early delinquency. *Journal of Criminal Justice, 56*, 127–139. https://doi.org/10.1016/j.jcrimjus.2017.07.002

Jia, Y., Gall, C. M., & Lynch, G. (2010). Presynaptic BDNF promotes postsynaptic long-term potentiation in the dorsal striatum. *The Journal of Neuroscience, 30*(43), 14440–14445. https://doi.org/10.1523/JNEUROSCI.3310-10.2010

Jing, D., Lee, F. S., & Ninan, I. (2017). The BDNF Val66Met polymorphism enhances glutamatergic transmission but diminishes activity-dependent synaptic plasticity in the dorsolateral striatum. *Neuropharmacology, 112*(Pt A), 84–93. https://doi.org/10.1016/j.neuropharm.2016.06.030

Jo, Y. S., Heymann, G., & Zweifel, L. S. (2018). Dopamine neurons reflect the uncertainty in fear generalization. *Neuron, 100*(4), 916–925.e3. https://doi.org/10.1016/j.neuron.2018.09.028

Joffe, R. T., Gatt, J. M., Kemp, A. H., Grieve, S., Dobson-Stone, C., Kuan, S. A., Schofield, P. R., Gordon, E., & Williams, L. M. (2009). Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: Implications for depressive illness. *Human Brain Mapping, 30*(4), 1246–1256. https://doi.org/10.1002/hbm.20592

Johnson, C. M., Peckler, H., Tai, L. H., & Wilbrecht, L. (2016). Rule learning enhances structural plasticity of long-range axons in frontal cortex. *Nature Communications, 7,* 10785. https://doi.org/10.1038/ncomms10785

Johnson, C., & Wilbrecht, L. (2011). Juvenile mice show greater flexibility in multiple choice reversal learning than adults. *Developmental Cognitive Neuroscience, 1*(4), 540–551. https://doi.org/10.1016/j.dcn.2011.05.008

Jyoti, D. F., Frongillo, E. A., & Jones, S. J. (2005). Food insecurity affects school children's academic performance, weight gain, and social skills. *The Journal of Nutrition, 135*(12), 2831–2839. https://doi.org/10.1093/jn/135.12.2831

Kalsbeek, A., Voorn, P., Buijs, R. M., Pool, C. W., & Uylings, H. B. (1988). Development of the dopaminergic innervation in the prefrontal cortex of the rat. *The Journal of Comparative Neurology, 269*(1), 58–72. https://doi.org/10.1002/cne.902690105

Kambali, M. Y., Anshu, K., Kutty, B. M., Muddashetty, R. S., & Laxmi, T. R. (2019). Effect of early maternal separation stress on attention, spatial learning and social interaction behaviour. *Experimental Brain Research, 237*(8), 1993–2010. https://doi.org/10.1007/s00221-019-05567-2

Karkhanis, A. N., Leach, A. C., Yorgason, J. T., Uneri, A., Barth, S., Niere, F., Alexander, N. J., Weiner, J. L., McCool, B. A., Raab-Graham, K. F., Ferris, M. J., & Jones, S. R. (2019). Chronic social isolation stress during peri-adolescence alters presynaptic dopamine terminal dynamics via augmentation in accumbal dopamine availability. *ACS Chemical Neuroscience, 10*(4), 2033–2044. https://doi.org/10.1021/acschemneuro.8b00360

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. Nature reviews. *Neuroscience, 8*(11), 844–858. https://doi.org/10.1038/nrn2234

Ke, J., & Ford-Jones, E. L. (2015). Food insecurity and hunger: A review of the effects on children's health and behaviour. *Paediatrics & Child Health, 20*(2), 89–91. https://doi.org/10.1093/pch/20.2.89

Kim, H., Sul, J. H., Huh, N., Lee, D., & Jung, M. W. (2009). Role of striatum in updating values of chosen actions. *The Journal of Neuroscience, 29*(47), 14701–14712. https://doi.org/10.1523/JNEUROSCI.2728-09.2009

Kim, Y. B., Huh, N., Lee, H., Baeg, E. H., Lee, D., & Jung, M. W. (2007). Encoding of action history in the rat ventral striatum. *Journal of Neurophysiology, 98*(6), 3548–3556. https://doi.org/10.1152/jn.00310.2007

Kim, J., & Ragozzino, M. E. (2005). The involvement of the orbitofrontal cortex in learning under changing task contingencies. *Neurobiology of Learning and Memory, 83*(2), 125–133. https://doi.org/10.1016/j.nlm.2004.10.003

Kjær, S. W., Damholdt, M. F., Callesen, M. B. (2018). A systematic review of decision-making impairments in Parkinson's disease: Dopaminergic medication and methodological variability. *Basal Ganglia, 14*, 31-40. https://doi.org/10.1016/j.baga.2018.07.003

Klanker, M., Feenstra, M., & Denys, D. (2013). Dopaminergic control of cognitive flexibility in humans and animals. *Frontiers in Neuroscience, 7*, 201. https://doi.org/10.3389/fnins.2013.00201

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience, 16*(8), 1412–1425. https://doi.org/10.1162/0898929042304796

Kosillo, P., Doig, N. M., Ahmed, K. M., Agopyan-Miu, A., Wong, C. D., Conyers, L., Threlfell, S., Magill, P. J., & Bateup, H. S. (2019). Tsc1-mTORC1 signaling controls striatal dopamine release and cognitive flexibility. *Nature Communications, 10*(1), 5426. https://doi.org/10.1038/s41467-019-13396-8

Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., & Moryś, J. (2018). BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. *Cellular and Molecular Neurobiology, 38*(3), 579–593. https://doi.org/10.1007/s10571-017-0510-4

