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The Effects of Early Life Stress on Reward Processing

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1. Introduction

Over 70 years ago, Renee Spitz described the phenomenon of anaclitic depression in institutionalized children, in which children deprived of social contact would eventually appear emotionally withdrawn and demonstrate impaired physical and intellectual development (Spitz and Wolf, 1946). Since then, an impressive amount of research has investigated the health consequences of early life adversity. Consistent with the biological vulnerability of the developing brain, early life stress (ELS; defined as childhood maltreatment, abuse or neglect) increases the risk for later psychopathology. ELS is associated with illnesses across the diagnostic spectrum, including major depressive disorder (MDD) (Heim and Binder, 2012), anxiety (Phillips et al., 2005), substance use (Andersen and Teicher, 2008), personality disorders (Ball and Links, 2009), attention-deficit/hyperactivity disorder (ADHD) (Harold et al., 2013), and psychotic disorders (Varese et al., 2012). The particular psychopathological trajectory might depend on the type of ELS (Carr et al., 2013) and the developmental window in which the stress was experienced (Andersen et al., 2008), as well as genetic and epigenetic risk and protective factors (Caspi et al., 2003; Palma-Gudiel and Fañanás, 2016). In this review, we argue that ELS, instead of being considered as having a direct association with specific diagnoses, is better conceptualized as altering core dimensional aspects of affective and cognitive function related to psychiatric illness.

That reward processing would be affected by exposure to ELS has a conceptual basis in learning and attachment theories, as well as in empirical data on stress neurobiology. Because learning about reward cues and contingencies occurs early on in the context of the parent-child relationship, when that relationship is abusive, inconsistent, or absent, learning how various cues and behaviors lead to reward is impaired (Pollak, 2015). For example,

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when a child grows up in an abusive home, they may become hypervigilant to cues predicting danger at the expense of attending to cues predicting reward. This is supported by evidence that those with a history of abuse demonstrate impairments in adjusting reward-seeking behavior based on changing environmental information (Guyer et al., 2006; Pechtel and Pizzagalli, 2013)

From a neurobiological perspective, perhaps one of the most well-known effects of ELS is alteration of the hypothalamic-pituitary-adrenal (HPA) axis (for reviews, see McCrory et al., 2010; Strüber et al., 2014; Tyrka et al., 2013). The HPA axis modulates the endocrine response to stress, regulating the release of glucocorticoids such as cortisol via interactions between corticotropin releasing factor (CRF), adrenocorticotropic hormone (ACTH) and receptors for glucocorticoids that provide negative feedback. CRF, besides inducing the release of ACTH, also acts within the brain to enhance sympathetic arousal (Dunn and Swiergiel, 2008; Valentino et al., 1983). Early life stress has been found to both exaggerate and attenuate the activity of the HPA axis in response to stress, both phenomena which have been linked to psychopathology (Carpenter et al., 2009; Heim C et al., 2000; Tyrka et al., 2008). Such alterations are relevant to reward processing, as receptors for CRF and glucocorticoids are located throughout the reward circuitry of the brain, with their activation or blockade affecting reward-sensitive neurotransmission and behaviors (Bryce and Floresco, 2016; Craenenbroeck et al., 2005; Walsh et al., 2014). This overlap between stress neurobiology and reward neurobiology suggests that any change in stress neurobiology is likely to influence reward.

Reward processing encompasses the response to rewarding stimuli, the ability to learn from reward, the anticipation of future rewards, and engagement in goal-directed behavior towards rewards (Berridge and Robinson, 2003; Rizvi et al., 2016). Deficits in reward processing are found in MDD (Admon and Pizzagalli, 2015), substance use disorders (Garfield et al., 2014; Tobler et al., 2016), posttraumatic stress disorder (PTSD) (Kalebasi et al., 2015), schizophrenia (McCarthy et al., 2016), and ADHD (van Hulst et al., 2016). Even in individuals who do not meet full diagnostic criteria, alterations in reward processing predict later diagnoses of MDD (Nelson et al., 2016), substance use disorder (Castellanos-Ryan et al., 2011; Garfield et al., 2014), and conduct disorder (Rubia et al., 2009). Accordingly, identifying at-risk individuals and tailoring interventions to target the reward processing system could represent an effective strategy to prevent later psychopathology (McCrory and Viding, 2015). While this remains to be tested, there are data showing that cognitive remediation, including working memory training and mindfulness, can enhance reward processing in non-clinical populations with high trait social anhedonia (Li et al., 2016) and in prescription opioid abusers (Garland, 2016).

The goal of this review is to summarize the research to date on ELS and reward processing, with the intent of providing clinicians and clinical scientists interested in ELS an introduction to this emerging field of inquiry and encouraging additional investigation. By integrating results from both the human and animal literatures, we aim to provide a perspective that synthesizes studies benefiting from the control and specificity of animal models with the more complex human work. For example, animal studies in ELS can utilize a specific strain of species (e.g., Sprague Dawley rats, rhesus monkeys) that are bred from a

limited number of parents, and are thus genetically similar. Furthermore, test animals are housed in uniform conditions, with precise control over the type, timing, and dosage of ELS. Variability and co-variation of these factors represent a major challenge in human studies. However, animal models cannot replicate the complexity of human ELS, and the significance of findings for human conditions is not always clear. Consideration of these two approaches together should provide perspective on the limitations of each approach and new insight into the effects of ELS on reward processing. We start with a brief overview of reward processing relevant to the ELS literature, introducing the neurobiological and conceptual basis of reward processing as well as methods employed in its measurement. Next, we review findings in humans and animals, followed by a synthesis of these two domains. Finally, we describe the implications of reward processing dysfunction, as a risk factor and target for intervention.

2. Methods

A systematic review was completed by searching PubMed to identify studies conducted in humans and animals evaluating the effects of ELS on reward processing. Keywords relevant to ELS and reward processing were chosen, based on keywords and terms used in prior research. For human studies, we used the following search terms: (“early life stress” OR “childhood maltreatment” OR “adverse childhood experiences” OR “childhood adversity” OR “childhood trauma” OR “emotional abuse” OR “emotional neglect” OR “ sexual abuse” OR “physical abuse” OR “physical neglect”) AND (“reward” OR “striatum” OR “reinforcement”). To identify animal studies, a similar strategy was used, except with keywords specific to common ELS paradigms: (“maternal separation” OR “social isolation” OR “early life stress”) AND (“reward” OR “reinforcement” OR “sucrose preference”). In addition, we cross-checked these search results with relevant studies cited by other authors.

We included studies published prior to December 9, 2017 in which humans or animals had experienced or been subjected to some form of ELS and that assessed some aspect of reward processing via measurements of behavior. In the case of humans, we only included studies in which functional magnetic resonance imaging (fMRI) was utilized in conjunction with a reward processing task. Studies that did not meet these criteria, such as animal studies that did not include a measurement of reward behavior or human studies that only utilized fMRI without a reward task, were excluded. Initial literature searches, especially within the animal literature, revealed that many of the studies evaluated reward processing in the context of drugs of abuse and risk for substance use disorders. Given that the topic of ELS and addiction is reviewed extensively elsewhere (Andersen and Teicher, 2009; Burke and Miczek, 2014; Delavari et al., 2016; Enoch, 2012), we restricted our review to studies that dealt with non-drug reward (food, social interaction, money, positive feedback). Data were extracted by no fewer than two separate authors to ensure accuracy and limit bias (Tables 1, 2).

3. Overview of Reward Processing

Reward processing broadly encompasses the biological and behavioral functions that serve to facilitate the acquisition of rewarding stimuli (Berridge and Robinson, 2003; Rizvi et al.,

2016). The three broad components of reward processing are drive towards a reward, hedonic experience/liking, and reward learning (Berridge and Robinson, 2003). There have been various attempts to parse out these processes with even greater specificity. The NIMH Research Domain Criteria (RDoC; https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) provides a framework for components of reward processing under its "Positive Valence Systems." This consists of several main constructs which map onto the above-noted components: approach motivation (similar to the drive component), initial responsiveness to reward (hedonic experience), and reward learning. Within approach motivation, RDoC has defined additional subconstructs, including reward valuation, willingness to work, expectancy, and preference-based decision making. Although the RDoC framework is relatively new, we have applied this terminology wherever possible for the purposes of this review (see Figure 1). It should be noted that parsing of various reward processes using the RDoC framework is limited by the precision of the paradigm used, with several paradigms engaging more than one process.

The importance of parsing out reward processes can be illustrated by the fact that in certain conditions, one reward function may be impaired while the others remain intact. For example, individuals with MDD have similar hedonic responses to sweet solutions compared to controls (Berlin et al., 1998), but are less likely to engage in tasks requiring higher amounts of effort (Treadway et al., 2012).

Evidence for these separate aspects of reward processing comes from research in animals on the neurobiological basis of reward and motivated behavior. In particular, attempts to understand the role of dopamine in the brain have demonstrated a differentiation between motivational and hedonic components of reward. Antagonism of dopamine receptors or dopamine depletion in the ventral striatum (specifically the nucleus accumbens) reduce the amount of effort an animal will expend to obtain a reward, but often leave intact reward consumption and positive hedonic responses (e.g., affective facial expressions) (Berridge and Robinson, 1998; Salamone and Correa, 2002). In addition, dopamine from the nucleus accumbens is important for the ability of rewarding cues to gain incentive salience and elicit instrumental behavior (Peciña et al., 2003; Wyvell and Berridge, 2000). Thus, dopamine in the nucleus accumbens appears to be necessary for the approach motivation aspects of reward processing, but is less involved in the hedonic experience/initial responsiveness to reward. Responsiveness to reward also involves the nucleus accumbens (in addition to other regions, such as the ventral pallidum), but opioids and endocannabinoids are the major neurochemical mediators of reward responsiveness (Mahler et al., 2007; Peciña and Berridge, 2005).

