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Review article

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.

Contents

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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, 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, 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–P34 correspond to early adolescence, P34–P46 correspond to mid-adolescence, and P46–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, 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 et al., 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, 2004; 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 al., 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 (Fig. 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,