Kozorovitskiy, Y., Peixoto, R., Wang, W., Saunders, A., & Sabatini, B. L. (2015). Neuromodulation of excitatory synaptogenesis in striatal development. *eLife, 4,* e10111. https://doi.org/10.7554/eLife.10111

Krajeski, R. N., Macey-Dare, A., van Heusden, F., Ebrahimjee, F., & Ellender, T. J. (2019). Dynamic postnatal development of the cellular and circuit properties of striatal D1 and D2 spiny projection neurons. *The Journal of Physiology, 597*(21), 5265–5293. https://doi.org/10.1113/JP278416

Lafuente, E., & Beldade, P. (2019). Genomics of developmental plasticity in animals. *Frontiers in genetics, 10*, 720. https://doi.org/10.3389/fgene.2019.00720

Lahiri, A. K., & Bevan, M. D. (2020). Dopaminergic transmission rapidly and persistently enhances excitability of D1 receptor-expressing striatal projection neurons. *Neuron, 106*(2), 277–290.e6. https://doi.org/10.1016/j.neuron.2020.01.028

Laraia B. A. (2013). Food insecurity and chronic disease. *Advances in Nutrition, 4*(2), 203–212. https://doi.org/10.3945/an.112.003277

Laube, C., van den Bos, W., & Fandakova, Y. (2020). The relationship between pubertal hormones and brain plasticity: Implications for cognitive training in adolescence. *Developmental Cognitive Neuroscience*, *42*, 100753. https://doi.org/10.1016/j.dcn.2020.100753

Lea, A. J., Tung, J., Archie, E. A., & Alberts, S. C. (2018). Developmental plasticity: Bridging research in evolution and human health. *Evolution, Medicine, and Public Health, 2017*(1), 162–175. https://doi.org/10.1093/emph/eox019

Lee, A. M., Tai, L. H., Zador, A., & Wilbrecht, L. (2015). Between the primate and 'reptilian' brain: Rodent models demonstrate the role of corticostriatal circuits in decision making. *Neuroscience, 296*, 66–74. https://doi.org/10.1016/j.neuroscience.2014.12.042

Lendvai, B., Stern, E. A., Chen, B., & Svoboda, K. (2000). Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. *Nature, 404*(6780), 876–881. https://doi.org/10.1038/35009107

Lex, B., & Hauber, W. (2010). The role of nucleus accumbens dopamine in outcome encoding in instrumental and Pavlovian conditioning. *Neurobiology of Learning and Memory, 93*(2), 283–290. https://doi.org/10.1016/j.nlm.2009.11.002

Lieberman, O. J., McGuirt, A. F., Mosharov, E. V., Pigulevskiy, I., Hobson, B. D., Choi, S., Frier, M. D., Santini, E., Borgkvist, A., & Sulzer, D. (2018). Dopamine triggers the maturation of striatal spiny projection neuron excitability during a critical period. *Neuron, 99*(3), 540–554.e4. https://doi.org/10.1016/j.neuron.2018.06.044

Lin, W.C., Delevich, K., Wilbrecht L. (in press). A role for adaptive developmental plasticity in learning and decision making. *Current Opinion in Behavioral Sciences.*

Lipton, D. M., Gonzales, B. J., & Citri, A. (2019). Dorsal striatal circuits for habits, compulsions and addictions. *Frontiers in Systems Neuroscience, 13*, 28. https://doi.org/10.3389/fnsys.2019.00028

Liu, S. J., & Cull-Candy, S. G. (2002). Activity-dependent change in AMPA receptor properties in cerebellar stellate cells. *The Journal of Neuroscience, 22*(10), 3881–3889. https://doi.org/10.1523/JNEUROSCI.22-10-03881.2002

Lu, B., Nagappan, G., Guan, X., Nathan, P. J., & Wren, P. (2013). BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nature Reviews. Neuroscience, 14*(6), 401–416. https://doi.org/10.1038/nrn3505

Luo, S. X., Timbang, L., Kim, J. I., Shang, Y., Sandoval, K., Tang, A. A., Whistler, J. L., Ding, J. B., & Huang, E. J. (2016). TGF-β signaling in dopaminergic neurons regulates dendritic growth, excitatory-inhibitory synaptic balance, and reversal learning. *Cell Reports, 17*(12), 3233–3245. https://doi.org/10.1016/j.celrep.2016.11.068

Macpherson, T., Morita, M., & Hikida, T. (2014). Striatal direct and indirect pathways control decision-making behavior. *Frontiers in Psychology, 5*, 1301. https://doi.org/10.3389/fpsyg.2014.01301

Majcher-Maślanka, I., Solarz, A., Wędzony, K., & Chocyk, A. (2017). The effects of early-life stress on dopamine system function in adolescent female rats. *International Journal of Developmental Neuroscience, 57*, 24–33. https://doi.org/10.1016/j.ijdevneu.2017.01.001

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science, 337*(6100), 1357–1360. https://doi.org/10.1126/science.1220845

Mandelman, S. D., & Grigorenko, E. L. (2012). BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association. *Genes, Brain, and Behavior, 11*(2), 127–136. https://doi.org/10.1111/j.1601-183X.2011.00738.x

Mani, A., Mullainathan, S., Shafir, E., & Zhao, J. (2013). Poverty impedes cognitive function. *Science, 341*(6149), 976–980. https://doi.org/10.1126/science.1238041

Maric, T., Sedki, F., Chafetz, D., Schoela, N., & Shalev, U. (2011). A role for neuropeptide Y Y5 but not the Y1-receptor subtype in food deprivation-induced reinstatement of heroin seeking in the rat. *Psychopharmacology, 218*(4), 693–701. https://doi.org/10.1007/s00213-011-2362-9

Mastwal, S., Ye, Y., Ren, M., Jimenez, D. V., Martinowich, K., Gerfen, C. R., & Wang, K. H. (2014). Phasic dopamine neuron activity elicits unique mesofrontal plasticity in adolescence. *The Journal of Neuroscience, 34*(29), 9484–9496.