Dopamine signaling to the basal ganglia, including the nucleus accumbens, also plays a role in what is known as the reward prediction error, a subconstruct of approach motivation. The reward prediction error, in which changes in dopamine firing encode differences between an expected vs. actual reward outcome, allows for dynamic learning from experience and updates in reward expectations (Gradin et al., 2011; Schultz, 2016).

While a complete discussion of all the neuroanatomical structures and molecules involved in reward processing is beyond the scope of this review, regions of the prefrontal cortex (PFC)

and amygdala are additional key brain areas involved in reward circuitry. Within the PFC, the orbital frontal cortex encodes and maintains reward value, while the anterior cingulate cortex plays a role in monitoring and determining effort required to obtain rewards (for review see (Rushworth et al., 2011)). Reward value and deviations of expected and actual outcomes are encoded via the amygdala through its projections to the PFC (Lichtenberg et al., 2017; Wassum and Izquierdo, 2015). Taken together, connections between midbrain dopamine cells, the basal ganglia (including structures within ventral striatum, such as the nucleus accumbens) and the PFC, with input from other structures, including the amygdala, thus form a reward circuit. It is in this circuit that information about reward cues, reward value, and required effort is processed, communicated, and then integrated to guide decision-making, facilitate motivation and readiness for action, and eventually result in the experience of pleasure (Rizvi et al., 2016) (Figure 2).

Normative development of the brain regions involved in reward processing demonstrates structural and functional changes from childhood to adulthood, with maturation of PFC regions typically delayed compared to that of subcortical regions (Galvan et al., 2006; Mills et al., 2014; Somerville et al., 2011). For example, animal models show protracted pruning of dopamine receptors in the PFC compared to the striatum and accumbens (Andersen et al., 2000; Tarazi et al., 1999). Given that brain regions undergoing the most extensive maturation are thought to be the most vulnerable to insult (Schneider et al., 1999), we might expect differing effects of ELS based on developmental timing. Thus, stressors occurring earlier in life might be more likely to affect subcortical reward functions (approach motivation and reward responsiveness), with those later in adolescence more likely affecting learning, valuation, and effort prediction.

4. ELS and Reward Processing: Preclinical Data

Early animal studies on developmental adversity, such as those by Harry Harlow (Harlow, 1958) and Seymour Levine (Levine, 1957), emerged in the 1950s, inspired both by early psychoanalytic theories and by the deprivations of civilian populations during World War II (Suomi et al., 2008). Observations of institutionalized children highlighted the importance of both maternal care and peer relationships (Spitz and Wolf, 1946). Accordingly, it is not surprising that the most common manipulations in animals to model ELS consist of maternal and peer separation. While the majority of available data on ELS and reward processing is from animals subjected to either neonatal maternal separation or juvenile peer isolation, we also highlight results from other paradigms, such as social defeat stress, social instability, and chronic variable stress.

4.1 Methods Used to Measure Reward Processing in Animals

Because most components of reward processing are ultimately subjective phenomena (motivation, hedonic experience), their occurrence in animals can only be inferred by the measurement of behavior. While there are multiple well-validated tests of reward behavior in animals that allow some differentiation between various reward processing components, close scrutiny often reveals that more than one component is likely involved.

4.1.1 Responsiveness to reward/Liking—Observation of orofacial movements is probably the only measure of liking independent of any learning or motivational process (Berridge and Robinson, 1998), but this is rarely studied. Reward consumption as a proxy for liking is frequently evaluated using the sucrose preference test (Rizvi et al., 2016). The test involves presentation of two identical bottles, one containing water and the other containing sucrose. One of the most common uses of the sucrose preference test is to assess stress-induced anhedonia in animal models of depression, where reduced consumption of sucrose is considered indicative of depressive-like behavior (Willner et al., 1996). While it can be argued that choosing between two containers and consuming the fluid from one requires aspects of learning and approach motivation, Hoffman (2015) has argued that the sucrose preference test is more specific to liking due to lack of work that the animal has to perform.

4.1.2 Approach Motivation—Two tasks from the ELS literature that probe more motivational components of reward processing are conditioned place preference and operant responses on a progressive ratio schedule. In the conditioned place preference task, a reward is repeatedly paired with a certain environment (i.e. getting food in a white painted cage), and then the animal is tested on the how much time it spends in the environment in the absence of primary reward. The conditioned place preference task is thought to measure incentive motivation to seek out cues previously associated with reward (Bardo and Bevins, 2000). As this measures the extent to which an environment acquires incentive salience for the animal, conditioned place preference can be conceptualized as probing the “reward valuation” subconstruct within approach motivation, but expectancy is arguably also involved, given the presence of Pavlovian conditioned approach behavior (Flagel et al., 2009; NIMH Research Domain Criteria). In progressive ratio responding, the animal is required to complete an increasing number of operant responses to obtain reward, thus testing its willingness to put forth effort for reward, and mapping onto the “willingness to work” subconstruct of approach motivation. While both of these tasks are thought to assess primarily the approach motivation components of reward processing, it should be noted that an element of reward learning is also required, particularly for conditioned place preference (Huston et al., 2013).

4.1.3 Learning—Beyond the simple associative learning processes that are likely involved in conditioned place preference and operant tasks, reward learning studies have utilized more complex paradigms that probe the animal’s ability to adjust behavior according to the value of a reward. For example, in contrast experiments, increasing reward value (i.e., increasing the concentration of sucrose) is expected to increase responding (Matthews et al., 1996b), and thus can reveal the extent to which an animal is able to appreciate changes in reward contingency. In addition, some studies utilize tasks that require reversal learning, testing the ability to change behaviors based on new reward contingencies. For example, in a reversal learning task, an animal that had learned to press the left of two levers to obtain reward must now begin pressing the right lever. Such reversal is known to depend on an intact orbitofrontal cortex to inhibit the prior learned response (Placek et al., 2013; Rolls, 2016).

4.2 Effects of ELS on Reward Processing in Animal Models

4.2.1 Maternal Separation—While maternal separation can refer to a range of postnatal manipulations, these paradigms usually involve separation of neonatal animals from the mother for at least three hours. Maternal separation interferes with the postnatal regulatory influence that the mother has on the animal's physiology and development, and is considered by many to be an analog of human child neglect (Carlyle et al., 2012; Pryce et al., 2005). However, it should be noted that the age at which maternal separation occurs in most animal experiments corresponds to a gestational age in humans, at least in terms of some aspects of brain development (Semple et al., 2013). For example, development of the limbic region and cortex on postnatal day (PND) 10 in the rat equates to that of a human fetus in the second to third trimester (Clancy et al., 2001). This might make it tempting to view maternal separation as relating more to a prenatal stressor in humans. However, development of the human brain is protracted compared to other species (Clancy et al., 2001; Miller et al, 2012; Semple et al., 2013), so despite having a more "mature" brain at birth compared to rats, vulnerability to insult remains.

Experiments assessing the effects of maternal separation on various components of reward are displayed in Table 1. One difficulty in characterizing the maternal separation literature is the wide variety of separation methods, control groups, and statistical methods that have been utilized (Lehmann and Feldon, 2000; Tractenberg et al., 2016). For example, studies of the effect of maternal separation on liking/responsiveness to reward are notable for such methodological differences as duration and frequency of maternal separation, temperature during separation, control group comparison, and sex of the animals. Not surprisingly, observed effects have been conflicting.

Numerous studies of the effects of maternal separation on sucrose preference have reported decreased preference (Amiri et al., 2016; Bolton et al., 2018; Hui et al., 2011; Sadeghi et al., 2016; Shu et al., 2015) or no change in sucrose preference (Matthews et al., 1996a; Mrdalj et al., 2016; Øines et al., 2012; Rüedi-Bettschen et al., 2005; Shalev and Kafkafi, 2002; Uchida et al., 2010), while others have reported increases in sucrose preference (Ferreira et al., 2013; Vazquez et al., 2005). Table 1 shows the methods employed in these studies. Review of the methodological approaches in relation to the pattern of findings did not reveal factors responsible for the variable outcomes, other than a likely role of strain of animal. Specifically, 4 out of the 5 studies using Sprague Dawley male rats demonstrated decreased sucrose preference following maternal separation. In Wistar male rats, decreased sucrose preference was found in only 1 out of 6 studies. Other factors, such as sex of animal or duration/length of separation, did not account for variation in results. That there were limited methodological factors underlying divergent results suggests the possible influence of a combination of subtle differences in methods and differences in laboratory conditions that tend not to be reported (e.g., sound levels and/or experience of the animal handlers).

Several studies found that while maternal separation by itself did not result in changes in sucrose preference, occurrence of a second stressor or challenge in adolescence or adulthood resulted in reduced sucrose preference (Hill et al., 2014; Klug and van den Buuse, 2012; Uchida et al., 2010). These studies support a "two hit" model in which ELS, such as

maternal separation, confers vulnerability to symptoms of psychiatric illness, but with symptom onset only occurring after exposure to a subsequent stressor (Bayer et al., 1999; Maynard et al., 2001).

Even when indices of liking are not altered by maternal separation, indices of approach motivation may be impaired. In one frequently cited study in marmoset monkeys, daily bouts of isolation from parents for the first month of life resulted in unchanged free consumption of a sweet solution at seven months, but decreased effort expenditure on a progressive reinforcement schedule (Pryce et al., 2004). Thus, it appears that separation preferentially affected the willingness to work subconstruct of approach motivation. A similar pattern in rodents was identified by two groups, in which there was decreased willingness to work via progressive reinforcement but unchanged consumption of sucrose when it was given freely (Rüedi-Bettschen et al., 2005) or provided on a fixed ratio (Campbell et al., 2017). Maternal separation was also associated with decreased conditioned locomotor activity to food-related cues (Matthews et al., 1996b, 1996a) as well as decreased conditioned place preference to chocolate (Sasagawa et al., 2017) indicative of a decreased reward valuation/incentive salience function within the approach motivation construct.

