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Impact of adolescent social experiences on behavior and neural circuits implicated in mental illnesses

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Abstract:

Negative social experiences during adolescence are central features for several stress-related mental illnesses. Social play fighting behavior in rats peaks during early adolescence and is essential for the final maturation of brain and behavior. Manipulation of the rat adolescent social experience alters many neurobehavioral measurements implicated in anxiety, depression, and substance abuse. In this review, we will highlight the importance of social play and the use of three separate social stress models (isolation-rearing, social defeat, and social instability stress) to disrupt the acquisition of this adaptive behavior. Social stress during adolescence leads to the development of anxiety and depressive behavior as well as escalated drug use in adulthood. Furthermore, sex- and age-dependent effects on the hormonal stress response following adolescent social stress are also observed. Finally, manipulation of the social experience during adolescence alters stress-related neural circuits and monoaminergic systems. Overall, positive social experiences among age-matched conspecifics during rat adolescence are critical for healthy neurobehavioral maturation.

Keywords: adolescence; social stress; play fighting; social interaction; isolation rearing; social isolation; social defeat; hypothalamic-pituitary-adrenal axis; corticosterone; medial prefrontal cortex; anxiety; depression; addiction; substance abuse; self-administration; psychostimulant; cocaine; amphetamine; dorsal raphe nucleus; corticotropin-releasing factor; dopamine; serotonin

Outline:

1. Introduction

Adverse experiences during adolescence increase risk for stress-related mental illnesses, including addiction, later in life (Andersen and Teicher, 2008; Gutman and Nemeroff, 2003; National Clearinghouse on Child Abuse and Neglect Report, 2005). The majority of young adults who report neglect or abuse during the course of development are diagnosed with at least one psychiatric disorder, including depression, anxiety, schizophrenia, substance use or behavioral disorders (Espejo et al., 2007; Gutman and Nemeroff, 2003; Heim et al., 2008; McFarlane et al., 2005; National Clearinghouse on Child Abuse and Neglect Report, 2005; Scheller-Gilkey et al., 2003). Early-life traumatic events also increase the likelihood of co-morbid psychiatric and substance abuse disorders in adulthood (Scheller-Gilkey et al., 2003). Thus, there is a great need to understand the effects of adverse experiences on the neural mechanisms underlying stress-related neuropsychiatric and substance use disorders. Although all aspects of human behavior cannot be modeled in non-human animals, animal models aid in discovery of relevant mechanisms for the effects of environmental and psychosocial stressors during adolescence in later neuropsychiatric disorders. Rat and mouse studies make up 93% of all neurodevelopmental research by one estimate (Clancy et al., 2007).

Neural and behavioral development of rodents is thought to mirror stages of human development (Adriani and Laviola, 2004; Andersen, 2003; Burke and Miczek, 2014; Laviola et al., 2003; Lukkes et al., 2009d; Spear, 2000). The specific ages when a rodent is considered an adolescent are quite variable across studies (e.g. Yetnikoff et al., 2013). For the laboratory rodent, adolescence is artificially introduced on postnatal day

(P) 21 when it is separated from its mother. For the purposes of this review, P21 to P34 correspond to early adolescence, P34 to P46 correspond to mid-adolescence, and P46 to P59 correspond to late adolescence (Burke and Miczek, 2014; Laviola et al., 2003; Lukkes et al., 2009d; McCormick and Mathews, 2007; Tirelli et al., 2003). These stages may correspond to early (10-13 years), middle (14-16 years) and late (17-21 years) stages of human adolescent life conceptualized by clinicians specializing in adolescent human health (Neinstein et al., 2009; Weiner et al., 2012). Physical markers of puberty typically appear in the mid-adolescent period in rats; preputial separation for males occurs around P40 to P48 and the vaginal opening for females takes place at approximately P32 to P35, but varies across studies and individuals (Lewis et al., 2002; McCormick and Mathews, 2007; Vetter-O'Hagen and Spear, 2012). While puberty takes place during adolescence, these are different constructs because puberty is a discrete measurable event, while adolescence is a gradual brain and behavioral maturation process that encompasses a more extensive portion of ontogeny (Sisk and Foster, 2004).

In humans, adolescence is a sensitive period of development that is characterized by increased risk-taking, sensation seeking, and moodiness (Fuhrmann et al., 2015; Kilford et al., 2016). During adolescence, more time is spent with peers and the quality of social interaction changes (Larson et al. 1996; Platt et al., 2013; Somerville, 2010). In humans, feelings of rejection become more common (Cairns et al., 1995) and psychopathology emerges (Cicchetti and Rogosch, 2002) during this time of life. During childhood, cognitive representations of peers are built that shape their future interactions and relationships with age mates based on their earlier experiences in peer groups (Cairns

et al., 1995). Furthermore, a greater reliance on peers for social support during adolescence occurs and adolescents become increasingly attuned to treatment by their peers (Brown et al., 1997; Ladd et al., 2014). Social relationships during childhood and adolescence have a role in either maintaining or promoting the development of maladaptive behavioral patterns (Hankin et al., 1998; Patterson et a., 1992).

Interactions with age-matched conspecifics during adolescence are also important for rodents. Rats are highly social animals and adolescent rats exhibit greater preference for social stimuli than do adults in the conditioned place preference test (Douglas et al., 2004; Yates et al., 2013). These peer-directed activities have a considerable incentive value during adolescence and are crucial for the development of social competence (Douglas et al., 2004; Pellis et al., 2014; Vanderschuren and Trezza, 2014). Early adolescence is characterized by increased social play, increased monoaminergic activity, and the development of proper cognitive strategies that lead to effective coping with adult situations (Spear, 2000; Vanderschuren et al., 1997). Manipulation of the rat adolescent social experience (Figure 1) alters many neurobehavioral measurements relevant to anxiety, depression, and substance abuse that are discussed in this review. Furthermore, the majority of studies reviewed here use male rats. If females were also examined, it will be noted within the text. The following manipulations of adolescent social experience discussed are:

1. Social play behavior emerges as early as P17 (Bolles and Woods, 1964) and peaks between P30 and P40 (Meaney and Stewart, 1981; Panksepp, 1981; Panksepp et al., 1984; Pellis and Pellis, 1990a, 1997). Juvenile play has been identified as one of the

essential mechanisms for healthy maturation of the social brain and social behavior, and many studies involving humans and rodents have illustrated the negative consequences associated with limited or abnormal play exposure in adolescence (Bell et al. 2010; Darwish et al., 2001; Hol et al., 1999; Pellis and Pellis, 2007; Pellis et al., 2010). Play fighting can be readily tested and quantified by pairing partners and scoring the various actions performed. Such measures can monitor both the frequency of play and the quality of the movements and counter movements by the partners and so assess different possible treatment effects (Himmler et al., 2013b).

2. Social isolation of rats has the most potent effects during a sensitive phase between weaning (P21) to early adulthood (P60) (Einon and Morgan, 1977; Leng et al., 2004; Weiss et al., 2004; Wilkinson et al., 1994). These changes are long-lasting and persist even after re-socialization (Einon and Morgan, 1977; Leng et al., 2004; Lukkes et al., 2009a; Lukkes et al., 2009b; Lukkes et al., 2009c; Weiss et al., 2004; Wright et al., 1991). A large number of preclinical studies employ post-weaning social isolation as a rodent model of adolescent adversity (as reviewed in Fone and Porkees, 2008; Hall, 1998; Lukkes et al., 2009d). Social isolation typically involves housing rats individually beginning on the day of weaning, which ranges from P21 and P28. Socially isolated rats are completely deprived of social contact but usually still have access to olfactory, auditory and visual cues from other rats within the holding room (Einon and Morgan, 1977; Leng et al., 2004; Weiss et al., 2004; Wilkinson et al., 1994). The controls for these experiments are typically group-reared in cages of two to four rats per cage (Einon and Morgan, 1977; Leng et al., 2004; Weiss et al., 2004). In the vast majority of studies, the

rats remain in isolation for four to six weeks or more (as reviewed by Hall, 1998; Fone and Porkess, 2008; Lapiz et al., 2003) and are then tested while still being housed in isolation. More recently, the isolation-rearing method has been designed so that animals are isolated specifically during a sensitive period in life when social play is most abundant (usually P21-P42), followed by a return to group housing before any collection of dependent variables (Baarendse et al., 2014; Lukkes et al., 2012b; Lukkes et al., 2009b; Lukkes et al., 2009c; Whitaker et al., 2013). This helps ensure that any behavioral or neurochemical effects observed can be attributed to isolation-induced disruption of particular phases of development (Lukkes et al., 2009a; Lukkes et al., 2009b; Lukkes et al., 2009c). Moreover, while studies using isolation-rearing over this period are the most common, it is important to note that when rats are reared with a non-playful partner or one that plays atypically during this critical period, they show cognitive and social deficits as well as neural changes (Bell et al., 2010; Einon et al., 1978; Schneider et al., 2016). This suggests that at least some of the effects of being reared in isolation arise from the lack of gaining appropriate social experiences. For this review, the term "isolation-rearing" will be used to describe isolation performed during discrete periods of development whereas the term "isolation housing" will be used when rodents are isolated from weaning through their entire lives.

3. Because of the importance of social learning in adolescence, it may be that the adolescent brain and hypothalamic pituitary adrenal (HPA) axis are more responsive to social context than the adult brain is when confronted with a stressor. The social instability stress (SS) model has been used in pair-housed Long Evans rats to investigate

this possibility. The SS procedure is applied postnatal days 30 through 45 (mid-adolescence) in adolescents. Daily during this period, rats are removed from the colony room and isolated in small, ventilated containers for one hour. Isolation produces a robust increase in corticosterone concentrations within 30 minutes that is maintained for the 60 minute duration (Hodges et al., 2014; McCormick et al., 2001). After isolation, rats are returned to the colony and are housed with a new cage partner that also is undergoing the SS procedure. The SS groups are compared with an isolation-only group (ISO) and a non-stressed control group (CTL). ISO rats undergo the daily one-hour isolation and return to their familiar cage partner (also undergoing ISO) each day. Pairs of CTL rats are undisturbed except for cage maintenance until the experimental test day, the last day of the SS and ISO procedures. In some studies, adolescent SS is compared to the same procedure applied in adult rats from postnatal day 70-85, which allows determination of the extent to which the effects of SS are greater when experienced in adolescence than in adulthood.