Matthews, M., Bondi, C., Torres, G., & Moghaddam, B. (2013). Reduced presynaptic dopamine activity in adolescent dorsal striatum. *Neuropsychopharmacolog, 38*(7), 1344–1351. https://doi.org/10.1038/npp.2013.32

McCutcheon, J. E., Conrad, K. L., Carr, S. B., Ford, K. A., McGehee, D. S., & Marinelli, M. (2012). Dopamine neurons in the ventral tegmental area fire faster in adolescent rats than in adults. *Journal of Neurophysiology, 108*(6), 1620–1630. https://doi.org/10.1152/jn.00077.2012

McLaughlin, K. A., Greif Green, J., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2012). Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry, 69*(11), 1151–1160. https://doi.org/10.1001/archgenpsychiatry.2011.2277

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews, 47*, 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012

Miller, G. E., Chen, E., Fok, A. K., Walker, H., Lim, A., Nicholls, E. F., Cole, S., & Kobor, M. S. (2009). Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proceedings of the National Academy of Sciences, 106*(34), 14716–14721. https://doi.org/10.1073/pnas.0902971106

Mittal, C., Griskevicius, V., Simpson, J. A., Sung, S., & Young, E. S. (2015). Cognitive adaptations to stressful environments: When childhood adversity enhances adult executive function. *Journal of Personality and Social Psychology, 109*(4), 604–621. https://doi.org/10.1037/pspi0000028

Miyajima, F., Ollier, W., Mayes, A., Jackson, A., Thacker, N., Rabbitt, P., Pendleton, N., Horan, M., & Payton, A. (2008). Brain-derived neurotrophic factor polymorphism Val66Met influences cognitive abilities in the elderly. *Genes, Brain, and Behavior, 7*(4), 411–417. https://doi.org/10.1111/j.1601-183X.2007.00363.x

Murphy, M., & Mercer, J. G. (2014). Intermittent feeding schedules--behavioural consequences and potential clinical significance. *Nutrients, 6*(3), 985–1002. https://doi.org/10.3390/nu6030985

Murray, S., & Chen, E. Y. (2019). Examining adolescence as a sensitive period for high-fat, high-sugar diet exposure: A systematic review of the animal literature. *Frontiers in Neuroscience, 13*, 1108. https://doi.org/10.3389/fnins.2019.01108

Nettle, D., & Bateson, M. (2015). Adaptive developmental plasticity: what is it, how can we recognize it and when can it evolve?. *Proceedings. Biological Sciences, 282*(1812), 20151005. https://doi.org/10.1098/rspb.2015.1005

Naneix, F., Marchand, A. R., Di Scala, G., Pape, J. R., & Coutureau, E. (2012). Parallel maturation of goal-directed behavior and dopaminergic systems during adolescence. *The Journal of Neuroscience, 32*(46), 16223–16232. https://doi.org/10.1523/JNEUROSCI.3080-12.2012

Nicholson, A., Reifsnyder, P. C., Malcolm, R. D., Lucas, C. A., MacGregor, G. R., Zhang, W., & Leiter, E. H. (2010). Diet-induced obesity in two C57BL/6 substrains with intact or mutant nicotinamide nucleotide transhydrogenase (Nnt) gene. *Obesity, 18*(10), 1902–1905. https://doi.org/10.1038/oby.2009.477

Nonomura, S., Nishizawa, K., Sakai, Y., Kawaguchi, Y., Kato, S., Uchigashima, M., Watanabe, M., Yamanaka, K., Enomoto, K., Chiken, S., Sano, H., Soma, S., Yoshida, J., Samejima, K., Ogawa, M., Kobayashi, K., Nambu, A., Isomura, Y., & Kimura, M. (2018). Monitoring and updating of action selection for goal-directed behavior through the striatal direct and indirect pathways. *Neuron, 99*(6), 1302–1314.e5. https://doi.org/10.1016/j.neuron.2018.08.002

Novick, A. M., Levandowski, M. L., Laumann, L. E., Philip, N. S., Price, L. H., & Tyrka, A. R. (2018). The effects of early life stress on reward processing. *Journal of Psychiatric Research, 101*, 80–103. https://doi.org/10.1016/j.jpsychires.2018.02.002

Nussenbaum, K., & Hartley, C. A. (2019). Reinforcement learning across development: What insights can we draw from a decade of research? *Developmental Cognitive Neuroscience, 40*, 100733. https://doi.org/10.1016/j.dcn.2019.100733

Opendak, M., Gould, E., & Sullivan, R. (2017). Early life adversity during the infant sensitive period for attachment: Programming of behavioral neurobiology of threat processing and social behavior. *Developmental Cognitive Neuroscience, 25*, 145–159. https://doi.org/10.1016/j.dcn.2017.02.002

Pan, Y., Chau, L., Liu, S., Avshalumov, M. V., Rice, M. E., & Carr, K. D. (2011). A food restriction protocol that increases drug reward decreases tropomyosin receptor kinase B in the ventral tegmental area, with no effect on brain-derived neurotrophic factor or tropomyosin receptor kinase B protein levels in dopaminergic forebrain regions. *Neuroscience, 197*, 330–338. https://doi.org/10.1016/j.neuroscience.2011.08.065

