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Impact of juvenile chronic stress on adult cortico-accumbal function: implications for cognition and addiction

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Abstract

Repeated exposure to stress during childhood is associated with increased risk for neuropsychiatric illness, substance use disorders and other behavioral problems in adulthood. However, it is not clear how chronic childhood stress can lead to emergence of such a wide range of symptoms and disorders in later life. One possible explanation lies in stress-induced disruption to the development of specific brain regions associated with executive function and reward processing, deficits in which are common to the disorders promoted by childhood stress. Evidence of aberrations in prefrontal cortex and nucleus accumbens function following repeated exposure of juvenile (pre- and adolescent) organisms to a variety of different stressors would account not only for the similarity in symptoms across the wide range of childhood stress-associated mental illnesses, but also their persistence into adulthood in the absence of further stress. Therefore, the goal of this review is to evaluate the current knowledge regarding disruption to executive function and reward processing in adult animals or humans exposed to chronic stress over the juvenile period, and the underlying neurobiology, with particular emphasis on the prefrontal cortex and nucleus accumbens. First, the role of these brain regions in mediating executive function and reward processing is highlighted. Second, the neurobehavioral development of these systems is discussed to illustrate how juvenile stress may exert long-lasting effects on prefrontal cortex-accumbal activity and related behavioral functions. Finally, a critical review of current animal and human findings is presented, which strongly supports the supposition that exposure to chronic stress (particularly social aggression and isolation in animal studies) in the juvenile period produces impairments in executive function in adulthood, especially in working memory and inhibitory control. Chronic juvenile stress also results in aberrations to reward processing and seeking, with increased sensitivity to drugs of abuse particularly noted in animal models, which is in line with greater incidence of substance use disorders seen in clinical studies. These consequences are potentially mediated by monoamine and glutamatergic dysfunction in the prefrontal cortex and nucleus accumbens, providing translatable therapeutic targets. However, the predominant use of male subjects and social-based stressors in preclinical studies points to a clear need for determining how both sex differences and stressor heterogeneity may differentially

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contribute to stress-induced changes to substrates mediating executive function and reward processing, before the impact of chronic juvenile stress in promoting adult psychopathology can be fully understood.

Keywords

Chronic juvenile stress; adolescence; drug reward; executive function; prefrontal cortex; nucleus accumbens

1. Introduction

More than one in five adults report being exposed to repeated instances of abuse or neglect during childhood (Adverse Childhood Experiences Study 2013). Individuals that experience such childhood stressors are at greater risk for the later development of behavioral and psychiatric disorders including attention deficit- hyperactivity disorder (ADHD), anxiety disorders, major depressive disorder, psychosis, substance use disorders and schizophrenia (Copeland et al., 2013; Espejo et al., 2006; Gutman & Nemeroff, 2003; Heim et al., 2008; McFarlane et al., 2005; Merrick et al., 2017; Niemala et al., 2011; Rossow & Lauritzen, 2001; Schilling & Christian, 2014; Seidenfaden et al., 2017; Sigurdson et al., 2014; Trotta et al., 2015; van Dam et al., 2012). The vulnerability to later psychopathology is positively related to the number of abusive/stressful events experienced during childhood, and is further increased by exposure to more than one type of abuse, e.g., emotional combined with physical or sexual abuse (Davis et al., 2001; Merrick et al., 2017; Rehan et al., 2016; Teicher et al., 2006). A central question is how exposure to repeated stressors during childhood translates into such a wide range of symptoms and disorders later in life. We hypothesize that this may be explained by stress-induced changes to brain regions associated with executive function and reward processing, deficits in which are common features of disorders associated with childhood stress.

Here, we sought to test our hypothesis by systematically evaluating published findings regarding the longer-term effects of chronic juvenile stress in both animal models and humans. The term chronic used throughout the review refers to repeated stress exposure (either multiple occurrences of the same stressor or experience of more than one stressor type), and our evaluation of pertinent literature is restricted to studies examining the effect of chronic stress. Juvenile is used here to encompass the pre-adolescent and adolescent stages, often considered within the stress literature as the post-weaning to adulthood period in rodents and ages under 18 years old in humans. Models of pre-weaning stress in rodents, such as maternal separation, were not included in this review. The pre-weaning period of rodents is a unique developmental period, with offspring exhibiting neural development during the first days of life equivalent to that seen in the human third trimester (Dwyer et al., 2009). The pre-weaning period thus represents a time of rapidly changing developmental processes in the rodent brain, which is accompanied by altered hypothalamic-pituitary-adrenal axis sensitivity to stressors (Levine, 2001; Dwyer et al., 2009). Combined with the complexity of the different maternal separation models (Nylander and Roman, 2013; Tractenberg et al., 2016), this means that the consideration of pre-weaning rodent stress

models and their findings requires more detailed consideration than can be given here. For further information in this field, see recent reviews such as Kosten et al., (2012), Nylander and Roman (2013), and Tractenberg et al., (2016).

The goal of this review is to provide an overview of the neural circuitry involved in top-down (executive) control of motivated behavior, along with examples of how aberrations in this functional circuitry as elicited by chronic juvenile stress may contribute to adult psychiatric disorders. To achieve this, we first introduce the concept that symptoms and disorders associated with chronic juvenile stress such as substance use disorders, major depressive disorder, and schizophrenia are typified by profound deficits in executive function and reward behavior. We then introduce brain regions and neurotransmitters associated with executive function and reward behavior, in order to highlight the complexity of the neural mechanisms underlying these behavioral processes, before summarizing the major developmental transitions in brain function and motivated behavior occurring from the juvenile to adult state that could provide targets for stress-induced insult. Finally, we critically evaluate findings from animal models and human studies investigating the impact of chronic juvenile stress on executive function and reward processing and their neurobiological substrates, to provide empirically-derived insight into how early-life stress increases the risk for neuropsychiatric illness in adulthood and to identify gaps in current knowledge that should be addressed by future research.

2. Childhood stress and later psychiatric illness – a function of disruption to executive function and reward processing?

Repeated exposure to stress during childhood may increase risk for a wide range of symptoms and disorders later in life due to disruption in the interplay between executive function and reward sensitivity. Executive function encompasses the higher order cognitive processes largely mediated by the prefrontal cortex (PFC), which are critical for maintaining a balance of behavioral focus and flexibility necessary to meet the demands of the current situation, and include working memory, attention, impulse control, and decision-making (Holmes & Wellman, 2009; Logue & Gould, 2014; Testa & Pantelis, 2009). Executive function is also essential for reward processing, allowing pursuit of reward when availability is indicated, but inhibiting goal-seeking behavior when reward contingencies change, such as when previously learned cues are either no longer predictive or value decreases in relation to the effort required to obtain the reward (Perry et al., 2011; Arnsten & Rubia, 2012; see Section 3.2). Notably, varying degrees of impairment in both executive function and reward processing are a common feature of the psychiatric disorders associated with childhood stress (e.g., Brown, 2008; Etkin et al., 2013; Green, 2006; Lewandowski et al., 2016; Whitton et al., 2015). As an example, working memory and other executive function deficits are seen in ADHD, substance abuse and other addictive disorders, bipolar disorder, major depressive disorder, and schizophrenia (Brown, 2008; Craig et al., 2016; Crews & Boettiger, 2009; Cullen et al., 2016; Etkin et al., 2013; Grant & Chamberlain, 2014; Kuswanto et al., 2016; Leeman et al., 2014). Furthermore, disrupted reward processing as a function of diminished executive processes is demonstrated in individuals with major depressive disorder (Whitton et al., 2015), who show deficits in working memory, sustained attention,

and task switching (Etkin et al., 2013). These factors combine to cause difficulty in the ability to change behavior in response to altered reward contingencies, resulting in a reduced reward anticipation and unwillingness to engage in effortful goal pursuit that is thought to promote the anhedonic state associated with depression (Whitton et al., 2015).

Schizophrenia, on the other hand, appears not to encompass a dichotomous extreme of reward hypo/hypersensitivity, but rather represents impairments in the ability to assign salience to relevant reward cues (Whitton et al., 2015). Thus, schizophrenic patients show difficulty in learning relevant cues and instead allocate greater attention to irrelevant stimuli, which one study found to be directly correlated with the degree of positive (psychotic, e.g., delusions, hallucinations) symptoms (Morris et al., 2012). Impairments in predicting the effort required to achieve goals of varying magnitude are also seen in schizophrenia, particularly in patients presenting with negative symptoms (e.g., flat affect, lack of motivation) (Fervaha et al., 2013; Gard et al., 2014; Gold et al., 2013). Diminished executive function (attention, working memory, flexibility etc.) in schizophrenics is also correlated with deficits in reward discrimination (Lewandowski et al., 2016). Combined, this lends support to the hypothesis that failure to update information about changes in reward cue salience in schizophrenia results from ineffective top-down modulation by the PFC of subcortical reward pathways.

Finally, disrupted cortical control of reward behavior appears to be fundamental to substance use disorders, which are characterized by a preference for impulsive choices in favor of an immediate or strongly reinforced reward, along with an inability to inhibit impulsive pre-potent conditioned motoric responses despite changes in reward contingency (Crews & Boettiger, 2009; Grant & Chamberlain, 2014; Perry et al., 2011). Interestingly, such increased impulsive choice and decreased response inhibition is characteristic across not only substance use disorders (MacKillop et al., 2011) but also appears to be a core feature of behavioral addictions such as pathological gambling (Grant & Chamberlain, 2014).

