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## Plasticity of the reward circuitry after early life adversity: mechanisms and significance

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### Abstract

Disrupted operation of the reward circuitry underlies many aspects of affective disorders. Such disruption may manifest as aberrant behavior including risk taking, depression, anhedonia and addiction. Early life adversity is a common antecedent of adolescent and adult affective disorders involving the reward circuitry. However, whether early life adversity influences the maturation and operations of the reward circuitry, and the potential underlying mechanisms, remain unclear.

Here we present novel information using cutting-edge technologies in animal models to dissect out the mechanisms by which early life adversity provokes dysregulation of the complex interactions of stress and reward circuitries. We propose that certain molecularly defined pathways within the reward circuitry are particularly susceptible to early life adversity. We examine regions and pathways expressing the stress sensitive peptide corticotropin releasing hormone (CRH), which has been identified in critical components of the reward circuitry and interacting stress circuits. Notably, CRH is strongly modulated by early life adversity in several of these brain regions. Focusing on amygdala nuclei and their projections, we provide evidence suggesting that aberrant CRH expression and function may underlie augmented connectivity of the nucleus accumbens with fear/anxiety regions, disrupting the function of this critical locus of pleasure and reward.

### Keywords

Anhedonia; CRH; Stress; Amygdala; Nucleus accumbens; Addiction

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## Introduction

Early life adversity is a common antecedent of adolescent and adult affective disorders involving disrupted operation of the reward circuitry. These include anhedonia, depression, excessive risk-taking (gambling) and drug and alcohol addiction. However, whether early life adversity influences the maturation and operations of the reward circuitry, and the potential underlying mechanisms, remain unclear.

The vulnerability of the developing (prenatal and early postnatal) brain to adversity derives from the fact that the mesolimbic reward circuitry undergoes significant growth, maturation and plasticity during this epoch (see Table 1). The nature of the eventual psychopathology engendered by early life adversity may depend on the nature or type of the insults and the developmental period in which they are experienced, as well as clear and well-established genetic and epigenetic factors that confer vulnerability to the insults. Indeed, genetics and early life adversity interact to modulate development of the reward circuitry, thus influencing its eventual functions[1,2]. In this review, we discuss reward circuit development and the mechanistic role of adversity in disrupting the normal maturation of this circuitry, conferring susceptibility to mental illness.

### **Causality of early life adversity and psychopathology: a conundrum in humans that requires experimental paradigms**

Whereas early life adversity, including poverty and chaotic environment, is associated with poor emotional outcomes and aberrant functional development of the reward system[3,4], the origins and mechanisms that underlie these observations are not fully understood. Specifically, it is not possible in human studies to dissociate genetics and environment. For example, poor parental care may predict anxiety and depression, yet the parent endows the child with both his/her behavior and DNA. Therefore, while well designed longitudinal human studies offer important clues and insights, they cannot conclusively establish causality and mechanisms[5]. Thus, the use of animal models of early life adversity is required[6]. Indeed, animal models for early life adversity (or stress) have been developed to probe the causal and mechanistic nature of these important observations in humans.

### **New experimental paradigms enable identifying causality and mechanisms of the role of early life adversity in aberrant maturation and operations of the reward circuitry**

The development of preclinical models for early life adversity offers scientists the ability to understand complex neural mechanisms using techniques and approaches that are not possible in humans. Indeed, numerous approaches have been used to generate stress or adversity early in life, including the prenatal and / or postnatal epochs considered sensitive[7]. Maternal separation has been used for decades to study the effects of such adversity/stress, and several variants exist including daily short (3–4 hour) separation or a single prolonged deprivation[8,9]. These models have generally yielded deficits in cognitive abilities[10–12] as well as anxiety-like and depression-like behaviors[13,14] and addiction-like behaviors[15,16]. Aiming to generate a naturalistic, highly reproducible model for early life adversity, a paradigm of simulated poverty, using cages with limited bedding and nesting material (LBN) in rodents, has been devised and used extensively around the world

[7,17,18]. This environment strongly disrupts caring behaviors in rodent dams and thus the sensory signals received by the developing pups. Whereas the overall duration and quality of maternal care remain unaltered, the pattern of caregiving is fragmented and unpredictable[17,19,20]. The fragmented, unpredictable sequences of maternal care cause chronic stress in the pups, which dissipates upon returning dams to normal bedded cages at the end of the one-week exposure. However, aberrant brain circuit maturation is generated in the pups, evident on magnetic resonance imaging (MRI) [27] and manifesting as impaired memory[21,22] as well as specific deficits in emotional-like behaviors[20,23]. Here we focus on alterations of the reward circuitry and their behavioral manifestations.