Panicker, S., Brown, K., & Nicoll, R. A. (2008). Synaptic AMPA receptor subunit trafficking is independent of the C terminus in the GluR2-lacking mouse. *Proceedings of the National Academy of Sciences of the United States of America, 105*(3), 1032–1037. https://doi.org/10.1073/pnas.0711313105

Park, H., & Poo, M. M. (2013). Neurotrophin regulation of neural circuit development and function. *Nature Reviews. Neuroscience, 14*(1), 7–23. https://doi.org/10.1038/nrn3379

Parker, N. F., Cameron, C. M., Taliaferro, J. P., Lee, J., Choi, J. Y., Davidson, T. J., Daw, N. D., & Witten, I. B. (2016). Reward and choice encoding in terminals of midbrain dopamine neurons depends on striatal target. *Nature Neuroscience, 19*(6), 845–854. https://doi.org/10.1038/nn.4287

Pattwell, S. S., Liston, C., Jing, D., Ninan, I., Yang, R. R., Witztum, J., Murdock, M. H., Dincheva, I., Bath, K. G., Casey, B. J., Deisseroth, K., & Lee, F. S. (2016). Dynamic changes in neural circuitry during adolescence are associated with persistent attenuation of fear memories. *Nature Communications, 7*, 11475. https://doi.org/10.1038/ncomms11475

Penner, M. R., & Mizumori, S. J. (2012). Neural systems analysis of decision making during goal-directed navigation. *Progress in Neurobiology, 96*(1), 96–135. https://doi.org/10.1016/j.pneurobio.2011.08.010

Piekarski, D. J., Boivin, J. R., & Wilbrecht, L. (2017). Ovarian hormones organize the maturation of inhibitory neurotransmission in the frontal cortex at puberty onset in female mice. *Current Biology, 27*(12), 1735–1745.e3. https://doi.org/10.1016/j.cub.2017.05.027

Piekarski, D. J., Johnson, C. M., Boivin, J. R., Thomas, A. W., Lin, W. C., Delevich, K., M Galarce, E., & Wilbrecht, L. (2017). Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex?. *Brain Research, 1654*(Pt B), 123–144. https://doi.org/10.1016/j.brainres.2016.08.042

Pinzón-Duarte, G., Arango-González, B., Guenther, E., & Kohler, K. (2004). Effects of brain-derived neurotrophic factor on cell survival, differentiation and patterning of neuronal connections and Müller glia cells in the developing retina. *The European Journal of Neuroscience, 19*(6), 1475–1484. https://doi.org/10.1111/j.1460-9568.2004.03252.x

Pothos, E. N., Creese, I., & Hoebel, B. G. (1995). Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *The Journal of Neuroscience, 15*(10), 6640–6650. https://doi.org/10.1523/JNEUROSCI.15-10-06640.1995

Powell, S. B., Geyer, M. A., Preece, M. A., Pitcher, L. K., Reynolds, G. P., & Swerdlow, N. R. (2003). Dopamine depletion of the nucleus accumbens reverses isolation-induced deficits in prepulse inhibition in rats. *Neuroscience, 119*(1), 233–240. https://doi.org/10.1016/s0306-4522(03)00122-2

Qin, L., Jing, D., Parauda, S., Carmel, J., Ratan, R. R., Lee, F. S., & Cho, S. (2014). An adaptive role for BDNF Val66Met polymorphism in motor recovery in chronic stroke. *The Journal of Neuroscience, 34*(7), 2493–2502. https://doi.org/10.1523/JNEUROSCI.4140-13.2014

Rago, A., Kouvaris, K., Uller, T., & Watson, R. (2019). How adaptive plasticity evolves when selected against. *PLoS Computational Biology, 15*(3), e1006260. https://doi.org/10.1371/journal.pcbi.1006260

Ragozzino, M. E., & Rozman, S. (2007). The effect of rat anterior cingulate inactivation on cognitive flexibility. *Behavioral Neuroscience, 121*(4), 698–706. https://doi.org/10.1037/0735-7044.121.4.698

Raskind, I. G., Haardörfer, R., & Berg, C. J. (2019). Food insecurity, psychosocial health and academic performance among college and university students in Georgia, USA. *Public Health Nutrition, 22*(3), 476–485. https://doi.org/10.1017/S1368980018003439

Reiner, D. J., Fredriksson, I., Lofaro, O. M., Bossert, J. M., & Shaham, Y. (2019). Relapse to opioid seeking in rat models: behavior, pharmacology and circuits. *Neuropsychopharmacology, 44*(3), 465–477. https://doi.org/10.1038/s41386-018-0234-2

Rescorla, R.A. & Wagner, A.R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical Conditioning II: Current Research and Theory*, 64–99.

Richardson, R., Cowan, C. S. M., Callaghan, B. L., & Kan, J. M. (2016). Effects of early-life stress on fear memory in the developing rat. *Current Opinion in Behavioral Sciences, 7*, 15–20. https://doi.org/10.1016/j.cobeha.2015.10.003

Ricon, T., Toth, E., Leshem, M., Braun, K., & Richter-Levin, G. (2012). Unpredictable chronic stress in juvenile or adult rats has opposite effects, respectively, promoting and impairing resilience. *Stress, 15*(1), 11–20. https://doi.org/10.3109/10253890.2011.572207

Riddle, M. C., McKenna, M. C., Yoon, Y. J., Pattwell, S. S., Santos, P. M., Casey, B. J., & Glatt, C. E. (2013). Caloric restriction enhances fear extinction learning in mice. *Neuropsychopharmacology, 38*(6), 930–937. https://doi.org/10.1038/npp.2012.268

Roff, D.A. (2002). *Life history evolution.* Sunderland, MA: Sinauer Associates.