3. Nucleus accumbens and prefrontal cortex - Modulation of executive function and reward behavior

The learning of and response to reward-associated stimuli is largely mediated by the mesolimbic system, with dopamine activity in the ventral striatum/nucleus accumbens (NAc) playing a pivotal role in the evaluation of stimulus salience (Berridge & Kringelbach, 2013; Wickens et al., 2007). However, fine-tuning of activity in this system is provided by input from various PFC regions (Perry et al., 2011; Arnsten & Rubia, 2012). As discussed below, this PFC mediation of NAc activity is critical for allowing reward-directed behaviors to be expressed in a manner appropriate to both the current and future situations.

3.1 Nucleus accumbens and reward

Afferents from the ventral tegmental area (VTA) release dopamine in the rodent NAc in response to presentation of either unconditioned reward or reward-associated stimuli (Berridge & Robinson, 1998), which in turn promotes goal-directed behavior (Grace et al., 2007). Accumbal dopamine appears to facilitate the formation of associations between

reward-related stimuli and incentive salience in both rodents and primates (Berridge & Robinson, 1998; Berridge et al., 2009), which presumably increases the likelihood that future perception of these cues will promote and maintain instrumental behavior necessary for obtaining the reward.

The mammalian NAc is divided both anatomically and functionally into core and shell regions (Fig. 1). Both contribute to reward-related behavior, with the NAc shell being most implicated in motivation and reward sensation, while the core contributes to reward cue learning/evaluation and initiation of goal-directed movement (Schofield et al., 2016; Sellings & Clarke, 2003; Sesack & Grace, 2010). The bulk (~90–95%) of neurons in both subregions of the NAc are GABAergic medium spiny neurons (MSN), which are segregated by dopamine receptor type (D₁ vs D₂) and neuropeptide (dynorphin/substance P vs enkephalin/neurotensin) co-expression (Schofield et al., 2016). In general, reward behavior appears to be enhanced by D₁-type MSNs but diminished by activation of D₂-type MSNs (Schofield et al., 2016). The actions of dopamine on the MSNs are modulated by excitatory glutamatergic afferents from cortical and allocortical areas, along with input from local cholinergic and GABAergic interneurons (Schofield et al., 2016), although the exact source of the cortical projections differs according to accumbal subregion (Perry et al., 2011; Schofield et al., 2016; Sesack & Grace, 2010). Both the NAc core and shell also receive excitatory input from the basolateral amygdala (BLA) and ventral hippocampus (Schofield et al., 2016). Output from the GABAergic NAc MSNs is mediated largely through the ventral pallidum, with some direct innervation of midbrain structures such as the lateral hypothalamus, subthalamic nucleus and the VTA (Sesack & Grace, 2010). The ventral pallidum in turn provides inhibitory GABAergic input to midbrain regions such as the lateral hypothalamus, subthalamic nucleus and mediodorsal thalamus, while also sending excitatory cholinergic (and some glutamatergic) afferents to the PFC and BLA (Root et al., 2015). The position of the NAc in this complex distributed network thus facilitates integration of cognitive and appetitive/motivational information with activity in motor pathways to mediate appropriate expression of goal-directed behavior, with dopamine activity playing a pivotal role.

Accumbal dopamine release can also be modulated by activation of serotonin receptors located either on VTA dopamine cell bodies or on dopaminergic and glutamatergic terminals and GABAergic interneurons in the NAc, with dopamine release being facilitated by 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT₃, and 5-HT₄ receptors and inhibited by 5-HT_{2C} receptors (Alex & Pehek, 2007). Similarly, norepinephrine from afferents arising in the locus coeruleus and nucleus of the solitary tract can increase dopamine release in the NAc shell via α_1 adrenergic receptors (Mitrano et al., 2012; Sesack & Grace, 2010). The serotonergic and adrenergic systems are highly responsive to stress-associated neuroendocrine activity (Dunn et al., 2004; Forster et al., 2006; 2008; Watt et al., 2007), offering a means by which accumbal dopamine activity and reward behavior can be modulated through perception and integration of the degree of stress associated with a particular context.

3.2 Prefrontal cortex and executive function

The mammalian PFC is critical for mediating executive function, such as regulation of attention, behavioral flexibility, decision making, impulsivity, planning, and working

memory (Logue & Gould, 2014). Distinct subregions of the PFC mediate different aspects of executive function (see Fig. 1; Arnsten & Rubia, 2012; Bari & Robbins, 2013; Hillman & Bilkey, 2010; Perry et al., 2011; Zeeb & Winstanley, 2011; Zeeb et al., 2015). For example, activity in the primate dorsolateral PFC (dlPFC), homologous to the rodent medial PFC (mPFC) (Seamans et al. 2008; Uylings et al. 2003), is observed during attentional processing, working memory, resolution of conflicting decisions, delay discounting, and cognitive flexibility (Arnsten & Rubia, 2012; Perry et al., 2011). On the other hand, the anterior cingulate cortex (ACC) regulates self-monitoring of internal state, cost-benefit discrimination learning and temporal assessment (Arnsten & Rubia, 2012; Perry et al., 2011) and the orbitofrontal cortex (OFC) appears to be primarily required for inhibition of pre-potent actions, reversal learning, and outcome prediction (Perry et al., 2011).

Recruitment of executive function as mediated by these PFC subregions is critical in directing the nature of goal-oriented behavior. Specifically, within a given context a choice must be made between yielding to impulsive choice for an immediate reward of small value vs. waiting for a delayed larger reward, while also either allowing or actively inhibiting pre-potent conditioned actions in favor of alternative strategies. This combination of delay discounting and behavioral flexibility is thought to allow the individual to control expression of goal-directed behavior according to changing contingencies in reward predictability, timing, and action outcome (Dreher, 2013; Kalenscher et al. 2006; Peters & Buchel, 2011). For instance, effective delay discounting requires the ability to focus attention while maintaining and updating task-relevant information (working memory, as mediated by the dl/mPFC), combined with the capability to inhibit inappropriate thoughts and actions (OFC-mediated) while evaluating reward value in comparison to internal motivational state (ACC-mediated). Further, a reduction in reward outcome signaled by a previously salient stimulus would promote discontinuation of the conditioned response in favor of attending to a different cue that now predicts reward (reversal learning, OFC-mediated), and/or adopting a different strategy to obtain the reward (behavioral flexibility/strategy shifting, dl/mPFC-mediated). Thus, modulation of reward behavior as a whole can be considered to be the result of a combination of executive processes, and so theoretically will depend upon graded activity in all regions of the PFC.

3.3 Interactions between prefrontal cortex and the mesoaccumbal pathway

The capacity for the PFC to exert top-down control over motivation and reward processing is principally mediated through excitatory projections to posterior cortical and subcortical regions (Arnsten & Rubia, 2012). Glutamatergic afferents from intratelencephalic and pyramidal cells in the PFC can modulate subcortical dopamine activity directly through monosynaptic connections with VTA dopaminergic cell bodies and/or NAc dopamine terminals, or indirectly via polysynaptic connections with other neurotransmitter systems that impinge upon the mesolimbic dopamine pathway (Buschman & Miller, 2014; Challis & Berton, 2015; Shepherd, 2013). Long-range GABAergic projections from the mPFC to the NAc shell in mice have also been recently identified, activation of which induces acute place avoidance (Lee et al., 2014), suggesting that the mPFC can influence reward-oriented behavior by directly inhibiting activity in the NAc. Excitatory afferents from the rat PFC have opposing effects on VTA dopamine neurons depending on their source, with those from

the infralimbic mPFC augmenting activity via direct connections to dopamine cell bodies, while projections from the OFC dampen firing by targeting inhibitory GABAergic neurons in the VTA (Lodge, 2011). Similarly, output from the PFC has a dichotomous effect on reward behavior depending on the target of innervation, with conditioned reward seeking being promoted by activation of PFC to NAc projections but inhibited by PFC-thalamus neurons (Otis et al., 2017). In turn, PFC activity is modulated by excitatory input from the ventral hippocampus and amygdala, along with monoaminergic afferents from cell bodies in the VTA, dorsal raphe, and locus coeruleus (Dembrow & Johnston, 2014; Riga et al. 2014; Robbins & Arnsten, 2009; Vertes et al., 2006).

Monoamine influence over PFC function appears especially important in regulating many of the aspects of executive function that contribute to reward processing and goal-directed behavior. For instance, attentional focus and working memory are heavily dependent on optimal adrenergic and dopaminergic activity in the primate dlPFC and rodent mPFC, as derived from the locus coeruleus and VTA, respectively. Specifically, activation of adrenergic α_2 receptors increases signal strength in PFC networks relevant to the task, while dopamine D_1 receptors act to decrease noise from competing non-relevant networks (Arnsten & Rubia, 2012; Robbins & Arnsten, 2009). Performance in sustained attentional focus and working memory tasks typically follows an inverted-U shaped curve of catecholamine release in the PFC, being impaired by either reduced or excessive norepinephrine and dopamine levels (Arnsten & Rubia, 2012). For example, working memory performance is reduced under conditions of low adrenergic signaling in the PFC (Berridge & Spencer, 2016), an effect replicated by blockade of α_2 receptors in the primate dlPFC (Li & Mei, 1994). Similarly, deficits in working memory are observed following pharmacological (Bubser & Schmidt, 1990; Clinton et al., 2006) or stress-induced reductions in mPFC dopamine activity (Mizoguchi et al., 2000; Novick et al., 2013), and poor performance at times when dopamine activity is low is rescued by intra-mPFC infusion of D_1 receptor agonists (Floresco & Phillips, 2001). At the other end of the curve, impairments in working memory are caused by pharmacological overstimulation of D_1 receptors in the rat mPFC (Zahrt et al., 1997) or by stress exposure (which is known to increase PFC catecholamine release, e.g., Finlay et al., 1995; Watt et al., 2014), and performance is restored by prior administration of D_1 receptor antagonists given either systemically or directly into the mPFC (Arnsten, 2009). Likewise, stress-induced increases in PFC norepinephrine appear to shift the balance of adrenergic receptor activation from high affinity α_2 receptors (which enhance working memory, Birnbaum et al., 2000) to low affinity α_1 receptors that impair performance (Birnbaum et al., 1999).