4. Clinical studies indicate that stressful adolescent experiences increase risk for substance abuse (DeWit et al., 1999; Dube et al., 2003; Dube et al., 2006; Nelson et al., 1995; Sullivan et al., 2006; Tharp-Taylor et al., 2009; Topper et al., 2011) and addiction (Dube et al., 2002; Dube et al., 2003; Hoffmann et al., 2000; Kaltiala-Heino et al., 2000). A wide range of stressful experiences are applied to adolescent rodents for the purpose of identifying neural mechanisms that underlie stress cross-sensitization to drugs of abuse. Social defeat is an ethologically and etiologically relevant stressor for the rat (Miczek, 1991; Miczek et al., 2008). The experimenter creates an imbalance of power where the

dominant rat (i.e., resident) forces submissive behavior of a subordinate rat (i.e., intruder) by repeated exposures to aggressive residents in an inescapable environment. Levels of the stress hormone, corticosterone, reach higher peaks during social defeat compared to many other stressful procedures (Koolhaas et al., 1997), and rats do not habituate to repeated confrontation with an aggressor (Covington and Miczek, 2005; Watt et al., 2009). A limited number of studies have investigated the effect of brief episodes of social defeat stress during adolescence on later sensitivity to drugs of abuse (reviewed in Burke and Miczek, 2014). The experiments discussed in this review apply social defeat to adolescent male intruders utilizing adult male residents selected for high levels of aggression. The episode of defeat is brief, typically 20 minutes, and occurs four or five times during mid-adolescence.

- insert Figure 1 here -

2. Social play fighting behavior during adolescence

Play fighting is a highly energetic behavior that involves bouts of close quarter wrestling, interspersed with chasing and pouncing on one another (Poole and Fish, 1976). This activity is organized around competing for access to the nape of a partner's nape of the neck (Figure 2), which is rubbed with the snout if contacted (Pellis and Pellis, 1987; Siviy and Panksepp, 1987). In serious fighting, bites are directed at the rump and lower dorsum (Blanchard et al., 1977). Thus, even though the tactics of attack and defense used during play fighting are superficially similar to those used during serious fighting, it is readily distinguished from serious fighting by the target of attack (Pellis and Pellis, 1987).

- insert Figure 2 here -

To remain playful, partners exhibit some degree of restraint during attack and defense while play fighting (Pellis and Pellis, 1998; Pellis et al., 2010), allowing for the partner to contact the playful attack target (Pellis et al., 2005). This self-handicapping behavior contributes to the rapid role reversals that are so characteristic of play fighting (Fagen, 1981; Himmler et al., 2016; Symons, 1978). This fast-paced social interaction requires the individual to monitor each other's actions and coordinate their movements quickly, which is highly demanding and involves multiple brain systems.

During play fighting, a rat defending against an attack to its nape can use two main types of maneuvers. First, they can turn their heads away from the attacker and swerve, run or leap away, thus evading nape contact with the attacker's snout (Figure 3A). Second, they can turn to face their attacker and then grapple with them so as to block access to their nape. When opting for the turning to face maneuver, it can take one of two forms. First, a defender can rotate to face its attacker by pivoting around its hind legs, thus producing a horizontal trajectory with its forequarters relative to the ground. Second, a defender can rotate around its longitudinal axis, starting with the head and progressing cephalocaudally. Rotation around the longitudinal axis can also take one of two forms: a defender can rotate fully so that it ends fully supine on its back (Figure 3B), or it can rotate only partially, so that one or both of its hind feet remain in contact with the ground (Figure 3C). See Himmler et al. (2013b) for more details.

- insert Figure 3 here -

The evasive and the horizontal rotation tactics are the least frequently used tactics

and are used at about the same frequency at all ages (Pellis et al., 1992). What changes with development, especially for males, is the frequency of use of the two versions of the rotation around the longitudinal axis of the body (Pellis & Pellis, 1990, 1997). About 60% of all defensive actions involve rotation around the longitudinal axis of the body, with partial rotation being the most frequent action used before early adolescence and following the onset of puberty. Complete rotation is the most frequently used tactic during early to mid-adolescence, around P30 to P40, when play fighting is most frequent (Thor and Holloway Jr, 1984).

During the early to mid-adolescent period, the greater use of the complete rotation tactic by the defender is associated with changes in the actions by the attacker that increase the experience of unpredictable postural instability and the losing control over one's own actions and over those of the partner. For example, a common postural context involves the attacker standing over the supine defender (see panel j in Figure 2) and when in this position the attacker maintains postural stability by keeping its hind feet on the ground (Figure 4a). However, sometimes the attacker will stand on the supine defender with all four feet (Figure 4b), reducing its stability as the supine partner squirms beneath (Foroud and Pellis, 2003). The ability of the attacker to prevent the supine partner from launching successful counterattacks is markedly diminished when adopting this 'unanchored' position (Pellis et al., 2005). Moreover, the frequency of using this unstable posture is greatest between P30 to P40 (Foroud and Pellis, 2002), the age at which play is most frequent (Thor and Holloway Jr, 1984) and the cortex most sensitive to the influences of interacting with peers (Vanderschuren and Trezza, 2014).

- insert Figure 4 here -

Learning to deal with such unpredictability has been postulated to be a major function of play in the adolescent period as it prepares animals to deal with the unexpected vicissitudes of life (Špinka et al., 2001), and aspects of the play present in both human children (Briggs, 1991; Pellegrini, 2009) and non-human juvenile animals (Foroud & Pellis, 2003; Petrū et al., 2008) are consistent with such a function. Indeed, prefrontal cortical areas of the brain that seem to be modified by playful experience (Pellis et al., 2010) are ones that have been shown to be important for learning form unexpected events (e.g., Takahashi et al., 2009). In the social domain, those vicissitudes involve dealing with conspecifics that may be encountered unpredictably or which act in unexpected ways. Two factors relevant to dealing with social partners, the social partner's identity (e.g., age, sex, dominance status, individual attributes) and the actions they perform during an encounter (e.g., are they aggressive or friendly, moving fast or slow) are important factors relevant to dealing with social partners (Pellis & Pellis, 2016).

3. Social deprivation during adolescence.

3.1. Social deprivation effects on play fighting behavior during adolescence

During the adolescent period, rats will play just as readily with unfamiliar partners as with familiar ones (Panksepp, 1981; Panksepp & Beatty, 1980; Pellis & Pellis, 1990). In natural colonies, in which multiple females synchronize their breeding (Calhoun, 1963; McClintock, 1984), young rats would have many peers, both siblings and non-siblings with whom to play, and given their penchant to play, the most likely source of novel partners is going to arise from seeking play partners. Thus, experience

with a diversity of partners is likely to arise as a byproduct of the adolescent's strong motivation to play.

Rats housed individually from the juvenile to the post-pubertal period show a variety of deficits in cognitive and social skills and impaired emotional regulation (e.g., Arakawa, 2003; da Silva et al., 1996; Einon and Morgan, 1977; Lukkes et al., 2009b; van den Berg et al., 1999). If a socially isolated adolescent is given exposure to a peer for just one hour a day, some of these deficits do not eventuate, but this is only the case if that peer is playful. A non-playful peer does not offer such protection from the effects of being reared in social isolation (Einon et al., 1978). Further, brief isolation increases play fighting when confronted with age-matched conspecifics (Panksepp et al., 1984). In this review, rat-specific anxious behavior or depressive behavior will be referred to as 'anxiety' or 'depression'.

3.2 Model of adolescent adversity increasing vulnerability to anxiety and mood disorders: isolation-rearing

Exposure to adverse experiences, such as social isolation, during adolescence can contribute to vulnerability to stress-related psychiatric disorders, including anxiety disorders and major depression, during adulthood (reviewed in Hall, 1998; Lukkes et al., 2009c). Adult rats exposed to adolescent social isolation exhibit increased aggression, anxiety, and fear (Einon and Morgan, 1977; Lukkes et al., 2009b; Wilkinson et al., 1994; Wright et al., 1991), altered responses to reward-related stimuli (Valzelli, 1973).

3.2.1 Isolation-rearing effects on anxiety behavior

A high comorbidity exists between anxiety and depression where 51% of depressed patients suffer from some type of anxiety disorder (Hirschfeld, 2001; Kessler et al., 1996). When anxiety behavior has been studied directly in rodents, isolation-rearing increased latency to both approach a novel object and emerge into an unfamiliar environment (Einon and Morgan, 1977). Further, re-socialization of isolates for 30 days failed to reverse these anxiogenic effects of social isolation (Wright et al., 1991). Male rats isolated from P28 to P72 exhibited increased anxiety behavior on the elevated plus maze (EPM) (Chappell et al., 2013). Isolation-rearing restricted to a sensitive period of adolescence (P21 to P42) increased anxiety states as suggested by decreased exploration in the EPM and increased hyponeophagic responses to a novel food (Parker, 1986). We also found that rats isolated during this time period exhibited a transient increase in anxiety behavior within a familiar brightly-lit open field as adults when compared to group-reared rats, even when re-socialized for two weeks prior to behavioral testing (Lukkes et al., 2009b). These animals also exhibited social withdrawal and increased freezing behavior during a social interaction test with an unfamiliar conspecific in adulthood (Lukkes et al., 2009b) and during adolescence (Burke and Miczek, 2014; van den Berg et al., 1999). These behaviors are indicative of increased anxiety (Lowry et al., 2005), suggesting that isolates exhibit pronounced social anxiety behaviors in adulthood when compared to group-reared controls. However, some studies do not replicate enduring anxiogenic effects of isolation-rearing, showing that isolates exhibit similar or decreased levels of anxiety-like behaviors compared to group-reared rats in an open field, during a social interaction test, or within an EPM (Gentsch et al., 1981; Hall, 1998; Rex

et al., 2004; Thorsell et al., 2006). For instance, Wall et al., (2012) found that isolation-housing from P21 to P49 increased social interactions in both males and females (Wall et al., 2012). Since the male rats from these studies were not exposed to any social contact from weaning until testing, such results may reflect a combination of increased novelty responses and chronic social deprivation.

3.2.2 Effects of isolation-rearing on depressive behavior

Abnormal social interaction and increased anxiety behavior predict the onset of depression during adolescence (Andersen and Teicher, 2008). Furthermore, peer influence is a powerful predictor of adolescent depression (Thapar et al., 2012). The fact that teenagers spend more time interacting with peers than during any other developmental period makes them more susceptible to peer influence (O'Brien et al., 1998) and social rejection (Sebastian et al., 2010).

To date, demonstration of depressive behaviors in an animal model has been rather inconsistent in traditional stress paradigms. Isolation-rearing from P30-P35 during adolescence increases depressive behavior of males in the forced swim test and impaired their ability to escape a shock in the controllable condition of the learned helplessness triad (Leussis and Andersen, 2008). Future studies should investigate the effects of isolation-rearing at discrete developmental time points during adolescence on depressive behavior using the learned helplessness paradigm and the sucrose preference test. Using the social instability paradigm discussed above, no evidence of increased depressive behavior in both males and females was observed in a forced swim stress test (McCormick and Green, 2013). In contrast, social defeat stress from P28 to P41 and

from P37 to P49 has been shown to increase immobility in females but not males in a forced swim stress test (Bourke and Neigh, 2011; Weathington and Cooke, 2012). Moreover, social deprivation from P21 to P53 increased female depressive behavior in the forced swim test (Jahng et al., 2012). Individually housed male mice (P21-P67) also exhibited increased immobility in the forced swim stress (Amiri et al., 2015).

Comparisons between studies that use similar methods and length of social deprivation state would aide in the interpretation of the outcomes of isolation housing protocols. Taking into account these differences between social isolation protocols might help elucidate some of the current discrepancies in the literature, especially in relation to anxiety and depressive behaviors. Regardless of the discrepancies in the literature, the use of adolescent isolation-rearing in rodents as a model of adverse experiences during adolescence in humans has provided many preclinical findings that can be translated into clinical research.

