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Acute locomotor responses to cocaine in adolescents vs. adults from four divergent inbred mouse strains

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Growing evidence suggests that adolescent mice display differential sensitivity to the acute locomotor activating effects of cocaine as compared to adults, but the direction of the difference varies across studies and the reasons are not clear. Few studies have directly examined genetic contributions to age differences in locomotor stimulation from cocaine. The goal of this study was to determine the extent to which reduced stimulation in C57BL/6J adolescents as compared to adults generalizes to other strains. Therefore, we examined male and female mice from four genetically divergent inbred stains (BALB/cByJ, C57BL/6J, DBA/2J and FVB/NJ) at two ages, postnatal day 30 and postnatal day 65. Mice received either saline or cocaine (15 or 30 mg/kg), and then immediately were placed back into their home cages. Locomotor activity was recorded continuously in the home cage by video tracking. Adolescents displayed reduced stimulation as compared to adults for C57BL/6J, BALB/cByJ and female FVB/NJ mice. No age differences were observed for DBA/2J or male FVB/NJ. No main effects of sex were observed. Strain differences in pharmacokinetics, neural development or physiology could contribute to the observed differences between ages across strains. Future comparative studies could discover biological differences between strains that explain age differences in cocaine sensitivity.

Keywords: BALB/cByJ, behavior genetics, C57BL/6J, DBA/2J, FVB/NJ, heritability, locomotor stimulation, mice, Mouse Phenome Database, psychostimulant

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Drug use in humans is commonly initiated during adolescence (Chen & Kandel 1995; Mathias 1996; Nelson *et al*. 1995). The brain is still undergoing substantial development during this time [e.g. prefrontal cortex (Giedd *et al*. 1999; Spear 2000), dopamine neurotransmitter system (Seeman *et al*. 1987; Tarazi *et al*. 1998, 1999; Teicher *et al*. 1995)]. Differences in brain morphology and physiology likely contribute to differential behavioral responses to drugs in adolescents as compared to adults (Zombeck *et al*. 2009). This is of concern because initial drug responses can predict future patterns of use (Davidson *et al*. 1993; Haertzen *et al*. 1983; Lambert *et al*. 2006).

In rodent models, distinct behavioral responses to drugs in adolescents as compared to adults have been observed using a variety of experimental paradigms (Belluzzi *et al*. 2004; Hollstedt *et al*. 1980; Levin *et al*. 2003; Shram *et al*. 2006; Silveri & Spear 2001; Torres *et al*. 2008; Vastola *et al*. 2002; Zakharova *et al*. 2009b). One clear example is locomotor activity following acute psychostimulant administration. Adolescent rodents typically display reduced sensitivity to the locomotor activating effects of cocaine (Laviola *et al*. 1995; Maldonado & Kirstein 2005a; Spear & Brake 1983; Zombeck *et al*. 2009, 2010), amphetamine (Adriani & Laviola 2000; Bolanos *et al*. 1998; Lanier & Isaacson 1977; Mathews & McCormick 2007; Mathews *et al*. 2009; Spear & Brake 1983) and methamphetamine (Zakharova *et al*. 2009a; Zombeck *et al*. 2009, 2010), when a wide range of doses and experimental paradigms are used. However, conflicting findings, particularly for cocaine, have been reported. For example, some studies have observed no differences between age groups (Adriani *et al*. 1998; Camarini *et al*. 2008; Collins & Izenwasser 2002; Niculescu *et al*. 2005; Parylak *et al*. 2008), while others have observed greater stimulation in adolescents as compared to adults in response to psychostimulants (Badanich *et al*. 2008; Caster *et al*. 2007; Catlow & Kirstein 2005). The explanation for this variability is not known, but probably involves both environmental sources, including differences in handling (Maldonado & Kirstein 2005a,b) and testing environment (Masur *et al*. 1980), as well as genetic, including species and strain differences between studies.

Genetic contributions to psychostimulant-induced locomotor activity among adult mice are well established (Bryant *et al*. 2009; Marley *et al*. 1998; Phillips *et al*. 2008). However, genetic contributions to variability between adolescent and adult sensitivity to psychostimulants are not well understood. Balda *et al*. (2008) showed that the neuronal nitric oxide synthase (*nNOS*) gene is involved in behavioral sensitization to cocaine in adult, but not adolescent, mice. This suggests that genes influencing behavioral effects of psychostimulants in adolescents may not be the same as adults. Further research is needed to determine the extent to which environmental and genetic background influence age differences in psychostimulant-induced locomotor activity.