The role of dl/mPFC D_2 receptors in working memory is less clear, with some studies either showing no effect (Seamans et al., 1998; Sawaguchi and Goldman-Rakic, 1994; Romanides et al., 1999) or a disruptive effect of D_2 receptor activation (Druzin et al., 2000). In contrast, adopting alternative strategies to obtain reward (set shifting) requires a balance of activation between D_1 and D_2 receptors in the rodent mPFC (Floresco, 2013). Antagonism of either α_2 or D_2 receptors in the rat OFC and ACC increases impulsive choice (Perry et al., 2011; Zeeb et al., 2010), while reduced serotonergic activity in the OFC and ACC is associated with impaired reversal learning and impulsive choice, respectively (Perry et al., 2011; Robbins & Arnsten, 2009). The ability to inhibit impulsive motoric actions, e.g., perseverating with a

conditioned response when cues no longer predict reward, appears to require a balance of 5-HT₂-like receptor activation between the mPFC and OFC, along with α_2 receptor stimulation in the OFC (Perry et al., 2011). In addition, shifting between maintenance of a conditioned reward response and strategy switching appears to depend on a balance of allocortical (specifically hippocampal) vs. mPFC excitation of the NAc, respectively, which is further governed by differential activation of accumbal D₁ and D₂ receptors (Goto & Grace, 2005).

Combined, these findings highlight the incredibly complex modulation of PFC activity and functional output as required to achieve fine-tuned top-down control of NAc-mediated reward behavior. Collectively, the literature suggests a balance of different executive functions as regulated by activity in specific PFC subregions is necessary for learning and maintaining conditioned behavior when reward is positively reinforced, while permitting behavioral flexibility when formerly predictive cues become irrelevant or conditioned responses are no longer contextually appropriate. Hence, the disruption of any PFC-mediated executive function could have serious ramifications for reward behavior, leading to maladaptive perseveration of impulsive choice and actions, or conversely, an inability to resolve conflicting decisions regarding alternative goal-directed actions to choose the most optimal strategy.

4. Development of executive control and reward-processing

The mammalian brain continues to undergo major developmental changes from birth to adulthood. These changes are especially pronounced in the juvenile brain during adolescence, particularly in cortical regions responsible for executive function and top-down control of motivation/reward responding. Details of the neural changes occurring in the juvenile brain are meticulously reviewed in Brenhouse & Andersen (2011), Crews et al. (2007) and Spear (2000). The major neuronal changes occurring in both the human and rat PFC and NAc as relevant to executive function and reward behavior are depicted in Figure 2. In brief, subcortical structures such as the mesolimbic dopamine system mature before cortical regions, with the PFC not reaching its final state until early adulthood (Giedd et al., 2004; Gogtay et al., 2004). This is reflected in changes to gray matter volume, which in the human NAc declines steadily in a linear fashion from childhood (approximately 7 years old) onwards (Wierenga et al., 2014; Fig. 2). In contrast, gray matter in the PFC follows a curvilinear developmental trajectory, such that maximal volumes are not attained until between 11 and 12 years of age (Giedd et al., 2004; Fig. 2), with reductions in volume then continuing into the mid-20's in subregions such as the dlPFC (Lenroot & Giedd, 2006). Conversely, white matter connectivity, both within the human PFC and between the PFC and striatal regions (including the NAc), increases linearly with age (Asato et al., 2010; Lenroot & Giedd, 2006; Whitaker et al., 2016; Fig. 2). Importantly, these connections do not mature until early adulthood (Asato et al., 2010; Whitaker et al., 2016), suggesting intra- and inter-PFC communication is at a suboptimal level in the juvenile brain. Dynamic reorganization of neurotransmitter systems within the human and rodent PFC and NAc also occurs during the adolescent portion of juvenile development, as reflected in the increased production and progressive elimination of synapses and receptors (pruning) seen in the monoaminergic pathways of the limbic system (Andersen, 2003; Dinopoulos et al., 1997).

There are distinct periods within rodent neural development that correspond with human juvenile periods, with the rat postnatal (P) days 21–28 considered pre-adolescence and P29–56 corresponding to adolescence (Lukkes et al., 2009a; Spear, 2000). In the rat mesocorticolimbic dopamine system, PFC concentrations of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) increase sharply from early to mid-adolescence (P30–45) (Chen et al., 1997; Fig. 2). Expression of dopamine D₁ and D₂ receptors also peaks at this time prior to pruning to adult levels (Fig. 2), with the reduction in dopamine receptors being developmentally delayed in the PFC compared to the NAc (Andersen et al., 2000; Brenhouse et al., 2008; Tarazi et al., 1998; Fig. 2). Related developmental alterations in mPFC presynaptic dopamine D₂ autoreceptor function also occur during adolescence. Specifically, these autoreceptors lose the ability to inhibit dopamine synthesis (Andersen et al., 1997), which combined with the increased expression of postsynaptic dopamine receptors may assist in maintaining an enhanced dopamine tone in the adolescent PFC. Of particular relevance to goal-directed behavior is the transient increase in dopamine D₁ receptors seen on mPFC excitatory projections to the NAc (Fig. 2), which appears to enhance salience attribution towards rewarding cues in adolescent rats (Brenhouse et al., 2008). Remarkably, expression of dopamine D₁ receptors in the human PFC also peaks in mid- to late adolescence (Weickert et al., 2007; Fig. 2), and reward anticipation elicits greater activity in the ventral striatum of human teenagers relative to both children and adults (Galvan 2010; Fig. 2). This enhanced ventral striatum response appears tied to teenage preferences for specific types of reward, with greater activity being elicited by stimuli associated with social attractiveness and risky behavior (Guyer et al., 2009; Galvan 2010; Fig. 2). Like humans, rodents also show peak social activity and novelty seeking/risk taking during adolescence (Douglas et al., 2003, 2004; Spear, 2000; Fig. 2). Together, this raises the intriguing possibility that the heightened reward salience attributed to social contact and sensation seeking in adolescents of both species is a function of increased D₁ receptor-mediated PFC output to the NAc/ventral striatum.

The delayed maturation of the PFC also has a functional effect on aspects of executive function that contribute to reward behavior. For instance, inhibitory control, working memory, and decision making continue to develop throughout human adolescence, with maximal performance appearing in late adolescence/early adulthood (Blakemore & Choudhury, 2006). This appears to follow the continuing maturation of white matter connections between the PFC and striatal regions and within the PFC itself (Asato et al., 2010; Whitaker et al., 2016). Understandably, this means that effective top-down control of reward processing and the ability to modulate reward behavior in a contextually-appropriate manner will also be developmentally delayed.

Combined, the available literature strongly suggests that the juvenile brain will be highly vulnerable to disruption by stressful experiences. This appears particularly the case during early to mid-adolescence, when the reorganization of the mesocorticolimbic dopamine system and salience for rewards associated with novelty and reward are both at peak levels. However, it is unclear if both social (e.g., aggression, isolation, change in peer group structure) and non-social (e.g., injury, nutritional deprivation, environmental disturbance) stressors result in similar perturbations to PFC and NAc function and associated behavioral expression that are evident in adulthood. Further, the majority of preclinical studies have

been conducted with male subjects, making it uncertain as to whether stress exposure during this sensitive period has comparable long-lasting effects in each sex. The following sections will attempt to answer these questions by comprehensively reviewing human and animal studies that examine the effects of chronic stress exposure over the pre- and adolescent period (collectively termed juvenile stress) on executive function and reward processing, and their neurobiological substrates, in adulthood.

5. Impact of chronic juvenile stress on prefrontal cortex and executive function

Long-lasting effects of chronic juvenile stress on adult PFC structure and function are observed both in animal models (Table 1) and humans (Table 2). The evidence points to reduced PFC activity in adult individuals with experience of juvenile stress, a finding that aligns with impairments in executive function reported by many animal and human studies (Tables 3–4). In terms of animal models, alterations to adult PFC monoaminergic function following chronic juvenile exposure to social stressors have been most commonly studied, with the majority showing reduced monoamine levels and alterations to autoreceptors and transporters that would indicate reduced monoaminergic function in the PFC (Table 1). This is particularly true of dopaminergic transmission in the PFC (e.g., Baarendse et al., 2013; Burke et al., 2010; 2013; Heidbreder et al., 2000; Novick et al., 2011; Watt et al., 2009; 2014; although see Han et al., 2011a). Whether monoaminergic activity in the adult PFC is similarly affected by repeated exposure to non-social juvenile stressors is not as clear, given the relatively few studies in this area (Table 1). Marquez et al. (2013) reported that predator odor and elevated platform exposure from P28–42 increased monoamine oxidase A and serotonin transporter levels in the adult mPFC and OFC, which could result in reduced monoaminergic transmission in these regions. However, a non-social mixed stressor paradigm over a similar developmental period actually increased dopamine content in the adult mPFC (Luo et al., 2014). Overall, studies using animal models indicate that monoaminergic activity in the adult PFC is reduced following experience of chronic social stress over the juvenile period, but further research is needed to understand whether non-social juvenile stress has equivalent or divergent impacts on monoaminergic function in the PFC.

