

# The effects of cannabidiol on cue- and stress-induced reinstatement of cocaine seeking behaviour are reverted by the CB1 receptor antagonist AM4113

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## Abstract

**BACKGROUND AND PURPOSE:** Pharmacological treatments are unavailable to patients with cocaine use disorders. Efforts to develop pharmacotherapies have led to the study of cannabidiol, a constituent of the *C. sativa* plant. However, the specific effects and mechanisms of action of cannabidiol in a rodent model of extinction-based abstinence and drug seeking relapse remain unclear. **EXPERIMENTAL APPROACH:** In this study, cannabidiol was provided during extinction training to male CD-1 mice trained to self-administer cocaine. We evaluated the reinstatement of cocaine seeking induced by cues, stress, and drug priming. To ascertain the participation of CB1 receptors in these behavioural changes, we administered the neutral CB1 antagonist AM4113 before each reinstatement session. **KEY RESULTS** The results document that cannabidiol did not modulate extinction learning. After cannabidiol treatment, increased levels of CB1 receptor protein were found in the prelimbic and orbitofrontal parts of the prefrontal cortex, as well as in the ventral striatum; an effect paralleled by a reduction of [?]FosB accumulation and increased GluR2 AMPA receptor subunits. Furthermore, cue-induced reinstatement of cocaine seeking was prevented in cannabidiol-treated mice. Unexpectedly, cannabidiol facilitated stress-induced reinstatement of cocaine-maintained responding. Cocaine-primed reinstatement remained unaltered by cannabidiol. Both, the blockade of cue-induced reinstatement and the facilitation of stress-induced reinstatement were abolished by AM4113 in cannabidiol-treated mice. **CONCLUSION AND IMPLICATIONS:** Our results reveal a series of complex CB1-related changes induced by cannabidiol with opposite implications for the reinstatement of cocaine seeking behaviour that may limit therapeutic opportunities.

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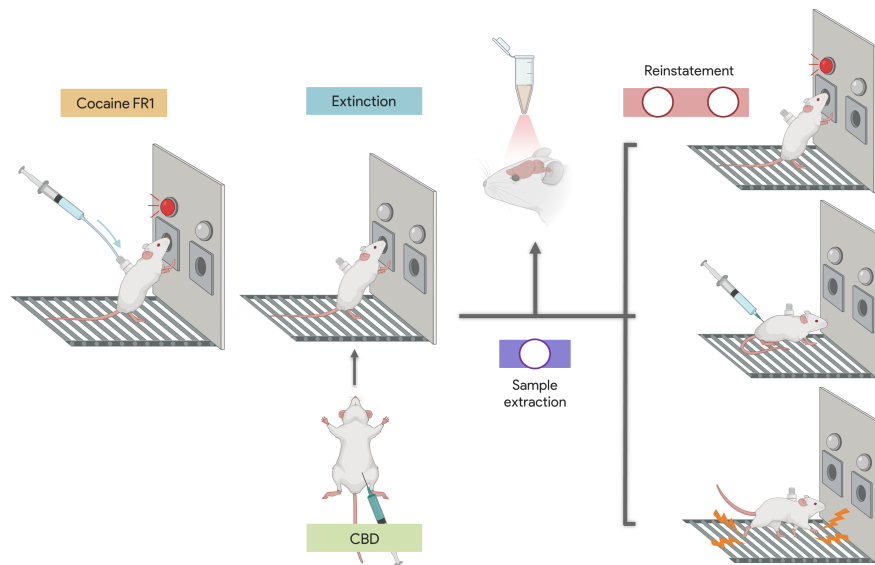
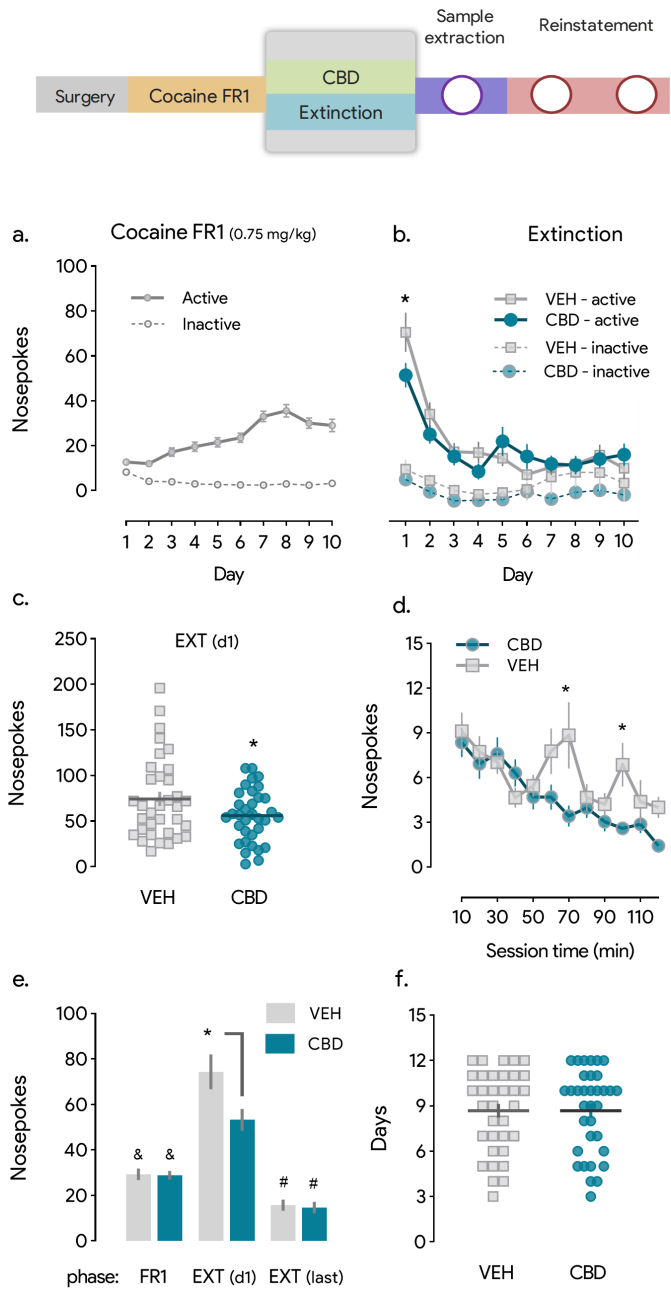