In addition to changes to approach motivation and reward responsiveness, evidence exists for alterations of various types of reward learning as a result of maternal separation. As mentioned above, reduced conditioning to predictive appetitive cues, while possibly reflecting decreased motivation, might also indicate impairments in associative learning (Matthews et al., 1996a, 1996b). Deficits in the ability to alter behavior based on changing reward cues, known as reversal learning, have also been reported with parental deprivation in monkeys (Pryce et al., 2004) and maternal separation in rats (Matthews et al., 1996a).

4.2.1.1 Neurobiology of Maternal Separation and Its Implications for Reward Processing: The neonatal rat relies upon the dam for protection from predators, nutrition, thermoregulation, and proper elimination of waste (Hofer, 1996). In addition to these basic protective and physiological functions, maternal care in the form of pup retrieval, nursing, licking and grooming have potent and long-lasting effects on the developing brain that translate into variations in adult behavior. In general, maternal care appears to promote decreased stress reactivity on both physiological and behavioral levels. Meaney and colleagues amply demonstrated this using rats with natural variations in maternal care. Pups raised by dams who exhibit high levels of maternal care demonstrate increases in hippocampal synaptogenesis (Liu et al., 2000), increased glucocorticoid receptor (GR) mRNA, decreased hypothalamic CRF mRNA (Liu et al., 1997), and increased benzodiazepine receptor binding in brain regions regulating emotion (Caldji et al., 2000b). Subsequent work revealed that such changes occurred via an epigenetic mechanism in which maternal care altered levels of gene methylation (Weaver et al., 2004). These changes suggest that high levels of maternal care enhance HPA axis regulation and allow more control of the endocrine stress cascade and better regulation of emotional behavior. Indeed, when adult rats exposed to high levels of maternal care as pups were challenged with an acute stressor as adults, they demonstrated decreased adrenocorticotrophic hormone (ACTH) and corticosterone levels, suggesting enhanced glucocorticoid negative feedback regulation

(Liu et al., 1997). These same rats were also found to demonstrate lower behavioral indications of fear and anxiety (Caldji et al., 2000a; Caldji et al., 2000b).

Given that maternal separation deprives rat pups from opportunities for maternal care, this paradigm would be expected to result in changes opposite to that seen in rats exposed to high levels of maternal care, and this does appear to be the case (Ladd et al., 2000). Similar to rats exposed to low levels of maternal care, maternal separation results in a greater peak and duration of glucocorticoid release in response to stress, decreased GR expression, increased CRF expression, and reduced benzodiazepine receptor binding (Sánchez et al., 2001). Further evidence of stress sensitivity is indicated by a decrease in alpha-2 adrenergic autoreceptor binding in the locus coeruleus, which promotes enhanced noradrenergic activity in response to stress (Liu et al., 2000; Swinny et al., 2010). Overall, these changes tend to result in a phenotype that is more reactive to stressful stimuli on a physiological level.

In addition to the association of stress-related pathways with fearful and depressive behavioral phenotypes, these pathways are closely linked to reward circuitry. This is an important concept in the field of addiction (Burke and Miczek, 2014b; George et al., 2012; Sinha, 2008), that is hypothesized to mediate the relationship between ELS and increased risk of substance use disorders (Andersen and Teicher, 2009). Glucocorticoid exposure *in utero* affects the development of dopaminergic neurons in the midbrain (Leão et al., 2007). Postnatally, CRF and glucocorticoids can potentiate dopamine release (Bagosi et al., 2006; Kalivas et al., 1987; Piazza et al., 1996). However, as with studies of reward-related behaviors, contradictory results exist on the effects of maternal separation on reward-related neurochemistry, as discussed below.

Maternal separation can result in both hypersensitive and hyposensitive mesolimbic dopamine function. For example, Matthews and colleagues have demonstrated decreased sensitivity to the enhancing effects of amphetamine and increased sensitivity to the blunting effects of D2 antagonists on behaviors related to approach motivation (Matthews et al., 1996bMatthews and Robbins, 2003). However, other studies demonstrate enhanced mesolimbic dopamine function, as evidenced by increased nucleus accumbens dopamine release in response to stress (Brake et al., 2004) or amphetamine (Hall et al., 1999), as well as increased locomotion in response to cocaine (Brake et al., 2004). The enhanced sensitivity to psychostimulants found in the latter studies might be due to decreases in dopamine transporter levels within the nucleus accumbens of maternally separated rats, limiting dopamine clearance (Brake et al., 2004; Meaney et al., 2002; Zhu et al., 2010). One reason for seemingly divergent findings may be variation in methodology, with Matthews et al. using a 6-hour separation procedure and Brake et al. using a 3-hour separation. Changes to the opioid system are also apparent with maternal separation, but conflicting results also exist based on specific methodology, demonstrating both increases and decreases in levels of endogenous peptides (Ploj et al., 2003; Vazquez et al., 2005) as well as sensitivity to ligands (Kalinichev et al., 2001; Vazquez et al., 2005). Such variations in the substrates of reward processing following maternal separation likely contribute to the differential findings in reward processing described in the previous section.

4.2.2 Social Isolation—While pre-weaning maternal separation is often conceptualized as early life neglect and results in a depressive-like phenotype (Pryce et al., 2005), post-weaning social isolation during the juvenile and adolescent period produces sensory processing deficits and increases in fear and anxiety-like behavior (Fone and Porkess, 2008; Lukkes et al., 2009). By depriving animals of the play experiences that normally guide cortical development, post-weaning social isolation is conceptualized as a rodent model of adolescent adversity with long-lasting effects on neurobiology and behavior (Fone and Porkess, 2008; Lukkes et al., 2009; Robbins, 2016).

As shown in Table 1, a preponderance of the evidence suggests that rodents subjected to post-weaning isolation demonstrate increased hedonic behavior. In tasks measuring liking, social isolation generally results in increased sucrose preference (Brenes and Fornaguera, 2008, 2009; Colonnello et al., 2011; Hall et al., 1998a; Van den Berg et al., 2000), although there are some discrepant reports (McCool and Chappell, 2009; Pisu et al., 2011). One explanation for these divergent findings might be the existence of differences in the timing and duration of separation. For example, while the majority of studies started isolation around postnatal day (PND) 21, McCool and Chappell (2009) started isolation when rats were between PND 28 and PND 32, thus allowing the rats to have experience with peers during a longer duration within their peak play period (Panksepp, 1981).

Increased indices of approach motivation are also found following social isolation, with evidence of enhanced responding for increasing concentrations of sucrose (Cuenya et al., 2015; Hall et al., 1997), as well as greater conditioned responses to sucrose-related stimuli (Jones et al., 1990). However, a study using a briefer isolation period during the juvenile/periadolescent period found the opposite effect for conditioned locomotor response to sucrose (Van den Berg et al., 1999).

In line with the developmental sensitivity of the prefrontal cortex during adolescence, post-weaning social isolation results in deficits in cognitive flexibility that impair reward learning processes (Fone and Porkess, 2008; Robbins, 2016). For example, despite enhanced approach motivation compared to socially housed controls, when a reward task requires fewer lever presses, socially isolated rats end up receiving less reward due to perseveration (Morgan and Einon, 1975). This paradigm also results in deficits in reversal learning (Amitai et al., 2014; Li et al., 2007), as well as in learning new strategies based on a previously unrelated cue (attentional set shifting) (Schrijver and Würbel, 2001).

Table 1 also includes additional models of ELS such as social defeat, as well as those that use a combination of stressors (e.g., in which the animal is exposed to different stressors, such as restraint, social defeat, isolation, and temperature changes). In terms of developmental timing, these paradigms are commonly utilized with juvenile or adolescent animals. While there are fewer studies of reward processing in studies using these other models of ELS compared to maternal separation and social isolation, there is some indication that female rats exposed to variable stressors in adolescence (restraint, social defeat) demonstrate subsequent deficits in sucrose consumption (Bourke and Neigh, 2011; Pohl et al., 2007) while male animals do not (Bourke and Neigh, 2011; Novick et al., 2013; Pohl et al., 2007; Toth et al., 2008).

4.2.2.1 Neurobiology of Social Isolation: As with maternal separation, post-weaning social isolation results in enhanced sensitivity of the HPA axis, especially in male rats (Holson et al., 1991; Viveros et al., 1988; Weiss et al., 2004), as well as an overall anxiogenic phenotype. The effects of post-weaning social isolation on reward related circuitry, while not without discrepancies, are much more consistent than those found with maternal separation. Specifically, the literature supports that there is an overall increase in nucleus accumbens dopamine function following social isolation, as evidenced by increased basal dopamine in the nucleus accumbens, increased firing of midbrain dopaminergic neurons (Fabricius et al., 2010), and increased dopamine release in the nucleus accumbens in response to psychostimulants (Hall et al., 1998b; Heidbreder et al., 2000; Yorgason et al., 2016, 2013).

Opposite to the effects on dopamine in the nucleus accumbens, PFC dopamine is decreased following social isolation, as evidenced by decreased turnover as well as decreased sensitivity to dopamine agonists (Baarendse et al., 2013; Heidbreder et al., 2000). This decreased dopamine activity in PFC may have a disinhibiting effect on dopamine release in nucleus accumbens, as prefrontal dopamine has an inhibitory function on subcortical release (del Arco and Mora, 2008). The combination of high accumbens dopamine activity with low cortical dopamine activity likely contributes to the reward processing findings in socially isolated animals which demonstrate increased behaviors indicative of approach motivation, but deficiency in aspects of reward learning that require greater executive control.