Interestingly, both social and non-social chronic juvenile stress within animal models appear to result in reduced capacity for NMDA-dependent synaptic plasticity in the adult PFC (Table 1; Leussis et al., 2008; Negron-Oyarzo et al., 2014; 2015; Quan et al., 2010). Decreases in markers of glutamatergic signaling and dampened PFC excitability are also noted (Ishikawa et al., 2015; Novick et al., 2016; Ver Hoeve et al., 2014; Zhao et al., 2009). Given the requirement of NMDA receptor-mediated activity within PFC circuits during cognitive tasks (Arnsten & Rubia, 2012), this would presumably result in less recruitment of the PFC as required for effective top-down control. In support of this, reduced neural activity within the PFC when performing a variety of executive function tasks is commonly observed in human adults reporting experience of chronic juvenile stressors (Table 2; e.g., Casement et al., 2015; Fonzo et al., 2016; Philip et al., 2013b; 2016). However, chronic juvenile stress is also associated with increased brain-derived neurotrophic factor (BDNF) in the PFC of

adult rats (Table 1; Han et al., 2011b; Meng et al., 2011; Shao et al., 2013), which is surprising given that reduced gray matter, reduced dendritic length or elaboration, and reduced plasticity are often observed in the adult PFC following juvenile stress in both humans and animal models (Tables 1 & 2). Whether upregulation of BDNF in the adult rat PFC following chronic juvenile stress reflects a compensatory mechanism in response to the reduced structural and neurophysiological capacity for plasticity in this brain region is a hypothesis that requires further testing.

Given reduced neural activity, diminished capacity for synaptic plasticity and dampened dopaminergic function in the adult PFC following chronic juvenile stress, it is not surprising that both animal and human studies show that repeated juvenile stress is associated with impaired executive function in adulthood (Tables 3 & 4). In animal models, these impairments are especially apparent if either social defeat or prolonged social isolation is experienced during early to mid-adolescence, and are commonly observed in measures of working memory in the radial arm maze, T-maze, and object recognition paradigms, in measures of inhibitory control within the 5-choice serial reaction time and rodent gambling paradigms, and in pre-pulse inhibition (Table 3). Similar deficits in working memory and inhibitory control are noted in human studies (Table 4; although see Feeney et al., 2013), with some indication that selective attention may also be impaired in adults reporting chronic exposure to juvenile stressors (e.g. Schalinski et al, 2017; Viola et al., 2013, although this latter study was complicated by simultaneous treatment for crack cocaine use). As discussed in section 3.2, these facets of executive function are dependent on PFC function. Therefore, it appears that the long-lasting effects of chronic juvenile stress exposure on executive function, particularly when experienced during early to mid-adolescence, are a direct result of reduced PFC activity in adulthood. We posit that this reduction in PFC activity result in part from over-activation of negative feedback mechanisms designed to restore PFC homeostasis following stressful events. For instance, increased PFC dopamine release is a normal response to stress exposure as measured in animal models (e.g., Nagano-Saito et al., 2014; Tidey & Miczek, 1996; Watt et al., 2014), but prolonged increases are detrimental to executive function (see section 3.2). However, repeated activation of restorative mechanisms may result in a hypofunctional state, especially if these continue to operate in the absence of further stress. This idea is supported by studies showing that deficits in adult mPFC dopamine caused by adolescent social defeat of rats can be prevented by pharmacological blockade of release-inhibiting D₂ autoreceptors in the mPFC during the defeat experience (Watt et al., 2014), and the finding that rats defeated in adolescence exhibit increased function of dopamine transporters in the mPFC (i.e., increased dopamine clearance) as adults (Novick et al., 2015). Such changes to regulatory mechanisms of neural activity suggest that chronic juvenile stress irreparably disrupts the normal trajectory of PFC development, and may explain why deficits in PFC function and cognition are evident in adulthood, well beyond the stress experience.

6. Impact of chronic juvenile stress on nucleus accumbens and reward processing

Findings related to the effects of chronic juvenile stress on adult accumbal dopamine levels or function are mixed (Table 5). Social isolation during juvenile development increases basal and stimulated dopamine levels in the NAc of adult rats, and increased D₂ receptor expression in the NAc is also often noted (Djouma et al., 2006; Fulford and Marsden, 1998; Han et al., 2011a; 2012; Karkhanis et al., 2014; Shao et al., 2009). Social defeat of rats in adolescence similarly increases both D₂ receptor expression and amphetamine-evoked dopamine tissue content in the NAc – in this case specifically in the core (Burke et al., 2010, 2011) - but the majority of findings in animal models of adolescent defeat fail to show altered dopamine levels in the NAc (Table 5). The disparity between effects of chronic social isolation vs defeat may be due to differences in the developmental time-frame in which each stressor is applied, with isolation typically initiated in pre-adolescence and continued through to adulthood, whereas social defeat was applied for a very specific time period over mid-adolescence (P35-39; see Table 5). Therefore, long-lasting changes to DA activity in the NAc may be more likely when chronic stress exposure occurs over a period encompassing pre/early adolescence. It should be noted that there is a paucity of information regarding the effects of non-social juvenile stressors on adult accumbal dopamine function, so it is not clear whether effects noted to date are specific to social stress.

Despite ambiguities in whether dopamine function is altered in the adult NAc following juvenile stress in the different social stress paradigms, it is clear that the reinforcing effects of drugs of abuse are enhanced in adulthood across all animal models of chronic juvenile social stress (Table 6). The few studies that have investigated effects of juvenile social stress on food-based reward behavior in adulthood have produced mixed results, finding either no effect (Novick et al., 2013) or increased seeking of palatable rewards (Coppens et al., 2012; Cumming et al., 2012), which may be a function of the types of social stress used and the age at which they were applied. Very few studies have examined the impact of chronic juvenile non-social stressors in animals, with repeated foot shock stress during adolescence failing to alter amphetamine conditioned place preference in adult rats (Burke et al., 2011). In contrast, chronic unpredictable non-social stress applied over the same time period increases ethanol intake in both adult male and female mice (Lopez et al., 2011). It could be hypothesized that the unpredictable nature of both social stressors and chronic unpredictable non-social stress is critical to the enhanced drug reinforcement observed in adulthood, but this requires further testing.

While the enhancement of drug reinforcement is observed in the overwhelming majority of studies of chronic juvenile social stress in animal models, effects on the locomotor-stimulating properties of drugs are not as clear-cut. Chronic juvenile social stress is reported to either increase, decrease or have no effect on stimulant-induced locomotion in rodents (Table 6). This suggests that the impact of chronic juvenile social stress may dissociate between the reinforcing and locomotor-stimulating effects of drugs of abuse.

Clinical studies indicate a strong positive relationship between repeated adverse childhood experiences and substance use disorders in adulthood (Fuller-Thomson et al., 2016; Gerra et

al., 2016; Giordano et al., 2014; Koskenvuo & Koskenvuo, 2015; LeTendre & Reed, 2017; Merrick et al., 2017; Rossow & Lauritzen, 2001). In the small number of clinical studies that have examined accumbal function in either human adolescents or adults reporting experiences of repeated social and non-social juvenile stress, hypoactivity of the NAc in response to either reward-related stimuli or reward anticipation is observed (Goff et al., 2013; Boecker et al. 2014; Corral-Frias et al., 2015; Hanson et al., 2015, 2016; but see Casement et al., 2014). Initially this would appear to stand in contrast both to the greater incidence of substance abuse disorders seen in victims of childhood stress, and to the increased dopamine activity in the NAc seen in some chronic juvenile stress animal models as discussed above (Table 5). This may be partially explained by likely inherent differences between accumbal responsiveness to drugs of abuse as employed in animal studies, and to the anticipation of monetary-based reward as is typically utilized in human experiments. However, it should be noted that the studies showing blunted accumbal responses to reward following chronic juvenile stress also found that NAc hypoactivity strongly predicted symptoms of anhedonia and depression (Goff et al., 2013; Boecker et al. 2014; Corral-Frias et al., 2015; Hanson et al., 2015). Moreover, anhedonia in participants exposed to repeated juvenile stress was linked to problematic alcohol use arising from the use of substances as a coping mechanism (Corral-Frias et al., 2015). Interestingly, hyperactivity of the NAc in response to amphetamine has been reported in individuals who experienced juvenile stress, with the strength of activation being positively correlated with the degree of stress exposure (Oswald et al., 2014). Combined, the results of these studies suggest that substance abuse following chronic juvenile stress in humans may result, in part, either from attempts to alleviate blunted NAc activity associated with anhedonic states, or from heightened accumbal responses upon drug consumption.

Regardless of differences in accumbal activity, the behavioral effects of chronic juvenile stress in animal models clearly translate to human experiences, with exposure to repeated childhood stress increasing risk for substance use disorders in both adult men and women (Kessler et al., 2010; LeTendre & Reed, 2017; Merrick et al., 2017; Newcomb and Harlow, 1986; Pesonen et al., 2012). Future work should focus on elucidating the mechanisms by which chronic juvenile stress affects accumbal function, and how this relates to increased sensitivity to the reinforcing properties of drugs of abuse.

