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Peer pressures: Social instability stress in adolescence and social deficits in adulthood in a rodent model

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ABSTRACT

Studies in animal models generate and test hypotheses regarding developmental stage-specific vulnerability that might inform research questions about human development. In both rats and humans, peer relationships are qualitatively different in adolescence than at other stages of development, and social experiences in adolescence are considered important determinants of adult social function. This review describes our adolescent rat social instability stress model and the long-lasting effects social instability has on social behaviour in adulthood as well as the possible neural underpinnings. Effects of other adolescent social stress experiences in rats on social behaviours in adulthood also are reviewed. We discuss the role of hypothalamic–pituitary–adrenal (HPA) function and glucocorticoid release in conferring differential susceptibility to social experiences in adolescents compared to adults. We propose that although differential perception of social experiences rather than immature HPA function may underlie the heightened vulnerability of adolescents to social instability, the changes in the trajectory of brain development and resultant social deficits likely are mediated by the heightened glucocorticoid release in response to repeated social stressors in adolescence compared to in adulthood.

1. Introduction

As outlined by Gottlieb and Lickliter (2004), the primary contribution of investigations in non-human animals for studies of people (and vice versa, as for comparative approaches in general) is to generate hypotheses and general principles of development that can then be tested. In the last ten or so years, there is increasing interest in understanding the neural plasticity of the adolescent period of development because of evidence that it may be a time of remediation (e.g., Bredy et al., 2004) for what were once thought to be relatively permanent programming effects of detrimental experiences in early life. The flip side is that this same plasticity may confer vulnerability in adolescence. Researches of the adolescent period in animal models may provide insights as to risk factors and the differential susceptibility at this stage of life.

Whether or not adolescence in humans is a bona fide developmental stage or a social construction that arose in modern history was a topic of debate as recently as the late 20th century (e.g., Fox, 1977; Schlegel and Barry III, 1991). Thus it is not surprising that adolescence also has been considered unique to the human species. For example, Bogin and Smith (1996) argued that while adolescence is an evolved stage of life, it appeared relatively recently (after the appearance of Homo erectus). Adolescence was considered a specialization in humans, with non-human species transitioning from a juvenile to adult

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stage without an adolescent stage. Researchers' acceptance nowadays of an adolescent period of development in non-human animals is exemplified in a figure by Brown and Spencer (2013) in which the developmental time course of circulating testosterone concentrations in males is illustrated in an altricial mammal (Norway rats), an altricial bird (zebra finches), a semi-precocial mammal (rhesus macaques), and a precocial bird (quail), all of which are depicted to show low testosterone concentrations during a juvenile period, a steep increase in an adolescent period, and high asymptotic concentrations in an adult period. The rise in testosterone, however, reflects the maturation of the hypothalamic–pituitary–gonadal axis that is a hallmark of puberty, and adolescence is not synonymous with puberty. Rather, adolescence extends beyond sexual maturation and is defined by the development of social and cognitive behaviour (Sisk and Foster, 2004).

Several parallels can be drawn between adolescence in humans and in rodent species, especially rats, for which the adolescent period has been investigated extensively in the laboratory. In both humans and rats, adolescence is a transitional period with no clear markers of onset or offset. A broad definition of adolescence in rats spans from about postnatal day 21 (approximately the time of weaning) to postnatal day 60 (approximately the time of sexual maturity), with physical indices of puberty evident at about postnatal day 35 in females and postnatal day 42 in males (reviewed in McCormick and Mathews, 2010). Changes in emotional and cognitive behaviour during adolescence are manifestations of ongoing brain development in both species (see reviews by Blakemore, 2012; Brenhouse and Andersen, 2011; Cooke and Shukla, 2011). Compared to adults, adolescents of both species show greater emotional reactivity, risk-taking, impulsivity, and novelty seeking (reviewed in Casey et al., 2010; Doremus-Fitzwater et al., 2010; Green and McCormick, 2013). In both humans and rats, there is extensive restructuring of social relationships in adolescence. For example, girls and boys switch their primary focus from relationships with the family to relationships with peers (Nelson et al., 2005). Adolescent rats spend more time in social interaction and social play, and find social interactions more rewarding than do adult rats (Spear, 2011; Trezza et al., 2010).

The importance of social learning in adolescence is underscored by the marked dysfunction that is evident when deprived of social interactions during that period of ontogeny. Social deprivation in rats typically involves housing the animals singly, and has been referred to as a form of "sociogenic brain damage", or social malnourishment (Montagu, 1977), but is more widely known as social isolation. The effects of social isolation in rats, a highly social animal, have been considered to model psychopathologies such as schizophrenia in humans (Fone and Porkness, 2008). It has long been recognized that the effects of social isolation are greater when experienced in adolescence than in adulthood (Einon and Morgan, 1977; Panksepp and Beatty, 1980). Marked deficits in brain chemistry, cognitive and emotional function are evident in adulthood after social isolation in adolescence, even when the social isolation is limited to the prepubertal, early adolescent period (e.g., Baarendse et al., 2013). Whereas some studies find that the effects of social isolation persist even if followed by a period of social housing (e.g., Lukkes et al., 2009), others have shown that partial remediation is possible by providing environmental enrichment (Hellemans et al., 2004) or that remediation is possible through social re-housing when social isolation is limited to either the fourth or fifth week of life (Hol et al., 1999).

Less severe manipulations of social relationships than deprivation in adolescence also modify the trajectory of brain and behavioural development. In this review, we describe our adolescent social instability model, which we have shown to result in mild impairments in emotional and cognitive behaviour in adulthood when administered in adolescence, but not when administered in adulthood (reviewed in Green and McCormick, 2013; McCormick and Green, 2013). Here we focus on our more recent evidence of impairments in social behaviour in adulthood after social instability in adolescence as well as review the effects of other social manipulations in adolescence on adult social function. We then discuss factors, notably hypothalamic–pituitary–adrenal responses to stressors, that may underlie the differential susceptibility of adolescents and adults to social stressors.

2. The social instability stress model

The social instability stress (SS) procedure involves pair-housed rats (Long Evans rats) that are removed from the colony room for one hour, after which rats are returned to the colony but to a new cage in which they are paired with a new cage partner of the same age that is also undergoing the SS procedure (see Fig. 1). The one hour isolation and pairings with new cage partners occur every day for 15 days. On the 16th day, after one hour isolation, all are returned to their original cage partner, at which time the SS procedure ends and rats are left undisturbed except for cage maintenance until time of behavioural testing. Control (non-stressed) rats are left undisturbed except for cage maintenance until time of behavioural testing throughout, except on postnatal days 30 and 45 when rats in both groups are weighed. When investigating the lasting effects of SS in adulthood, behavioural tests typically begin after postnatal day 70. In our initial studies, we applied the SS procedure in adolescence from postnatal day 33 to postnatal day 45 (McCormick et al., 2004, 2005), but then changed the age range to between postnatal days 30 and 45 to capture a pre- and post-pubertal period in both sexes. Nevertheless, the use of the same ages for manipulation in both males and females means the sexes are at different developmental stages during the SS procedure. This problem is not easily resolved; although females attain pubertal milestones earlier than males, not all developmental milestones are attained earlier in females. For example, microglial colonization of the hippocampus, cortex, and amygdala (Schwarz et al., 2012) and neuronal numbers in the locus coeruleus (Pinos et al., 2001) reach plateaus earlier in males than in females. Thus, we focus more on the sex-specificity of our SS procedure rather than on sex differences per se. In this review, we describe our results for males only.

The daily one hour isolation part of the SS procedure involves confining the adolescents in small containers