3.2.3 Role of isolation housing for social defeat behavior during adolescence

Studies in socially defeated adult rats suggest that isolation housing impairs the ability of intruders to cope with an aggressor (van den Berg et al., 1999; Von Frijtag et al., 2002) and increases freezing during introduction of a novel conspecific (Lukkes et al., 2009a; Lukkes et al., 2009b). The first investigation of how social deprivation influences social behavior *during adolescence* manipulated housing conditions and social defeat experience in a 2 x 2 experimental design. Rats were single housed at weaning (P21) and compared to rats that were housed with cage-mates. Single housed intruders exhibit less non-social activity during confrontation with an adult intruder, but increase social play

and crawl under the resident more compared to pair housed adolescent intruders (Buwalda et al., 2013). Using a similar 2 x 2 design, single housed adolescents freeze more often in response to an attack bite upon the first encounter with an aggressive adult resident, but as pair housed adolescents increase freezing during an attack bite over repeated social defeat encounters, the single housed rats do not (Burke and Miczek, 2015). Pair-housed intruders are quicker to freeze than are single housed adolescents and display increased freezing in response to repeated social defeat encounters. The increased freezing exhibited by pair-housed rats suggests an adaptive coping style that agrees with a previous report that adolescent pair-housed rats exposed to adolescent social defeat are quicker to show submission from the first to the last defeat (Watt et al., 2009). For adult rats, the reduction in locomotion over repeated social defeats is attributed to increased freezing in the presence of the resident and is thought to reduce the probability of further attacks (Buwalda et al., 2012; Nocjar et al., 2012; Paul et al., 2011), which suggests that the pair-housed adolescent's increase in freezing from the first to fourth defeat is more similar to adult observations than is the reduction in freezing observed in the single housed adolescents.

In contrast to pair-housed rats, single-housed males exhibit decreased freezing during attack bites in response to repeated defeats. Furthermore, the residents during the defeat session execute more foreleg attacks (appearance of swatting) and perhaps more attack bites toward these socially deprived rats (Burke and Miczek, 2015). Thus, reduced freezing observed in single housed adolescents over the four defeats is probably a maladaptive behavior, leading to greater attacks as previously suggested for adults (van

den Berg et al., 1999). The greater following and crawling under residents by single housed intruders puts the intruder in an inaccessible position for normal social behavior, which probably explains the reduced allogrooming and anogenital sniffing, but greater kicking of single housed intruders by the resident compared to pair-housed intruders (Burke and Miczek, 2015). Nevertheless, the resident shows much interest as shown by greater time sniffing single housed compared to pair-housed intruders. Behavioral strategies for coping with repeated social defeats may rely on experience with social interactions in the home cage because socially housed rats exposed to adolescent social defeat and subordinate cage-mates initiate play fighting bouts more often than controls (Buwalda et al., 2013; Pellis and Pellis, 1992). The nature of the home cage social interactions between social defeats requires further investigation to determine the role of social buffering in adaptive coping behaviors that characterize pair-housed adolescents versus the maladaptive behavior that characterizes single-housed adolescent intruders.

During adolescent social defeat confrontations, single housed intruders exhibit an increased amount of social play behaviors directed toward the resident (approach, socially investigate, follow and crawl under resident; Trezza et al., 2010; Burke and Miczek, 2015). These types of behaviors are considered to be rewarding (Douglas et al., 2004; Varlinskaya et al., 1999; Yates et al., 2013). This observation along with the lack of conditioned freezing behavior over the course of repeated social defeats suggest that the stressfulness of the social defeat encounter may be different for pair-housed adolescent rats compared to single housed adolescents. Perhaps rats reared in isolation have increased motivation for social interaction, even when that social interaction is with

an aggressive adult, causing the social defeat less aversive for single housed rats. Singly housed adolescent intruders may not find the social defeat as stressful as pair-housed intruders. This could be an explanation for why only pair-housed intruders escalate cocaine self-administration following adolescent social defeat (Burke and Miczek, 2015). Future studies should investigate measures of stress (e.g., corticosterone, 20 kilohertz vocalizations) during social defeat experiences and compare between group- and singly housed adolescent rats.

4. Age differences in social and hormonal stress responses

Through its control of the production and release of glucocorticoid hormones, the HPA axis modulates many functions of the body, including energy storage, cardiovascular, immune, and reproductive functions. Thus, the HPA axis is an important means through which an organism copes with stressors because glucocorticoids can alter the functioning of many systems to meet the demands. Further, because glucocorticoid hormones influence learning and memory systems in the central nervous system (CNS), the HPA response to stressors shape the animal's future behavior (McEwen, 2012). Although the HPA response to stressors is adaptive, excessive and chronic elevations of glucocorticoids can have maladaptive consequences. During times of biological transitions, such as the transitional period of adolescence, the CNS may be more vulnerable to chronic stressors and high concentrations of glucocorticoids and the trajectory of ongoing brain development may be comprised.

4.1. The HPA response to stressors

The perception of stressors activates a broad array of neural systems that project to the paraventricular nucleus (PVN) of the hypothalamus to cause the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which travel to the anterior pituitary to cause the release of adrenocorticotropic hormone (ACTH). Then ACTH reaches the adrenal cortex to release glucocorticoid hormones (primarily corticosterone in rats) into general circulation, in which the majority (~95%) will be bound to corticosteroid binding globulin (CBG). There is negative feedback control of the release of glucocorticoids at all levels of the HPA axis and at higher neural regions, notably the hippocampus and medial prefrontal cortex (Ulrich-Lai and Herman, 2009). Efficiency of negative feedback systems is an important means of limiting the organism's exposure to glucocorticoids.

The actions of glucocorticoids are mediated primarily by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Because the affinity of MR for glucocorticoids is about 10 fold that of GR, the majority of MR are bound under low basal concentrations. Thus, GR signaling is sensitive to a broader range of concentrations of hormone and is considered more relevant for the effects of HPA activation in response to stressors, whereas MR is more relevant for basal tone. When bound, MR and GR form dimers and either can enhance or repress the expression of many genes by binding directly on DNA or through binding with cofactors. Nongenomic effects, such as changes in neuronal excitability and changes to intracellular signaling cascades, have been described that account for some of the more rapid effects of glucocorticoids (Groeneweg et al., 2011).

4.2. The HPA axis in adolescence

Some features of the HPA axis are adult-like in early adolescence (e.g., GR and MR binding capacities in the brain; Vazquez, 1998), and other features are continuing to mature (e.g., AVP heteronuclear RNA in the PVN is higher prepubertally in males (Romeo et al., 2007; Viau et al., 2005); lower baseline corticosterone and CRH mRNA in prepubertal females (Viau et al., 2005); greater expression of adrenal melanocortin 2 receptor accessory protein mRNA in prepubertal males (Romeo et al., 2014). Most studies of HPA function that have compared adolescents and adults involved studies of pre-pubertal adolescents and responses to an acute stressor. When restraint is used as the stressor, prepubertal adolescents typically have higher and/or more prolonged release of ACTH and corticosterone than do adults (e.g., Bingham et al., 2011; Doremus-Fitzwater et al., 2009; Foilb et al., 2011, but see Cao et al., 2010; Goble et al., 2011). The direction of difference between adolescents and adults in HPA response is also stressor-specific in studies of post-pubertal adolescents (reviewed in McCormick et al., 2015). Thus, it may be that adolescent-adult differences in HPA function are related to the perception of stressors and the brain regions projecting to the PVN rather than in the HPA axis specifically.

Consistent with this hypothesis, pre- and post-pubertal adolescents differ from adults in the expression of immediate early genes in several hypothalamic and extra-hypothalamic brain regions in response to a stressor, with adolescents typically showing greater and/or more prolonged expression than adults (Hodges et al., 2014; Lui et al., 2012; Novak et al., 2007; Viau et al., 2005). In addition, there are widespread changes in

the brain (e.g., neurotransmitter receptor densities, myelination; cell proliferation) during adolescence, and there is increasing evidence that adolescence is a second window for sexual differentiation of several brain regions (Cooke and Woolley, 2009; De Lorme et al., 2012).

There are fewer studies of HPA function in response to repeated stressors in adolescent rats compared with in adult rats. The typical finding from these studies is a higher corticosterone response to the last of a repeated stress exposure in adolescence than in adults (7th episode restraint stress (Lui et al., 2012; Romeo et al., 2006); 5th exposure to predator scent (Wright et al., 2012); 5th episode of restraint stress (Doremus-Fitzwater et al., 2009)). Greater neuronal activation of the PVN, as indicated by immediate early gene expression, was found after repeated restraint in adolescents than in adults (Lui et al., 2012; Romeo et al., 2006).

4.3. Social context, social stress, and the HPA axis in adolescence

Following social instability stress, episode behavior with the cage partner was monitored for an hour. No age difference was evident in the controls; male rats at both ages spent about half their time in physical contact with their partner (Hodges and McCormick, 2015). Active interaction with the cage partner was high after isolation in both groups compared with controls, but higher when returning to an unfamiliar partner (SS) than when retuning to a familiar partner (ISO). The only age difference was that whereas adolescent SS and ISO rats spent more time in physical contact with their cage partners than did CTL rats, adult SS and ISO spent less time in physical contact than did CTL rats. Thus, whereas adolescents increased affiliative behavior after isolation stress,

adults decrease affiliative behavior, irrespective of being housed with a familiar or unfamiliar cage partner (Hodges and McCormick, 2015).

There were no age differences in the corticosterone response to the first episode of isolation, which occurred at P30 or P70 days of age. The elevated corticosterone after isolation declined significantly after one hour back in the colony, and was higher in rats with an unfamiliar partner (SS) than with a familiar partner (ISO) at both ages (Hodges et al., 2014). After the 16th isolation, SS and ISO rats showed evidence of habituation; SS and ISO had lower corticosterone concentrations compared with age-matched CTL rats undergoing a 1st isolation, and adolescents and adults did not differ (Hodges and McCormick, 2015). After one hour back in the colony, when with a familiar partner, rats at both ages had low corticosterone concentrations irrespective of whether it was the 1st or 16th isolation. The same was observed for adult rats returned to an unfamiliar partner after isolation. In contrast, adolescents had a potentiated release of corticosterone when confronting their 16th unfamiliar cage partner than when with a new cage partner for the first time. In a study of adolescents only, CRH mRNA expression in the PVN was higher at baseline on the 16th day of the procedure compared with CTL such that neither ISO nor SS showed an increase to the 16th isolation that CTL rats showed to a 1st isolation on postnatal day 45 (McCormick et al., 2007). CRH mRNA expression in the central nucleus of the amygdala did not increase after the 16th isolation in ISO rats, but SS rats had increased expression to a 16th isolation as did CTL rats undergoing a 1st isolation (McCormick et al., 2007). In sum, social context moderated the effects of daily isolation. Although both adolescents and adults show similar social buffering effects, with

corticosterone returning faster to baseline when with a familiar than an unfamiliar partner, only adolescents showed evidence of sensitization of corticosterone release to repeated partner unfamiliarity (Hodges and McCormick, 2015). These results are consistent with the hypothesis that social context is a greater factor in the HPA functioning of adolescents than of adults.