7. Conclusions and future directions

It is clear that in both human and animal studies, chronic juvenile stress is associated with deficits in executive function along with enhanced drug reinforcement. Impaired executive function and altered reward sensitivity are shared among many psychiatric disorders such as substance abuse/addiction, depression, anxiety disorders and schizophrenia (Brown, 2008; Etkin et al., 2013; Green, 2006; Grant & Chamberlain, 2014; Lewandowski et al., 2016; MacKillop et al., 2011; Whitton et al., 2015). Reduced activity in the PFC and NAc during tasks such as delay discounting and reward contingency/reversal learning is also seen in these disorders (Culbreth et al., 2016; Hall et al., 2014; Hoffman et al., 2008; Miedl et al., 2012; Pizzagalli et al., 2009; Schlagenhauf et al., 2014). Therefore, it is likely that long-lasting reductions in PFC function combined with poor top-down regulation of subcortical areas like the NAc are neurobiological substrates linking the effects of repeated childhood

stress with neuropsychiatric symptoms in later life (Fig. 3). Restoration of PFC function, particularly of monoaminergic and glutamatergic activity as discussed in earlier sections, would thus appear to be an important goal for a more comprehensive treatment for the neuropsychiatric consequences of repeated childhood stress exposure.

These conclusions are somewhat tempered by the observation that the majority of animal literature informing our understanding of these mechanisms has been conducted in male rodents. Hence, there is a pressing need for future work to determine whether similar neural bases of the negative consequences of chronic juvenile stress exist for both males and naturally reproductively-cycling females. In addition, the majority of preclinical studies assessing the effects of pre- and adolescent stress exposure on later executive function and reward processing are conducted using social-based stressors. Furthermore, human studies rarely either distinguish the different types of stressors experienced by participants or establish the precise age of stress exposure (Tables 2 & 4; but see Schalinski et al., 2017). Additional confounds arise from differences between preclinical and clinical studies in the type of reward used to assess changes in reward processing following juvenile exposure to chronic stress, with animal studies primarily focusing on responses to drugs of abuse, whereas monetary rewards have typically been used for humans. Therefore, it would be informative for future work to determine whether the neurobiological bases of psychiatric symptoms and given symptom clusters associated with chronic juvenile stress are related to specific stressor experiences and age of exposure, and if changes to substrates mediating disrupted reward processing can be generalized across different reward types.

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Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
5-HT	5-Hydroxytryptamine
ADHD	Attention Deficit-Hyperactivity Disorder
ACC	Anterior Cingulate Cortex
BDNF	Brain-Derived Neurotrophic Factor
BLA	Basolateral Amygdala
CB	Cannabinoid
Cg	Cingulate Cortex
CPP	Conditioned Place Preference
CRF	Corticotrophin-Releasing Factor
CTQ	Childhood Trauma Questionnaire

DA	Dopamine
DAT	Dopamine Transporter
dIPFC	Dorsolateral Prefrontal Cortex
DOPAC	3,4- dihydroxyphenylacetic acid
fEPSP	Field Excitatory Post-Synaptic Potential
GABA	γ -Aminobutyric acid
Glu	Glutamate
GR	Glucocorticoid Receptor
IL	Infralimbic Cortex
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MAOa	Monoamine Oxidase A
MDMA	3,4-Methylenedioxymethamphetamine
mOFC	Medial Orbitofrontal Cortex
mPFC	Medial Prefrontal Cortex
MSN	Medium Spiny Neurons
NAA	N-acetylaspartate
NAc	Nucleus Accumbens
NAcC	Nucleus Accumbens Core
NAcSh	Nucleus Accumbens Shell
NE	Norepinephrine
NMDA	N-methyl-D-aspartate
OFC	Orbitofrontal Cortex
P	Postnatal
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PPI	Prepulse Inhibition
PrL	Prelimbic Cortex
SD	Sprague-Dawley

SERT	Serotonin Transporter
VTA	Ventral Tegmental Area

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Highlights

- Chronic juvenile stress is associated with executive function deficits in adulthood
- Deficits are mediated by lasting stress-induced alterations to prefrontal cortex
- Increased drug sensitivity also seen in adults exposed to chronic juvenile stress
- Greater accumbal responsivity and less top-down control can explain such outcomes
- Normalizing cortico-accumbal activity may reduce lasting effects of juvenile stress

Figure 1. Summary of behaviors related to executive function and motivation mediated by subregions of the prefrontal cortex (PFC) and nucleus accumbens (NAc) of both the primate (left) and rodent (right)

Colors denote functionally homologous subregions between primates and rodents. ACC: Anterior cingulate cortex (green), OFC: orbitofrontal cortex (purple), NAcC: NAc core (orange), NAcSh: NAc shell (red). Note that the rodent medial PFC (mPFC; right, blue) is functionally homologous to the primate dorsolateral PFC (dlPFC; left, blue), with some functional homology to the primate ACC (Seamans et al., 2008).

Figure 2. Summary of developmental changes to the prefrontal cortex and nucleus accumbens occurring in both humans and rats over the juvenile/adolescent period, along age-related changes to executive function and reward behaviors

Peak changes in measured neural variables are represented by enclosed text, with the length of the box corresponding to their approximate duration in relation to the developmental timeline, while short vertical lines denote span of ages tested in cited studies (see text for details).

Figure 3. Summary of major effects of juvenile stress on adult mesoaccumbocortical activity and cognitive/behavioral outcomes

Typically dopamine activity in the prefrontal cortex (PFC), as derived from the ventral tegmental area (VTA), inhibits glutamatergic input to the nucleus accumbens (NAc), thus reducing excitatory input to the NAc. The majority of animal and human studies demonstrate that chronic juvenile stress is associated with reduced PFC activity. Human studies also show accumbal hypofunction in anticipation of reward, with animal studies demonstrating increased dopaminergic activity in the NAc in response to drugs of abuse. Combined, this dysregulation of the mesoaccumbocortical system is thought to result in poorer executive functioning and increased sensitivity to drugs of abuse in adult individuals exposed to chronic juvenile stress, thus contributing to neuropsychiatric illness.

Table 1
Effects of Chronic Juvenile Stress on the Adult Medial Prefrontal Cortex of Animal Models

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Monoaminergic Systems						
Social Stressors						
Social Defeat (1/day intermittently over 13 days: 5 days total)	P45-57	Rat Wistar	Male	P75+	No change in any monoamine examined in PFC.	Vidal et al., 2007
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Decreased mPFC DA content. No change in mPFC NE, DOPAC, 5-HT or 5-HIAA.	Watt et al., 2009
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Blunted amphetamine-induced mPFC DA levels.	Burke et al., 2010
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	No change in mPFC D ₁ or D ₂ receptor expression.	Burke et al., 2011
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+	Increased DAT expression in the IL mPFC. No change in DAT expression in Cg or PrL.	Novick et al., 2011
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Blunted amphetamine-induced mPFC DA release.	Burke et al., 2013
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+ P55+	Decreased mPFC DA activity (DOPAC/DA). Local D ₂ autoreceptor antagonism during adolescent defeat prevents decreased mPFC DA activity at P56.	Watt et al., 2014
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+	Increased DAT function in the IL mPFC.	Novick et al., 2015
Social Isolation (24 h/day until end of study)	P21-110+	Rat Wistar	Male	P110+	Decreased DA turnover in IL mPFC.	Heidbreder et al., 2000
Social Isolation (24 h/day until end of study)	P28-55+	Rat Lister-Hooded	Male	P55+	No change in basal DA or 5-HT extracellular levels in PrL mPFC. Blunted amphetamine-induced 5-HT release in PrL mPFC.	Dalley et al., 2002
Social Isolation (24 h/day until end of study)	P28-190+	Rat Lister-Hooded	Male	P190+	Increased PrL and Cg mPFC 5-HT _{2A} receptor binding. Decreased PrL PFC 5-HT _{1A} receptor binding.	Preece et al., 2004
Social Isolation (24 h/day until end of study)	P21-100+	Rat Long-Evans	Male	P100+	Increased 5-HT _{1A} receptor binding in frontal pole of cerebral cortex. No change in 5-HT _{1A} receptor binding in mPFC or OFC.	Helleman et al., 2005
Social Isolation (24 h/day for 14 days)	P38-51	Rat Wistar	Male	P65+	No change in mPFC DA levels.	Shao et al., 2009
Social Isolation (24 h/day until end of study)	P21-85+	Rat SD	Male	P85+	Increased DA, 5-HT and 5-HIAA in mPFC.	Han et al., 2011a