## The reward circuitry and its development

**A. overview**—Reward processing encompasses the biological and behavioral functions to drive the acquisition of rewarding stimuli[24,25]. The hypothalamus is central to processing basic rewards, whereas higher cortical and subcortical forebrain structures are engaged when complex choices about these fundamental needs are required. The reward circuitry is a complex entity that includes the prefrontal cortex (PFC), nucleus accumbens (NAc), ventral tegmental area (VTA), amygdala (Amyg) and hippocampus (HC) acting as a neural network to effectively assess the likely outcomes of different choices. Studies have focused on the glutamatergic and dopaminergic input pathways to the NAc, a key brain region that integrates excitatory and inhibitory input to signal the salience of rewarding stimuli[26–31]. The primary function of the NAc is to modulate the response to reward-related cues, as well as the value of deviations of expected versus actual reward outcomes, which are encoded via projections to and from the amygdala, thalamic nuclei and prefrontal cortex[32–34] (Figure 1).

**B. development**—A tremendous body of work has elucidated the connectivity, operation and function of the mature reward circuitry, yet much remains unknown about the early development of this system and of its functionality in both humans and experimental models. This information is required in order to assess the nature of the influence on the circuitry by early life adverse events, and the potential impact.

In addition, although a large majority of mechanistic studies involve rodent models, there is a striking dearth of information regarding the comparative early development and maturation of the reward circuitry across species. Because the timing of adversity critically influences the outcome, this lack of information might result in imprecise inferences and difficulties in translating major preclinical studies to the human. It is important to note that because the development of distinct circuits occurs at different time-points and velocities across species[35,36], it is not optimal to consider global ‘brain development’ across species. Hence, milestones such as neurogenesis, synaptogenesis, connectivity and specific functions of a given circuit should be compared across species (Table 1). For example, studies examining over twenty distinct milestones across species suggest that, for the hippocampal circuit, the state of maturation of a 5–7 day old Sprague Dawley rat seems to approximate that of a human full-term neonate[35]. As shown in Table 1, such a comparison is far more difficult and complex for milestones within the reward circuitry. This is partially a result of very few studies as well as the different methods used across species and the different

sensitivities of methods employed in historical and current work. Yet, in the aggregate, it can be gleaned that reward circuitry development during the first postnatal week in the rodent may approximate that of a full-term human neonate.

### **Neurotransmitter pathways of the reward circuitry**

The role of dopamine in reward and motivated behaviors has been extensively studied and reviewed[37–39]. The ventral striatum and dopaminergic neurons of the substantia nigra are vital for processing reward. However, differential roles of dopamine in motivational and hedonic components of reward have been reported. For example, dopamine receptor antagonism in the NAc reduced the amount of effort an animal will expend to obtain a reward, whereas consumption and positive hedonic responses remained intact[40,41]. In addition, increased D2/D3 receptor availability in the ventral pallidum, nucleus accumbens, right ventral caudate and putamen correlated with the severity of anhedonia in clinically assessed patients with depression[42]. In rodents, incentive salience and instrumental behaviors from rewarding cues were also driven by dopaminergic control[43,44]. Together, these data support the notion that dopamine in the NAc is required for motivation of reward but not for hedonic experience and responsiveness to reward. Instead, opioids and endocannabinoids act as major neurochemical mediators of reward responsiveness[45–47].

The excitatory neurotransmitter glutamate plays a major role in the function of the reward circuit[48]. In the rodent, glutamate projections to the NAc originate from cortical, thalamic, hippocampal and amygdalar regions and function via AMPA, NMDA and mGluR receptors[49]. Further, blocking NMDA and AMPA receptors impaired the conditioned rewarding effects of drugs of abuse[50]. In humans, reward processing-driven ventral striatal activation correlated with hippocampal glutamate levels[51], and in rodents, glutamatergic ventral pallidal neurons increased activity in the lateral habenula, rostromedial tegmental nucleus and GABA VTA neurons, which resulted in constrained reward seeking[52].

