What makes people under stress more vulnerable to become addicted to cocaine? Brain BDNF may be the key

Annually, drug addiction leads to 0.5 - 1.3% of mortality for people between 15-64 years of age and has an estimated economic impact of $524 billion in the U.S, due to addiction-related health care, loss of productivity, accidents, and crime. Its impact stretches beyond the addicted individual to family members and society. There are individual differences and environmental factors that contribute to vulnerability to addiction. One such factor is social stress, which for some is experienced on a daily basis, ranging from domestic abuse to bullying. Since people under social stress are more susceptible to abuse drugs, it is critical to understand the brain mechanism of stress-induced vulnerability to addiction.

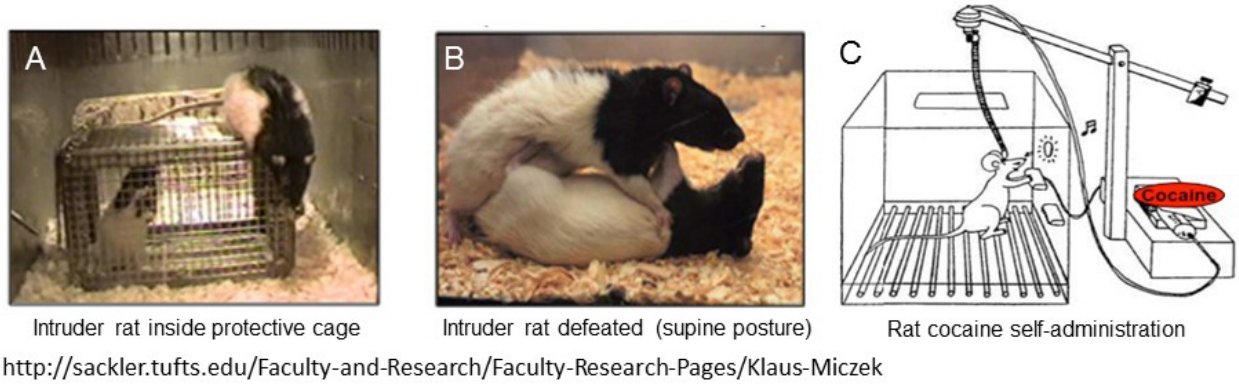

Fig. 1. A. At the beginning of social defeat stress, intruder rat is put inside the resident's home cage under the protective cage, with the resident around. B. After the removal of the protective cage, the resident will fight with the intruder till it lay down on the ground showing supine posture. C. The cartoon shows the rat inside the self-administration chamber pressing the lever to gain cocaine infusion.

Brain-derived neurotrophic factor (BDNF) is a brain-enriched molecule that supports neural survival and the generation of new connections among neurons. In the brain, drugs of abuse activate neurons in the ventral tegmental area (VTA), which contains many dopaminergic neurons that respond to all kinds of natural rewards and addictive drugs. Previously, we found that repeated social defeat stress in rats significantly increases BDNF expression in the VTA, which associates with an augmented locomotor response to amphetamine. Since BDNF also regulates signaling strength between neurons, it may initiate stress-induced neural adaptations that make an organism more sensitive to the rewarding effects of drugs. Thus, we hypothesized that individuals with high levels of BDNF in the VTA would be extremely vulnerable to cocaine following stress.

To test our hypothesis that BDNF is involved in stress-induced vulnerability to cocaine abuse, we

artificially increased expression of BDNF in the VTA of male rats. Rats were then exposed to either brief handling by the experimenter or received intermittent social defeat stress consisting of a brief physical attack/defeat (~3 min) from a larger, territorial rat, and continued psychological stress from the threatening behavior of the intruder (15 min). Then to measure aspects of drug self-administration, both handled and socially defeated rats were trained to press a lever for intravenous cocaine infusions. We placed the animals on a training procedure where the number of the lever pressing to gain the next cocaine infusion increased, so the animal would eventually need to press hundreds of times to receive one infusion. At some point, the demand is too great that the animal gives up, which allows us to measure how hard the animal is willing to work for cocaine (i.e., motivation). We also placed the animals in a cocaine binge session, where rats were given 12 hours of unlimited access to cocaine to measure compulsive drug intake.

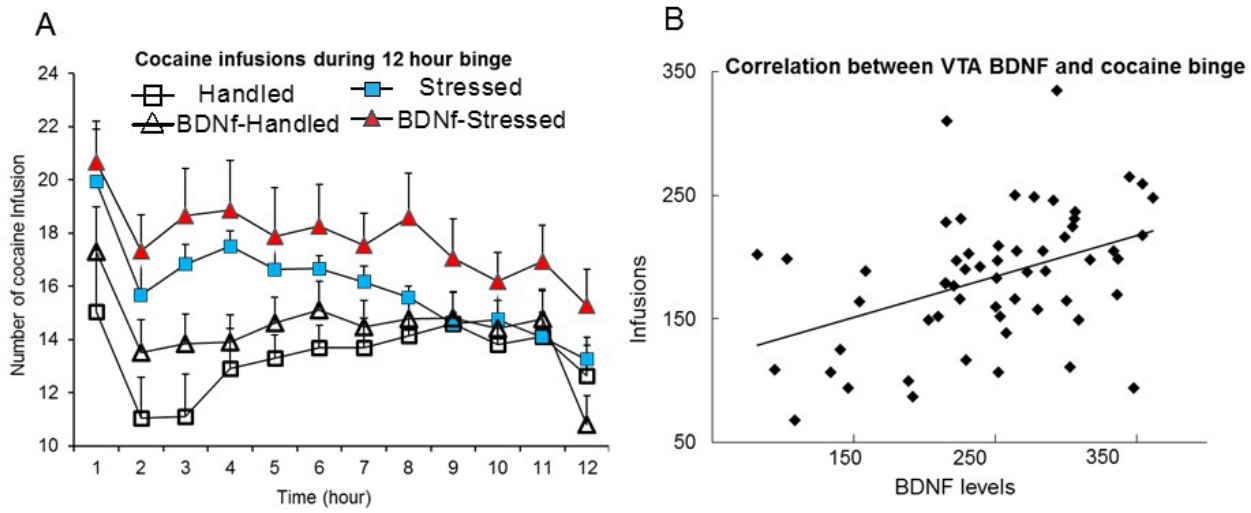

Fig. 2. A. The group with higher BDNF and history of social defeat stress showed highest cocaine intake during 12-hour binge session. B. The significant positive correlation between BDNF expression in the VTA and cocaine intake during 12 hour binge.

Our results indicate that social defeat stress alone increases the motivation to self-administer cocaine and potentiates compulsive cocaine intake during a binge session, demonstrating stress-induced vulnerability to drug abuse. Importantly, we found that artificially increasing BDNF in the VTA further potentiates stress-induced compulsive cocaine intake during the binge session. Moreover, we measured levels of BDNF in the VTA of all the animals after cocaine self-administration and found that animals that self-administered the highest amount of cocaine during the binge session also had the greatest amount of BDNF in the VTA. This finding suggests these two events are positively related.

In summary, our research has uncovered a brain mechanism that may play a critical role in how

stress may increase vulnerability to addiction. Developing treatments that reduce BDNF in the VTA may provide a new therapeutic strategy to prevent and treat cocaine addiction, particularly in individuals that have a history of repeated social stress.

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