5. Human Neuroimaging Studies (Table 2)

Compared to the animal literature, there are fewer studies investigating reward processing in humans with ELS. While there is a literature on automatic emotional processing in ELS, many of these studies focus on threat processing and amygdala activity rather than reward (McCrory et al., 2017). Within the studies that do assess reward, variation in terms of type and developmental time point of ELS, age of testing, and method used for testing also presents challenges for drawing definitive conclusions.

While numerous tasks have been used to measure reward processing in humans (reviewed in Rivzi et al. 2016), the two most commonly employed in the literature relevant to ELS are the monetary incentive delay task and the reward guessing task, or variants thereof. Both tasks have two phases, an anticipation phase, in which the subject is given information about the potential for reward, and a delivery phase, in which the reward is received. By measuring brain activity during the anticipation and delivery phases, a motivational component and a reward responsiveness component can be inferred, respectively (Knutson et al., 2000; Lutz and Widmer, 2014; Wang et al., 2016). In line with reward circuitry, studies utilizing fMRI to measure reward processing revealed increased brain activation signals in response to the anticipation and receipt of reward (Wang et al., 2016).

Using the monetary incentive delay task, four studies demonstrated decreased activity in regions of basal ganglia during the anticipation phase, suggesting reduced approach motivation in individuals who were exposed to institutionalization or early life adversity prior to adolescence (Boecker et al., 2014; Boecker-Schlier et al., 2016; Dillon et al., 2009; Mehta et al., 2010). However, in one study, while activation in the ventral striatum and

putamen was decreased during anticipation, activity was increased during the delivery phase, but only for positive verbal feedback as opposed to monetary reward (Boecker et al., 2014). The authors suggested that individuals experiencing ELS might be particularly sensitive to social feedback.

Despite the capacity to differentiate phases corresponding to approach motivation and reward responsiveness on the reward guessing tasks, data on both components were not available for all studies. In two studies by the same group, ELS was associated with decreased ventral striatal activity to positive feedback (Hanson et al, 2015; Hanson et al, 2016). This relationship was significant when the stress was experienced earlier in life (kindergarten through grade 3) but not later (Hanson et al., 2016). Similarly, individuals with a history of reactive attachment disorder and early life maltreatment demonstrated reduced activation of caudate and nucleus accumbens during the reward guessing task (delivery versus anticipation was not differentiated) (Takiguchi et al., 2015). In these studies, stressors experienced in early childhood most powerfully modulated the relationship between ELS and activation in reward-related brain regions.

There are divergent findings in studies of responses to viewing positive emotional stimuli. While institutionally reared children had decreased ventral striatal response to positive emotional faces (Goff et al., 2013), adolescents with a history of physical and sexual abuse demonstrated increased reactivity to positively valenced social stimuli (Dennison et al., 2016), suggesting a potential difference in the effects of neglect vs abuse. Despite this difference, in both groups decreased activation of the ventral striatum correlated with increased depressive symptoms.

While most studies demonstrate decreased activation of the striatal regions in tasks engaging motivational and reward responsiveness processes, this was not the case when the specific stressor investigated was variations in parental warmth. In young adult males, low maternal warmth in early childhood was associated with increased medial prefrontal cortex and striatal activation during anticipation of monetary reward (Morgan et al., 2014). A similar association was found for adolescent females with low maternal warmth in early adolescence, although increased activity was associated with increased depressive symptoms (Casement et al., 2014). These two studies suggest that, depending on gender and developmental timing of stressor and testing, low maternal warmth may increase the brain's sensitivity to anticipation of reward.

A major difference between the human fMRI studies and the animal studies is that while the animal studies rely almost solely on behavioral measures to infer reward processes, behavioral measures (reaction times, performance) are reported much less frequently in the human literature. The monetary incentive delay task and the reward guessing task, while well adapted for use with imaging, are less suited to capturing differences in reward behavior. Reaction times on the monetary incentive delay task could be interpreted as a function of motivation or reward sensitivity. Dillon et al. (2009) and Boeker et al. (2014) found increased reaction times in individuals with prior ELS in the monetary incentive delay task, while decreased reaction times were noted in children with reactive attachment disorder in a gambling task (Takiguchi et al., 2015), although the remainder of studies either

did not measure behavior (Casement et al., 2015, 2014; Goff et al., 2013; Hanson et al., 2016, 2015; Morgan et al., 2014) or reported a lack of differences (Boecker-Schlier et al., 2016; Mehta et al., 2010). It should be noted that in various studies utilizing fMRI and the monetary incentive delay task, changes in ventral striatal activation are often found in the absence of changes in reaction time (Jansma et al., 2013; Saji et al., 2013; Smoski et al., 2011), suggesting that reaction time may lack sensitivity as a marker for reward processing.

Differences in reward behavior have been found using a probabilistic reward task. For example, women with a history of both childhood sexual abuse and MDD (Pechtel and Pizzagalli, 2013), adolescents exposed to physical abuse (Hanson et al., 2017), and young adults who had high levels of various adversities in early life (Birn et al., 2017) demonstrate decreased reinforcement learning. Hanson (2017) suggests that growing up in adverse environments where there is inconsistency in caregiver behavior, the individual is taught that positive and negative outcomes happen randomly. In such environments, there would be less value in utilizing information to predict reward, and more value in a generalized state of emotional arousal, as evidenced by enhanced activation of the subgenual cingulate cortex (Pechtel and Pizzagalli, 2013). Such increased emotional hyperarousal might explain why children with a history of ELS failed to modulate their reaction time based on the probability of reward (Guyer et al., 2006).

Overall, a limited literature in humans does suggest that ELS is associated with decreased neural responsiveness to reward on both measures of approach motivation and reward responsiveness, although studies evaluating decreased maternal warmth appear to be an exception. There is also indication that the earlier in life that maltreatment or neglect is experienced, the more likely it is to result in decreased striatal responses to reward. Interestingly, this is similar to the developmental pattern that is seen in the animal literature, with maternal separation more likely to result in deficits in approach motivation and responsiveness to reward compared to post-weaning social isolation. While it does appear that decreased striatal responsiveness in humans is linked to anhedonia and depressive symptoms, studies measuring how this impacts actual behavior are lacking.

6. Discussion

Compared to work on reward processing in specific psychiatric disorders, interest in the effects of ELS on reward processing is relatively recent. Despite limitations in the available human and animal literature, decreased indices of approach motivation and responsiveness to reward appear to be more common when the stressor is experienced earlier in life (i.e., maternal separation in animals, or early institutionalization in humans). Stressors experienced closer to the periadolescence period, such as social isolation in rats or lack of parental warmth in teenage girls, can have the opposite effect. This may be due to the fact that stressors later in adolescence could potentially have greater effects on the prefrontal cortex (Andersen et al., 2008; Leussis and Andersen, 2008), facilitating a central disinhibition of subcortical reward function.

When interpreting these findings, it is important to consider that differences in physiology and behavior should not simply be viewed as pathological insults, but can also be seen as

adaptations to facilitate survival in an adverse environment. Viewed from such a lens, one could speculate that decreased approach motivation might be adaptive in environments where reward seeking behavior might be particularly risky. Similarly, shunting cognitive resources away from reward learning and towards hypervigilant attention to threat might also be adaptive. This might be especially true in the case of early life physical and sexual abuse, where inconsistency in caregiver behavior would preclude early experiences of using cues to predict reward outcome (Hanson et al., 2017; Pollak, 2015). In addition, in situations such as social isolation in juvenile animals or lack of parental warmth in humans, enhanced sensitivity to motivated behavior and sensitivity to reward might be adaptive in order to facilitate acquisition of needs in a deprived environment.

Findings of alterations in reward processing following ELS have several implications. As posited in the introduction, ELS likely alters core aspects of affect and cognition that in turns makes individuals susceptible to psychopathology. In support of this idea, in many of the human studies reviewed, decreased activation in regions of the basal ganglia to the anticipation or receipt of reward was not only associated with depressive symptoms (Dillon et al., 2009; Goff et al., 2013), but often found to mediate the relationship between ELS and depression (Corral-Frías et al., 2015; Hanson et al., 2015). A similar mediating effect of reduced activity in the mPFC during reward anticipation was found with alcohol dependence (Casement et al., 2015). While changes to reward processing did not mediate the association between ELS and ADHD, similar patterns of ventral striatal activity were found (Boecker et al., 2014). All of these studies suggest that changes to reward processing represents a transdiagnostic marker for susceptibility to psychiatric illness.

Viewing deficits in reward processing as a risk factor for the development of psychopathology in individuals who have experienced abuse, maltreatment, or neglect opens the possibility for early interventions prior to the development of diagnosable psychopathology (Casement et al., 2014; McCrory and Viding, 2015). To our knowledge, interventions meant to target subclinical anhedonia or impairments in reinforcement learning in at risk populations have yet to be tested, however there is evidence for potential efficacy. When individuals who have completed behavioral activation therapy are challenged with a monetary incentive delay task, they demonstrate increased activation of the ventromedial PFC during anticipation of a loss, which is interpreted as allowing for ongoing engagement in rewarding activity despite negative emotions (Mori et al., 2016). Another example is specialized mindfulness training for addiction, which has been hypothesized to restructure associative learning and valuation of natural rewards via alterations to anterior cingulate and ventral striatal activity (Garland, 2016). Given the role of dopamine in various aspects of reward processing, dopaminergic agents might have utility in enhancing reward learning and approach motivation when used in conjunction with behavioral training (Acheson et al., 2013; Admon et al., 2016). While the available literature in this area is still small, this represents an exciting area of research with the potential to reduce or ameliorate the lifelong burden of risk for psychiatric illness faced by individuals exposed to ELS.

