Report

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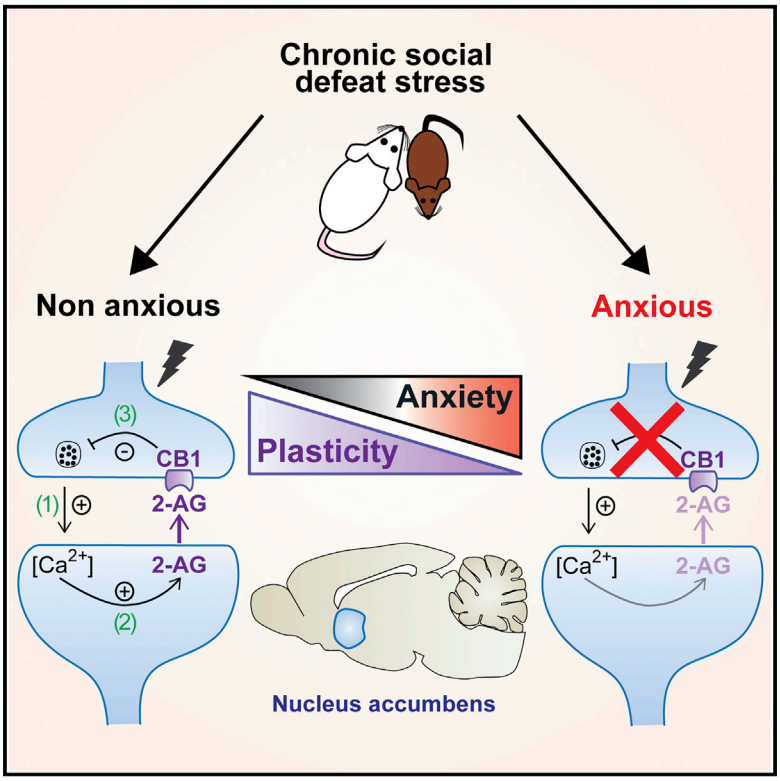
# Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress

## Graphical Abstract

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## In Brief

Bosch-Bouju et al. used cluster analysis to segregate mice into anxious and non-anxious populations following social defeat. Endocannabinoid spike-timing-dependent plasticity is abolished in anxious mice only. Enhancement of endocannabinoid signaling in the nucleus accumbens restores anxiety-like behaviors and synaptic plasticity. Endocannabinoid plasticity is thus a synaptic marker of anxiety following social defeat.

## Highlights

- Socially defeated mice were clustered into anxious and non-anxious groups
- Spike-timing endocannabinoid plasticity was abolished in anxious mice
- Elevation of 2-AG levels in the nucleus accumbens restores behavior and plasticity
- Endocannabinoid plasticity is a synaptic marker of anxiety following social defeat

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# Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress

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## SUMMARY

**Chronic social defeat stress (CSDS) is a clinically relevant model of mood disorders. The relationship between the CSDS model and a physiologically pertinent paradigm of synaptic plasticity is not known. Here, we found that cluster analysis of the emotional behavior states of mice exposed to CSDS allowed their segregation into anxious and non-anxious groups. Endocannabinoid-mediated spike-timing dependent plasticity (STDP) in the nucleus accumbens was attenuated in non-anxious mice and abolished in anxious mice. Anxiety-like behavior in stressed animals was specifically correlated with their ability to produce STDP. Pharmacological enhancement of 2-arachidonoyl glycerol (2-AG) signaling in the nucleus accumbens normalized the anxious phenotype and STDP in anxious mice. These data reveal that endocannabinoid modulation of synaptic efficacy in response to a naturalistic activity pattern is both a molecular correlate of behavioral adaptability and a crucial factor in the adaptive response to chronic stress.**

## INTRODUCTION

The neural and molecular mechanisms responsible for individual vulnerability and resilience to neuropsychiatric illnesses such as depression and anxiety disorders are poorly understood. Endocannabinoids have been linked to psychiatric illness, in particular the pathophysiology of depressive- and anxiety-like behaviors (Lafourcade et al., 2011; Hill and Gorzalka, 2009; Hillard et al., 2012; Mangieri and Piomelli, 2007; Mechoulam and Parker, 2013; Vinod and Hungund, 2006). In depressed patients, blood levels of endocannabinoids (eCBs) are decreased (Hill et al., 2009), while in animal models of depression, altered brain levels of eCBs and functionality of the cannabinoid type 1 receptor (CB1R) are reported (Bluett et al., 2014; Hill et al., 2005; Qin et al., 2015). In addition, pharmacological and genetic disruption of CB1R or eCB production results in enhanced anxiety, stress, and fear response (Hill and Patel, 2013; Jenniches et al., 2016; Marsicano et al., 2002; Qin et al., 2015; Shonesy et al., 2014; Steiner et al., 2008), reinforcing the idea that this system may play a significant role in the pathogenesis of neuropsychiatric diseases.

Endocannabinoids are lipid mediators with essential modulatory functions in the brain (Katona and Freund, 2012). Produced in the postsynapse, the two major eCBs, anandamide and 2-arachidonoyl glycerol (2-AG), signal in a retrograde direction to modulate synaptic strength via presynaptic CB1R (Castillo et al., 2012). By integrating and translating environmental changes into synaptic changes, eCBs regulate a range of brain functions (for review, see Morena et al., 2016). Activation of CB1R leads to acute depression of synaptic transmission, which with extended eCB signaling engages an endocannabinoid-mediated long-term depression (LTD) originally discovered in the nucleus accumbens (Robbe et al., 2002), a key structure to stress resiliency (Duval et al., 2015; Francis et al., 2015; Levita et al., 2012; McLaughlin et al., 2014; Vialou et al., 2010). However, it is not known whether eCBs produced in response to a naturalistic pattern of synaptic activity participate in stress resiliency.

Here, we focused on eCB spike-timing dependent plasticity (STDP) at excitatory synapses in the accumbens in a clinically relevant model of anxiety- and depressive-like behaviors: chronic social defeat stress (CSDS) (Berton et al., 2006; Krishnan et al., 2007; Larrieu et al., 2014). CSDS induces individual differences across behavioral endpoints (Krishnan et al., 2007). We automated classification of behavioral endpoints to segregate defeated mice based on their anxiety-like behaviors. Our findings demonstrate that impairment of eCB STDP in the accumbens is a synaptic signature of anxiety-like behavior after social defeat stress. The restoration of eCB signaling in the accumbens through the enhancement of 2-AG signaling protects against CSDS-induced anxiety-like behavior. Altogether, these data establish eCB STDP in the accumbens as a central regulator of adaptive capacity in animals exposed to CSDS, offering a