Comparing inbred mouse strains is one method of discovering genetic influences on behavior. Of the studies in mice, age differences in locomotor activity following psychostimulant administration have been examined in only a few

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different strains. Adolescent C57BL/6J mice consistently display reduced stimulation to cocaine and methamphetamine as compared to adults (McCarthy *et al*. 2004; Zombeck *et al*. 2009). Outbred CD1 mice commonly show no age differences in stimulation to cocaine or amphetamine (Adriani *et al*. 1998; McCarthy *et al*. 2004; Niculescu *et al*. 2005), but Adriani & Laviola (2000) found reduced stimulation in adolescents as compared to adults following 2 mg/kg amphetamine. Inbred DBA/2J mice also apparently show no age differences (Camarini *et al*. 2008). However, these data do not include information on females for either the C57BL/6J or the DBA/2J strains. Information on many of the other inbred strains (e.g. as represented in the Mouse Phenome Database) is also lacking.

The goal of this study was to determine the extent to which the phenomenon of attenuated stimulation in adolescents as compared to adults in C57BL/6J mice extends to other inbred strains. We hypothesized that adolescents would stimulate less than adults across strains, but that the magnitude of this difference would depend significantly on genotype.

Methods

Subjects

A total of 192 animals were used in this study from four different inbred stains: C57BL/6J, FVB/NJ, BALB/cByJ and DBA/2J. All four strains are listed as Tier 1 priority in the Mouse Phenome Database and were chosen because each represents different branches of the phylogenetic tree for inbred mouse strains, as represented in Rhodes *et al*. (2007).

Male and female mice ($n = 4$/sex/age/strain/dose) arrived from Jackson Laboratory (Bar Harbor, ME, USA) in two different age groups: postnatal day 21 and postnatal day 56. Mice were initially housed in groups of three to four for 5 days before being transferred to custom-made acrylic home cages conducive for video tracking (Fig. 1) where they remained for 4 additional days (Zombeck *et al*. 2009, 2010). All mice were housed on a 12:12 reverse light/dark cycle (lights off at 0700 h and on at 1900 h), with the room temperature maintained at $21 \pm 1^{\circ}$C. Mice had *ad libitum* access to food and water at all time. Adolescent mice were tested at postnatal day 30 and adults at day 65. This is a commonly accepted period for adolescents and adults in rodents (Spear 2000; Spear & Brake 1983). All procedures were approved by the University of Illinois Institutional Animal Care and Use Committee and adhered to National Institutes of Health (NIH) guidelines. The Beckman Institute Animal Facility where the mice were held is Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) approved.

Behavioral testing

All behavioral testing was conducted in the animal's home cage using custom-made home cages with clear plastic lids and food and water delivered from the side (Zombeck *et al*. 2009). Two different types of bedding were used depending on whether the mouse had a white or a dark coat color. Corncob bedding (Harlan 7097, Harlan Teklad, Madison, WI, USA) was used for dark mice, whereas Shepherd Paperchip® (Shepherd Specialty Papers, Milford, NJ, USA) bedding was used for white mice (Fig. 1). Following Zombeck *et al*. (2009, 2010), horizontal distance traveled in the home cage was recorded continuously using TopScan (Clever Sys, Vienna, VA, USA) video tracking software. Behavioral testing began at the onset of the dark cycle. Red lights were placed overhead in various positions in the room to illuminate the cages during the dark phase for continuous video tracking (mice cannot see red light). All mice were tracked under baseline conditions for 1 h without being disturbed. Following the 1-h baseline, all mice received an intraperitoneal injection of saline and were then immediately returned to their home cage to monitor the response to injection. After 1 h, the mice were administered another saline injection or cocaine (15 or 30 mg/kg) and locomotor activity was recorded for an additional 1 h. Doses were chosen based on previous studies that have shown reliable behavioral differences between age groups in C57BL/6J males (Zombeck *et al*. 2009, 2010).

Figure 1: Photograph of the custom-made home cages where animals were tested for cocaine-induced locomotor stimulation by continuous overhead video tracking. Note that FVB/NJ and BALB/cByJ were tested in cages with dark type bedding (Shepherd Paperchip®), whereas C57BL/6J and DBA/2J were tested with light colored bedding (Harlan Corncob) to facilitate video tracking (dark object on light background or light object on dark background). Red light was used to illuminate the cages during the dark cycle when locomotor activity testing occurred.