Figure 2



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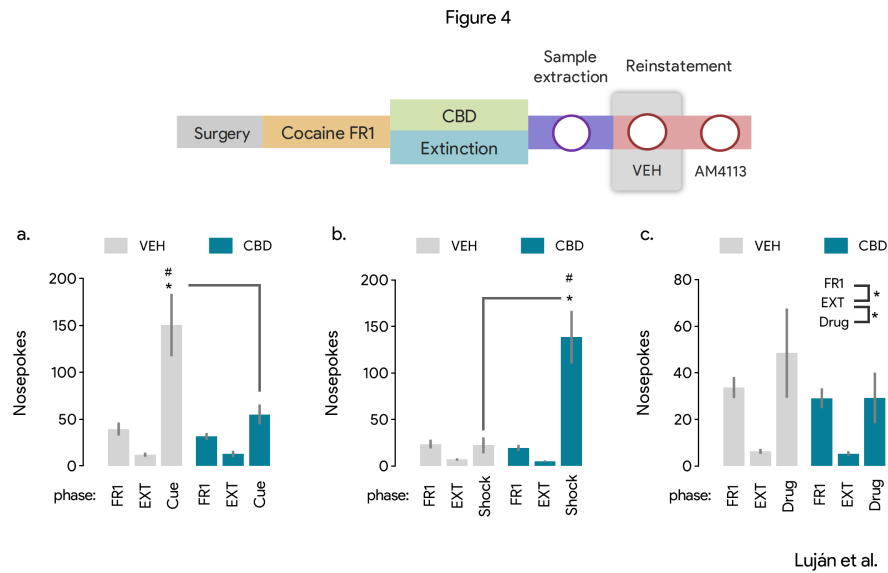
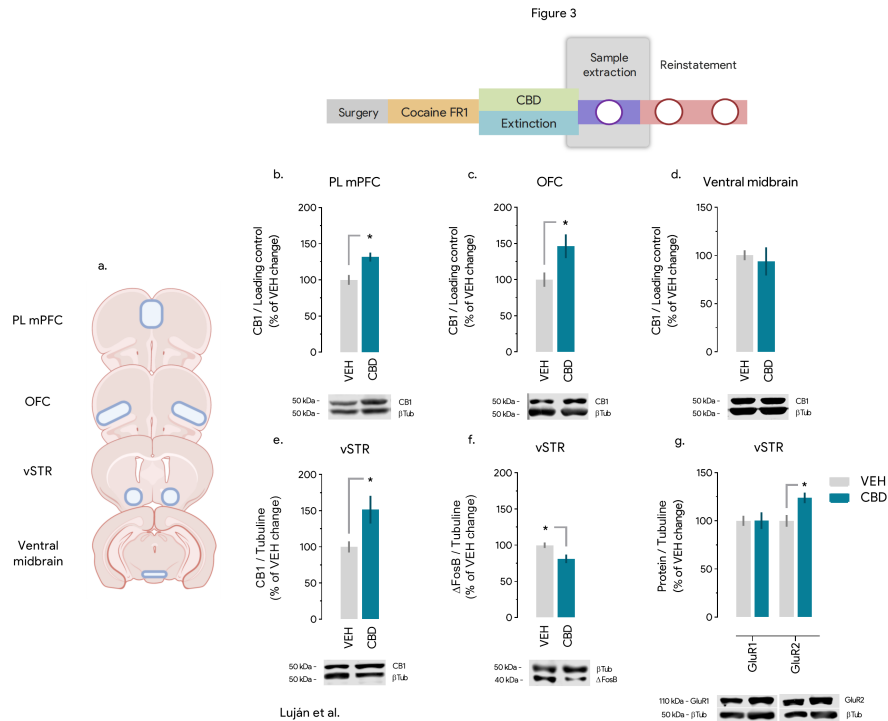
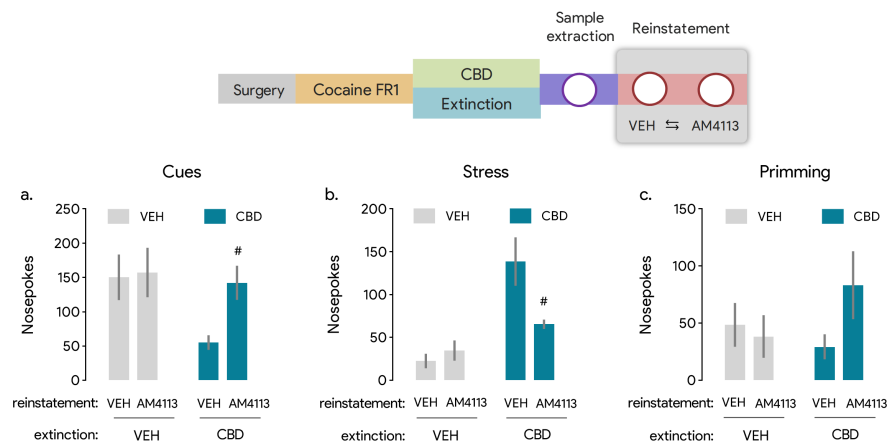


Figure 5



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