Habituation, the reduction in glucocorticoid release to repeated stressor, is considered adaptive when the stressor is not harmful; habituation reduces the metabolic costs associated with activating the HPA axis and reduces the possibility of the negative consequences associated with high concentrations of glucocorticoids (Grissom and Bhatnagar, 2009). The reduced habituation evident in adolescent SS males and SS females means they were exposed to higher concentrations of glucocorticoids than both ISO and CTL rats. Further, both SS males and SS females have lower plasma CBG concentrations compared with CTL and ISO by the end of the procedure, which means a higher percentage of corticosterone is unbound (McCormick et al., 2007). The lack of habituation in adolescent SS rats may also be a basis for the heightened susceptibility of adolescents than adult to the lasting consequences of the procedure (McCormick et al., 2005; Morrissey et al., 2011).

Repeated exposure to SS sensitized the corticosterone response in adolescent male rats in response to a novel cage-mate, whereas in adults there was habituation of this corticosterone response. Male rats confronted with novel adult aggressors during adolescence exhibit sensitized corticosterone release from the first and last social defeat (Watt et al., 2009), while in adults the corticosterone response remains similar (Covington

and Miczek, 2005). These findings in socially defeated rats should be compared within the same experiment, which could be problematic because adolescent social defeat is quite different from adult social defeat. Nevertheless, these results support the idea that HPA output during adolescence in response to repeated stressors is hyper-excitable compared to adult rats (Romeo et al., 2006). Furthermore, the sensitized corticosterone response after repeated stressors may influence adaptive social behavior of socially housed rats during repeated confrontations with novel adult aggressors and perhaps also the pruning of neurons projecting to the medial prefrontal cortex (mPFC) during adolescence (reviewed in Burke and Miczek, 2014).

4.4 Effects of social instability stress (SS) in adolescence on social behavior

Glucocorticoids are recognized as a primary means through which environmental stressors experienced early in life have "programming effects", effects that persist well beyond the time of exposure, on brain development. There is increasing evidence that adolescence may be another window for such programming effects, particularly for the development of the social brain (Tzanoulinou and Sandi, 2016). In keeping with this possibility, when administered in adolescence, the SS procedure modifies several social behaviors, producing effects that are evident in adulthood several weeks after the end of the procedure. To date, we have only investigated effects on social behavior in males, although we have evidence for effects in females for other endpoints (e.g., increased locomotor sensitization to psychostimulants (Mathews et al., 2008); impaired spatial location memory (McCormick et al., 2010); reduced fear extinction (McCormick et al., 2013b)). In adulthood, adolescent SS males spent less time in social interactions with a

novel male in a test arena than did CTL rats (Green et al., 2013). SS males and CTL males did not differ in social approach, with the two groups spending the same amount of time near a novel male that was confined behind wire mesh (Green et al., 2013). We recently found the same difference in social interaction and lack of difference in social approach in rats tested soon after the SS procedure while still in adolescence (Hodges & McCormick, unpublished observations). These results suggest that SS males are socially anxious or perhaps did not develop an appropriate social repertoire, and that they may not be different in social motivation. An altered social repertoire in male SS rats is also evident in their behavior with receptive females. In five test sessions that began in adulthood six weeks after the SS procedure, SS rats had reduced sexual performance (completed fewer ejaculatory sequences and had reduced copulatory efficiency) compared with CTL rats and no evidence of reduced sexual motivation (McCormick et al., 2013a).

A study of performance against a cage mate in a food competition task provides additional evidence of a modified social repertoire in adolescent SS males in adulthood (Cumming et al., 2014). The food competition task provided the opportunity to investigate whether SS in adolescence alters the formation of dominant-submissive relationships (DSR) in dyadic pairs, a process that emerges after puberty (Adams and Boice, 1989; Pellis and Pellis, 1990). One proposed function of DSRs is to reduce overt aggression in the acquisition of resources, with priority access attained by the dominant of the pair (Berdoy et al., 1995; Hillman and Bilkey, 2012). Consistent with the latter proposal, more aggression was found in dyads for which there was no DSR than in dyads

for which there was a DSR during food competition sessions in which the dyads had access to a highly palatable food (sweetened condensed milk) in a feeder that allowed access only to one at a time (Cumming et al., 2014). Irrespective of DSR status (and SS and CTL dyads did not differ in terms of number of DSR and no-DSR dyads), however, SS dyads were more aggressive than CTL dyads during food competition sessions. The increased aggression may stem from an impoverished social repertoire and/or a heightened motivation for sweetened condensed milk in SS rats compared with CTL rats.

Lastly, evidence from ongoing studies also suggests that SS in adolescence has far-ranging effects on social function. SS males have impaired social memory compared with CTL males when tested in adolescence, and we are currently investigating to see if this deficit persists into adulthood (Hodges & McCormick, unpublished observations). We also have preliminary evidence that SS and CTL rats do not differ in their preference for ethanol vs water when ethanol is provided in the home cage. When access to ethanol is in test arenas, however, SS rats do not show the typical social effects on ethanol intake exhibited by CTL rats as adolescents; CTL rats drank more in test arenas when another rat was in an adjacent compartment separated by wire mesh than when alone, whereas SS rats drank the same amount when alone or when another rat was present (Marcolin & McCormick, unpublished observations).

5. Social defeat of adolescent rats and drugs of abuse

5.1. Social defeat cross-sensitization to drugs of abuse.

Brief episodes of social defeat stress activate the HPA axis in a fashion similar to the SS procedure described above. Under specific conditions, social defeat of adult rats

consistently increases: 1) psychostimulant self-administration during a progressive ratio schedule of reinforcement (PR) (Covington et al., 2008; Quadros and Miczek, 2009), 2) a 24-hour unlimited access binge (Covington and Miczek, 2001; Miczek et al., 2011), 3) acquisition of psychostimulant self-administration (Haney et al., 1995; Kabbaj et al., 2001), and 4) reinstatement of extinguished cocaine self-administration behavior (Manvich et al., 2015). In addition, adult social defeat also abolishes the circadian pattern of cocaine self-administration (Miczek et al., 2004). Taken together, social defeat of adult rats is a useful model for studying the neural basis for the connection between human social stress and drug abuse. The effects of social defeat during adolescence on subsequent drug reward behaviors have been investigated much less.

Social defeat during adolescence (≈P34) was first investigated for its impact on psychostimulant-induced behavior in adulthood using hamsters by Trzcinska et al. (2002), but the single episode of social defeat did not increase behavioral sensitization to systemic cocaine (20 mg/kg) and decreased the initial motor response to cocaine later in adulthood. Kabbaj et al. (2002) also found that a wide array of social stressors administered randomly during adolescence decreased systemic amphetamine-stimulated locomotion in adulthood. When a brief episode of social defeat was applied for five days from P35 to P39, it increased locomotion in response to a lower dose (1.0 mg/kg, ip.) of amphetamine (Burke et al., 2013). This dose was important because adolescent social defeat had no effect on the motor response to a higher dose (2.5 mg/kg) of systemic amphetamine (Burke et al., 2010). Based on these few studies, the timing and repetitive nature of the social stress procedure appears essential for motor cross-sensitization from

stress to psychostimulants to occur.

Social defeat of adolescent rats also increases the preference for an environment previously paired with an experimenter-administered dose of cocaine and amphetamine (Burke et al., 2011; Stelly et al., 2016). As behavioral responses to experimenter-administered psychostimulants do not always equate to voluntary drug self-administration behavior (Thomsen and Caine, 2011), an investigation of voluntary self-administration was necessary. The first study found that adolescent social defeat (four defeats from P31 to P35) did not affect nicotine self-administration that began on P36 (Zou et al., 2014). Adolescent social defeat on an intermittent schedule (four defeats from P35 to P44) increased the acquisition of cocaine self-administration in early adulthood and responding for cocaine during limited and extended access conditions about 40 days later in adulthood (Table 1) (Burke and Miczek, 2015). The differing results between these two studies are possibly due to the age of testing (adolescence vs adult), the type of psychostimulant tested (nicotine vs. cocaine), or the inclusion of a stress-free incubation period that may allow for gradual neural changes to complete. Intermittent social defeat of adolescent mice (four defeats P27 to P36) also increased acquisition of ethanol self-administration in adulthood, extending the long-term effects of adolescent social defeat to a different drug of abuse (Rodriguez-Arias et al., 2014).

- insert Table 1 here -

5.2. Housing conditions during social defeat and cocaine taking.

A critical factor for social defeat to exert negative outcomes is the housing condition of the intruder. Single housing, which deprives the adolescent of social play

fighting, increases measures of drug self-administration and preference in adulthood, but only when the rat is isolated from weaning onward (Lopez et al., 2011; Ribeiro Do Couto et al., 2009; Robbins et al., 1996; Schenk et al., 1985; Schenk et al., 1990). A critical period for single housing to increase drug conditioned place preference is P21 to P42 (Whitaker et al., 2013). In our study, single housed rats acquired the self-administration task at a higher rate than pair-housed rats (Burke and Miczek, 2015), which agrees with increased acquisition rates of psychostimulant self-administration in rats reared in isolation (Baarendse et al., 2014; Bardo et al., 2001; Ding et al., 2005; Howes et al., 2000). The general behavioral state of hyperarousal is common to isolation-reared rats (Einon et al., 1978; Powell et al., 2002) and might have contributed to the increased percent acquiring cocaine self-administration in the single housed groups. Isolation housing effects on acquisition of cocaine taking are observed at lower unit doses of cocaine (0.083 mk/kg) (Baarendse et al., 2014; Howes et al., 2000). Isolation-rearing usually shifts the dose response function to the left (Boyle et al., 1991; Phillips et al., 1994; Schenk et al., 1987), but see (Baarendse et al., 2014). In our study (Burke and Miczek, 2015), a standard dose of 0.75 mg/kg/infusion was used during acquisition to keep in line with previous adult social defeat studies (Miczek et al., 2011), but future studies should investigate the effect of single housing and social defeat stress on a dose response function. Single housed rats were unaffected by adolescent social defeat stress, whereas socially reared rats exhibited an elevated rate of acquisition of cocaine self-administration (Table 1) (Burke and Miczek, 2015). This suggests an important role of adolescent social experience in ability of social defeat stress during adolescence to

increase the acquisition of cocaine self-administration.