Statistics

Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). Analysis of variances (ANOVAs) were performed separately for each strain with age, sex and dose as factors and across strains with strain, age and dose as factors. Pair-wise differences were evaluated using Tukey *post hoc* tests. Heritability was estimated by one-way ANOVA for each age and dose with strain as the factor (Belknap *et al*. 1993; Crabbe *et al*. 1990; Rhodes *et al*. 2007). For all tests, a P value of <0.05 was considered significant.

Results

Saline

The response to a saline injection was measured 1 h following onset of the dark cycle, before cocaine administration. Total distance traveled was summed over the 1 h following injection. Adolescent and adult mice displayed similar levels of locomotor activity in all strains except BALB/cByJ. This was reflected in a significant age × strain interaction in the three-way ANOVA with age, strain and sex as factors ($F_{3,174} = 4.1$, $P = 0.007$). *Post hoc* analysis showed that BALB/cByJ adolescent mice traveled less far than adults (main effect of age, $F_{1,44} = 15.2$, $P = 0.0003$). No significant age effects

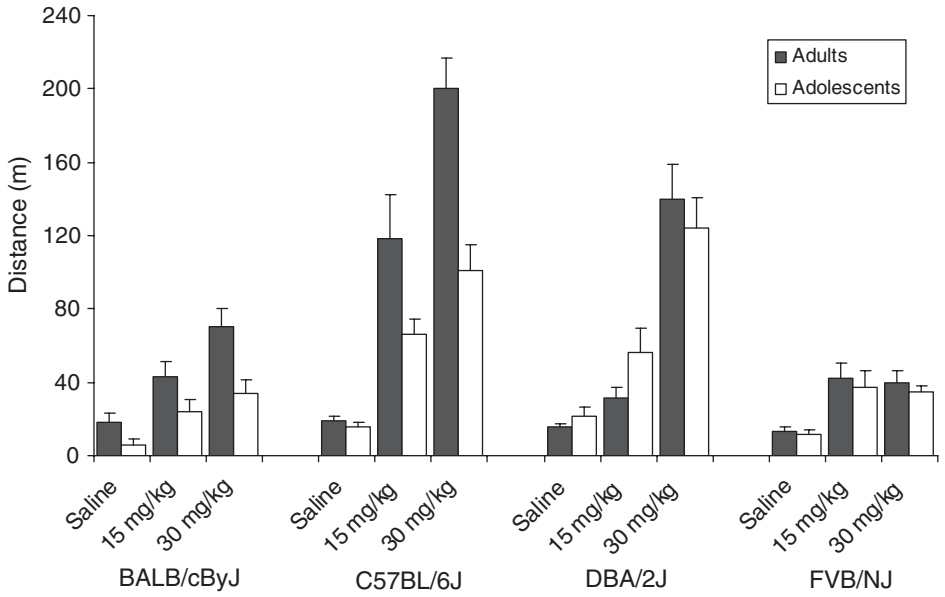

Figure 2: Average (±SE) distance traveled summed over 60 min following acute i.p. injection of saline or cocaine. Each bar represents the average of eight individuals (collapsed across sex; four males, four females). Adults are shown as solid bars and adolescents open bars.

were observed in the other strains. No significant strain or sex differences were observed collapsed across age ($P > 0.05$).

Cocaine

The magnitude and direction of the difference in locomotor stimulation between adolescents and adults differed depending on genotype (Fig. 2). All main effects and interactions were significant in the overall three-way ANOVA including the age × strain interaction ($F_{3,166} = 8.8$, $P < 0.0001$) and the age × dose × strain interaction ($F_{6,166} = 2.4$, $P = 0.03$). C57BL/6J and BALB/cByJ adolescents showed the predicted pattern of reduced locomotor stimulation as compared to adults (C57BL/6J main effect of age, $F_{1,36} = 19.7$, $P < 0.0001$; BALB/cByJ main effect of age, $F_{1,36} = 15.5$, $P = 0.0004$). Within BALB/cByJ mice, the age × sex interaction was marginally non-significant ($F_{1,36} = 3.5$, $P = 0.07$). This is because for the high dose, 30 mg/kg, adolescents displayed attenuated stimulation only in females ($P = 0.01$) not in males ($P = 0.46$) (Fig. 3). However, this difference was not large enough to produce a significant age × dose × sex interaction ($F_{2,36} = 1.5$, $P = 0.23$). Age differences were significantly sex dependent within FVB/NJ mice (age × sex interaction, $F_{1,36} = 10.4$, $P = 0.003$). Female FVB/NJ mice showed the typical attenuated response in adolescents compared with adults ($P = 0.0002$), but no age difference was observed in males (Fig. 4). No significant age or sex differences in locomotor stimulation from cocaine were observed in DBA/2J mice (all $P > 0.05$).