The involvement of dorsal raphe serotonin transporter (SERT) terminals, which synapse onto VTA dopaminergic neurons has also been implicated in driving rewarding behaviors. In rodents, dorsal raphe serotonin fibers synapse on VTA dopaminergic neurons that co-express vesicular glutamate transporter 3 (VGLUT3) and target the NAc to initiate a rapid release of dopamine via dual serotonin-glutamate input [53], yet optogenetic activation of dorsal raphe serotonin neurons prolonged the waiting time for future reward[54,55].

### **Neuromodulators contribute to molecular-defined pathways within the reward circuitry**

In addition to classical neurotransmitters, several peptides and neuromodulators are expressed in structures involved with the reward circuitry. As noted above, opioids and endocannabinoids act as major neurochemical mediators of reward responsiveness[46,47]. Several neuropeptides are co-expressed in neurons within the reward circuitry[56,57] and specifically within the NAc. These include orexin[58], neuropeptide Y[59], and CRH and its receptors CRHR1 and CRHR2 [60–63]. More recently, Itoga et al. 2019, using viral genetic mapping and anterograde and retrograde tracing, mapped CRH expressing projection sources to the NAc in mice[64]. Intriguingly, the authors identified an enrichment of CRH-expressing inputs to the NAc from brain regions involved in aspects of sensing, processing

and retrieval of emotionally salient events. These findings are intriguing because CRH, a stress-regulated peptide and a mediator of stress, is poised to execute the effects of adversity, including early-life adversity, on the reward circuitry[65–67].

### The role of CRH in the reward circuitry

CRH is an essential, evolutionarily conserved stress neuropeptide that is expressed in specific neuronal populations throughout the brain to crucially modulate the functions of several circuits including those involved in processing of emotion and cognition[68,69]. CRH and its cognate receptors have been shown to exhibit experience-dependent plasticity in different nodes of the reward and stress circuitries such as the amygdala, locus coeruleus, dorsal raphe and hippocampus[21,70–73]. For instance, CRH in the NAc increases dopamine release promoting appetitive behavior, via CRH receptors that have been identified in rodent[74], and primate[75] NAc. However following prior stress exposure, CRH-mediated dopamine release was abolished and the behavioral consequence of CRH release in the NAc switched from appetitive to aversive [61]. Further, CRH in the NAc increased cholinergic interneuron firing and acetylcholine tone[76,77], as well as cFos activity[62] and phosphorylation of CREB in NAc medium spiny neurons[78].

Whereas CRH-expressing fibers have been identified in the NAc that originate from the basolateral amygdala, the function of this BLA-NAc pathway remains unclear (Figure 2). Better information is available for other CRH-expressing pathways: Dopaminergic neurons co-expressing CRH in the ventral tegmental area (VTA) drive the aversive effects of nicotine withdrawal, activating CRHR1 to block the GABAergic input to these neurons[79]. CRH-expressing projections between the amygdala and VTA modulate dopamine release[65]. A CRH-expressing projection between the VTA and the hypothalamic paraventricular nucleus (PVN) has been identified[80], which is interesting because CRH-expressing cells in the PVN fire during aversive events and their activity is decreased in response to appetitive stimuli [81,82]. Thus, reward, such as palatable food might relieve stress by specifically targeting the CRH-expressing PVN neurons. Recently, an additional role for CRH within the reward circuitry has been identified. Following early life adversity, CRH mRNA and protein expression were augmented in several nodes of the reward and stress circuitries including amygdala and hippocampus[21,83]. Concomitantly, adult rats that experienced early-life adversity were rendered anhedonic in several measures (Figure 3). Partial silencing of CRH in the central amygdala resulted in reversal of this anhedonia [23], further supporting a complex role for CRH-dependent modulation of reward and motivational behaviors.. Whereas the evidence presented above is derived from animal models, analogous functions of CRH in humans is supported by the finding that genetic variations in the CRH receptor CRHR1 are linked to stress related psychiatric disorders [84–88].