Housing adult rats individually intensifies adult social defeat stress, whereby single housing during social defeat attenuates body weight gain, sensitizes HPA axis, increases anxiety behavior, inhibits behavioral anticipation of sucrose reward, and impairs memory for conspecifics compared to group-housed defeated rats (de Jong et al., 2005; Nakayasu and Ishii, 2008; Ruis et al., 1999; Von Frijtag et al., 2000). The interaction of single housing and social defeat during adolescence was recently investigated. Social housing was necessary for social defeat during adolescence to escalate cocaine self-administration (Burke and Miczek, 2015). Cocaine self-administration acquisition, infusions obtained under a PR schedule of reinforcement, and infusions obtained during an unlimited access binge were all increased in adulthood after social defeat of pair-housed adolescent rats (Burke and Miczek, 2015). In single housed adolescents, only the acquisition of cocaine self-administration was increased with no escalation of cocaine taking observed during maintenance, PR or 24-hour binge, which agrees with a report that the most consistent effects of single housing on drug self-administration are found during the early stages of access to drugs of abuse, such as acquisition, and rarely impact subsequent measures of self-administration (Lu et al., 2003). Social defeat of single housed adolescents had no impact on cocaine taking in early adulthood at all. This suggests that social experience in the home cage during adolescence in some unknown way is required for social defeat stress to intensify drug-taking behavior later in life.

It was predicted that single housing and adolescent social defeat stress would have synergistic effects on cocaine self-administration based on previous studies in adults suggesting reduced stress reactivity in pair housed rats during social defeat, an effect referred to as "social buffering" (de Jong et al., 2005; Nakayasu and Ishii, 2008; Ruis et al., 1999; Von Frijtag et al., 2000). As mentioned above, there was no compounding effect of isolation housing and adolescent defeat on cocaine self-administration. In fact, single housed defeated rats self-administered less cocaine during the PR and 24 hour binge sessions than pair-housed defeated rats (Burke and Miczek, 2015). In adults, continuous subordination social defeat stress reduced cocaine self-administration and cocaine stimulated locomotion, while increasing anhedonia-like behavior, which is characterized by a reduced dopaminergic response to cocaine in the nucleus accumbens shell (Miczek et al., 2011; Shimamoto et al., 2015). During adolescence, isolation-rearing and brief daily episodes of social defeat increase depressive behavior compared to socially housed non-defeated control rats (Bourke et al., 2014). Perhaps isolation housed rats that gained the least amount of weight during adolescence and exhibited no motor cross-sensitization to a cocaine injection (Burke and Miczek, 2015), could potentially self-administer less cocaine than pair-housed defeated rats due to a state of anhedonia. The combination of single housing in conjunction with intermittent social defeat during adolescence may cause a depressive phenotype to manifest in adulthood. Further studies are needed to assess depressive-related behavior and anhedonia following social defeat of pair vs single housed adolescents to support this hypothesis.

The change in behavior over repeated social defeats during adolescence is relevant to drug abuse because it predicts the degree of cocaine self-administration in early adulthood. Specifically, the probability to freeze when attacked after repeated social defeats during adolescence is positively correlated with adult cocaine self-administration approximately 30-40 days later during PR and during the 24 hour binge (Burke and Miczek, 2015). In a follow up study, there was a strong correlation between adolescent rats that were quicker to adopt a supine posture after repeated social defeat episodes and self-administration behavior during limited and extended access to cocaine (Burke et al., 2016). Submissive behaviors that predict drug self-administration in adulthood are useful to identify neural mechanisms altered by adolescent social stress that increase risk for drug abuse without adding the confounding variable of cocaine, which would likely alter those very neural mechanisms under investigation. Further studies are needed to replicate this correlation and investigate causal relationships between submissiveness and conditioned defeat behavior during adolescence and drug seeking during adulthood.

There are clear differences in resident behavior toward adolescent and adult intruders. Even though great effort is made to select the most aggressive residents by screening with novel non-experimental adolescents repeatedly prior to each experimental cohort, residents attack adult pair-housed intruders faster and force submission quicker than when confronted with adolescent pair-housed intruders (Burke and Miczek, 2015). This confirms earlier reports of increased time to submission for adolescent intruders compared to adult (Ver Hoeve et al., 2013; Zou et al., 2014) and faster attack latencies

towards adult intruders compared to adolescent intruders (Garcia-Pardo et al., 2014). Adult residents threaten adolescent intruders differently than adult intruders as indicated by greater lateral threat toward adult and greater frontal threat toward adolescent intruders (Burke and Miczek, 2015). The lateral threat is often preceded and followed by intruder upright defensive postures (Koolhaas et al., 1980) and is thought to give the intruder the opportunity to submit without being attacked (Plyusnina et al., 2011). This difference in resident threat style dependent on intruder age is probably driven by the intruder's defensive behavior (Blanchard and Blanchard, 1977), in this case by reduced upright defensive and supine postures among adolescents (Burke and Miczek, 2015). Ver Hoeve et al. (2013) also report less upright defensive behavior in female adolescent intruders compared to adults, suggesting this adolescent reduction in upright defensive posture occurs independent of sex. Overall, territorial aggression from the resident is reduced when the intruder is adolescent and behavioral measures of submission and aggression are quite different.

The adolescent behavior that is correlated with adult cocaine taking is a behavior unique to adolescent rats under these experimental parameters. In response to an attack bite, adolescent intruder rats exhibit reduced probability of adopting the supine posture and the upright defensive posture, but increased freezing and immobility, while adults show the opposite behavioral pattern (Burke and Miczek, 2015). Perhaps adolescent rats have underdeveloped social skills and lack experience with aggressors, resorting to freezing. There are no differences in freezing in response to a tone or acute foot-shock in adolescent and adult rodents (Broadwater and Spear, 2013), suggesting this age

difference in freezing could be unique to social contexts. To date, the influence of housing condition during adult social defeat and its role in escalation of drug self-administration has not been investigated. One would predict remarkable age differences in the connection between social experience and subsequent drug taking because adolescence is a particularly vulnerable period for social development. However, one important issue is that social defeat of adolescent rats is quite different than adult social defeat on a behavioral level, which makes a comparison of adolescent and adult social defeat within the same experiment problematic.

Overall, there are several important factors to consider based on the limited number of published studies regarding the rodent model of the link between socially stressed adolescents and subsequent elevated risk for drug abuse. 1) The social defeat confrontations need to be brief and intermittent in order for the stress to increase later brain and behavioral responses to drugs of abuse and drug self-administration. 2) Social experience (group housing) during the intermittent exposure to brief social defeats is required for adolescent social defeat to cross-sensitize to psychostimulants and escalate self-administration. 3) Social deprivation during adolescence results in maladaptive behavioral coping strategies when confronted with an adult aggressor during mid-adolescence. 4) The manner in which an individual copes with an attack after repeated social defeats during adolescence may be related to the degree of cocaine self-administration in adulthood, whereby more submissive behavior (freezing) during attacks is correlated with more cocaine taking later in life. 5) There are clear age differences in

both resident and intruder behavior during social defeat of pair-housed rats that make direct comparisons of adult and adolescent social defeat challenging.

Future studies should investigate the face validity of this model by measuring drug-seeking despite negative consequences (punished drug self-administration) and risk for relapse (reinstatement of drug seeking) following adolescent stress. Adolescent behavioral phenotypes that predict adult drug self-administration are useful to identify neurobiological, neuroendocrine, and genetic risk alterations without having the confounding variable of drug exposure. This line of research may also prove useful for testing potential pharmacological, behavioral, and genetically based interventions that could eventually lead to therapeutics useful to treat those at risk for substance use disorder following a history of social stress.

6. Neural basis for adolescent social experiences to alter brain development.

6.1. Cortex and social play behavior

Systems related to motivation and reward (hypothalamus, ventral striatum), as well as ones related to emotional regulation and motor control (amygdala, dorsal striatum) are involved in social play behavior (Siviy and Panksepp, 2011; Trezza et al., 2010; Vanderschuren et al., 2016). Cortical systems, especially the prefrontal cortex, are activated during play (Gordon et al., 2003; Gordon et al., 2002). Increased social play, but not increased solitary play (i.e., playing with objects or engaging in locomotion-related play) among a range of primate species, was correlated with increased size of the cortex, amygdala, hypothalamus and striatum (Graham, 2011; Lewis et al., 2002; Lewis and Barton, 2006).

In rats, removal of the cortex at birth does not affect the age related increase in play fighting in the juvenile and early adolescent periods and its decrease with the onset of puberty. Moreover, the frequency of play at its peak is not different to that of intact controls (Panksepp et al., 1984; Pellis et al., 1992). Nor does decortication prevent rats from using the full repertoire of playful tactics (Pellis et al., 1992) and produce normal levels of role reversals (Himmler et al., 2016). These findings suggest that the ability to motivate, produce and maintain play fighting does not require the cortex. However, the cortex appears to be involved in contextually modulating behavioral actions both during play by adolescents and play and other social interactions by adults (Pellis & Pellis, 2016).

Rats deprived of play experience in the juvenile period as adults have difficulty in coordinating their movements with social partners (Moore, 1985; Pellis et al., 1999) and fail to behave in a submissive manner when confronting a dominant male leading to them being attacked aggressively (Byrd & Briner, 1999; van den Berg et al., 1999). Closer inspection of the play fighting in post-pubertal decorticate rats indicate comparable deficits (Pellis et al., 1992). Given the activation and involvement of the prefrontal cortex during play (Siviy, 2016), lesion studies were conducted to ascertain its role in social interactions. Damage to the orbital frontal cortex (OFC), an area known to be involved in social behavior (Kolb, 1984), lead to rats failing to modify their behavior with the identity of their partner (Pellis et al., 2006). Damage to the mPFC, an area known to be involved in attention and impulse control, and shown to be affected by juvenile social experiences (Baarendse et al., 2013), lead to rats with a reduced ability to effectively

coordinate their movements with those of their social partner (Bell et al., 2009; Himmler et al., 2014a).

6.2. Effects of isolation-rearing during adolescence on the brain

Functional changes in the mPFC and in abilities such as impulse control that are known to depend on these prefrontal cortical systems, are altered by rearing animals under social isolation conditions throughout adolescence (Baarendse et al., 2013). Socially reared rats that have had the opportunity to interact with peers show a pruning of the dendritic arbor and changes in the density of synapses in the neurons of the mPFC (Bell et al., 2010; Himmler et al., 2013a). This pruning may be associated with the play-induced functional changes in the activity of the mPFC that corresponds to improved behavioral performance (Baarendse et al., 2013; Himmler et al., 2014a). One playful peer is sufficient to produce this pruning, whereas being reared with a relatively non-playful adult is not. Being reared with multiple peers, whether playful or not, has the effect of maintaining a complex dendritic arbor and a high density of synapses in the neurons of the OFC (Bell et al., 2010), which may correspond to functional changes in the activity of the OFC that corresponds to improved ability to discriminate between partners (Pellis et al., 2006). It is also worth noting that once weaned: 1) adults do not readily interact with adolescents (Cramer et al., 1990), 2) adolescent rats are highly motivated to play with peers (Douglas et al., 2004) and 3) breeding is synchronized in colonies containing multiple mature females (Calhoun, 1963) with the result of their being many same-age play partners available. Therefore, much of the experience gained in interacting with multiple partners derives from playing with peers. Either directly (for the mPFC) or

indirectly (for the OFC), play with peers during the adolescent period is critical for the modification of neural circuits of the prefrontal cortex that are essential for being able to modulate responses in social and non-social contexts (Pellis et al., 2014; Vanderschuren and Trezza, 2014).