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Social Isolation (24 h/day for 14 days)	P21-34	Rat SD	Male	P55+	Increased number of D ₂ receptor positive cells in mPFC.	Han et al., 2012
Social Isolation (24 h/day until end of study)	P23-75+	Rat SD	Male	P75+	Decreased dendritic D ₂ receptor labeling in PrL PFC.	Fitzgerald et al., 2013
Social Isolation (24 h/day for 21 days)	P21-P43	Rat Lister-Hooded	Male	P80+	Loss of sensitivity to combined D ₁ and D ₂ receptor agonists in mPFC pyramidal cells (mainly IL).	Baarendse et al., 2013
<i>Non-Social Stressors</i>						
Foot Shock (1/day for 5 days)	P21-25	Rat Wistar	Male	P70+	Blunted mPFC c-Fos expression in response to 5-HT1A receptor activation. Lack of negative feedback on mPFC 5-HT release after local application of 5-HT1A agonist.	Matsuzaki et al., 2009
Predator Odor (1/day intermittently over 8 days; 5 days total)	P40-48	Rat Long-Evans	Male & Female	P60+	Increased D ₂ receptors in ventral mPFC (IL and dorsopeduncular). No change in D1 receptors in ventral mPFC (IL and dorsopeduncular).	Wright et al., 2008
Predator Odor and Elevated Platform (1-2/day intermittently over 14 days; 7 days total)	P28-42	Rat Wistar-Han	Male	P90+	Increased PFC (mPFC + OFC) MAOa and SERT mRNA levels. Increased histone (H3) acetylation of MAOa promoter in PFC. Reduced OFC activity in response to social challenge.	Marquez et al., 2013
Restraint, Elevated Platform and Foot Shock (1-2/day every other day for 7 days)	P27-33	Rat Wistar	Male	P70+	Increased mPFC DA content. Decreased mPFC 5-HIAA content. No change in mPFC NE, DOPAC or 5-HT. No change in any monoamine in OFC.	Luo et al., 2014
<i>Amino Acid Systems</i>						
<i>Social Stressors</i>						
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+	Decreased NMDA receptor binding in IL mPFC.	Novick et al., 2016
Social Isolation (24 h/day until end of study)	P21-75+	Rat SD	Male	P75+	Decreased PFC NR2A mRNA expression.	Zhao et al., 2009
<i>Other Systems</i>						
<i>Social Stressors</i>						
Abusive Mother Paradigm (24 h/day for 7 days)	P7-14	Rat	Male & Female	P100+	Increased GR protein levels in the IL mPFC of both males and females.	Alteba et al., 2016

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Social Isolation (24 h/day for 28 days)	P21-48	Rat SD	Male	P75+	Increased BDNF in mPFC.	Meng, et al., 2011
Social Isolation (24 h/day for 14 days)	P21-34	Rat SD	Male	P60+	Increased number of BDNF-positive cells in mPFC.	Han et al., 2011b
Social Isolation (24 h/day for 14 days)	P38-51	Rat Wistar	Male	P65+	Increased BDNF in mPFC.	Shao et al., 2013
<i>Non-Social Stressors</i>						
Foot Shock, Forced Swim and Predator Odor (1/day for 6 days)	P23-28	Rat SD	Male	P75	No change in mPFC GR mRNA levels.	Fuentes et al., 2014
Restraint (1/day for 10 days)	P35-44	Rat SD	Male	P80+	Decreased CB ₁ receptor binding in PFC.	Lee & Hill, 2013
<i>Alterations to Structure and Activity</i>						
<i>Social Stressors</i>						
Intermittent Separation from social group	P91-147	Squirrel Monkey	Male & Female	3-6 y	Increased gray matter volume in the ventral medial, dorsolateral, and prefrontal cortices.	Lyons et al., 2002
Intermittent Separation from social group	P91-147	Squirrel Monkey	Male	9 y	Decreased GR expression in Layer I and Layer II of the dorsolateral PFC.	Patel et al., 2008
Social Defeat (1/day for 7 days)	P36/38-42/44	Rat SD	Female	P80+	Decreased restraint-induced c-Fos protein levels in PrL mPFC. No change in restraint-induced c-Fos protein levels in IL or Cg mPFC.	Ver Hoeve et al., 2014
Social Defeat (1/day for 7 days)	P14-21	Mice-DBA2/J	Male & Female	P80+	No change in cocaine-induced c-Fos expression.	Lo Iacono et al., 2016
Social Isolation (24 h/day for 15 days)	P18-32	Rat SD	Male	P60+	Decreased dendritic arborization in mPFC pyramidal cells.	Pascual et al., 2006
Social Isolation (24 h/day for 5 days)	P30-35	Rat SD	Male	P60+	Decreased synaptic plasticity in IL and Cg mPFC. Reversed through post-stress (P40-55) administration of GABA _A agonist (adinazolam) or NMDA antagonist (MK-801).	Leussis et al., 2008
Social Isolation (24 h/day until end of study)	P21-75+	Rat Wistar	Male	P75+	Reduced LTP in PrL mPFC.	Quan et al., 2010
Social Isolation (24 h/day until end of study)	P21-75+	Rat Lister-Hooded	Male	P75+	Decreased IL and PrL volume. Increased c-Fos expression in IL mPFC pyramidal cells. Decreased GABAergic interneurons in IL mPFC. Decreased GAD67 protein in mPFC (layers V + VI).	Gilbert-Juan et al., 2013
Social Play Deprivation (24 h/day for 39 days)	P21-60+	Rat Long-Evans	Female	P60+	Increased mPFC dendritic length, apical spines, and basilar spines.	Bell et al., 2010

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
<i>Non-Social Stressors</i>						
Chronic Unpredictable (2/day for 12 days)	P26-37	Rat SD	Male	P65+	Decreased Fos-positive cell density in superficial layer of the IL mPFC. Slower response of IL neurons to basolateral amygdala stimulation.	Ishikawa et al., 2015
Limited bedding and nesting material (24 h/day for 7 days)	P2-9	Mice C57BL/6J	Male & Female	P70+	Decreased number of dendritic intersections in Layer V of the Cg mPFC.	Yang et al., 2015
Restraint (3 h/day for 7 days)	P42-49	Rat SD	Male	P50 P70+	Decreased fEPSP potential amplitude in PrL mPFC. fEPSP amplitudes in PrL mPFC return to control levels.	Negrón-Oyarzo et al., 2014
Restraint (3 h/day for 7 days)	P42-49	Rat SD	Male	P50 P70+	Impaired expression of LTD in PrL mPFC. Expression of LTD in PrL mPFC returns to control levels.	Negrón-Oyarzo et al., 2015

Abbreviations: 5-HIAA 5-Hydroxyindoleacetic acid, 5-HT 5-Hydroxytryptamine, BDNF Brain Derived Neurotrophic Factor, CB Cannabinoid, Cg Cingulate, DA Dopamine, DAT Dopamine Transporter, DOPAC 3,4-Dihydroxyphenylacetic acid, fEPSP field Excitatory Post-Synaptic Potential, GABA γ -Aminobutyric acid, GR Glucocorticoid Receptor, IL Infralimbic, LTD Long-Term Depression, LTP Long-Term Potentiation, MAO Monoamine Oxidase, (m)OFC (medial) Orbitofrontal Cortex, NE Norepinephrine, NMDA N-methyl-D-aspartate, PrL Prelimbic, SERT Serotonin Transporter, SD Sprague-Dawley

Table 2

Effects of Chronic Juvenile Stress on the Adult Frontal Cortex in Humans

Chronic Early-Life Stressor	Age Stressor Experienced	Sex	Age at Testing	Effects of Stressor	Reference
Structural Changes					
Emotional Abuse/Neglect	Childhood	Male & Female	30–31 y	Decreased dorsolateral PFC gray matter volume partially mediated the relationship between childhood emotional maltreatment and adulthood anxiety.	Fonzo et al., 2016
Sexual Abuse	14–16 y	Female	19–20 y	Reduced frontal gray matter volume.	Andersen et al., 2008
Mixed	0–17 y	Male & Female	30–40 y	Reduced frontal gray matter volume (right and left ACC).	Baker et al., 2013
Mixed	Childhood	Male & Female	19–20 y	Significant negative correlation between CTQ score and mPFC gray matter volume.	Gorka et al., 2014
Functional Changes					
Emotional Abuse/Neglect	Childhood	Male & Female	30–31 y	Decreased dorsolateral PFC recruitment partially mediated the relationship between childhood emotional maltreatment and adulthood anxiety.	Fonzo et al., 2016
Mixed	Childhood	Male & Female	30–40 y	Decreased PCC to mPFC connectivity. Trend-level increased amygdala to mPFC connectivity.	Philip et al., 2013a
Mixed	Childhood	Male & Female	35–40 y	Decreased mPFC activity during the N-Back Working Memory Task.	Philip et al., 2013b
Mixed	15–18 y	Male	20 y	Decreased PFC response to reward anticipation.	Casement et al., 2015
Mixed	Childhood	Male & Female	22–23 y	CTQ scores correlated negatively with mPFC Glu/NAA concentrations. CTQ scores correlated positively with resting state entropy during eyes-closed conditions.	Duncan et al., 2015
Mixed	Childhood	Male & Female	30–40 y	Decreased mPFC activity during the 2-Back Working Memory Task.	Philip et al., 2016

'Mixed' refers to inclusion of participants with a range of chronic childhood trauma, including physical, emotional and sexual abuse, and neglect. 'Childhood' refers to anytime up to 18 years of age. Abbreviations: ACC Anterior Cingulate Cortex, CTQ Childhood Trauma Questionnaire, Glu Glutamate, (m)PFC (medial) Prefrontal Cortex, NAA N-acetylaspartate, PCC Posterior Cingulate Cortex

Table 3
Effects of Chronic Juvenile Stress on Adult Executive Function Associated with the Medial Prefrontal Cortex in Animal Models