### Functional output of the reward circuitry: Anhedonia as a readout.

Anhedonia, defined as the reduced ability to experience pleasure, is a prominent symptom of several neuropsychiatric disorders and is considered a trans-diagnostic marker for disrupted function of the reward circuitry [93]. In U.S. Marine Corps recruits, anhedonia was identified as a predictor for post-combat PTSD[89] and a potent harbinger of suicide[90]. Notably, anhedonia is a predictor of treatment outcome of cocaine dependence [91], chronic

pain, and prescription opioid use[92]. Further support for altered reward circuitry in anhedonia comes from imaging studies: Structural MRI revealed that smaller right nucleus accumbens correlated with anhedonic symptoms, and that left and right putamen volume could predict the severity of present and future anhedonic states [93].

### **Early-life adversity induces anhedonia**

Early life adversity induced by simulated poverty and unpredictable maternal behaviors resulted in decreased preference for sweets[20,94] a reduction in social play [23,95], and a reduced hedonic set point for cocaine[96] (Figure 3). All these behaviors are considered manifestations of anhedonia in rodents[20,97]. Notably, maternal separation stress alone did not result in anhedonia measured by sucrose preference; rather, a second stressor during adulthood was necessary to induce it[98,99]. Because both paradigms result in evidence of stress in the pups, these studies suggest that aberrant patterns of maternal-derived sensory signals rather than stress alone influence the development of the reward circuitry. Human studies using fMRI have probed the functional activation of components of the reward circuitry in individuals that had experienced early life adversity and identified several deficits. For examples, decreased activity was observed in the basal ganglia [100,101], and the development of ventral striatum activation in adolescents exposed to early life adversity was attenuated [102]. These authors identified a more robust effect when the stress was experienced earlier in life, indicating the importance of the timing of the insult[3].

### **How does early life adversity modify the reward circuitry?**

Reward circuit function requires the integration and coordination of molecular, cellular, synaptic and network signaling. Failure to mature during sensitive developmental periods may result in neuropsychiatric disorders. The visual and auditory networks require patterned sensory signals of light and sound tones, respectively, to strengthen and prune synapses to form functional circuits[103,104]. In parallel, patterns of sensory signals from the mother early in life may influence the sculpting of the reward circuitry. There is evidence suggesting that predictable maternal signals enhance circuit maturation across species[22]. Conversely, unpredictable fragmented maternal care in rats and mice resulted in manifestations of anhedonia and in altered amygdala-PFC connectivity on MRI[20,23,96,105]. Thus, it is tempting to speculate that early-life adversity alters the maturation and function of the reward circuitry via several overlapping mechanisms. First, it leads to upregulation of CRH expression and neurotransmission in several nodes such as BLA-NAc and perhaps others. This aberrant CRH neurotransmission may disrupt the critically balanced combinatorial signaling within the circuit (Figure 4). In addition, aberrant sensory signal patterns during sensitive periods may promote inappropriate synaptic strengthening and pruning within the reward circuit (in analogy to visual and auditory circuits[106,107]) leading to aberrant functional signaling of the reward circuitry later in life (Figure 4).

### **Identifying predictive markers of early life adversity**

The risk of early life adversity resulting in susceptibility to mental illness has led researchers to seek either genetic or epigenetic predictive markers to enable preventative or intervention approaches. For instance, meta-analysis supported an association between telomere length and early life adversity in humans, and further identified that adversity earlier in



development resulted in greater negative effects compared with exposure later[108]. Genetic susceptibility might be conferred by variants in molecules involved in the functions of stress-related hormones. Thus, interactions between FKBP5 and early life adversity have been identified as markers for stress related disorders including post-traumatic stress disorder[109], and as mentioned above, polymorphisms in the CRHR1 gene were associated with greater depressive reactivity to chronic stress in those previously exposed to early life adversity[110].

A key goal in addressing the consequences of early life adversity and especially those that predict vulnerability or resilience to subsequent mental illness is identifying predictive ‘signatures’ of these consequences. In rat, distinct patterns of maternal care resulted in differences in histone acetylation and DNA methylation in stress-regulating targets[111] and BDNF methylation has been identified as a marker of early life adversity[112]. In human neonates, the glucocorticoid receptor promoter was more methylated in newborns exposed to prenatal maternal depression[113,114]. Peripheral indicators of early life adversity via DNA methylation have been identified in numerous studies[111,115,116], and more recently, repeated measurement in the same individual was successful in delineating an epigenetic ‘scar’ of early life adversity[117]. To date, the relevance of such markers for predicting early life adversity-provoked alterations of the reward circuitry is unclear, and longitudinal prospective imaging studies in humans[118,119] might uncover imaging changes that predict pathology associated with dysregulated reward circuitry following this insult.