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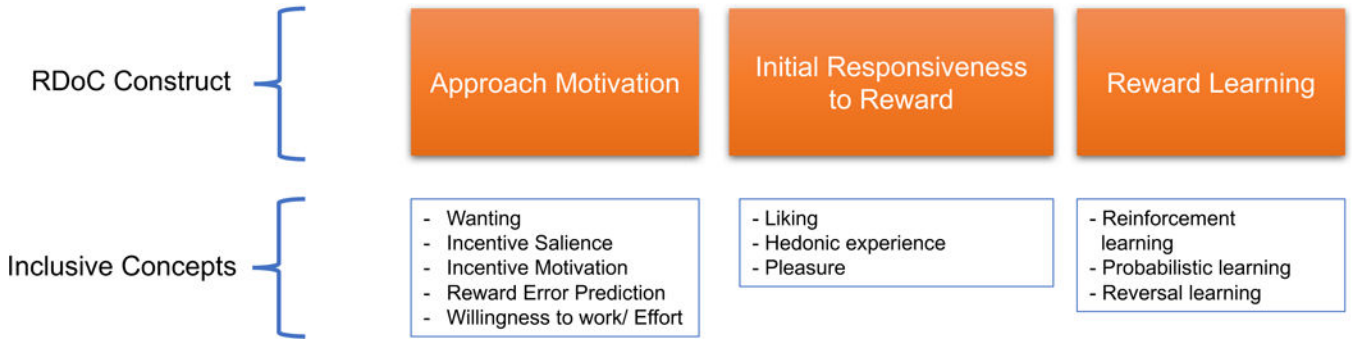

Figure 1.

Three of the major NIMH Research Domain Criteria constructs relevant to reward processing. Inclusive concepts are subconstructs as well as phrases/concepts used in the reward processing literature that map onto each construct.

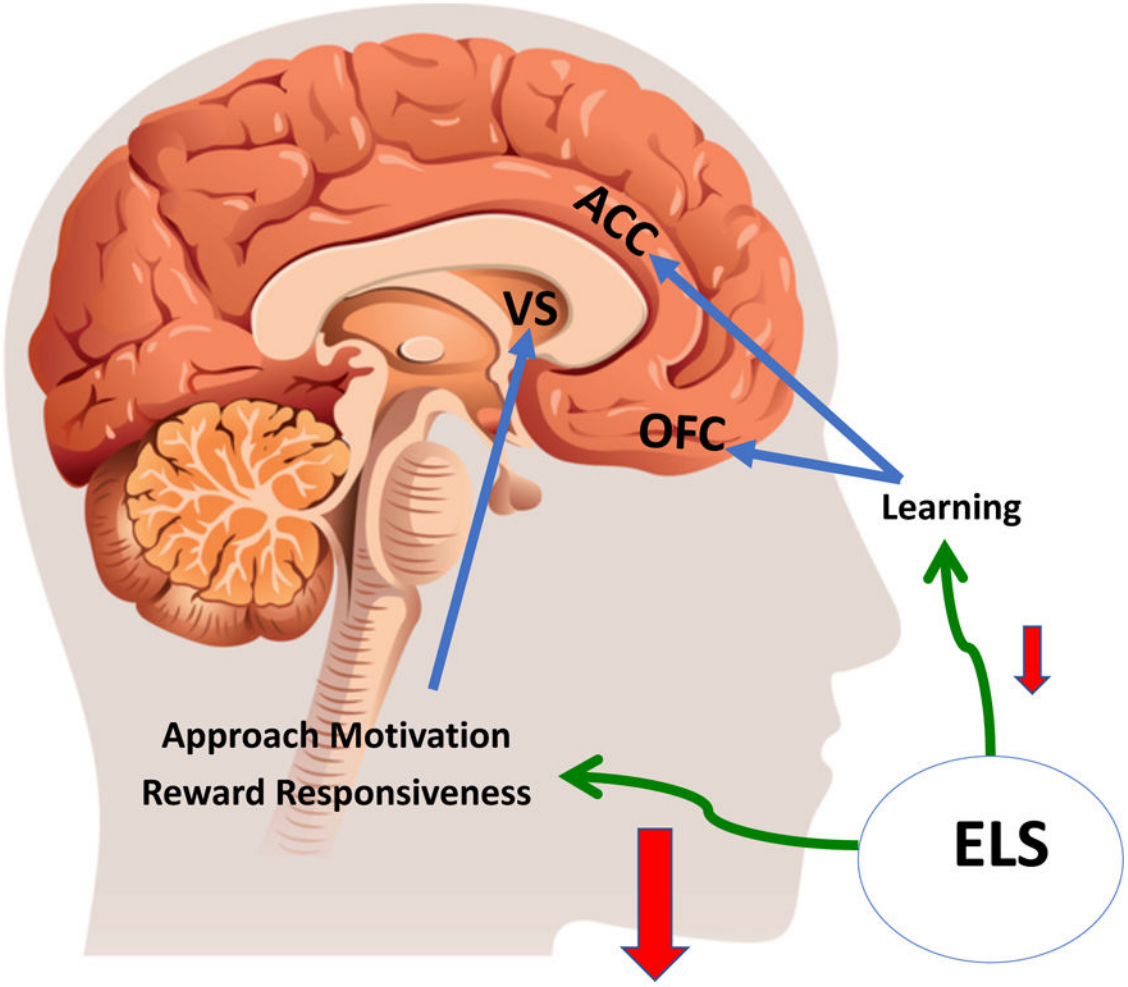

Figure 2.

A simplified overview of brain regions involved in reward processing and the influence of early life stress. Areas of the ventral striatum (VS) are involved in approach motivation and reward responsiveness via activity of dopamine and endogenous opioids, respectively. The anterior cingulate cortex (ACC) and orbital frontal cortex (OFC) are linked to reward learning. Available evidence suggests overall decrease in approach motivation and reward responsiveness functions by ELS. While ELS can also impair reward learning, there is less available evidence for this, as indicated by the size of the red arrow.

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Table 1

Studies of Reward Processing in Animals.

Maternal Separation											
Author, year	**Species/ Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Reward Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
Amiri et al., 2016	NMRI mice	M	PND 2-14	MS	**MS**: separated from their mothers for 180 min/ day.	Reward responsiveness	SPT	1% sucrose solution	PND 50	Reduced consumption of sucrose compared to control rats.	Decreased reward responsiveness.
Bai et al., 2014	Sprague Dawley rats	M+F	**MS**: PND 1-13 **CUPS**: 10 weeks	MS, CUPS, MS+CUPS	**MS**: separated from their mothers for 6 hrs/day for 2 wks. **CUPS**: exposed to one of various stressors once a day for 3 wks beginning at PND 70. **DUAL STRESS:** MS + CUPS. **CONTROL**: standard husbandry care.	Reward responsiveness	SPT	1% sucrose solution	13 wks	Reduced consumption of sucrose in male MS and CUPS, but not MS + CUPS rats compared to controls. Female MS+CUPS rats consumed less than control rats.	Decreased reward responsiveness in males with only one exposure and in females with only dual exposure.
Bolton et al., 2017	Sprague Dawley rats	M	PND 2-9	Limited bedding	**Limited bedding:** Pups and dam reduced nesting material PND 2-9. Standard bedding on PND 10. **Controls**: Normal bedding.	Reward responsiveness, approach motivation	SPT, social interaction	1.5% sucrose solution, social play with conspecific	PND 56	Decreased sucrose preference and duration of social play in rats exposed to limited bedding.	Decreased reward responsiveness.
Campbell et al., 2017	Wistar rats	M	PND 2-14	MS	**MS:** separated from mother for 3 hrs/day. **Control:** undisturbed.	Approach motivation	Sucrose self-administration (PR)	10% sucrose solution	PND 70-75	MS rats similar self-administration on FR, decreased self-administration on PR.	Decreased approach motivation.
Ferreira et al., 2013	Wistar rats	M	PND 1-10	MS	**MS**: pups removed from home cages and placed in separate cages for 3 hrs/day. **NH**: not handled until weaning. **H**: pups were removed from home cages and placed in separate cages for 10 min/day.	Reward responsiveness	SPT	1% sucrose solution	Not specified	MS rats consumed more sucrose in the second hr of exposure.	Increased reward responsiveness.
Hill et al., 2014	Wistar rats	M+F	PND 2-14	MS	**MS**: pups separated from dam 3 hrs/day. **CONTROL**: pups exposed to 10-15s of separation/day. At 8 wks, all rats randomly assigned to receive 2 wks of cort or vehicle.	Reward responsiveness	SPT	1% sucrose solution	Wk 14	No difference with MS in male or female. Decreased preference in MS females receiving cort.	Decreased reward responsiveness with “two hit” of MS + cort in females but not males.
Hui et al., 2011	Sprague Dawley rats	M+F	PND 2-14	MS with or without EE post-weaning	**MS**: litters separated from dams for 180 min/day. **Non-MS**: stayed with dams. Post weaning on PND 21, half the pups housed in standard conditions and half the pups housed in EE.	Reward responsiveness	SPT	1% sucrose solution	PND 61-75	Reduced sucrose preference in MS rats. EE rescued effect of MS sucrose preference.	Decreased reward responsiveness.
Klug and Van de Bluse., 2012	Wistar rats	M+F	PND 2-14	MS	**MS**: pups separated from dam 3 hrs/day. **CONTROL**: exposed to 10-15s of separation. At 8 wks, all rats received 2 wks of cannabinoid receptor agonist or vehicle.	Reward responsiveness	SPT	1% sucrose solution	Wk 12	No difference with just MS in either sex. Decreased preference in MS males receiving cort.	Decreased reward responsiveness with “two hit” of MS + cannabinoid in males but not females.
Kosten et al., 2006	Sprague Dawley rats	F	PND 2-9	MS	**MS**: pups isolated individually for 1 hr/day. **CONTROL**: NH.	Approach motivation	Food self-administration (PR)	Food pellets	~PND 90 (adult rats≥ 90)	MS females demonstrated increased lever pressing for food on escalating PR schedule.	Increased approach motivation/ willingness to work.
Kundakovic et al. 2013	Balb/cJ (Balb/c) mice and C57BL/6J (B6) mice	M+F	PND 1-14	MS + Matemal Unpredictable stress	**MS:** pups isolated together for 2 hours daily. **Maternal Stress:** Dams exposed to either 20 min restraint stress or 2 min forced swim during separation. **Controls:** left undisturbed.	Reward responsiveness, approach motivation	SPT	1% sucrose	PND 36-39 (SPT)	-MS C57BL/6J males and females decreased sucrose preference vs controls. -MS Balb/c males decreased sucrose preference vs controls. -MS Balb/c females increased sucrose preference vs controls.	Decreased reward responsiveness in C57BL/6J M+F and Balb/c M. Increased reward responsiveness in Balb/c females.
Lomanowska et al., 2006	Sprague Dawley rats	M	PND 5-17	Artificial Rearing	**Artificial Rearing:** feeding though gastric cannulae. **Maternal Rearing:** reared by foster dam.	Reward responsiveness	SPT	Table sugar	PND 42-63	Increased sucrose preference in artificially reared rats.	Increased reward responsiveness.
Maniam &; Morris, 2010	Sprague Dawley rats	M+F	PND 2-14	MS	**NH**: litters not handled **MS15**: litters separated from dams for 15 min/ day. **MS180**: litters separated from dams for 180 min/ day.	Reward responsiveness	SPT	2.5% sucrose solution	PND 34	Male MS180 rats decreased sucrose preference compared to NH and MS15 rats. No differences in females.	Decreased reward responsiveness in males only.