Rogers R. D. (2011). The roles of dopamine and serotonin in decision making: evidence from pharmacological experiments in humans. *Neuropsychopharmacology, 36*(1), 114–132. https://doi.org/10.1038/npp.2010.165

Roseberry A. G. (2015). Acute fasting increases somatodendritic dopamine release in the ventral tegmental area. *Journal of Neurophysiology, 114*(2), 1072–1082. https://doi.org/10.1152/jn.01008.2014

Ruther, J., Meiners, T., & Steidle, J. L. M. (2002). Rich in phenomena-lacking in terms. A classification of kairomones. *Chemoecology, 12*(4), 161–167. https://doi.org/10.1007/pl00012664

Sala-Bayo, J., Fiddian, L., Nilsson, S., Hervig, M. E., McKenzie, C., Mareschi, A., Boulos, M., Zhukovsky, P., Nicholson, J., Dalley, J. W., Alsiö, J., & Robbins, T. W. (2020). Dorsal and ventral striatal dopamine D1 and D2 receptors differentially modulate distinct phases of serial visual reversal learning. *Neuropsychopharmacology, 45*(5), 736–744. https://doi.org/10.1038/s41386-020-0612-4

Salamone, J. D., & Correa, M. (2012). The mysterious motivational functions of mesolimbic dopamine. *Neuron, 76*(3), 470–485. https://doi.org/10.1016/j.neuron.2012.10.021

Sanchez, A. L., Matthews, B. J., Meynard, M. M., Hu, B., Javed, S., & Cohen Cory, S. (2006). BDNF increases synapse density in dendrites of developing tectal neurons in vivo. *Development, 133*(13), 2477–2486. https://doi.org/10.1242/dev.02409

Sasagawa, T., Horii-Hayashi, N., Okuda, A., Hashimoto, T., Azuma, C., & Nishi, M. (2017). Long-term effects of maternal separation coupled with social isolation on reward seeking and changes in dopamine D1 receptor expression in the nucleus accumbens via DNA methylation in mice. *Neuroscience Letters, 641,* 33–39. https://doi.org/10.1016/j.neulet.2017.01.025

Sasi, M., Vignoli, B., Canossa, M., & Blum, R. (2017). Neurobiology of local and intercellular BDNF signaling. Pflugers Archiv : *European Journal of Physiology, 469*(5-6), 593–610. https://doi.org/10.1007/s00424-017-1964-4

Saunders, B. T., Richard, J. M., Margolis, E. B., & Janak, P. H. (2018). Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. *Nature Neuroscience, 21*(8), 1072–1083. https://doi.org/10.1038/s41593-018-0191-4

Schofield, P. R., Williams, L. M., Paul, R. H., Gatt, J. M., Brown, K., Luty, A., Cooper, N., Grieve, S., Dobson-Stone, C., Morris, C., Kuan, S. A., & Gordon, E. (2009). Disturbances in selective information processing associated with the BDNF Val66Met polymorphism: evidence from cognition, the P300 and fronto-hippocampal systems. *Biological Psychology, 80*(2), 176–188. https://doi.org/10.1016/j.biopsycho.2008.09.001

Schultz W. (2016). Dopamine reward prediction-error signalling: A two-component response. *Nature Reviews. Neuroscience, 17*(3), 183–195. https://doi.org/10.1038/nrn.2015.26

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593–1599. https://doi.org/10.1126/science.275.5306.1593

Scott, W. A. (1962). Cognitive complexity and cognitive flexibility. *Sociometry, 25*(4), 405–414. https://doi.org/10.2307/2785779

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology, 74*(1), 1–58. https://doi.org/10.1016/j.pneurobio.2004.05.006

Seelke, A. M., Perkeybile, A. M., Grunewald, R., Bales, K. L., & Krubitzer, L. A. (2016). Individual differences in cortical connections of somatosensory cortex are associated with parental rearing style in prairie voles (Microtus ochrogaster). *The Journal of Comparative Neurology, 524*(3), 564–577. https://doi.org/10.1002/cne.23837

Sevak, R. J., Koek, W., Owens, W. A., Galli, A., Daws, L. C., & France, C. P. (2008). Feeding conditions differentially affect the neurochemical and behavioral effects of dopaminergic drugs in male rats. *European Journal of Pharmacology, 592*(1-3), 109–115. https://doi.org/10.1016/j.ejphar.2008.07.002

Shalev, U., Highfield, D., Yap, J., & Shaham, Y. (2000). Stress and relapse to drug seeking in rats: studies on the generality of the effect. *Psychopharmacology, 150*(3), 337–346. https://doi.org/10.1007/s002130000441

Shen, W., Flajolet, M., Greengard, P., & Surmeier, D. J. (2008). Dichotomous dopaminergic control of striatal synaptic plasticity. *Science, 321*(5890), 848–851. https://doi.org/10.1126/science.1160575

Shetty, A. K., & Turner, D. A. (1998). In vitro survival and differentiation of neurons derived from epidermal growth factor-responsive postnatal hippocampal stem cells: inducing effects of brain-derived neurotrophic factor. *Journal of Neurobiology, 35*(4), 395–425. https://doi.org/10.1002/(sici)1097-4695(19980615)35:4<395::aid-neu7>3.0.co;2-u

Shin, J. H., Kim, D., & Jung, M. W. (2018). Differential coding of reward and movement information in the dorsomedial striatal direct and indirect pathways. *Nature Communications, 9*(1), 404. https://doi.org/10.1038/s41467-017-02817-1

Sinclair, D., Purves-Tyson, T. D., Allen, K. M., & Weickert, C. S. (2014). Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain. *Psychopharmacology, 231*(8), 1581–1599. https://doi.org/10.1007/s00213-013-3415-z