## Conclusions

There is a strong association between early life adversity throughout infancy and early childhood and the subsequent development of mental illnesses associated with reward circuitry dysfunction. The key challenge is disentangling the preexisting genetic factors from the causal role of adversity and the mechanisms by which it might modify the normal functional and structural maturation of the reward circuitry. This goal is important, because it is required for identifying biomarkers and targets for prevention and intervention.

Experimental animal models and novel circuit technologies are enabling both hypothesis-driven and data driven investigations of these issues. Because adversity activates and influences the brain’s ‘stress system’, focusing on stress-related molecules is reasonable, and is supported by human genomic analyses [84]. The current review focused on aspects of these questions and investigations, highlighting areas of knowledge gaps. Notably, a key challenge is discovering sufficient information about the comparative development of the reward circuitry across species, which will allow for true translation of clinical questions to lab-based mechanistic studies, and to the translation of discoveries in experimental models back to the clinic.

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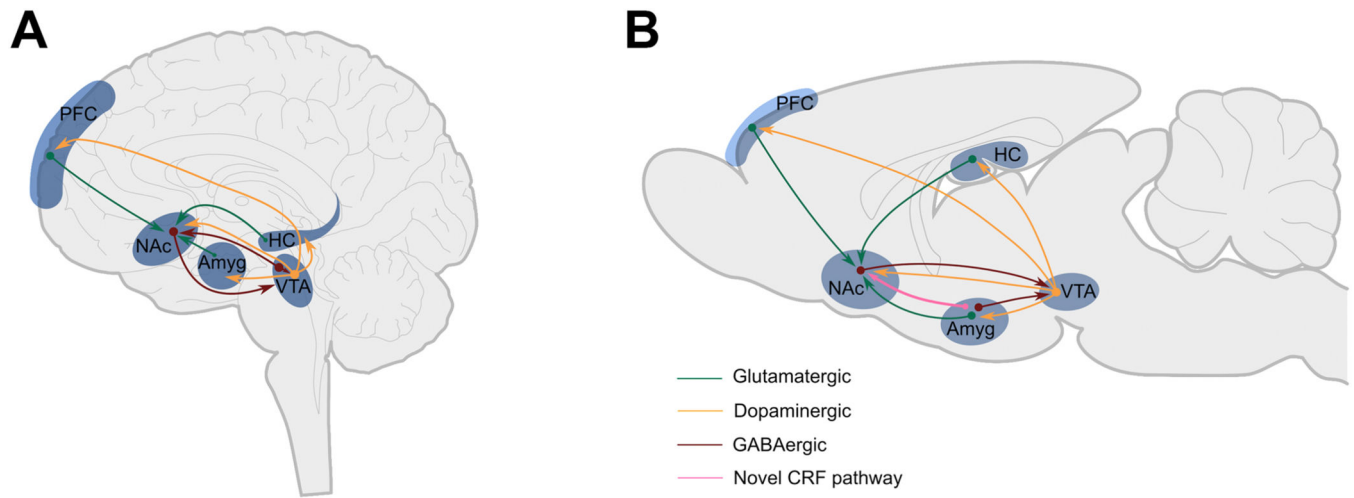


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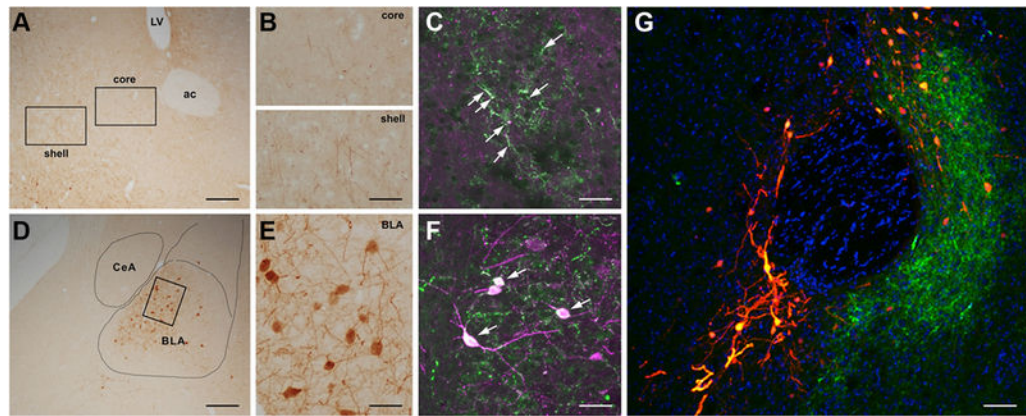