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Radial Arm Maze						
<i>Social Stressors</i>						
Chronic Unpredictable (6/week for 40 days)	P30-70	Rat SD	Male	P380+	No impairments in working memory.	Chaby et al., 2015b
Chronic Unpredictable (6/week for 40 days)	P30-70	Rat SD	Male	P260+	Enhanced reversal learning (behavioral flexibility), no change in associative learning within daily training sessions (trials separated by 30 s intervals). Decreased working memory after exposure to a novel environment.	Chaby et al., 2015a
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Increased working memory errors at shortest (5 min) delay of the win-shift task.	Novick et al., 2013
Social Isolation (6 h/day for 7 days)	P15-21	Rat Long-Evans	Male	P110+	Increased number of working memory errors during acquisition, no change in reference memory.	Sandstrom & Hart, 2005
<i>Non-Social Stressors</i>						
Restraint (1/day for 21 days)	P28-49	Rat Wistar	Male	P75+ P115+	No impairments in working memory. Decreased working memory 30 days following a second stressor (cold swim stress).	Jin et al., 2013
Morris Water Maze						
<i>Social Stressors</i>						
Social Instability (1 h of social isolation and then rehoused with new cage mate: 15 days)	P30-45	Rat Long-Evans	Male	P90+	No impairments in working memory or reversal learning.	Green & McCormick, 2013
Social Isolation (24 h/day until end of study)	P21-75+	Rat Wistar	Male	P75+	Decreased reversal learning.	Quan et al., 2010
Social Isolation (24 h/day for 14 days)	P21-34	Rat SD	Male	P60+	Decreased reversal learning.	Han et al., 2011b
T-Maze or Y-Maze						
<i>Social Stressors</i>						
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Impaired working memory at 90 sec delay of the delayed alternating T-maze.	Novick et al., 2013

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Social Defeat (1/day for 10 days)	P45-54	Rat Long-Evans	Male & Female	P70+	No impairment in correct choices (no delay imposed) in either males or females in the alternating T-maze.	Furuta et al., 2015
Social Instability (1 h of social isolation and then rehousing with new cage mate: 15 days)	P30-45	Rat Long-Evans	Male	P130+	No impairment in working memory at any delay (5-90 sec) of the delayed alternating T-maze.	Green & McCormick, 2013
<i>Non-Social Stressors</i>						
Chronic Unpredictable * (2/day for 5 days)	P38-42	Rat	Male & Female	P65+	Impaired working memory with 30 sec delay in the delayed alternating T-maze.	Comeau et al., 2014
Chronic Unpredictable Noise Events (24 h/day for 15 days)	P21-35	Rat Swiss-Wistar	Male	P90+	Impaired working memory at 60 sec delay of the delayed alternating T-maze.	Ruvalcaba-Delgadillo et al., 2015
Limited Nesting and Bedding Material (24 h/day for 5 days)	P2-7	Mice C57BL/6J	Male & Female	P70+	Increased 'same arm returns' as a measure of attentional deficit in the Y-maze	Yang et al., 2015
<i>Attentional Set-Shifting Task</i>						
<i>Social Stressors</i>						
Social Defeat (1/day for 10 days)	P28-37 P38-47	Mice C57BL/6J	Male	P80+	Increased number of trials to reach criterion and errors in reversal learning, and extra-dimensional set-shifting. No impairments observed in any dimension.	Zhang et al., 2016
<i>Non-Social Stressors</i>						
Restraint, Elevated Platform and Foot Shock (1-2/day every other day for 7 days)	P27-33	Rat Wistar	Male	P65+	No impairment in the number of trials to reach criterion in reversal learning, and intra- and extra-dimensional set-shifting.	Luo et al., 2014
<i>5-Choice Serial Reaction Time Task</i>						
<i>Social Stressors</i>						
Social Isolation (24 h/day for 28 days)	P28-56	Rat Lister-Hooded	Male	P100+	Increased number of perseverative responses after a brief burst of white noise. No impairments in accuracy, impulsivity and correct latency measures.	Dalley et al., 2002
Social Isolation (24 h/day for 21 days)	P21-43	Rat Lister-Hooded	Male	P90+	Deficits in inhibitory control (increased premature responses), but no effect on attention, accuracy or perseverative responses.	Baarendse et al., 2013
<i>Non-Social Stressors</i>						

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Chronic Unpredictable (2/day for 5 days)	P38-42	Rat	Male & Female	P65+	Deficits in inhibitory control (increased premature responses) and attention (increased omissions). No effect on perseverative responses.	Comeau et al., 2014
Operant Strategy Shifting Task						
<i>Social Stressors</i>						
Social Defeat (1/day for 5 days)	P28-32 P42-46	Rat SD	Male	P70+	General impairment in performance. Impairment in strategy-shifting performance.	Snyder et al., 2015
Object Recognition Task						
<i>Social Stressors</i>						
Social Defeat (1/day for 10 days)	P42-52	Mice C57BL/6J	Male	P55+	Decreased recognition index with a 60 min delay in defeat-susceptible mice.	Huang et al., 2013
Social Instability (1 h of social isolation and then rehousing with new cage mate: 15 days)	P30-45	Rat Long-Evans	Male	P120+	No impairment in novel object recognition at shorter (15 or 60 min) delays.	Green & McCormick, 2013
Rat Gambling Task						
<i>Social Stressors</i>						
Social Isolation (24 h/day for 21 days)	P21-43	Rat Lister-Hooded	Male	P90+	Failure to distinguish advantageous (smaller gains with little loss) and disadvantageous choices (larger gains but larger losses).	Baarendse et al., 2013
Social Isolation (24 h/day until end of study)	P22-70+	Rat Long-Evans	Male	P70+	Increase in disadvantageous choices.	Zeeb et al., 2013
Pre-Pulse Inhibition						
<i>Social Isolation</i>						
Social Isolation (24 h/day until end of study)	P21-110+	Rat Wistar	Male	P110+	Impaired PPI.	Heidbreder et al., 2000
Social Isolation (24 h/day until end of study)	P21-90+	Rat Wistar	Male	P90+	Impaired PPI in minimally-handled isolated rats. Impaired PPI is reversed with increased handling	Rosa et al., 2005
Social Isolation (24 h/day until end of study)	P28-70+	Rat Long-Evans	Male	P70+	Impaired PPI.	McCool et al., 2009
Social Isolation (24 h/day for 21 days)	P21-35 P21-90+	Rat SD	Male	P90+	Impaired PPI. Impaired PPI and increased startle amplitude.	Liu et al., 2011
Social Isolation (24 h/day until end of study)	P23-70+	Rat SD	Male	P70+	Impaired PPI.	Fitzgerald et al., 2013

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Social Isolation (24 h/day for 14 days)	P38-51	Rat Wistar	Male	P65+	Impaired pre-exposure inhibition in latent inhibition task.	Shao et al., 2013

Abbreviations: PPI Pre-pulse Inhibition, SD Sprague-Dawley

* included 12 hours of social isolation but the other unpredictable stressors were all non-social

Table 4
Effects of Chronic Juvenile Stress on Adult Executive Function Associated with the Frontal Cortex in Humans

Chronic Early-Life Stressor	Age Stressor Experienced	Sex	Age at Testing	Effects of Stressor	Reference
Chronic Stress as determined by Allostatic Load (assessed at age 9 and 13)	Childhood	Male & Female	17 y	Significant negative correlation between allostatic load and working memory	Evans & Fuller-Rowell, 2013
Physical Neglect	Childhood	Female	28–32 y	Impaired selective attention and inhibitory control as assessed by the Stroop Color-Word Task. Impaired cognitive flexibility and inhibitory control as indicated by increased time necessary to complete the Trail Making Test B. Impaired working memory as indicated by decreased total score in the N-Back Task. Impaired working memory as indicated by decreased number of correct answers in the Letter Number Sequencing Task. No impairment in decision making as assessed by the Iowa Gambling Task.	Viola et al., 2013
Physical Neglect	Childhood	Male & Female	24–32 y	Impaired social cognition in individuals diagnosed with psychosis, as assessed using the MCCB	Schalinski et al., 2017
Emotional, Physical & Sexual Abuse	Childhood	Male & Female	24–32 y	Impairments in attention, working memory, verbal and visual learning, and social cognition in individuals diagnosed with psychosis, as assessed using the MCCB	Schalinski et al., 2017
Sexual Abuse	Childhood	Male & Female	50+ y	Improved performance on tests examining global cognitive function and immediate word recall.	Feeney et al., 2013
Unpredictable Childhood Environment	< 10 y	Male & Female	18–64 y	Impaired inhibition during uncertain conditions in the Antisaccade task. Enhanced set-shifting during uncertain conditions in the Stroop Color-Word task.	Mittal et al., 2015
Mixed	Childhood	Male & Female	31–69 y	Impaired spatial working memory associated with high emotional and physical abuse.	Majer et al., 2010
Mixed	< 13 y	Male & Female	18–45 y	Impairments in memory and executive function as measured by the Cambridge Neuropsychological Test Automated Battery.	Gould et al., 2012
Mixed	Childhood	Female	19–20 y	Impaired visuospatial working memory as indicated by decreased accuracy on the Spatial Emotional Match to Sample task.	Cromheeke et al., 2014
Mixed	Childhood	Male & Female	35–40 y	No working memory impairment as assessed by the N-Back task.	Phillip et al., 2013b
Mixed	Childhood	Male & Female	36–46 y	Impaired working memory as indicated by decreased accuracy in 2-Back task.	Fuge et al., 2014
Mixed	Childhood	Male & Female	30–40 y	Impaired working memory as indicated by decreased accuracy in the N-Back task.	Phillip et al., 2016
Mixed	Childhood	Male & Female	30–35 y	Impaired affective control as indicated by increased errors in the Affective Go/No-Go task.	Corbo et al., 2016

Chronic Early-Life Stressor	Age Stressor Experienced	Sex	Age at Testing	Effects of Stressor	Reference
No attention impairments as assessed by the Test of Variable Attention task.					