Snell-Rood, E. C. (2012). Selective processes in development: implications for the costs and benefits of phenotypic plasticity. *Integrative and Comparative Biology, 52*(1), 31–42. https://doi.org/10.1093/icb/ics067

Snell-Rood, E. C. (2013). An overview of the evolutionary causes and consequences of behavioural plasticity. *Animal Behaviour, 85*(5), 1004–1011. https://doi.org/10.1016/j.anbehav.2012.12.031

Snell-Rood, E., & Snell-Rood, C. (2020). The developmental support hypothesis: adaptive plasticity in neural development in response to cues of social support. *Philosophical Transactions of the Royal Society B: Biological Sciences, 375*(1803), 20190491. https://doi.org/10.1098/rstb.2019.0491

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews, 24*(4), 417–463. https://doi.org/10.1016/s0149-7634(00)00014-2

Stamford J. A. (1989). Development and ageing of the rat nigrostriatal dopamine system studied with fast cyclic voltammetry. *Journal of Neurochemistry, 52*(5), 1582–1589. https://doi.org/10.1111/j.1471-4159.1989.tb09212.x

Stamps J. A. (2016). Individual differences in behavioural plasticities. *Biological Reviews of the Cambridge Philosophical Society, 91*(2), 534–567. https://doi.org/10.1111/brv.12186

Stearns, S. C. (1989). The evolutionary significance of phenotypic plasticity: Phenotypic sources of variation among organisms can be described by developmental switches and reaction norms. *BioScience, 39*(7), 436–445. https://doi.org/10.2307/131113

Stearns, S. C. (1992). *The evolution of life histories*. Oxford: Oxford University Press.

Steinberg, E. E., Boivin, J. R., Saunders, B. T., Witten, I. B., Deisseroth, K., & Janak, P. H. (2014). Positive reinforcement mediated by midbrain dopamine neurons requires D1 and D2 receptor activation in the nucleus accumbens. *PloS One, 9*(4), e94771. https://doi.org/10.1371/journal.pone.0094771

Steinberg, E. E., Keiflin, R., Boivin, J. R., Witten, I. B., Deisseroth, K., & Janak, P. H. (2013). A causal link between prediction errors, dopamine neurons and learning. Nature Neuroscience, 16(7), 966–973. https://doi.org/10.1038/nn.3413

Stelly, C. E., Tritley, S. C., Rafati, Y., & Wanat, M. J. (2020). Acute stress enhances associative learning via dopamine signaling in the ventral lateral striatum. *The Journal of Neuroscience, 40*(22), 4391–4400. https://doi.org/10.1523/JNEUROSCI.3003-19.2020

Stuber, G. D., Evans, S. B., Higgins, M. S., Pu, Y., & Figlewicz, D. P. (2002). Food restriction modulates amphetamine-conditioned place preference and nucleus accumbens dopamine release in the rat. *Synapse, 46*(2), 83–90. https://doi.org/10.1002/syn.10120

Sugama, S., Sekiyama, K., Kodama, T., Takamatsu, Y., Takenouchi, T., Hashimoto, M., Bruno, C., & Kakinuma, Y. (2016). Chronic restraint stress triggers dopaminergic and noradrenergic neurodegeneration: Possible role of chronic stress in the onset of Parkinson's disease. *Brain, Behavior, and Immunity, 51*, 39–46. https://doi.org/10.1016/j.bbi.2015.08.015

Sutton, R. S., & Barto, A. G. (2018). *Reinforcement learning: an introduction*. The MIT Press.

Suzuki, Y., & Nijhout, H. F. (2006). Evolution of a polyphenism by genetic accommodation. *Science, 311*(5761), 650–652. https://doi.org/10.1126/science.1118888

Sweatt, J. D. (2016). Neural plasticity and behavior - sixty years of conceptual advances. *Journal of Neurochemistry, 139*(Suppl 2), 179–199. https://doi.org/10.1111/jnc.13580

Tai, L. H., Lee, A. M., Benavidez, N., Bonci, A., & Wilbrecht, L. (2012). Transient stimulation of distinct subpopulations of striatal neurons mimics changes in action value. *Nature Neuroscience, 15*(9), 1281–1289. https://doi.org/10.1038/nn.3188

Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, G. C., & Kasai, H. (2008). Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. *Science, 319*(5870), 1683–1687. https://doi.org/10.1126/science.1152864

Tarazi, F. I., & Baldessarini, R. J. (2000). Comparative postnatal development of dopamine D(1), D(2) and D(4) receptors in rat forebrain. *International Journal of Developmental Neuroscience, 18*(1), 29–37. https://doi.org/10.1016/s0736-5748(99)00108-2

Taylor, P., & Lewontin, R. (2017, June 06). The Genotype/Phenotype Distinction., from https://plato.stanford.edu/archives/sum2017/entries/genotype-phenotype/

Teicher, M. H., Andersen, S. L., & Hostetter, J. C., Jr (1995). Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. *Brain Research. Developmental Brain Research, 89*(2), 167–172. https://doi.org/10.1016/0165-3806(95)00109-q

Tennyson, S. S., Brockett, A. T., Hricz, N. W., Bryden, D. W., & Roesch, M. R. (2018). Firing of putative dopamine neurons in ventral tegmental area is modulated by probability of success during performance of a stop-change task. *eNeuro, 5*(2), ENEURO.0007-18.2018. https://doi.org/10.1523/ENEURO.0007-18.2018

