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Spatial discrimination reversal and incremental repeated acquisition in adolescent and adult BALB/c mice

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ABSTRACT

Adolescence is characterized by neural and behavior development that includes increases in novel experiences and impulsive choice. Experimental rodent models can characterize behavior phenotypes that typify adolescence. The present experiment was designed to characterize differences between adolescent (post-natal day (PND) 34–60) and adult (PND 70–96) BALB/c mice using a response-initiated spatial discrimination reversal (SDR) and incremental repeated acquisition of response chains (IRA) procedures. During SDR, adolescents omitted more trials and were slower to initiate trials than adults, but the age groups did not differ on accuracy and perseveration measures. During IRA, adolescents displayed poorer overall performance (measured by progress quotient), lower accuracy at individual chain links, and completed fewer long response chains (>3 links) than adults. In both procedures (SDR and IRA), the poorer performance of adolescents appeared to be related to the use of a response device that was spatially removed from reinforcer delivery. These results indicate that SDR and IRA performance can be established during the brief rodent adolescent period but that these two age groups' performances differ. We hypothesize that adolescent behavior is more sensitive than adult behavior to the spatiotemporal distance between response device and location of reinforcer delivery.

1. Introduction

Adolescence is marked by increased risky and often impulsive decision-making (e.g., substance abuse, unprotected sex), the emergence of many psychiatric illnesses, and rapid development of academic skills (Moffitt, 1993; Spear, 2000; Swendsen et al., 2012). Critical changes in the volume of cortical grey and white matter, receptor pruning, and development of cortical connections occur throughout the brain, often between 12 and 18 years of age (Brenhouse and Andersen, 2011; Giedd et al., 1999; Jacobus et al., 2013). The development of the pre-frontal cortex (PFC) and subcortical structures such as the nucleus accumbens (NAc) are especially important during adolescence because they are among the last regions to mature (Giedd et al., 1999; Paolicelli et al., 2011). The PFC has been implicated in processes ranging from behavior inhibition, task switching, attentional selection, and resistance to disruption in studies with rodents (Dalley et al., 2004, 2008). Imbalances in the development of brain regions like the PFC and NAcc during development may leave adolescents increasingly vulnerable to developing maladaptive patterns of behavior (Adriani and Laviola, 2004; Galvan et al., 2006; Moffitt, 1993; Pinkston and Lamb 2011). Evidence from clinical and experimental studies implicate dysfunctions in fronto-striatal pathways, connecting frontal cortices with the basal ganglia, in a range of disorders, including ADHD and autism spectrum disorders (Cherkasova and Hechtman, 2009; Jentsch and Taylor, 1999; Langen et al., 2012). Less is known about how adolescents and adults respond to challenging behavioral demands and these may exacerbate differences between age groups.

Experimental models of adolescent behavior often use rat and mouse strains because they are cost-effective and share similarities in anatomy and physiology with primates (Spear, 2000). Rodent adolescence "encompasses the week preceding the onset of puberty and the first few days thereafter (Macrìèt al., 2002)" and contains three sub-periods: early (also prepubescent or juvenile; PND 21–34), middle (sometimes "periadolescence;" PND 34–46), and late adolescence (sometimes young adulthood; PND

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46–59) (Laviola et al., 2003). Several behavior assays with rodents model characteristic patterns of adolescent behavior, including behavior rigidity, disinhibition, and impulsivity (Evenden, 1999; Madden and Johnson, 2010). Recent investigations have adapted these procedures to meet the time constraints presented by the rapid progression of rodent development (e.g., Adriani et al., 2003; Andrzejewski et al., 2011; Pinkston and Lamb, 2011; Sturman et al., 2010). Relative to adults, adolescent rodents spend more time exploring novel environments, develop an exaggerated sensitization response to psychostimulants, and discount delayed and probabilistic reinforcers more steeply (Adriani et al., 1998; Laviola et al., 2001; Pinkston and Lamb, 2011; Zoratto et al., 2013). Also, adolescents learn to discriminate multiple stimuli more slowly (Spear and Brake, 1983) and display greater persistence under extinction compared to adults (Andrzejewski et al., 2011; Myslivecek and Hassmannová, 1979). The current study sought to extend the classes of behavior that can be studied during rodent adolescence by adapting two procedures: spatial discrimination reversal (SDR) and incremental repeated acquisition (IRA).

Discrimination reversal procedures first assess the acquisition of a simple discrimination and then reverse it such that the previously reinforced behavior is now under extinction while the previously unreinforced behavior now is reinforced. Discrimination reversal procedures have been used in humans and a range of non-human animals (Fellows and Farah, 2003; Pagani et al., 2005) and are sensitive to disruption of the orbitofrontal cortex in rodents, nonhuman primates, and humans (Dalley et al., 2004; Zald and Andreotti, 2010). The first reversal is especially sensitive to disruption of the orbitofrontal cortex by lesions, by altering neurotransmitter (especially dopamine) activity in this region (Dalley et al., 2004), and by gestational methylmercury (MeHg) exposure in rodents (Paletz et al., 2007; Reed et al., 2006). SDR procedures present an opportunity to examine behavioral flexibility in adolescent mammals, a period marked by transient dopaminergic (DAergic) functioning and structural development. The SDR procedure used here required that a mouse initiate a trial by pressing a back lever, an approach taken to increase the likelihood that a mouse was on-task and to displace it from the choice levers at the beginning of a trial.

