

TITLE: Age differences in *bdnf* gene expression after cocaine self-administration or cue-induced reinstatement of cocaine-seeking in male rats

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Introduction: Results from our behavioral pharmacology laboratory indicate that male rats that self-administer cocaine as adolescents exhibit decreased vulnerability to subsequent cue-induced reinstatement of cocaine-seeking, as compared with adults. An important neuroplasticity-related gene that influences such drug-seeking behavior and differs across age groups is brain-derived neurotrophic factor (*bdnf*). BDNF mRNA is expressed in regions of the brain known to be critical for reward and reinforcement-related behavior. Based on reports that BDNF in the prefrontal cortex attenuates cue-induced reinstatement in adult rats, whereas BDNF in the nucleus accumbens increases reinstatement, we hypothesized that cocaine-seeking would correlate with higher expression of BDNF mRNA in the prefrontal cortex but lower expression in the nucleus accumbens of younger animals compared with adults.

Methods: Adolescent and adult male Wistar rats were allowed to acquire lever-pressing maintained by intravenous (i.v.) infusions of cocaine in daily two-hour sessions over 13 days. A subset of rats in both age groups received only saline infusions. At three experimental time points (immediately after last self-administration session, after extinction and reinstatement at 1 day abstinence from cocaine, and after extinction and reinstatement at 60 days abstinence), rats were sacrificed and brain tissue was collected to analyze BDNF mRNA levels by *in situ* hybridization. Initially, tissue was analyzed in the entire medial prefrontal cortex (mPFC) and the entire nucleus accumbens (NAc). Then *bdnf* expression was re-analyzed to account for sub-regions of the mPFC (prelimbic and infralimbic cortex) and the NAc (core and shell), with additional measurements of the claustrum (Cl) and caudate putamen (CPu).

Results: Although *bdnf* expression varied across drug treatment and time point in brain region-dependent ways, *bdnf* expression was similar across age groups in almost all cases. Expression levels were extremely low in the nucleus accumbens.

Conclusions: These data generally fail to support the hypothesis that age differences in BDNF mRNA levels correlated with cue-induced reinstatement of cocaine-seeking. Future studies should analyze BDNF protein across age and drug conditions.