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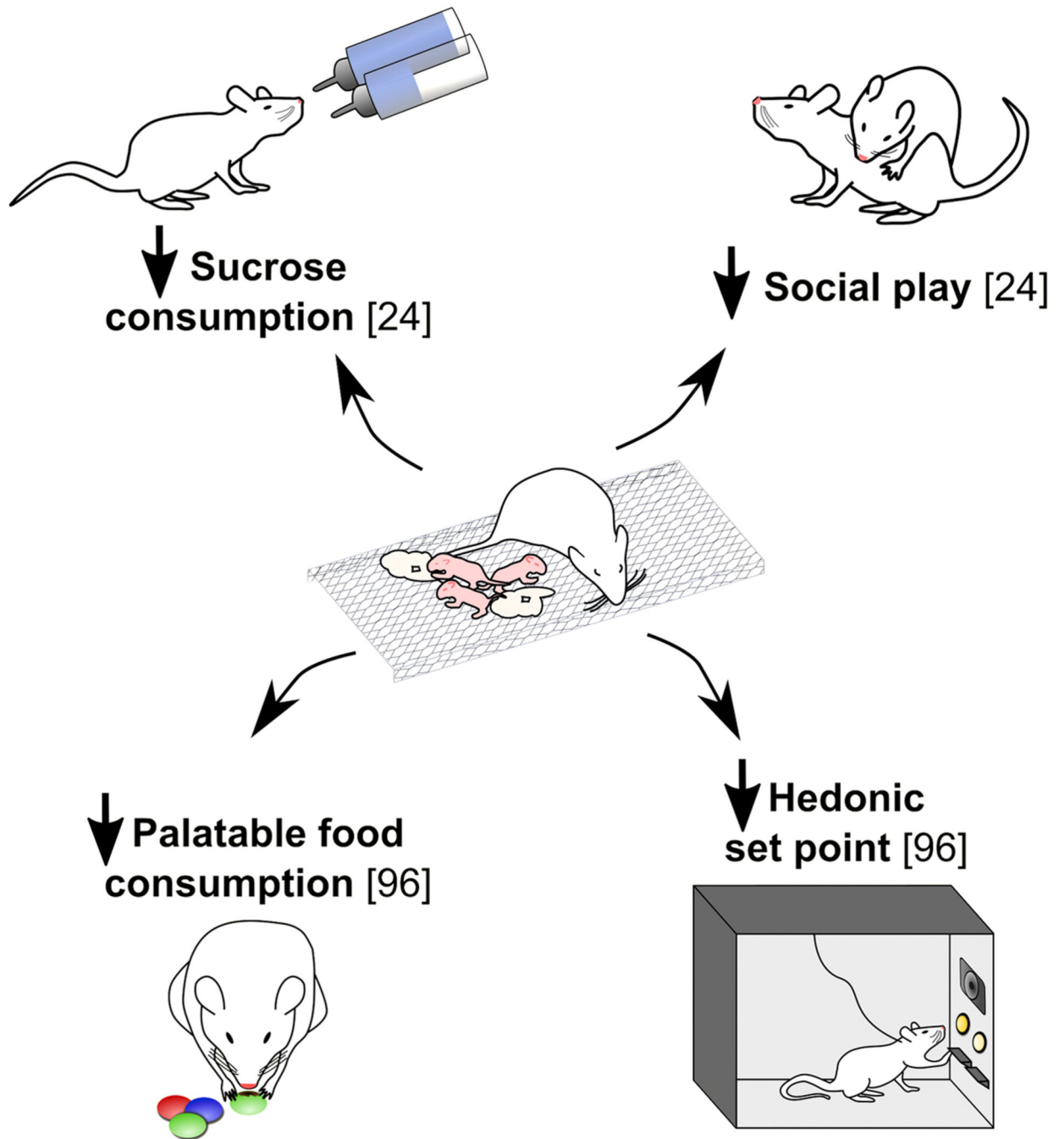
**Figure 1. The reward circuitry in the human and rodent brain.**