'Mixed' refers to inclusion of participants with a range of chronic childhood trauma, including physical, emotional and sexual abuse, and neglect. 'Childhood' refers to anytime up to 18 years of age. MCCB = Measurement and Treatment Research in Schizophrenia (MATRICS) Consensus Cognitive Battery

Table 5
Effects of Chronic Juvenile Stress on the Adult Nucleus Accumbens in Animal Models

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
<i>Monoaminergic Systems</i>						
<i>Social Stressors</i>						
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	No change in any monoamine/metabolite measured in the NAcC or NAcSh.	Watt et al., 2009
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Increased amphetamine-induced DA tissue content in NAcC. No change in amphetamine-induced DA tissue content in NAcSh.	Burke et al., 2010
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Increased amphetamine-induced D ₂ receptor expression in NAcC but not NAcSh. No change in amphetamine-induced D ₁ receptor expression in either NAcC or NAcSh.	Burke et al., 2011
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	No change in amphetamine-induced NAcC DA release.	Burke et al., 2013
Social Isolation (24 h/day until end of study)	P21-60+	Rat Lister-Hooded	Male	P60+	Heightened and prolonged NAcSh DA release in response to foot shock. Heightened and prolonged NAcSh DA release in response to contextual stimulus.	Fulford & Marsden, 1998
Social Isolation (24 h/day until end of study)	P21-110+	Rat Wistar	Male	P110+	Decreased basal 5-HT turnover in NAc.	Heidbreder et al., 2000
Social Isolation (24 h/day until end of study)	P30-110+	Mongolian Gerbil	Male	P110+	No effect on 5-HT fiber density in either NAcC or NAcSh.	Lehmann et al., 2003
Social Isolation (24 h/day until end of study)	P21-80+	Rat Fawn-Hooded	Male	P80+	No change in D ₁ receptor density in NAc. Increased D ₂ receptor density in NAcC and NAcSh.	Djouma et al., 2006
Social Isolation (24 h/day for 21 days)	P21-42	Rat SD	Male	P55+	Augmented CRF-induced 5-HT release in NAc.	Lukkes et al., 2009b
Social Isolation (24 h/day for 14 days)	P38-51	Rat Wistar	Male	P65+	Increased DA content in NAc.	Shao et al., 2009
Social Isolation (24 h/day until end of study)	P21-85+	Rat SD	Male	P85+	Increased DA, DOPAC, 5-HT and 5-HIAA in NAc.	Han et al., 2011a
Social Isolation (24 h/day for 14 days)	P21-34	Rat SD	Male	P55+	Increased number of D ₂ receptor positive cells in NAc.	Han et al., 2012
Social Isolation (24 h/day until end of study)	P28-80+	Rat Long-Evans	Male	P80+	No change in basal DA or NE in NAc. Increased ethanol-induced DA and NE in NAc.	Karkhanis et al., 2014
<i>Other Systems</i>						

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
<i>Social Stressors</i>						
Social Defeat (1/day every 3 days for 10 days; 4 days total)	P27-36	Mice-OF1	Male	P55+	Decreased μ -opioid receptor gene expression in NAc.	Rodriguez-Aria et al., 2014
<i>Alterations to Structure and Activity</i>						
<i>Social Stressors</i>						
Social Defeat (1/day every 3 days for 10 days; 4 days total)	P27-36	Mice-OF1	Male	P55+	Decreased NAc blood-brain barrier integrity.	Rodriguez-Aria et al., 2015

Abbreviations: 5-HIAA 5-Hydroxyindoleacetic acid, 5-HT 5-Hydroxytryptamine, CRF Corticotrophin-Releasing Factor, DA Dopamine, DOPAC 3,4-Dihydroxyphenylacetic acid, NAc Nucleus Accumbens, NAcC Nucleus Accumbens Core, NAcSh Nucleus Accumbens Shell, NE Norepinephrine, SD Sprague-Dawley

Effects of Chronic Juvenile Stress on Adult Reward-Related Behaviors Associated with the Nucleus Accumbens in Animal Models

Table 6

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Conditioned Place Preference						
<i>Social Stressors</i>						
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	Increased amphetamine-induced CPP.	Burke et al., 2011
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P60+	No change in food reward CPP.	Novick et al., 2013
Social Defeat (1/day every 3 days for 10 days; 4 days total)	P29-38	Mice OF1	Male	P70+	Increased MDMA-induced CPP during reinstatement.	Garcia-Pardo et al., 2015
Social Defeat (1/day every 3 days for 10 days; 4 days total)	P27-36	Mice-OF1	Male	P55+	Increased cocaine-induced CPP; enhanced reinstatement and decreased extinction.	Rodriguez-Aria et al., 2016
Social Defeat (1/day for 7 days)	P14-21	Mice-DBA2/J	Male & Female	P80+	Increased cocaine-induced CPP and enhanced reinstatement.	Lo Iacono et al., 2016
Social Instability (1 h of social isolation and then rehoused with new cage mate; 15 days)	P30-45	Rat Long-Evans	Male & Female	P70+	Trend-level decrease in amphetamine-induced CPP in both males and females.	Mathews et al., 2008
<i>Non-Social Stressors</i>						
Foot shock (1/day for 5 days)	P35-39	Rat SD	Male	P55+	No change in amphetamine-induced CPP.	Burke et al., 2011
Drug-Induced Locomotion						
<i>Social Stressors</i>						
Chronic Unpredictable (1/day for 28 days)	P28-56	Rat SD	Male	P60+	No change in amphetamine-induced locomotion. Prevented amphetamine-induced sensitization.	Kabbaj et al., 2002
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+	Decreased amphetamine-induced locomotion.	Burke et al., 2010
Social Defeat (1/day for 5 days)	P35-39	Rat SD	Male	P55+	Increased acute amphetamine-induced locomotion. No change in chronic amphetamine-induced locomotion.	Burke et al., 2013
Social Defeat (1/day every 3 days for 10 days; 4 days total)	P35-44	Rat Long-Evans	Male	P55+	No change in cocaine-induced locomotion.	Burke & Miczek, 2015
Social Instability (1 h of social isolation and then	P33-48	Rat Long-Evans	Male & Female	P70+	Increased nicotine-induced locomotion in females only.	McCormick et al., 2004

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
reoused with new cage mate: 15 days						
Social Instability (1 h of social isolation and then reoused with new cage mate: 15 days)	P30-45	Rat Long-Evans	Male & Female	P70+	Increased amphetamine-induced locomotion.	Mathews et al., 2008
Social Isolation (24 h/day for 36 days)	P21-55+	Rat Long-Evans	Male	P55+	No change in cocaine-induced locomotion.	Burke and Miczek, 2015
Plus Social Defeat (1/day every 3 days for 10 days: 4 days total)	P35-44				Decrease in cocaine-induced locomotion.	
<i>Non-Social Stressors</i>						
Chronic Unpredictable (1/day for 28 days)	P28-56	Rat SD	Male	P60+	No change in amphetamine-induced locomotion. No change in amphetamine-induced sensitization.	Kabbaj et al., 2002
<i>Drug Self-Administration</i>						
<i>Social Stressors</i>						
Social Defeat (1/day every 3 days for 10 days: 4 days total)	P35-44	Rat Long-Evans	Male	P65+	Enhanced cocaine self-administration.	Burke and Miczek, 2015
Social Defeat (1/day every 3 days for 10 days: 4 days total)	P27-36	Mice-OF1	Male	P55+	Increased ethanol consumption and increased breakpoint as a measure of motivation to consume ethanol.	Rodriguez-Aria et al., 2015
Social Defeat (1/day every 3 days for 10 days: 4 days total)	P27-36	Mice-OF1	Male	P55+	Delayed acquisition for cocaine self-administration.	Rodriguez-Aria et al., 2016
Social Isolation (24 h/day for 36 days)	P21-57	Rat Long-Evans	Male	P65+	No change in cocaine self-administration.	Burke and Miczek, 2015
Plus Social Defeat (1/day every 3 days for 10 days: 4 days total)	P35-44					
Social Isolation (24 h/day until end of study)	P28-70+	Rat Long-Evans	Male	P70+	Increased ethanol consumption and self-administration. No change in sucrose consumption or self-administration.	McCool et al., 2009
Social Isolation (24 h/day until end of study)	P21-60+	Mice-C57BL/6J	Male & Female	P60+	Increased ethanol intake in both males and females.	Lopez et al., 2011
Plus Non-Social Chronic Unpredictable (2/day for 14 days)	P35-49				Increased ethanol intake in both males and females.	
<i>Non-Social Stressors</i>						

Chronic Early-Life Stressor (Duration)	Age Stressor Applied	Species & Strain	Sex	Age at Testing	Effects of Stressor	Reference
Chronic Unpredictable (2/day for 14 days)	P35–49	Mice-C57BL/6J	Male & Female	P60+	Increased ethanol intake in both males and females.	Lopez et al., 2011
Food-seeking						
Social Stressors						
Social Defeat	P45–57	Rat Roman high avoidance				Coppens et al., 2012
Social Instability (1 h of social isolation and then rehoused with new cage mate; 15 days)	P30–45	Rat Long-Evans	Male	P59+	Increased aggression when competing for food reward	Cumming et al., 2014

Abbreviations: CPP Conditioned Place Preference, MDMA 3,4-Methylenedioxymethamphetamine, SD Sprague-Dawley