Maternal Separation											
Author, year	**Species/ Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Reward Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
Matthews et al., 1996a	Lister-hooded rats	M+F	PND 5-20	MS	**MS**: removed from home cages for 6-hr periods on 10 random days. **CONTROL**: litters removed from home cages and placed into identical wire baskets for 5 min/ separation day.	Approach motivation, learning (valuation)	Conditioned locomotor activity to food, contrast effects on sucrose preference	Food pellets, sucrose solutions	10 wks, 12 wks (experimentally naïve) or 28 wks	MS females failed to develop conditioned locomotor response. No effect on sucrose preference. Controls greater downward shift in lick frequency during negative contrast. Controls increased lick frequency more than MS during positive contrast.	Decreased approach motivation and decreased learning.
Matthews et al., 1996b	Lister- hooded rats	M+F	PND 5-20	MS	**MS**: 6-hr separations on 10 random days. **CONTROL**: separated for 2 min/separation day.	Approach motivation	Conditioned locomotor response to food, effects of amphetamine, sulpiride, SCH-23390, and clonidine	Food pellets	10 wks	MS rats attenuated and delayed conditioned locomotor response; blunted response to enhancing effect of amphetamine and enhanced sensitivity to depressant effects of D2 blockade.	Decreased approach motivation. Pharmacological manipulations suggestive of decreased DA tone.
Matthews and Robbins, 2003	Lister-hooded rats	F	PND 5-20	MS	**MS**: 6-hr separations performed on 10 random days. **CONTROL:** separated for 2 min/separation day.	Approach motivation, "hedonic capacity"	Intracranial self-stimulation threshold	Electrical current to lateral hypothalamus	>20 wks	No difference in baseline threshold for stimulation. MS rats more sensitive to D2 antagonist.	No baseline differences.
Michaels and Holtzman, 2006	Long-Evans hooded rats	M	PND 3-14	MS	**MS**: 15 1-hr or 3-hr separations. **CONTROL**: NH.	Reward responsiveness	SPT	10% sucrose solution vs deionized water	~ 3 months	MS rats drank more fluid total, but no differences in sucrose preference.	No differences.
Mrdalj et al., 2016	Wistar rats	M	PND 2-14	MS with or without CMS	**LMS**: offspring separated from dams 180 min/ day. **BMS**: offspring separated from dams 10 min/day. **NH CONTROL**: no separation. At PND 90, half of each group was exposed to CMS for 4 wks.	Reward responsiveness	SPT	1% sucrose solution	~PND 90, 120	No effect of early life condition on sucrose preference. Decreased preference with CMS.	Reduced reward responsiveness in rats with CMS.
Øines, Murison, Mrdalj, Grønli, &; Milde, 2012	Wistar rats	M	PND 2-14	MS with or without SIS	**LMS**: offspring separated from dams for 180 min/day. **BMS**: offspring separated from dams for 10 min/ day. **NH CONTROL**: dams and offspring left completely undisturbed. From PND 72-75 until PND 85-88, rats from each group exposed to SIS or received standard animal care. SIS consisted of pairing each rat with a new rat daily for 14 days.	Reward responsiveness	SPT	1% sucrose solution	PND 64-68, 86-90	No difference in preference for LMS offspring compared to NH and BMS offspring. No effect of SIS observed on sucrose preference, but overall liquid consumption less for LMS rats.	No differences: LMS rats exhibited decreased liquid consumption overall.
Paul et al., 2000	Rhesus-Macaque monkeys	M+F	3 days-7 months	MS	**MS**: separated from mothers at 3 days old to be hand/nursery reared. Pair housed at 7 months. **CONTROL**: reared normally.	Reward responsiveness	Sucrose and quinine consumption	Sucrose (2.74-175.0 mM) and quinine-HCl (0.1-5.0 mM) solutions	4-5 years	MS monkeys consumed less sucrose containing solutions and more quinine containing solution.	Unclear; authors speculate there may be reduced gustatory sensitivity overall.
Pryce et al., 2004	Marmoset monkeys	M+F	PND 2-28	MS	**MS**: infant brought to remote isolation chamber for 30-120 min/day. **CONTROL**: carrying parent restrained briefly and released. Monkeys' performance on VD/VR/VRR task was assessed.	Reinforcement learning, approach motivation, reward responsiveness	CANTAB (stimulus response with reversal learning, PR), free consumption	Banana flavored milk	9 months	MS monkeys made more errors during reversal learning, decreased responding on PR. Similar consumption of freely available reward.	Decreased learning and approach motivation, similar reward responsiveness.
Rüedi-Bettschen et al., 2005	Wistar rats	M	PND 1-14	MS	**MS** – pup isolated for 4 hrs/day. MSxLightxWarm. MSxLightxCold. MSxDarkxWarm. MSxDarkxCold. **NH**: NHxDark. NHxLight. Light (lights on 0700-1900) vs dark phase (lights off 0700-1900). Cold (21° C) vs warm (32-33° C).	Approach motivation, reward responsiveness	PR responding, free consumption	7% sucrose solution	6 months	MS during dark cycle (warm or cold) resulted in decreased responding and reinforcement on PR. No difference in free consumption.	Decreased approach motivation and no change in reward responsiveness.
Sadeghi, Peeri, &; Hosseini, 2016	Albino Wistar rats	M	PND 2-14	MS	**CONTROL**: no maternal separation. **MS**: litters separated from mothers for 180 min/ day.	Reward responsiveness	SPT	1% sucrose solution	PND 60	Reduced sucrose consumption in MS rats compared to control rats.	Decreased reward responsiveness.

Maternal Separation											
Author, year	**Species/ Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Reward Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
					MS + fluoxetine: 5 mL administered intraperitoneally from PND 28 to 60. **MS + voluntary wheel running**: free access to running wheel 24 hrs/day from PND 28 to 60. **MS + mandatory treadmill**: rats treated to exercise for increasing interval of time over 4 wk period.						
Sasagawa et al., 2017	C57BL/6N mice	M+F	PND 1-14	MS+SI	**MS+SI:** Each pup separated from dam and placed in separate container for 3 hours daily. **Control:** Left undisturbed until weaning. All mice rehoused at weaning in groups of 3-4.	Reward responsiveness, approach motivation	Free consumption + CPP	Milk Chocolate	3-4 Months	Similar free consumption of chocolate in MS+SI mice. Reduced CPP for chocolate in MS+SI females.	Decreased approach motivation in females but not males.
Shalev and Kafkafi., 2002	Long-Evans rats	M	PND 3-14	MS	**EH**: pups separated from dams for 15 min/day at room temperature. **MS**: pups handled similarly to EH pups, but separated from dams for 180 min/day. **NH**: pups were undisturbed.	Reward responsiveness, reinforcement learning, approach motivation	SPT, concentration response test, progressive reinforcement test	1%, 3% and 0.5% sucrose solutions	10 wks, 3 months, 11 wks	No differences for SPT, concentration response test or progressive reinforcement test. MS rats increased locomotor response compared to NH rats.	No changes.
Shu et al., 2015	Sprague Dawley rats	M	PND 2-14	MS with or without CMS	**MS**: litters separated 3 hrs/day from mothers. **CONTROL:** no separation. After reaching adulthood, half of pups in control group and half of pups in MS group randomly assigned to CMS from PND 91 to 112.	Reward responsiveness	SPT	1% sucrose solution	PND 91, 112	Decreased sucrose consumption in rats with MS compared to control rats without MS. Sucrose consumption of rats with CMS alone was lower than sucrose consumption of rats with MS.	Decreased reward responsiveness.
Uchida et al., 2010	Sprague Dawley rats	M+F	PND 2-14	MS with or without repeated restrained stress	**AFR**: animals handled twice a wk during regular cage changes. **MS15**: pups separated from dams 15 min/day. **MS180**: pups separated from dams 180 min/day. At 8 wks old, adult rats subjected to 2 hrs/day of restraint stress for 14 days (held in wire mesh restrainers with head and feet secured).	Reward responsiveness	SPT	1% sucrose solution	10 wks	No effect of MS alone on sucrose preference. MS180 rats given repeated restraint stress had decreased sucrose preference compared with non-restrained controls and MS 180 rats.	Decreased reward responsiveness with combination of MS and restraint.
Vazquez et al., 2005	Long-Evans rats	M	PND1-14	MS	**MS**: pups separated from dam for 3 hrs/day. **CONTROL**: no handling other than cage cleaning.	Approach motivation, reward responsiveness	SPT, morphine CPP, morphine consumption	0.025% sucrose solution, 2mg/kg morphine for CPP, 25mg/L morphine solution for consumption	2.5-3 months	Slightly increased sucrose preference in MS rats. Increased CPP and morphine consumption for morphine in MS rats.	Increased approach motivation and reward responsiveness for morphine; increased reward responsiveness for sucrose.
Zhang et al., 2005	Sprague Dawley rats	M	PND 2-9	MS	**MS**: pups isolated individually for 1 hr/day. **CONTROL**: NH. Responding for food under FR15 and PR5 and PR escalation schedules was tested.	Approach motivation	Food self-administration (FR, PR)	Food pellets	~PND 70-90	Lower responding rates at FR15 for food for MS rats than NH rats, but similar performance at PR for food.	Decreased approach motivation.
Social Isolation											
Author, year	**Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
Amitai et al., 2014	Long- Evans rats	M	PND 24	SI	**SI**: single-housed **Socials**: housed in groups of 3.	Reward learning	Reversal learning	Strawberry milkshake	18 and 52 wks post-weaning	SI rats required more sessions in order to reach criterion performance when reward contingencies were reversed.	Decreased reward learning.
Brenes &; Fornaguera, 2008	Sprague Dawley rats	M	PND 30- 114	SI	**SI**: housed individually under standard conditions. **GH**: housed under standard conditions in groups of 3. **EE**: housed in special cages with plastic objects, PVC tubes, food dispensers and water bottles.	Reward responsiveness	SPT	32% sucrose solution	PND 65-66, 93-94, 108-109	SI rats showed greater preference for sucrose at PND 66 and consumed significantly more sucrose at PND 94 than GH and EE groups.	Increased reward responsiveness.
Brenes &; Fornaguera, 2009	Sprague Dawley rats	M	PND 28- 94	SI	**SI**: housed singly in cages. **GH**: housed in groups of 3.	Reward responsiveness	SPT	32% sucrose solution	PND 90-91, 94-95	SI rats had significantly increased sucrose consumption at PND 91 compared with GH rats.	Increase reward responsiveness.
Colonnello, Iacobucci, Anderson, &; Panksepp, 2011	Octodon Degus	M+F	PND 25	SI	**SI**: housed in isolation for 4 wks; handled daily to be moved to treatment cages alone 1 hr/day. **Partial SI**: housed in isolation for 4 wks; allowed 1 hour of socialization with 2 same-sex sibs/day.	Reward responsiveness	SPT	2% sucrose solution	PND 25, 39 and 53-56	Greater preference for sucrose at wk 4 in SI group than the partial SI and social groups.	Increased reward responsiveness.