Thomas, A. W., Caporale, N., Wu, C., & Wilbrecht, L. (2016). Early maternal separation impacts cognitive flexibility at the age of first independence in mice. *Developmental Cognitive Neuroscience, 18*, 49–56. https://doi.org/10.1016/j.dcn.2015.09.005

Thomas, A. W., Delevich, K., Chang, I., & Wilbrecht, L. (2020). Variation in early life maternal care predicts later long range frontal cortex synapse development in mice. *Developmental Cognitive Neuroscience, 41*, 100737. https://doi.org/10.1016/j.dcn.2019.100737

Torres, C., Glueck, A. C., Conrad, S. E., Morón, I., & Papini, M. R. (2016). Dorsomedial striatum lesions affect adjustment to reward uncertainty, but not to reward devaluation or omission. *Neuroscience, 332*, 13–25. https://doi.org/10.1016/j.neuroscience.2016.06.041

Toye, A. A., Lippiat, J. D., Proks, P., Shimomura, K., Bentley, L., Hugill, A., Mijat, V., Goldsworthy, M., Moir, L., Haynes, A., Quarterman, J., Freeman, H. C., Ashcroft, F. M., & Cox, R. D. (2005). A genetic and physiological study of impaired glucose homeostasis control in C57BL/6J mice. *Diabetologia, 48*(4), 675–686. https://doi.org/10.1007/s00125-005-1680-z

Tractenberg, S. G., Levandowski, M. L., de Azeredo, L. A., Orso, R., Roithmann, L. G., Hoffmann, E. S., Brenhouse, H., & Grassi-Oliveira, R. (2016). An overview of maternal separation effects on behavioural outcomes in mice: Evidence from a four-stage methodological systematic review. *Neuroscience and Biobehavioral Reviews, 68*, 489–503. https://doi.org/10.1016/j.neubiorev.2016.06.021

Tsai, S. J., Hong, C. J., Yu, Y. W., & Chen, T. J. (2004). Association study of a brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and personality trait and intelligence in healthy young females. *Neuropsychobiology, 49*(1), 13–16. https://doi.org/10.1159/000075333

Tseng, K. Y., & O'Donnell, P. (2007). Dopamine modulation of prefrontal cortical interneurons changes during adolescence. *Cerebral Cortex, 17*(5), 1235–1240. https://doi.org/10.1093/cercor/bhl034

van der Plasse, G., van Zessen, R., Luijendijk, M. C., Erkan, H., Stuber, G. D., Ramakers, G. M., & Adan, R. A. (2015). Modulation of cue-induced firing of ventral tegmental area dopamine neurons by leptin and ghrelin. *International Journal of Obesity, 39*(12), 1742–1749. https://doi.org/10.1038/ijo.2015.131

Valenti, O., Lodge, D. J., & Grace, A. A. (2011). Aversive stimuli alter ventral tegmental area dopamine neuron activity via a common action in the ventral hippocampus. *The Journal of Neuroscience, 31*(11), 4280–4289. https://doi.org/10.1523/JNEUROSCI.5310-10.2011

Vandenberg, A., Lin, W. C., Tai, L. H., Ron, D., & Wilbrecht, L. (2018). Mice engineered to mimic a common Val66Met polymorphism in the BDNF gene show greater sensitivity to reversal in environmental contingencies. *Developmental Cognitive Neuroscience, 34*, 34–41. https://doi.org/10.1016/j.dcn.2018.05.009

Velanova, K., Wheeler, M. E., & Luna, B. (2008). Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex, 18*(11), 2505–2522. https://doi.org/10.1093/cercor/bhn012

Ventura, R., Coccurello, R., Andolina, D., Latagliata, E. C., Zanettini, C., Lampis, V., Battaglia, M., D'Amato, F. R., & Moles, A. (2013). Postnatal aversive experience impairs sensitivity to natural rewards and increases susceptibility to negative events in adult life. *Cerebral Cortex, 23*(7), 1606–1617. https://doi.org/10.1093/cercor/bhs145

Verharen, J., de Jong, J. W., Roelofs, T., Huffels, C., van Zessen, R., Luijendijk, M., Hamelink, R., Willuhn, I., den Ouden, H., van der Plasse, G., Adan, R., & Vanderschuren, L. (2018). A neuronal mechanism underlying decision-making deficits during hyperdopaminergic states. *Nature Communications, 9*(1), 731. https://doi.org/10.1038/s41467-018-03087-1

Wahlstrom, D., Collins, P., White, T., & Luciana, M. (2010). Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. *Brain and Cognition*, *72*(1), 146–159. https://doi.org/10.1016/j.bandc.2009.10.013

Wang, L., Jiao, J., & Dulawa, S. C. (2011). Infant maternal separation impairs adult cognitive performance in BALB/cJ mice. *Psychopharmacology, 216*(2), 207–218. https://doi.org/10.1007/s00213-011-2209-4

Wang, D., Levine, J., Avila-Quintero, V., Bloch, M., & Kaffman, A. (2020). Systematic review and meta-analysis: effects of maternal separation on anxiety-like behavior in rodents. *Translational Psychiatry, 10*(1), 174. https://doi.org/10.1038/s41398-020-0856-0

Wang, Q., Li, M., Du, W., Shao, F., & Wang, W. (2015). The different effects of maternal separation on spatial learning and reversal learning in rats. *Behavioural Brain Research, 280*, 16–23. https://doi.org/10.1016/j.bbr.2014.11.040

Wang, C., Liu, B., Long, H., Fan, L., Li, J., Zhang, X., Qiu, C., Yu, C., & Jiang, T. (2015). Epistatic interaction of BDNF and COMT on the frontostriatal system. *Neuroscience, 298*, 380–388. https://doi.org/10.1016/j.neuroscience.2015.04.014