A schematic of the known major dopaminergic, glutamatergic and GABAergic connections between the ventral tegmental area (VTA), amygdala (Amyg) nucleus accumbens (NAc), hippocampus (HC) and prefrontal cortex (PFC) in human (A) and rodent (B) brain. The sine qua non of pleasure/reward in this system is a release of dopamine in the NAc from terminals of VTA-origin neurons. The NAc is further innervated by glutamatergic projections from the PFC, Amyg and HC. A CRH+ projection from the BLA to the NAc has recently been identified.



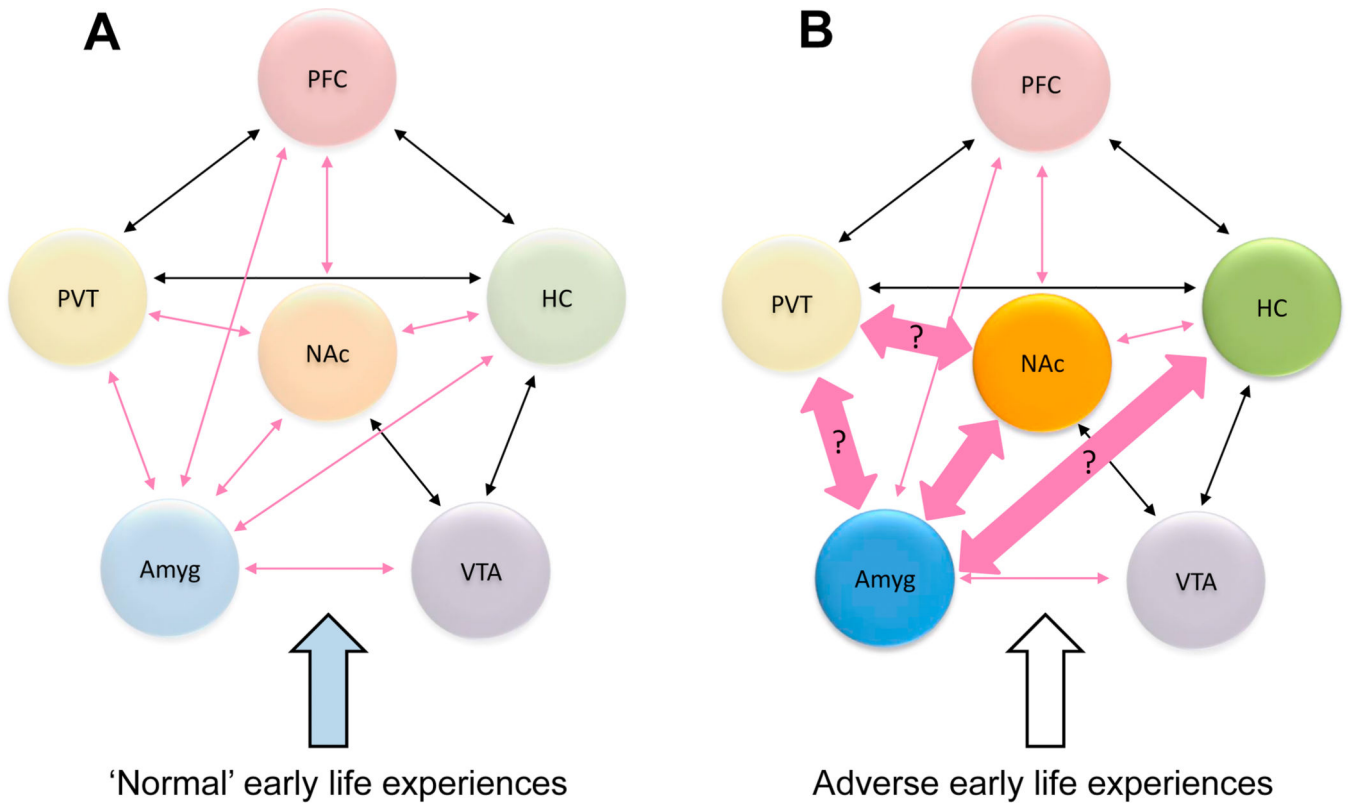
**Figure 2. A CRH expressing pathway between the basolateral amygdala (BLA) and the nucleus accumbens (NAc).**