Although the timing and duration of isolation protocols used vary, isolation-rearing during adolescence appears to alter markers of serotonergic activity in the mPFC. Adult rats exposed to adolescent social isolation exhibit altered serotonergic activity in various forebrain regions (Fulford and Marsden, 1998; Jones et al., 1992; Lukkes et al., 2012b; Lukkes et al., 2013; Lukkes et al., 2009c). For instance, social isolation has been shown to increase 5-HT_{1A} and 5-HT_{2A} receptor binding (Gunther et al., 2008) and enhance serotonergic turnover (Brenes and Fornaguera, 2009) as well as concentrations of serotonin (Miura et al., 2002a, b; Rilke et al., 1998). Reduced freezing behavior in adult rats is associated with an increased release of serotonin in the mPFC (Forster et al., 2006). In contrast, increased anxiety-like behavior in rats coincides with depletion of serotonin in the PFC (Pum et al., 2009). Serotonergic activity in the mPFC appears to be an important component of the stress-coping response (Forster et al., 2006; Forster et al., 2008). Therefore, up-regulation of serotonergic activity in the PFC may represent an adaptive compensatory change in response to adolescent isolation-rearing.

Poor regulation of stress responses play a role in depression and anxiety and are partially mediated by mPFC projections to the dorsal raphe nucleus (DR) (Amat et al., 2005; Robbins, 2005). The DR is a serotonergic cell body region of topographically organized, functional subsets of serotonergic neurons that regionally react to stress-

specific stimuli. For instance, the dorsal DR (DRD) and caudal DR (DRC) are involved in affect processing (Hale et al., 2012; Lowry et al., 2005; Van Bockstaele et al., 1993). Specifically, serotonergic neurons concentrated within the DRD project to structures associated with neural circuits modulating anxiety states and are selectively activated by a variety of anxiety-related stimuli (Abrams et al., 2005; Commons et al., 2003; Lowry et al., 2005; Van Bockstaele et al., 1993), including the CRF type 2 (CRF_2) receptor ligand, urocortin 2 (Staub et al., 2006; Staub et al., 2005). This neurochemically distinct area of the DR projects to the nucleus accumbens (NAc), basolateral nucleus of the amygdala (BLA), and mPFC (Lowry et al., 2005; Van Bockstaele et al., 1993) and receives input from the bed nucleus of the stria terminalis (BNST), which plays an important role in mediating anxiety-related behavior (Davis, 1998; Gewirtz et al., 1998; Levita et al., 2004; Walker et al., 2003). These unique connections projecting from and into the DRD suggest that this subregion of the DR may play an important role in the regulation of anxiety-related physiological and behavioral responses (Lowry et al., 2005; Maier and Watkins, 2005), and affective disorders (Commons et al., 2003). The DRVL is selectively sensitive to panicogenic agents such as CO2 and sodium lactate (Johnson et al., 2005; Johnson et al., 2008b), and are implicated in vulnerability to panic-like responses (Hale et al., 2012; Johnson et al., 2008a; Johnson et al., 2011; Johnson et al., 2008b). Stressor controllability is regulated by mPFC projections to the DR (Maier and Watkins, 2005). In turn, serotonergic activation of the DR projecting to the mPFC is required for the production of anxiety- and depressive-like behavior (Amat et al., 2004; Lowry et al., 2005).

Another neural circuit that plays a role in isolation-induced anxiety, particularly in females, is the DR-BLA pathway. The anxiogenic drug, *N*-methyl-beta-carboline-3-carboxamide (FG-7142; a partial inverse agonist at the benzodiazepine allosteric site on the γ-aminobutyric acid (GABA)A receptor) increased neural activity as measured by c-Fos expression. Isolation-reared female rats injected with FG-7142 had greater c-Fos expression within the BLA and in serotonergic neurons in the DRD, ventrolateral DR (DRVL), and DRC relative to appropriate vehicle-injected control groups (Lukkes et al., 2012a). In contrast, group-reared rats displayed no such increase in c-Fos expression (Lukkes et al., 2012a). These data suggest that activation of the BLA-DRD pathway requires an additional subsequent stressor following isolation-rearing during adolescence. Isolation-reared female rats also exhibited decreased mRNA expression in the rate-limiting enzyme for serotonin synthesis, tryptophan hydroxylase 2 (*tph2*) in the DRVL (Lukkes et al., 2013), a pattern observed previously in a rat model of panic disorder. These data suggest that adolescent social isolation alters *tph2* expression in specific subregions of the DR and alters the effects of stress-related stimuli on behavior and serotonergic systems. In contrast, we did not observe this effect of adolescent social isolation on *tph2* mRNA expression in males (Lukkes et al., unpublished observations). Furthermore, isolation-reared females may have an increased excitability of the amygdala, which in turn selectively alters *tph2* mRNA expression in DRVL serotonergic neurons that are heavily innervated by the amygdala (Donner et al., 2012; Peyron et al., 1998). Consistent with this hypothesis, we have found that adolescent isolation-rearing results in a decrease in c-Fos immunostaining in a parvalbumin-expressing subset of local

GABAergic interneurons within the BLA (Lukkes et al., 2012a). These data suggest that post-weaning social isolation of female rats interferes with the normal, adaptive activation of a subpopulation of local inhibitory GABAergic interneurons within the BL by stress-related stimuli, which may lead to an increased vulnerability to stress-and anxiety-related responses in adulthood. Chronic anxiety states in female rats exposed to adolescent social isolation may be due to a dysregulation of resilience mechanisms involving serotonergic activation of 5-HT_{2A} receptor expressing GABAergic interneurons in the BLA. Overall, adolescent isolation-rearing of female rats sensitizes a DR-BLA system to stress-related stimuli, which may lead to an increased sensitivity to stress- and anxiety-related responses in adulthood.

Corticotropin-releasing factor and CRF-related peptides are important neurotransmitters involved in integrating multiple components of the stress response. CRF-synthesizing neurons are widely distributed in the brain, including in the central nucleus of the amygdala (CeA) and BNST (Gray, 1993). Consistent with a role for extrahypothalamic CRF in regulating stress-related behaviors, extracellular CRF concentrations in the CeA are increased in response to a stressor (Merlo et al, 1995; Merali et al, 1998). The CeA provides CRF innervation to the serotonergic DR (Gray, 1993), which in turn provides serotonergic innervation to stress-related forebrain regions such as the mPFC, NAc, and BLA (Lowry et al., 2005; Van Bockstaele et al., 1993). The behavioral effects induced by CRF, such as increased anxiety, are thought to be mediated, in part, by CRF effects on serotonergic systems within the DR (Kirby et al, 2000; Hammack et al, 2002; Forster et al, 2006; Lowry and Moore, 2006). Both CRF_1 and

CRF_2 receptors have been detected in the DR (Commons et al, 2003; Funk et al, 2003, Day et al, 2004) and have opposing effects on serotonergic release (Kirby et al, 2000; Pernar et al, 2004; Lukkes et al, 2008). CRF_1 receptors are high affinity and inhibit serotonergic activity, whereas CRF_2 receptors are low affinity and facilitate serotonergic activity in the DR (Kirby et al., 2000; Pernar et al., 2004).

Dysregulation of CRF receptors in the DR may contribute to the increased vulnerability to anxiety- and depressive behavior after a stressful event (Bangasser et al., 2010; Weathington et al., 2014). The anxiogenic effects of isolation-rearing are attenuated by CRF receptor antagonism within the DR (Lukkes et al., 2009a). Furthermore, isolation-rearing up-regulates CRF_2 receptor expression in the DR resulting in prolonged serotonin release in the NAc in male rats (Lukkes et al., 2009c). Our limited studies in young adult female rats also show that isolation-rearing enhanced stress sensitivity in anxiety-related subregions of the DR that project to the NAc and BLA (Lukkes et al., 2013). These findings suggest that the isolation-induced behavioral alterations in anxiety and stress responses could be due to modifications of the mechanisms regulating stress-related CRF release in the DR during adolescence.

We recently investigated the ontogeny of CRF receptors in specific sub-regions of the DR of both males and females to help elucidate their role during adolescence (Lukkes et al., 2016). Surprisingly we found few age-related changes throughout adolescent development. However, females had higher levels of CRF_2 receptor mRNA than males in the key DR sub-regions of the DRD and the DRVL. These sub-regions are known to project to the PFC and NAc, where they modulate anxiety- and depressive-like behavior

(Hale et al., 2012; Van Bockstaele et al., 1993). Sex differences in CRF_2 in the DRD and DRVL may be related to elevated anxiety. Higher CRF_2 expression in the DRVL of adolescent females may underlie sex differences in response to stress-related situations. Differential sex-dependent behavioral responses to stressful situations are consistent with previous studies (Lukkes et al., 2013; Doremus-Fitzwater et al., 2009; McCormick et al., 2008). Furthermore, Weathington et al., (2014) found that females have less CRF_2 receptors than males in BNST and more CRF_2 receptors in the lateral septum (Weathington et al., 2014). Overall, these studies suggest that the ontogeny of CRF receptors may underlie sex-differences in the emergence of stress-related psychiatric disorders and provide insight into the efficacy of sex-dependent treatment options for these disorders.

6.3 Effects of social defeat stress during adolescence on the brain

The social defeat stress that adolescent rats experience under experimental conditions has long-term effects on the brain. For instance, adolescent social defeat reduces mPFC dopamine levels and attenuates the mPFC dopaminergic response to amphetamine in early adulthood (Burke et al., 2013; Burke et al., 2010; Watt et al., 2009). Social experience during adolescence or adulthood is important for dendritic arborization in the OFC and prefrontal cortex regulation of social behavior and an intact mPFC is important for play fighting behavior to occur (Bell et al., 2009; Pellis et al., 2006). Furthermore, deprivation of social play (isolation-rearing) alters dopaminergic modulation of mPFC function underlying impulse control (Baarendse et al., 2013) later in

life. These findings suggest an intricate relationship between adolescent social experience and the mPFC.

The mPFC projects to the NAc and low levels of dopamine in the mPFC are hypothesized to allow for higher levels of NAc dopamine to be stimulated by drug and naturally rewarding stimuli (Mitchell and Gratton, 1992). Indeed, social defeat also enhanced the NAc core dopamine response to amphetamine in adulthood (Burke et al., 2010). Repeated restraint stress during adolescence also increased NAc dopamine tissue content in response to amphetamine, but this effect was short lasting and disappeared by adulthood (Cruz et al., 2012). Social defeat stress during adolescence may effectively cause long-lasting changes in the mesoaccumbal dopamine system to increase the dopaminergic response to drugs of abuse in adulthood.