Magnitude of locomotor stimulation varied greatly between strains (main effect of strain, $F_{3,166} = 43.0$, $P < 0.0001$) (Fig. 2). C57BL/6J displayed the greatest increase in locomotor activity in response to cocaine administration (all pair-wise comparisons with C57BL/6J were $P < 0.01$), followed by DBA/2J (DBA/2J > FVB/NJ and BALB/cByJ, both $P < 0.0001$). FVB/NJ and BALB/cByJ stimulated the least and were not statistically different from each other ($P > 0.05$). Heritability estimates were conducted separately for each age group because the age × strain interaction was significant (described above). Strain accounted for 48–74% of the variation in locomotor stimulation in adults and 30–65% in adolescents (Table 1). Smaller and non-significant heritability estimates were observed following a saline injection.

Discussion

The purpose of this study was to determine the extent to which attenuated locomotor stimulation to cocaine in adolescent vs. adult male C57BL/6J mice (Zombeck *et al*. 2009, 2010) could be generalized to other genotypes. The major finding is that the phenomenon extends to BALB/cByJ, but DBA/2J and FVB/NJ showed a qualitatively different result (Fig. 2). This is consistent with a previous study that found no age differences in stimulation from cocaine in DBA/2J (Camarini *et al*. 2008). To the best of our knowledge, this is the first comparison of locomotor stimulation between adolescents and adults for FVB/NJ, although this strain is related to the outbred CD-1 strain that has been tested (Adriani *et al*. 1998; Adriani & Laviola 2000; McCarthy *et al*. 2004; Niculescu *et al*. 2005).

The finding that age differences varied among strains is interesting and implies that there are tractable biological differences between strains that underlie the age differences in behavior. By tractable, we mean that it should be possible

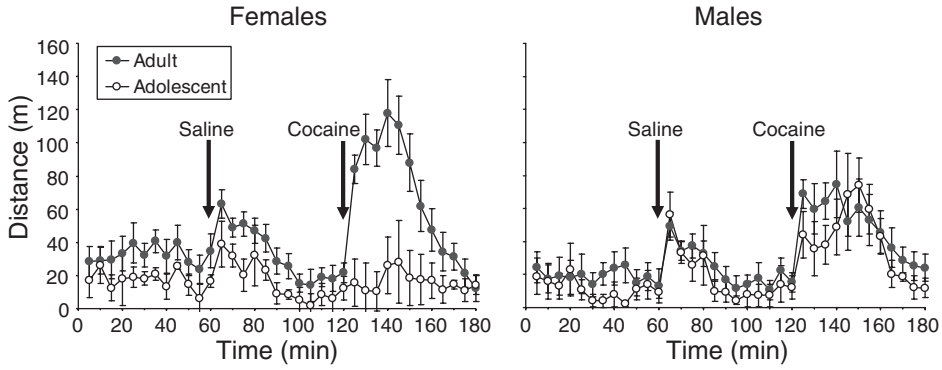

Figure 3: Comparison of female and male BALB/cByJ mice following 30 mg/kg cocaine. Average distance traveled in 5 min bins (±SE) is plotted against time for adults (filled symbols) and adolescents (open symbols). Animals were given a saline injection at 60 min and 30 mg/kg cocaine injec=tion at 120 min. Each data point represents the average of four individuals. Both graphs share the same *y*-axis.

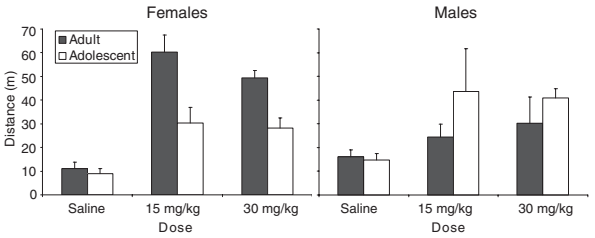

Figure 4: Comparison of female and male FVB/NJ mice following cocaine injection. Average (±SE) distance traveled summed over 60 min following acute i.p. injection of saline or cocaine plotted separately for adults (solid bars) and adolescents (open bars). Each bar represents the average of four individuals. Both graphs share the same *y*-axis.