A Cre-driven retrograde adeno-associated virus (AAV2-retro-CAG-FLEX-tdTomato-WPRE) was injected into the NAc of CRH-IRES-Cre mice. (A) Low and (B) high magnification images of CRH+ fiber terminals in the NAc core and shell. (C) High magnification image of antibody-immunolabeled CRH+ fiber terminals colocalized with virus-labeled CRH+ fiber terminals in the NAc. (D-F) The virus retrogradely labels CRH+ cells in the BLA. (G) A low magnification image of the NAc. The tdTomato reporter is shown in orange, immunostaining to confirm CRH localization is shown in green. The section was counter stained with DAPI (blue). Bar = 200um in (A, D), 80um in (B), 35um in (C, F), 40um in (E) and 60um in (G).



**Figure 3. Early life adversity induces anhedonia.**

Rearing mice and rats in a model of simulated poverty results in adolescent and adult anhedonia. This is apparent as measured by reduced sucrose and M&M consumption, as well as diminished social play and hedonic set point for cocaine.



**Figure 4. Proposed changes to CRH+ connectivity of the reward circuitry following early life adversity.**

(A) Connectivity between nodes of the reward circuitry following normal early life experiences. (B) Early life adversity results in aberrant connectivity of key nodes of the reward circuitry. Black arrows = known connectivity, pink arrows = known CRH+ connectivity. NAc -Nucleus accumbens, Hippo = Hippocampus, VTA = Ventral tegmental area, Amyg = Amygdala, PVT = Paraventricular thalamus, PFC = Prefrontal cortex.

**Table 1.**

The development of the reward circuitry across species

<b>Human</b>	<b>Rodent</b>	<b>Developmental milestone</b>	<b>Reference(s)</b>
<b>Ventral tegmental area</b>			
4 wk gestation (1 <sup>st</sup> trimester)	Rat: E14	Medial forebrain bundle appears	[120,121]
5.5 wk gestation (1 <sup>st</sup> trimester)	Mouse: E8.5 Rat: E12.5	TH detectable in ventral mesencephalon	[122,123]
19 wk gestation (2 <sup>nd</sup> trimester)	Mouse: E16 Rat: E18	VTA DA neurons distinguishable from neighboring groups	[124,125]
<b>Nucleus accumbens</b>			
10 wk gestation (1 <sup>st</sup> trimester)	Rat: E15	Nucleus accumbens appears*	[126,127]
12 wk gestation (1 <sup>st</sup> trimester)	Rat: E15	D1R detectable in striatum	[128,129]
3.5 postnatal months	Rat: P11	Loss of AChE striosomes in NAc	[130,131]
<b>Amygdala</b>			
4 wk gestation (1 <sup>st</sup> trimester)	Mouse: E11 Rat: E13	Amygdala appears*	[132,133]
6 wk gestation (1 <sup>st</sup> trimester)	Rat: E17	Basolateral nuclear group is identifiable	[134,135]
12.5–16 wk gestation (2 <sup>nd</sup> trimester)	Mouse: E11-E15 Rat: E15-E19	Lateral amygdala generation	[133,136]
30 wk gestation (3 <sup>rd</sup> trimester)	Rat: E13	Pyramidal neurons identifiable in basolateral amygdala	[137,138]
<b>Prefrontal cortex</b>			
3.5 years	Rat: P35	Peak PFC synaptic density	[139,140]
17–25 years	Rat: P90	Synaptogenesis and myelination complete	[141]
<b>Connectivity</b>			
8 wk gestation (1 <sup>st</sup> trimester)	Mouse: E10 Rat: E14	Dorsal thalamocortical radiations appear	[142,143]
26–32 wk gestation (3 <sup>rd</sup> trimester)	Mouse: E15 Rat: E16	Thalamocortical afferents reach the cortical plate	[144,145]
<b>Functions</b>			
2 months	Mouse: P3 Rat: P1	Emergence of appetitive learning	[146,147]
Newborn	Rat: P6	Emergence of sucrose preference	[148,149]
9 months-1 year	Rat: P14-P28	Emergence of social play	[150]