Warnault, V., Darcq, E., Morisot, N., Phamluong, K., Wilbrecht, L., Massa, S. M., Longo, F. M., & Ron, D. (2016). The BDNF valine 68 to methionine polymorphism increases compulsive alcohol drinking in mice that is reversed by tropomyosin receptor kinase B activation. *Biological Psychiatry, 79*(6), 463–473. https://doi.org/10.1016/j.biopsych.2015.06.007

Watabe-Uchida, M., Eshel, N., & Uchida, N. (2017). Neural circuitry of reward prediction error. *Annual Review of Neuroscience, 40*, 373–394. https://doi.org/10.1146/annurev-neuro-072116-031109

Watt, M. J., Weber, M. A., Davies, S. R., & Forster, G. L. (2017). Impact of juvenile chronic stress on adult cortico-accumbal function: Implications for cognition and addiction. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 79*(Pt B), 136–154. https://doi.org/10.1016/j.pnpbp.2017.06.015

Weigel, M. M., & Armijos, R. X. (2018). Household food insecurity and psychosocial dysfunction in Ecuadorian elementary schoolchildren. *International Journal of Pediatrics, 2018*, 6067283. https://doi.org/10.1155/2018/6067283

Weiss, L. C. (2019). Sensory Ecology of Predator-Induced Phenotypic Plasticity. *Frontiers in Behavioral Neuroscience, 12*, 330. https://doi.org/10.3389/fnbeh.2018.00330

Whitaker, R. C., Phillips, S. M., & Orzol, S. M. (2006). Food insecurity and the risks of depression and anxiety in mothers and behavior problems in their preschool-aged children. *Pediatrics, 118*(3), e859–e868. https://doi.org/10.1542/peds.2006-0239

Willing, J., Cortes, L. R., Brodsky, J. M., Kim, T., & Juraska, J. M. (2017). Innervation of the medial prefrontal cortex by tyrosine hydroxylase immunoreactive fibers during adolescence in male and female rats. *Developmental Psychobiology, 59*(5), 583–589. https://doi.org/10.1002/dev.21525

Winicki, J., & Jemison, K. (2003). Food Insecurity and Hunger in the Kindergarten Classroom: Its Effect on Learning and Growth. *Contemporary Economic Policy, 21*(2), 145–157. https://doi.org/10.1093/cep/byg001

World Health Organization. (2019, August 20). *The state of food security and nutrition in the world 2019*. World Health Organization. https://www.who.int/nutrition/publications/foodsecurity/state-food-security-nutrition-2019/en/.

Yagishita, S., Hayashi-Takagi, A., Ellis-Davies, G. C., Urakubo, H., Ishii, S., & Kasai, H. (2014). A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science, 345*(6204), 1616–1620. https://doi.org/10.1126/science.1255514

Yin, H. H., & Knowlton, B. J. (2006). The role of the basal ganglia in habit formation. *Nature Reviews. Neuroscience, 7*(6), 464–476. https://doi.org/10.1038/nrn1919

Yin, H. H., Knowlton, B. J., & Balleine, B. W. (2004). Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *The European Journal of Neuroscience, 19*(1), 181–189. https://doi.org/10.1111/j.1460-9568.2004.03095.x

Yohn, N. L., & Blendy, J. A. (2017). Adolescent chronic unpredictable stress exposure is a sensitive window for long-term changes in adult behavior in mice. *Neuropsychopharmacology, 42*(8), 1670–1678. https://doi.org/10.1038/npp.2017.11

Young, E. S., Griskevicius, V., Simpson, J. A., Waters, T., & Mittal, C. (2018). Can an unpredictable childhood environment enhance working memory? Testing the sensitized-specialization hypothesis. *Journal of Personality and Social Psychology, 114*(6), 891–908. https://doi.org/10.1037/pspi0000124

Zalosnik, M. I., Pollano, A., Trujillo, V., Suárez, M. M., & Durando, P. E. (2014). Effect of maternal separation and chronic stress on hippocampal-dependent memory in young adult rats: Evidence for the match-mismatch hypothesis. *Stress, 17*(5), 445–450. https://doi.org/10.3109/10253890.2014.936005

Zelazo, P. D. (2015). Executive function: Reflection, iterative reprocessing, complexity, and the developing brain. *Developmental Review, 38*, 55–68. https://doi.org/10.1016/j.dr.2015.07.001

Zeeb, F. D., Wong, A. C., & Winstanley, C. A. (2013). Differential effects of environmental enrichment, social-housing, and isolation-rearing on a rat gambling task: dissociations between impulsive action and risky decision-making. *Psychopharmacology, 225*(2), 381–395. https://doi.org/10.1007/s00213-012-2822-x

Zheng, D., Cabeza de Vaca, S., & Carr, K. D. (2012). Food restriction increases acquisition, persistence and drug prime-induced expression of a cocaine-conditioned place preference in rats. *Pharmacology, Biochemistry, and Behavior, 100*(3), 538–544. https://doi.org/10.1016/j.pbb.2011.10.021

Zhu, X., Li, T., Peng, S., Ma, X., Chen, X., & Zhang, X. (2010). Maternal deprivation-caused behavioral abnormalities in adult rats relate to a non-methylation-regulated D2 receptor levels in the nucleus accumbens. *Behavioural Brain Research, 209*(2), 281–288. https://doi.org/10.1016/j.bbr.2010.02.005

Zwosta, K., Ruge, H., & Wolfensteller, U. (2015). Neural mechanisms of goal-directed behavior: Outcome-based response selection is associated with increased functional coupling of the angular gyrus. *Frontiers in Human Neuroscience,* 9, 180. https://doi.org/10.3389/fnhum.2015.00180