Table 1: Heritability estimates of locomotor activity following saline or cocaine administration

	Saline	15 mg/kg	30 mg/kg
Adults	0.05	**0.48**	**0.74**
Adolescents	**0.30**	**0.30**	**0.65**

Bold font represents R^2 values were significant at $P < 0.05$ level.

to identify common biological features consistently altered in the strains showing the age differences but not in the others, although the features could have disparate biological explanations. For example, in certain strains, adolescents might experience lower concentrations of cocaine in their brains as compared to adults for reasons related to distribution of the cocaine in the whole animal (i.e. the pharmacokinetic hypothesis) (Zombeck *et al*. 2009). Alternatively, the differences could be related to developmental, biochemical or molecular changes in the brain associated with the transition in age (pharmacodynamic) (Zombeck *et al*. 2010). A third possibility is that the ontogeny for reduced sensitivity to cocaine could vary depending on genotype. For example, it is possible that had we compared slightly younger or older adolescents, we might have observed reduced sensitivity in FVB/NJ males and DBA/2J males and females. Previous studies have found age differences to change over the course of adolescence in rats (Badanich *et al*. 2008; Lanier & Isaacson 1977).

With respect to the pharmacokinetic hypothesis, the literature suggests that it may contribute to some of the differences shown in Fig. 2, but probably is not a major factor. In C57BL/6J, an extensive analysis suggested that large differences in stimulation occur between adults and adolescents at equivalent doses of cocaine in the brain (Zombeck *et al*. 2009). With respect to strain differences among adult mice, slightly lower concentrations of cocaine were observed in BALB/cByJ mice compared with C57BL/6ByJ, which is consistent with reduced stimulation in BALB/cByJ vs. C57BL/6J (Fig. 2) (Wiener & Reith 1990). On the other hand, C57BL/6J displayed much greater stimulation than DBA/2J in our study, particularly at the 15 mg/kg dose (Fig. 2) even though cocaine concentrations in the brains of C57BL/6J and DBA/2J are reported to be similar (Ruth *et al*. 1988; Tolliver *et al*. 1994).

The reduced locomotor stimulation in adolescents as compared to adults in C57BL/6J, BALB/cByJ and FVB/NJ females, most likely reflects reduced sensitivity to the drug rather than increased sensitivity or transition into stereotypy (i.e. repetitive behaviors that would compete with horizontal movement). First, higher doses are needed to produce stereotypy in mice (Atkins *et al*. 2001; Schlussman *et al*. 2003; Tilley & Gu 2008; Tolliver & Carney 1994a,b). Second, 30 mg/kg cocaine produced greater locomotor activity than the 15 mg/kg dose in all strains except FVB/NJ, suggesting that both age groups were on the ascending limb of the inverted U-shape dose–response curve. Stereotypy contributes more to the descending limb of the curve (Shuster *et al*. 1977; Tolliver & Carney 1994a). It is important to note that because FVB/NJ did not show a difference in locomotor response between the two doses of cocaine, it is not clear if mice are on the ascending or descending limb of the dose–response curve. Further research is needed to

make definitive conclusions about sensitivity to cocaine in adolescent and adult FVB/NJ mice.

Sex differences

It was surprising to observe age differences in female but not in male FVB/NJ mice (Fig. 4). None of the other strains showed sex-dependent effects across both doses. BALB/cByJ showed a trend for sex differences at 30 mg/kg, but not 15 mg/kg cocaine, suggesting subtle differences in sensitivity between the two sexes (Fig. 3). Previous studies report mixed results as to whether age differences in sensitivity to psychostimulants are sex dependent. Parylak *et al*. (2008) and Mathews *et al*. (2007) have reported attenuated locomotor stimulation in female adolescents as compared to adults at doses that do not produce similar age differences in males for cocaine and amphetamine, respectively. However, these findings have not been replicated in other studies of age differences to cocaine and amphetamine in male and female rodents (Adriani & Laviola 2000; Laviola *et al*. 1995; Mathews *et al*. 2009). The cause for inconsistencies among the findings is unclear; however, differences in handling procedures may contribute. Maldonado *et al*. (2005a,b) discovered that the direction of age differences (i.e. whether adolescents show more, less or no differences compared with adults) in locomotor stimulation to cocaine varies depending on both sex and whether or not the rats were habituated to handling prior to the experiment.