Maternal Separation											
Author, year	**Species/ Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Reward Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
					Social Housing Group: housed with sex-matched sib; allowed 1 hour of socialization with sex-matched partial SI sib/day.						
Cuenya et al., 2015	Wistar rats	M	PND 21-36	SI	**SI**: housed alone. **CONTROL**: housed in groups of 5-6. From PND 36-60, isolated subjects were regrouped.	Reinforcement learning, Approach motivation	Sucrose consumption following shifts in concentration	32% and 4% sucrose solution	PND 90	SI enhanced consumption compared to controls following increase positive contrast (4%-32%).	Increased approach motivation.
Hall et al., 1997	Lister-hooded rats	M	PND 21 onward	SI	**SI**: housed individually. **CONTROL**: housed 4 rats/cage .	Reward responsiveness, approach motivation	SPT in fed and deprived states, positive and negative contrast	0.7%, 2.1%, 7.0%, 21.0%, 34.0% sucrose solutions under non-deprived conditions, 0.7%, 7.0% and 34.0% sucrose solutions under deprived conditions and for tests of positive and negative contrast	8 wks	No difference between groups in consumption of sucrose in fed or deprived conditions. SI rats consumed more sucrose under conditions of positive and negative contrast and were more sensitive to positive contrast/less sensitive to negative contrast.	Increased approach motivation due to isolation.
Hall et al., 1998a	Fawn- hooded and Wistar rats	M	PND 21	SI	**SI**: housed singly for 8 wks. **CONTROL**: housed 2 animals per cage for 8 wks.	Reward responsiveness	Voluntary consumption of sucrose and saccharine	0.7%, 2.1%, 7.0%, 21.0% and 34% sucrose solutions, 0.01%, 0.04%, 0.16%, and 0.64% saccharin solutions	~PND 77	SI rats had increased sucrose consumption at all concentrations. Isolated rats increased saccharin consumption at high concentrations.	Increased reward responsiveness.
Hong et al., 2012	Sprague Dawley rats	M+F	PND 30-49	SI	**SI:** housed one per cage. **CONTROL**: housed in groups of 2-3. Forced swim test at P49-50. All rats group-housed P50-P70. 2nd FST P70-P71. Rats isolated around ~P90 for habituation to sucrose.	Reward responsiveness	SPT following 30 min of restraint	1% sucrose solution	~PND 100	Females but not males increased sucrose intake during SPT.	Increased reward responsiveness in female rats isolated in adolescence.
Jones, Marsden, &; Robbins, 1990	Lister- hooded rats	F	PND 21	SI	**SI**: housed individually for the duration of the experiment. **GH**: housed 6 rats/cage for the duration of the experiment.	Approach motivation	Exp 1: Locomotor activity conditioned to food presentation Exp 2: Operant responding to a conditioned reinforcer (stimulus previously associated with sucrose)	Standard rat chow, 10% sucrose solution	~14 wks	SI resulted in increased conditioned locomotor activity and increased responding for conditioned reinforcer.	Increased approach motivation.
Li et al., 2007	Sprague Dawley rats	M	PND 21	SI	**SI**: housed individually. **Control:** housed 3 per cage.	Reward learning	Reversal learning in alternating T-maze	Food pellets	8 wks post-weaning	No differences in initial acquisition of task. SI rats required more trials to acquire reversal learning.	Decreased reward learning.
McCool and Chappell, 2009	Long-Evans rats	M	Starting between PND 28-32	SI	**SI**: housed individually. **GH**: housed 4 animals/cage. Wks 1, 2 &; 4: self-administration of either 10% ethanol or 3% sucrose. Wks 3&; 5: extinction trials.	Reward responsiveness, approach motivation	Sucrose self-administration (FR)	3% sucrose solution	~PND 70	No difference in response rate for sucrose between SI and GH animals.	No differences.
Morgan and Einon, 1975	Lister-hooded rats	F	PND 25-120	SI	**SI**: housed in plastic mesh cages. **CONTROL**: housed in groups of 4.	Reinforcement learning, Approach motivation	Two-lever DRL in which rat must alternate levers for food reward, waiting 30s in between responding	45 mg Noyes sucrose pellet	PND 120	SI rats show both increased perseverative (pressing same lever before 30s interval is up) and anticipatory (pressing alternate lever before 30s interval is up) responses compared to controls.	Increased approach motivation.
Pisu et al., 2011	Sprague Dawley CD rats	M	~ PND 25	SI	**SI**: housed individually in smaller cages for 30 days. **GH**:6-8 rats/cage for 30 days.	Reward responsiveness	SPT	32% sucrose solution	PND 55-60	SI rats exhibited reduced intake and preference for sucrose compared to group-housed animals.	Decreased reward responsiveness.
Schrijver and Würbel, 2001	Lister-hooded rats	M	PND 21	SI	**SI**: housed individually. **Control:** housed 3 per cage.	Reward learning	Reversal Learning and Set Shifting Spatial and Non-Spatial Radial Arm Maze	Food pellets	PND 80	No difference on acquisition or reversal learning within Spatial or Non-Spatial task. SI rats required more trials to acquire shift between spatial and non-spatial cues.	Decreased reward learning.
Van den Berg et al., 1999	Wistar rats	M	PND 22-35	SI	**SI**: individually housed at 4 wks. **GH**: pair housed in cages.	Approach motivation	CPP for social interaction, anticipation	Social interaction, 5% sucrose solution	~Wks 8-11	Isolation resulted in decreased CPP for social interaction and	Decreased approach motivation for social and food rewards.

Maternal Separation											
Author, year	**Species/ Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Reward Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
										decreased anticipatory locomotion for sucrose.	
Van den Berg, Van Ree, &; Spruijt, 2000	Wistar rats	M	PND 21	SI	**SI**: housed in isolation with no social contact. **PARTIAL SI**: housed in isolation with 30 min of social contact/day. **GH**: housed 5 rats per cage.	Reward responsiveness	Sucrose consumption	5% sucrose solution	PND 22-35	Increased sucrose consumption in SI rats compared to partial SI and GH. Partial SI rats had increased consumption compared to non-isolated rats.	Increased reward responsiveness.
Other ELS Paradigms											
Author, year	**Strain**	**Sex**	**Timing of Exposure**	**Nature of Exposure**	**Methods/Group Design**	**Inferred Construct**	**Method to Assess Reward**	**Object**	**PND Test**	**Main Findings**	**Effect on Reward**
Bourke and Neigh., 2011	Wistar rats	M+F	PND 37-49	Combination SD and restraint	**Stress group**: 6 total exposures to social defeat, 6 total exposures to 60-min restraint over 12 days. **Adolescent CONTROL**: pair-housed rats of each sex. **Adult CONTROL**: individually housed.	Reward responsiveness	Sucrose consumption	0.8% sucrose solution	**Adoles-cent**: PND 48-55 **Adult**: PND 96-103	Adolescent stress resulted in decreased sucrose consumption in adolescence and adulthood in female but not male rats.	Decreased reward responsiveness in females but not males.
Novick et al., 2013	Sprague Dawley rats	M	PND 35-40	SD	**SD**: put in cage of larger, aggressive adult rat 1x/day for 5 days. **CONTROL**: adolescent rats removed from home cages and put into novel cages for duration of SD task each day.	Approach motivation	Sweetened condensed milk (SCM) consumption &; CPP	SCM	~PND 60	No difference in CPP or total consumption.	No difference.
Pohl et al., 2007	Long-Evans rats	M+F	PND 23-51	CMS, SSS	**CMS**: exposed to variable stressors everyday for 4 weeks. **SSS**: exposed to 45 min restraint during water immersion or 5 min of 3x0.6 shocks, at random intervals twice a wk throughout the stress period. **CONTROL**: handled twice per wk.	Reward responsiveness	Sucrose consumption	0%, 7%, and 10% sucrose solutions	45 wks	Females but not males in SSS and CMS stress groups consumed significantly less 10% sucrose solution.	Decreased reward responsiveness in females following stress.
Toth et al., 2008	Sprague Dawley rats	M	PND 30	CMS	**CMS**: exposed to variable stressors. everyday for 4 weeks **CONTROL:** ordinary care.	Reward responsiveness	SPT	0.2% sucrose solution	~PND 60 (directly after CMS)	No difference in sucrose preference between CMS and control animals.	No difference.