The ventral tegmental area (VTA) is the dopamine cell body region that is the primary dopaminergic projection to the NAc and also has projections to the mPFC. Neural plasticity in the VTA as measured by long-term potentiation of NMDA receptor-mediated glutamatergic transmission, was enhanced following social defeat stress during adolescence (Stelly et al., 2016) and isolation rearing (Whitaker et al., 2013) and associated with cocaine conditioned place preference. This implicates the VTA as a site of action for adolescent social adversity to alter the brain in a way that increases drug reward. Antagonism of the CRF_1 receptor in the VTA of adolescent rats blocked the ability of social defeat to increase cocaine self-administration some 40 days later in adulthood (Burke et al., 2016). Thus, CRF_1 receptors in the VTA are required for adolescent social defeat stress to increase adult cocaine taking. The same effect was

observed in adult rats that were socially defeated during adulthood (Boyson et al., 2014), suggesting that this CRF_1 role may be not unique to adolescence. Recent analysis of the ontogeny of VTA CRF receptors support this idea because CRF_1 receptors mRNA in the VTA during adolescence are no different than in adulthood (Lukkes et al., 2016). More investigation is needed to isolate neural mechanisms involved in the link between adolescent stress and later risk for drug abuse that are unique to adolescence.

Recent evidence implicates the VTA CRF_1 receptor in behavioral adaptations to repeated social defeat stress during adolescence. Over repeated social defeat encounters, vehicle infused adolescents reduced non-social exploration and increased social investigation of the aggressive resident (Burke et al., 2016). These adaptive behavioral changes to repeated social defeats were blocked by the intra-VTA infusion of a CRF_1 receptor antagonist just prior to the social defeat interaction (Burke et al., 2016). These results support a role for VTA CRF_1 receptors in behavioral adaptations under high stress conditions.

6.4 Effects of social instability stress during adolescence on the brain.

Our initial investigations on the effects of SS on the brain focused on the hippocampus for several reasons. The hippocampus has a high density of corticosteroid receptors, is involved in negative feedback regulation of HPA function, and hippocampal neurogenesis and dendritic arborization are highly sensitive to stressors in adults (McEwen, 2012), and thus likely to be even more sensitive in adolescence. The hippocampus is continuing to mature in adolescence; for example, neurogenesis and the density of dendritic spines are higher in early adolescence and begin to decline to adult

levels soon after puberty (He and Crews, 2007; Yildirim et al., 2008) and adolescents perform differently from adults on hippocampal dependent tasks (McCormick and Mathews, 2010). In female adolescents, SS rats had reduced hippocampal neurogenesis compared with control female adolescent rats (McCormick et al., 2010), consistent with the dampening effects of chronic stress on neurogenesis reported for adults (e.g., Mirescu and Gould, 2006). We investigated hippocampal neurogenesis more extensively in males, and found a different pattern of effects than we had found for females. Initially, the daily stress procedure increased cell proliferation, although there was no increased hippocampal cell proliferation by the end of the SS procedure or later on in adulthood (McCormick et al., 2012). There appeared instead to be a longer survival of immature neurons in the hippocampus in SS male rats compared with control male rats, and the increased survival also was found in adults, suggesting that the SS procedure affected hippocampal neurogenesis long after its termination. What is unclear, though, is how these two different effects in males and females are related to the decreased performance on hippocampal-dependent tasks found in both male and female rats after the SS procedure (McCormick et al., 2010, 2012).

6.5 Potential treatment for stress-related neuropsychiatric disorders

These data may have a significant impact on identifying novel targets for the development of therapeutic treatment and interventions, with the ultimate aim for the prevention of depression, anxiety, and substance abuse disorders. Although serotonergic based treatments seem logical given this circuitry, clinical studies have shown that they are not as effective in adolescents or have too many other limitations for their use (March

et al., 2004; Sussman et al., 2001; Weintrob, 2002; Weintrob et al., 2002). One plausible avenue of treatment for adolescent anxiety and depression is the use of CRF receptor antagonists. Currently, CRF_1 receptor antagonists are failing in clinical trials for the treatment of stress-related disorders (Kehne and Cain, 2010). Our preclinical data and others suggest that CRF_2 receptor antagonists may be a novel target for the treatment of anxiety and depression but this needs further investigation (Hammack et al., 2003; Lukkes et al., 2009a). Our previous data shows that DR CRF_2 receptors are elevated in isolation-reared males (Lukkes et al., 2009a). However, we do not know how social stressors affect CRF receptors in the DR in males and females. Future research should determine how CRF_1 or CRF_2 receptors are altered in the DR throughout adolescence following social stress.

7. Sex differences following adolescent adversity

Sex differences in stress-related neuropsychiatric disorders, such as depression and anxiety, emerge during adolescence when females are 70% more likely to develop depression and 60% more likely to experience an anxiety disorder in their lifetime compared to males, possibly due to an increased sensitivity to stress (Paus et al., 2008). Despite the evidence that females have an increased risk for the development of neuropsychiatric illnesses, most studies have focused on males, and females have been insufficiently studied

7.1. Role of hormones in sex differences

While the precise mechanisms for these sex differences are poorly understood, gonadal hormones probably play a role. For instance, low levels of estrogen are

associated with greater depressive-like symptoms in rodents (Hajszan et al., 2010). Furthermore, hormonal changes precipitated by puberty are thought to be one of the most important influences driving social reorientation in adolescence in humans (Forbes and Dahl, 2010) and are most likely a neural underpinning of adolescent social processes. Puberty-related hormonal changes increase the salience of peers and coincide with early stages of pubertal development (Blakemore et al., 2010; Forbes and Dahl, 2010; Steinberg, 2004). Prefrontal cortical activity during reward processing is linked to puberty (Forbes et al., 2010). In rats, ovarian hormones play an important role in maintaining female-typical patterns of play behavior (Pellis, 2002). A hypersensitivity to social exclusion has been reported in teenage girls (O'Brien and Bierman, 1988; Sebastian et al., 2011). This hypersensitivity may be related to pubertal timing although current data are equivocal. For instance, earlier pubertal timing in girls has been associated with more depressive symptoms (Benoit et al., 2013; Graber et al., 1997; Miller and Gur, 2002). In contrast, social stress during the juvenile period delays pubertal timing in female non-human primates (Wilson et al., 2013). These data implicate altered pubertal timing in the risk for emotional dysregulation possibly by altering the course of developing limbic neurocircuitry.

In addition to a role for gonadal hormones influencing sex differences, hormones associated with the HPA axis may also be important. Function of the HPA axis differs in males and females, partly from the process of sexual differentiation early in development (late fetal, early neonatal periods), and partly from activational effects of gonadal hormones when concentrations rise after puberty (McCormick and Mathews, 2007). In

brief, testosterone tends to inhibit, and estradiol tents to potentiate, HPA responses to stressors. Thus, females tend to have higher CRH, ACTH, and corticosterone release in response to stressors compared with males. Sex hormones influence the HPA axis through actions in the periphery, but also through actions in the PVN and at upstream neural regions (e.g., medial preoptic area) (Handa and Weiser, 2014).

7.2. Effects of social stress on brain and behavior in females

The peak in play fighting for adolescent females occurs at a different time than for adolescent males (Pellis and Pellis, 1990; reviewed in Burke and Miczek 2014). Overall, same sex play behavior is greater in males than in females, especially when reared in mixed sex groups (Meaney and Stewart, 1981; Pellis and Pellis, 1990), but can be diminished when: 1) rats are reared in isolation (Panksepp, 1981), 2) reared with a single same sex partner (Himmler et al., 2013c; Himmler et al., 2014b), or 3) the sex of the partner with which the subject is tested (Argue & McCarthy, 2015).

In the few studies that have investigated the effects of post-weaning social isolation on behavioral measures in female rodents, findings have been inconsistent. Methodological differences amongst isolation studies that include differences in onset and duration of isolation as well as strain differences may account for the lack of consistency in the expression of heightened anxiety states. However, the limited number of studies that have used female rats suggest that isolation-rearing and/or isolation housing appears to increase anxious behavior of female rats (e.g.; (Arakawa, 2007; Leussis and Andersen, 2008). For example, female rats isolated from pre- to mid-adolescence, compared to group-reared rats, showed increased latency to emerge into an

unfamiliar open-field, decreased center entries, and decreased defensive burying (indicative of reduced proactive coping) when tested in a state of social deprivation between P40 and P45 (Arakawa, 2005, 2007; Einon and Morgan, 1977). In addition, a shorter isolation period of female rats from P30 to P35 also reduced time spent in open arms when tested on EPM at P36 (Leussis and Andersen, 2008). In a recent study by Hermes et al. (2011), female rats that were isolated from P19 to P70 exhibited increased anxiety behavior in an open-field and social interaction test when compared to group-reared controls (Hermes et al., 2011). In contrast, Weiss et al. (2004) isolated rats from P21 until day of EPM testing in adulthood (P91), and found female rats did not exhibit increased anxiety behavior. Similarly, Ferdman et al. (2007) found no effect of 13 to 14 weeks of social isolation in female rats on anxiety behavior in the social interaction test. Adolescent isolation-rearing of female rats from P21 to P42 followed by re-socialization, relative to group-rearing, had no effect on anxiety behavior in the social interaction test during adulthood (Lukkes et al., 2013). However, isolation-reared female rats, in contrast to group-reared rats, did respond with increased arousal and vigilance behaviors during adulthood in a home cage environment, associated with decreased exploration, following challenge with the anxiogenic drug FG-7142 (a partial inverse agonist at the benzodiazepine allosteric site on the γ-aminobutyric acid (GABA)A receptor) (Lukkes et al., 2013). When isolated from P30 to P35, increased anxiety-like behavior was only observed in females (Leussis and Andersen, 2008). Combined, these data suggest that social isolation restricted to a sensitive window of development has both immediate and enduring effects on anxiety, including social anxiety.

Using the SS model in adolescent females, daily isolation had only a modest effect on social interactions when returned to the colony in females, irrespective of whether they returned to a familiar or unfamiliar partner compared with males (McCormick et al., 2007). Further, whereas ISO females had reduced corticosterone release to the 16th isolation than did age-matched CTL undergoing a first isolation, SS rats showed no evidence of habituation to repeated isolation. Thus, social context moderated the habituation of corticosterone release to repeated isolation in females, whereas in males the effects of social context were only evident in the sensitized response to repeated pairings with new cage partners rather than in response to repeated isolation. It is important to note that utilizing social defeat in females is difficult because females only exhibit territorial aggression during specific stages of lactation. Overall, more research is needed to determine the sex-dependent effects of adverse experiences during adolescence on both behavioral and neural changes. A better understanding of these changes will lead to more effective treatments and novel targets in females with stress-related neuropsychiatric disorders.

8. Conclusions

Social stress during adolescence has long lasting effects on both behavior and stress-related neural circuits. Increased anxiety and depressive behavior as well as heightened drug use occur when the normal developmental trajectory of social play is altered. This heightened sensitivity to social stressors in adolescence may reflect the importance of social learning and the building of the social brain in adolescence. Furthermore, the reviewed data suggest that the quality of social experiences in

adolescence has marked effects on social development. The findings presented in this review suggest that adolescents have a greater sensitivity to social context compared to adults in the regulation of stress-induced corticosterone release. Social interactions in the home cage are necessary for social defeat stress to increase drug taking and display adaptive social behaviors when confronted with an adult aggressor based on a study manipulating housing conditions of adolescent male rats throughout adolescent social defeat exposure. In addition, social deprivation during adolescence alters serotonergic function in stress-sensitive neural regions, which may underlie the anxious and depressive behavioral phenotypes observed in animals exposed to social stress paradigms during this formative period. Increased sensitivity to stressors following social stress may be due to alterations in CRF-mediated serotonergic function in the limbic system. However, the sex-dependent effects of adolescent social stress on later anxiety, depressive, and substance abuse behavior as well as on serotonergic function requires further investigation, given that females are more likely to suffer from mood disorders (Becker et al., 2007; Nestler et al., 2002). Disruptions in stress-related neural networks may help explain how stressful experiences during adolescence heighten the risk of developing anxiety, depression, and substance abuse disorders in adulthood.