Repeated acquisition (RA) procedures, pioneered by Boren (1963), require subjects to acquire chains of responses within a session. Incremental repeated acquisition (IRA), an extension of RA, allows for the assessment of acquisition and performance in such a way that the length of the chain increases gradually, often according to some behavior criterion, within a single session (Cohn and Paule, 1995; Paule et al., 1990). IRA may be viewed as an apical procedure that captures many of the functions thought to be mediated by the prefrontal cortex and higher-order functioning (Cohn and Paule, 1995; Paule et al., 2012). There is high correlation, $r = 0.53$, between measures of IRA accuracy and IQ scores in human children (Paule et al., 1999) and improvement demonstrates a developmental time course (Baldwin et al., 2012). Specifically, the dependent measure progress quotient (PQ), directly related to the number of reinforcers earned at a given chain length, can vary over a dynamic range and serve as an independent, overall measure of performance (Bailey et al., 2010; Johnson et al., 2010). The IRA procedure has been used with a wide variety of species, including rats, mice, pigeons, and non-human primates (Cohn and Paule, 1995) and has garnered extensive use when evaluating acute drug effects and chronic exposure to environmental contaminants (Bailey et al., 2013; Paule and McMillan, 1984). A mastery-based approach allows task difficulty to adjust in real time according to the animal's performance, an approach that has led to the production of very long response chains by mice (Bailey et al., 2010; Johnson et al., 2010). The dynamic, within-session adjustment of difficulty allows for identification of influential factors within individual animals.

The present study investigated middle to late adolescent (PND 34–60) and adult (PND 70–90) BALB/c mouse behavior in SDR and IRA procedures. These procedures allowed for age-based comparisons between a discrete-trials operant procedure and a more rate-based free operant procedure.

2. Materials and methods

2.1. Subjects

Nineteen adolescent and 18 adult male BALB/c mice, purchased from Harlan Laboratories, arrived when they were 28 and 63 days old, respectively. Adolescent mice were group housed; five mice per cage in clear *Plexiglas*© cages with ash chip bedding. The adults, whom had been group-housed as adolescents at Harlan Laboratories, arrived at the vivarium individually housed and were kept separate for the duration of the experiment. In our experience, group-housed adult male BALB/c mice engage in aggressive barbering and fighting which can result in grievous injury and sometimes death. Adult mice were singly housed in cages that contained a clear *Plexiglas*© divider that prevented physical contact but allowed visual, olfactory, and auditory interactions between two mice in the same cage. Adolescent mice weighed between 12 and 15 g upon arrival and were initially given ad libitum access to standard rodent chow (Purina Mills Inc., St. Louis, MO). Upon the start of testing, food was removed 4 h before experimental sessions and returned at the end of the session. Adult mice were maintained at a weight 23–25 g by feeding approximately 2.5–3.0 g standard rodent chow per day. Autoshaping (see Section 2.3) began on PND 34 for adolescent mice and PND 70 for adult mice.

Mice were housed in an AAALAC-accredited vivarium, temperature and humidity-controlled, and maintained on a 12 h light-dark cycle (lights on at 6:00 am). All mice had ad libitum access to water. Prior to the start of autoshaping, mice were acclimated to a sweetened condensed milk and water solution (3:1 water to milk) over a two-day period (4 and 8 h per day). All procedures were approved by the Auburn University IACUC.

Following autoshaping, adolescent and adult mice were randomly assigned to either the IRA or the SDR group with the constraint that the groups acquired lever-pressing similarly during autoshaping. The IRA group included 10 adolescent and 11 adult mice and the SDR group included nine adolescent and seven adult mice. Subjects were exposed to either the IRA or SDR procedure for the duration of the study.

2.2. Apparatus

Daily experimental sessions for both IRA and SDR procedures were conducted in 10 Med Associates operant conditioning chambers (Med Associates Inc., product #ENV-007). Each chamber, measuring 30.5 cm L × 24.1 cm W × 29.2 cm H, contained two stainless steel front and back walls and two *Plexiglas*© side walls. Mounted on the front wall were two retractable levers (product #ENV-307W), separated by a dipper reservoir. One non-retractable lever (product #ENV-307A) was mounted in the center of the back wall. Dipper presentation allowed 4 s access to 0.1cc solution of sweetened condensed milk and water (3:1 ratio). Pressing the levers with 2 g of force registered a response. A single 2.8 W house light was located near the ceiling of the chamber on the back wall, a Sonalert™ tone generator was located in the top left, and a white noise generator was located in the top right of the back wall. The operant chambers were enclosed in sound-attenuating cabinets, with a fan for ventilation and masking noise.