Abbreviations: AFR, animal facility rearing; BMS, brief maternal separation; CMS, chronic mild stress; cort, corticosterone; CPP, conditioned place preference; CUPS, chronic unpredictable stress; EE, enriched environment; EH, early handling; FR, Fixed Ratio; GH, group housed; H, neonatal handling; LMS, long maternal separation; MS, maternal separation; NH, non-handled; ; PND, post-natal day; PR, Progressive Ratio; SD, social defeat; SI, Social Isolation; SIS, Social Instability Stress; SPT, sucrose preference test; SSS, severe sporadic stress

Table 2

Studies using fMRI and Reward Tasks.

Study Characteristics					Early Stress Exposure Characteristics			Reward Task Characteristics			Results in ELS Group				
											Neural response findings				Other findings
Author, year	Study N (N exposed)	Gender	Mean Age	Diagnosis or symptoms	Nature of exposure	Timing of exposure	Method to assess exposure	Reward phase/type	Task	Object	Striatum*	mPFC	Amygdala	Other Areas and Striatal Subregions	
Baranger, 2016	665 (-)	Both	19.6	7.8% met DSM-IV criteria for Axis I disorder, including alcohol use disorder	Abuse and neglect	<17 years	CTQ	Delivery	Reward-guessing task	Monetary	↑ ventral striatal reactivity to reward-related stimuli, NS after controlling for confounders				*PER1* rs3027172 genotype interacted with ELS to predict both problematic drinking.
Bim, 2017	42 (23)	Both	20.5	NR	"Severe negative life events and circum-stances"	< 11 years	YLSI	Anticipation and delivery	MID	Monetary				↓posterior cingulate, middle temporal gyrus, lingual gyrus, right middle frontal gyrus and cerebellum in anticipation, but not delivery of reward vs no-reward	On separate gambling task, high childhood stress correlated with decreased latency to place bets, the choice of low probability targets, and failure to adjust behavior to feedback.
Boecker, 2014	162 (-)	Both	24.4	Lifetime ADHD symptoms	Early family adversity (low educational level, overcrowd-ing, parental psychiatric disorder, etc.)	3 months	Parent interview	Anticipation and delivery	MID	Monetary or verbal feedback	↓ during anticipation ↑during delivery of verbal, but not monetary, reward			↓ putamen, pallidum, left thalamus, left insula, left ACC and right anterior hippocampus during anticipation; ↑ bilateral insula, right pallidum and bilateral putamen during delivery of verbal, but not monetary, reward	↑ reaction time. No effect on number of win trials. ↓ contingent negative variation on EEG.
Boecker-Schlier, 2016	168 (-)	Both	24.5	None meeting DSM criteria	Childhood family adversity (low educational level, overcrowd-ing, parental psychiatric disorder, etc.)	<11 years	Parent interview	Anticipation and delivery	MID	Monetary and verbal	↓left ventral striatum during anticipation, ↑right ventral striatum during delivery in COMT Met homozygotes			↓ACC and left medial frontal gyrus during anticipation, ↑ACC during delivery in COMT Met homozygotes	↓EEG contingent negative variation signal during anticipation. No significant effect of adversity on reaction time.
Casement, 2014	120 (-)	Female	16	2.5% major depression	Social stressors (low parental warmth, peer victimiza-tion)	11–12 years	PCRS and PES	Anticipation	Reward-guessing task	Monetary	↑ for low parental warm	↑ for low parental warm ↓ for higher peer victimization	↑ for low parental warm	= OFC	Stress-related neural response to potential rewards correlated with depressive symptoms.
Casement, 2015	157 (-)	Male	20	NR	Cumulative stressful life events	15–18 years	LEQ and IPSI	Anticipation and delivery	Reward-guessing task	Monetary		↓ for anticipation and delivery			↑ cumulative stressful life events associated with more problematic alcohol use. mPFC response mediated association between stressful life events and later symptoms of alcohol dependence.
Dennison, 2016	59 (21)	Both	17	14% of maltreated sample met criteria for MDD	Abuse and neglect	<17 years	CTQ and CECA	Response to positive and neutral stimuli	Viewing social images	Socio-affective cues	↑			↑left NAcc, and left putamen for positive relative to neutral stimuli	Higher levels of reward response in left putamen associated with decreased depression in maltreated youth.
Dillon, 2009	44 (13)	Both	24.6	77% of ELS group met DSM-IV criteria for an Axis I disorder at some time	Abuse	≤13 years	AAI, TSS, CTS and protective services records	Anticipation	MID	Monetary				↓ left globus pallidus	↑ symptoms of anhedonia and depression. Rated reward cues less positively. ↑ reaction time. ↑ putamen volumes.
Goff, 2013	69 (38)	Both	9.9	33% in ELS group with clinically significant	Previously institutional-ized	< 2 years	-	Viewing happy faces	Emotional faces task	Socio-affective cues	↓			↓ NAcc	↑ depression.

Study Characteristics					Early Stress Exposure Characteristics			Reward Task Characteristics			Results in ELS Group				
											Neural response findings				Other findings
Author, year	Study N (N exposed)	Gender	Mean Age	Diagnosis or symptoms	Nature of exposure	Timing of exposure	Method to assess exposure	Reward phase/type	Task	Object	Striatum *	mPFC	Amygdala	Other Areas and Striatal Subregions	
				externalizing/internalizing symptoms											Atypical NAcc development. Ventral striatum activation to happy faces negatively correlated with depression scores in ELS individuals.
Hanson, 2015	106 (-)	Both	13.8	Free of all psychopath-ology, except for anxiety disorders, at baseline	Emotional neglect	< 15 years	CTQ	Delivery	Reward-guessing task	Monetary	↓ to positive feedback = to negative feedback				↓ in this reward-related ventral striatum activity associated with ↑ symptomatology and partially mediated association between emotional neglect and subsequent depression.
Hanson, 2016	72 (-)	Male	26.3	High risk for long-term antisocial behavior	Parental loss, medical problems, other major life stressors	<Grade 12	Life Changes measure	Delivery	Card-guessing task	Monetary	↓ response to reward ↓ response to positive feedback = for negative feedback				Effect significant for stress during early, but not later, childhood. No association between ventral striatum activity and adult internalizing or externalizing symptoms.
Holz, 2017	171(-)	Both	25	Conduct Disorder	Childhood family adversity (low educational level, overcrowd-ing, parental psychiatric disorder, etc.)	<11 years	Parent interview	Anticipation	MID	Monetary and verbal	↓ventral striatum and dorsal striatum during anticipation				Conduct disorder partially mediated effects of adversity on brain activity. Negative relationship between reward dependence and adversity.
Mehta, 2010	23 (12)	Both	16	“Quasi-autism,” hyper-activity, cognitive impairment, disinhibited attachment	Romanian adoptees – previously institutional-ized	< 2 years	-	Anticipation	MID	Monetary	↓		=	↓ Caudate nucleus = Insula and thalamus	Adoptees did not recruit striatum during reward anticipation despite comparable performance accuracy and latency. Accuracy on MID task did not differ.
Morgan, 2014	120 (-)	Male	20	13% MDD or dysthymia, 14% history of substance dependence, 8% history of ASPD	Low maternal warmth and maternal depression	< 2 years	Observation during mother–child interactions and SCID with mothers	Anticipation and delivery	Reward-guessing task	Monetary	↑ for anticipation	↑ for anticipation			
Takiguchi, 2015	36 (16)	Both	12.6	RAD	Abuse and neglect	< 12 years	CATS		Gambling task	Monetary	↓			↓NAcc and caudate	Earlier age of stress better predictor of decreased activity. Negative correlations between bilateral striatal activity and avoidant attachment. ↓ reaction time.

Notes: AAI, Adult Attachment Interview; ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; ASPD, antisocial personality disorder; CATS, Child Abuse and Trauma Scale; CS, conditioned stimulus; COMT, catechol-o-methyltransferase; CTQ, Childhood Trauma Questionnaire; CTS, Conflict Tactics Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ELS, early life stress; fMRI, functional magnetic resonance imaging; IPSI, Interpersonal Problem Situations Inventory for Urban Adolescents; LEQ, Life Event Questionnaire for Adolescents; MDD, major depressive disorder; met, methionine; MID, monetary incentive delay; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; NR, not reported; NS, not significant; PCRS, Parent-Child Rating Scale; PES, Peer Experiences Scale; RAD, reactive attachment disorder; SCID, Structured Clinical Interview for DSM; TSS, Traumatic Stress Schedule; YLSI, Youth Life Stress Interview.

*, Neural response findings included under striatum whenever subregions or whole striatum was activated

↑, higher relative to non-exposed subjects

=, same as non-exposed subjects

↓, lower relative to non-exposed subjects