mine poses unique challenges, in that it's highly addictive nature is compounded by drug-induced cognitive deficits. Here we show the utility of an animal model for conditioned cue and drug induced relapse by using a reinstatement model of methamphetamine-seeking behavior in rats. In addition, cognitive performance was assessed in order to determine the deficits that arise from chronic methamphetamine exposure and the relationship of these changes in cognitive performance to methamphetamine-seeking behavior.
Methods: Male rats were trained to lever press during 1, 2, or 6 hr daily sessions for intravenous methamphetamine (0.06 mg/kg/infusion) paired with the presentation of a compound stimulus cue (light + tone). Responding was then allowed to extinguish in the absence of either methamphetamine or the drug-paired cue. Reinstatement of methamphetamine-seeking behavior (i.e. responding on the previously methamphetamine-paired lever) was then tested either in the presence of the compound stimulus or after a methamphetamine priming injection (1.0 mg/kg, IP). Before and after chronic methamphetamine self-administration, animals were assessed using a novel object recognition test, a behavioral task in rats that is analogous to cognitive assessments previously used in methamphetamine dependent human subjects.
Results: Animals showed robust methamphetamine self-administration over time, followed by a decrease in responding across extinction sessions, and significant increases in reinstated responding for methamphetamine-paired cues, or after a methamphetamine injection. Animals showed a pattern of more persistent lever pressing across extinction trials compared to responding seen after other drugs (e.g. cocaine). Furthermore, longer methamphetamine access regimens increased responding during reinstatement testing. Changes in novel object recognition and the relationship of cognitive performance to reinstatement behavior will be presented and discussed.
Discussion: Methamphetamine-trained animals showed high drug intake, resistance to extinction, and robust reinstatement of methamphetamine-seeking behavior. We will discuss the utility of this model for understanding the relationship of various risk factors, including cognitive deficits, with drug-taking and drug-seeking behavior. The use of this model for assessment of novel pharmacotherapies aimed at relapse prevention and cognitive dysfunction in methamphetamine dependence will also be discussed. These studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health. This research was supported by NIH grants RO1 DA10462 and P50 DA15369.

17. Affective Circuitry in Unaffected Adolescent/Young Adult Offspring from Multiplex Alcohol Dependence Families: Structural and Functional MRI Studies

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Background: Yearly longitudinal follow-up of offspring from multiplex families using imaging and ERP has pointed to developmental differences in cognitive functioning including P300 amplitude differences in these high-risk offspring. Previously we reported morphometric differences in amygdala volume in the right hemisphere in these high-risk offspring and slower pruning of cerebellar grey through adolescence. These morphometric differences appear to be minimally influenced by exogenous factors, as the majority of the offspring had not yet developed alcohol or drug dependence. These results suggested the importance of further study of components of cognitive and affective circuits that may place these offspring at higher risk for developing substance use disorders.
Methods: Anatomic brain MRI scans are being obtained at regular intervals as part of a longitudinal study. In a morphometric analysis of first time scans, orbitofrontal volumes were obtained in the right and left hemisphere for high and low risk participants. Data for a total of 107 children, adolescents and young adults (50 female and 57 male) were analyzed. A functional imaging study was completed for sixteen high and low risk adolescent/young adults (mean age 22 years). Groups were matched for age and gender and fMRI completed using an emotion recognition test (the Reading the Mind in the Eyes test of Baron-Cohen).
Results: For the structural imaging analysis, a right/left ratio for total OFC in each hemisphere was calculated (right-left/right +left) for each participant. OFC volumes were larger in the right hemisphere for both groups. Risk group comparisons were performed adjusting for ICV, age, BMI and hand preference. This analysis revealed significantly smaller Right/Left ratios in the high-risk group ($F = 8.95$, $p = 0.003$). For the functional imaging study, SPM5 fMRI analyses were performed. Contrast maps (Emotion >Fixation) were submitted to random effects analyses (HR, LR, and HR vs. LR; threshold, $p < .005$). Intra-group analyses indicated that whereas LR showed robust and bilateral activation of the OFC, such activation was absent in HR subjects. Inter-group analyses indicated reduced activation in the inferior frontal and orbital-frontal regions.
Discussion: The significantly reduced Right/Left OFC ratio in these HR offspring suggests involvement of the affective fronto-limbic system that includes the OFC, cingulum, and amygdala. Dysregulation of this circuit has been associated with pediatric bipolar disorder, impulsive disorders and cocaine dependence. Our preliminary findings indicating reduced activation of the OFC in HR offspring seen in our fMRI analyses are consistent with our structural findings, and are in accord with observations that D2 receptors and dopamine release are associated with reduced activation of the OFC (Volkow et al 2004). Functional polymorphisms in D2 receptor gene (C957T) appear to be associated with alcohol (Hill et al., unpublished) and heroin (Xu et al 2004) dependence. These findings suggest that offspring from multiplex families may be at genetic risk for alterations in affective circuitry that may increase their susceptibility for substance use disorders.

18. Effects of Naltrexone on Ethanol Self-Administration in Rhesus Macaques Exposed to Early-Life Stress

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Background: Preclinical and clinical studies have shown that opiate receptors may play an important role in alcohol reinforcement, as demonstrated by the effectiveness of the opiate receptor antagonist naltrexone in reducing alcohol consumption. Rodent studies have revealed that maternal separation can induce long-lasting changes in brain levels of the endogenous opioids, and in nonhuman primates, early-life stress, modeled using a mother-absent, peer-rearing condition, produces increases in alcohol consumption during late adolescence and adulthood. However, whether naltrexone's efficacy in reducing ethanol consumption differs according to exposure to early-life stress is yet to be tested.
Methods: The present study aimed to assess naltrexone's efficacy in reducing oral ethanol self-administration in female rhesus macaques that were reared with their mothers (mother-reared: MR; n=6) or without adults in peer only groups (peer-reared: PR; n=6) during the first 6 months of life. At approximately 8 months of age, all monkeys were housed together as a single same-age cohort until adolescence (~4.5 years of age). Using a five-station computer-automated liquid dispensing apparatus, all monkeys, each equipped with a neck-collar identification chip, were trained in daily 1-hr sessions 4-5 days per week to self-administer an aspartame-sweetened vehicle solution.