The lack of an overall main effect for sex is consistent with other mouse studies that have observed no difference in locomotor activity between males and females following cocaine administration (Kikusui *et al*. 2005; Wahlsten *et al*. 2003). However, Morse *et al*. (1993) found male C57BL/6J and DBA/2J mice to travel greater distances than females following cocaine. It is interesting that in rat studies, females are often found to stimulate more than males to cocaine (Craft & Stratmann 1996; Heyser *et al*. 1994; Laviola *et al*. 1995; Parylak *et al*. 2008; van Haaren & Meyer 1991). Variability in sex differences among rats and mice has been reported before (Jonasson 2005) and highlights the importance of accounting for species when considering sex differences.

Heritability

Many previous studies have established significant genetic influences on locomotor responses to cocaine in adult mice. These include selective breeding experiments (Marley *et al*. 1998) and comparisons across inbred strains (Reith & Selmeci 1992; Ruth *et al*. 1988; Wiener & Reith 1990). Consistent with previous reports, BALB/cByJ adults displayed lower levels of locomotor stimulation in comparison with adult C57BL/6J- and DBA/2J-related strains (Reith & Selmeci 1992; Ruth *et al*. 1988; Wiener & Reith 1990). However, unlike previous studies (Cook *et al*. 1998; Rocha *et al*. 1998; Tolliver & Carney 1994a, 1995), C57BL/6J displayed greater stimulation than DBA/2J (Fig. 2), but Kafkafi *et al*. (2003) found greater stimulation in C57BL/6J than DBA/2J. Two major differences between our study and many previous studies could explain discrepancies. The first is that we tested our mice at night during their normal active period whereas the majority of previous studies tested animals during the light cycle. Another major difference is that we measured locomotor activity in the animal's home cage using continuous video tracking. To the best of our knowledge, all previous studies placed animals into a new cage or arena during measurement of locomotor activity. Placing animals into a new environment or one that is different from home induces a state of arousal and increases locomotor activity on its own. Moreover, the response is strongly strain dependent (Lad *et al*. 2010; Orsini *et al*. 2004). Therefore, testing in the home cage may reduce noise in the data from reaction to novelty and explain discrepancies in heritability estimates reported for adults in Table 1, as compared to previous studies.

The heritability estimates in Table 1 must be interpreted with caution. They are equal to r^2 values from a one-way ANOVA with strain as the factor. The common assumption when using a panel of inbred strains to estimate heritability is that all animals experienced the same environment (Crabbe *et al*. 1990; Hegmann & Possidente 1981). However, this assumption is blatantly false. Most studies, including this one, did not transfer embryos or cross foster pups. In most cases including the current study, all C57BL/6J mice were raised by C57BL/6J dams and reared around other C57BL/6J mice, whereas all BALB/cByJ mice were raised by BALB/cByJ dams and reared around their own kind. If social environment matters for cocaine responses, then the heritability estimates in Table 1 and many others of the same kind (Rhodes *et al*. 2007; Turner *et al*. 2005) will be inflated. Another note of caution is that heritability as measured from r^2 using a panel of inbred strains does not represent a narrow-sense or a broad-sense estimate. The estimate is not narrow-sense because it includes genetic variance from epistasis, but it is not broad-sense either because it excludes genetic variance from dominance. Finally, the higher estimates of heritability in adults as compared to adolescents (Table 1) are a direct result of greater stimulation in adults. The proportion of variation attributed to strain is magnified when the range in phenotypes is increased and individual variance within strains is relatively uniform (Fig. 2).

Summary

The main finding was that differential locomotor stimulation from cocaine between adolescents and adults is strongly dependent on genetic background. Certain strains, including C57BL/6J and BALB/cByJ, showed the typical pattern of reduced stimulation in adolescents as compared to adults. However, others such as DBA/2J and male FVB/NJ showed no differences between ages. Sex differences were only apparent as interactions with age for BALB/cByJ and FVB/NJ strains, suggesting a minor contribution of sex in explaining the age or strain differences. Disparate biological explanations could contribute to the strain differences including developmental differences in brain physiology, morphology or pharmacokinetics. Future studies testing these specific hypotheses as well as examining more strains at multiple time points during adolescence are needed to develop a richer understanding of the phenomenon of age differences in cocaine-induced stimulation.

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