Peer relations during childhood and adolescence have been identified as one of the most powerful predictors of concurrent and future psychiatric disorders (Thapar et al., 2012). Early identification of abnormal social interactions and/or active coping strategies has the potential to predict individuals that may require intervention to prevent stress-related neuropsychiatric disorders. As indicated in this review, social interactions during

adolescence have an essential role in healthy maturation for the laboratory rat, and many studies involving humans and rodents have illustrated the negative consequences associated with limited or abnormal play exposure in childhood (Bell et al., 2010; Darwish et al., 2001; Schneider et al., 2016). A major advantage to the development of appropriate animals models such as those reviewed here (social defeat, social instability, and social isolation in adolescence) is that researchers can manipulate social stress experience and identify possible neural mechanisms under highly controlled experimental conditions. Applying cutting edge neuroscience techniques to these models should identify precise neural mechanisms and interventions that are potentially useful to improving human mental health.

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Figure Captions:

Figure 1. Schematic timeline of the experimental procedures and terminology discussed in this review.

(Note to editor as requested by the author guidelines: The authors request Figure 1 appear in color online, but black and white in print.)

Figure 2. A sequence of play fighting is shown for a pair of juvenile rats. The rat on the left approaches another rat from the rear (a) and pounces towards its partner's nape (b). Before contact is made, the defender rotates around its longitudinal axis (c) to face its attacker (d), but the attacker continues to move forward pushing the defender onto its side (e). The defender then rolls over onto its back as its attacker stands over it, restraining the defender's movements while continuing to reach for its nape (f–h). The supine defender launches a counterattack to its partner's nape (i), which is blocked (j, k). With continued squirming by the supine partner, the rat on top (l) is pushed off by the supine animal (m). The original defender then stands up (n) and lunges towards its partner's nape (o). The sequence involves repeated attack and defense of the nape and role reversals to which partner attacks and which defends. Reprinted from Pellis & Pellis (1987) with permission.

Figure 3. Three types of defense to a playful nape attack are illustrated in 61-day-old male rats. A. Evasion: Following the attacker's lunge at the nape (a, b), the defender

swerves away from the attacker (c). B. Complete rotation: A nape contact from behind (a) leads the defender to rotate (b, c) until lying supine and blocking the attacker with its outstretched paws (d). C. Partial rotation: A lunge to the nape from the side (a, b) is followed by a rotation of the head, neck and shoulders by the defender, withdrawing the nape from the attacker's snout (c). Reprinted from Pellis et al. (1992) with permission.

Figure 4. A common position that is adopted during play fighting is for one animal to stand over its supine partner. The rat standing on top usually does so by standing on the ground with its hind paws and using its forepaws to restrain its supine partner (a). However, sometimes the rat on top stands on its partner with all four of its paws (b), greatly diminishing its postural stability. Reprinted from Foroud & Pellis (2003) with permission.

Tables:

Table 1. Summary of how social defeat during adolescence impacted cocaine self-administration in adulthood for socially (pair housing) and isolation (single housing) reared rats (based on Burke and Miczek 2014). An up arrow indicates adolescent social defeat increased the above measure for that housing condition, while an equals sign indicates no change.

Effect of Adolescent Social Defeat	Cocaine Self-Administration			
	Acquisition	Maintenance	Progressive Ratio	24-Hour Binge
Social (Pair) Housing	↑	=	↑	↑
Single Housing	= *	=	=	=

*Indicates greater than socially housed rats for both controls and socially defeated adolescents

Figure 1

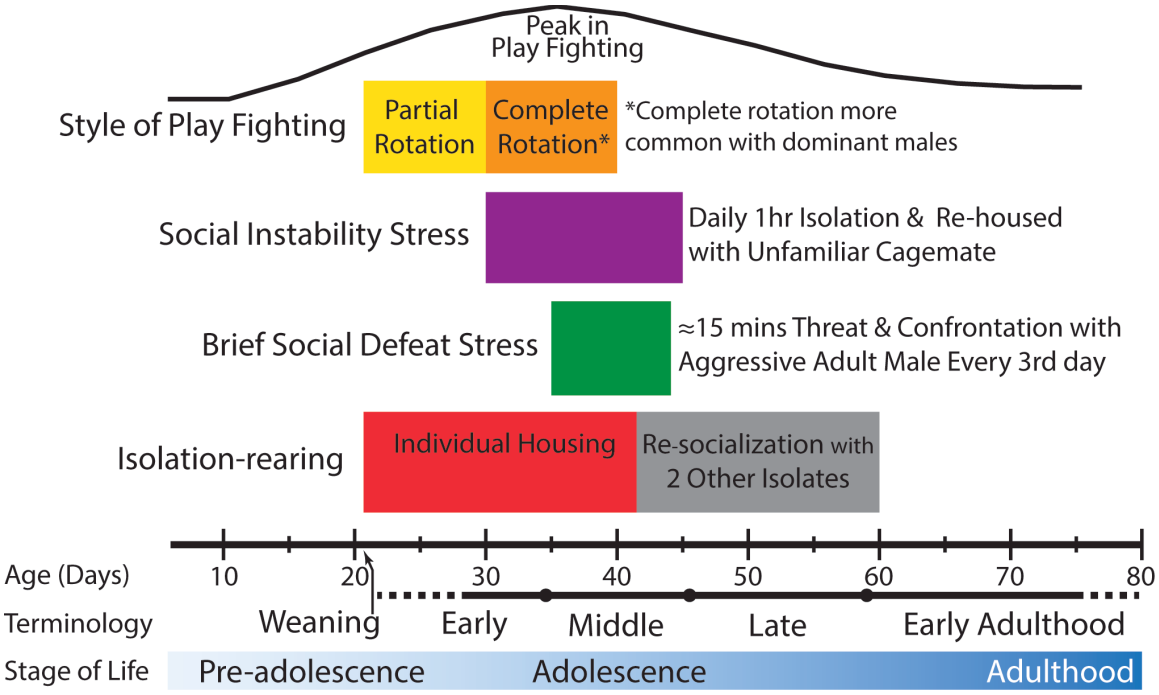
Peak in
Play Fighting
Style of Play Fighting
Partial Rotation
Complete Rotation*
*Complete rotation more common with dominant males
Social Instability Stress
Daily 1hr Isolation & Re-housed with Unfamiliar Cagemate
Brief Social Defeat Stress
≈15 mins Threat & Confrontation with Aggressive Adult Male Every 3rd day
Isolation-rearing
Individual Housing
Re-socialization with 2 Other Isolates
Age (Days)
10
20
30
40
50
60
70
80
Terminology
Weaning
Early
Middle
Late
Early Adulthood
Stage of Life
Pre-adolescence
Adolescence
Adulthood

Figure 2

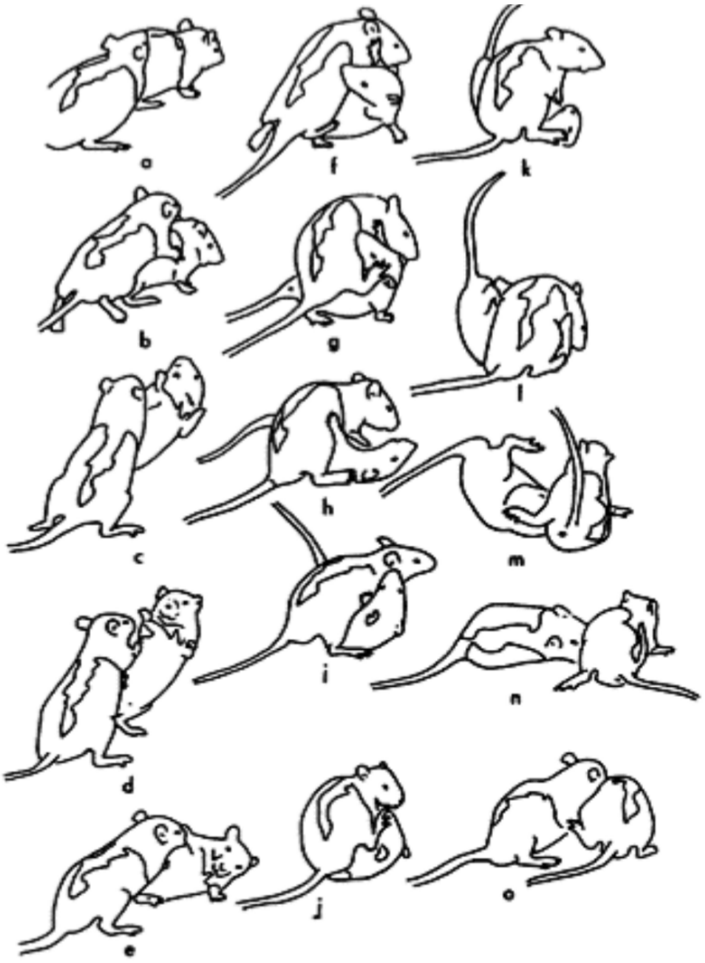

Figure 3

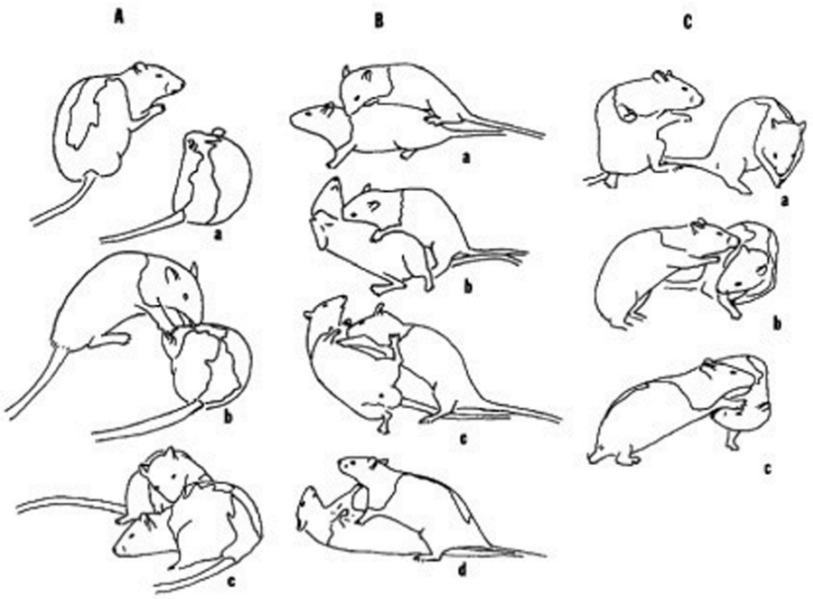

Figure 4