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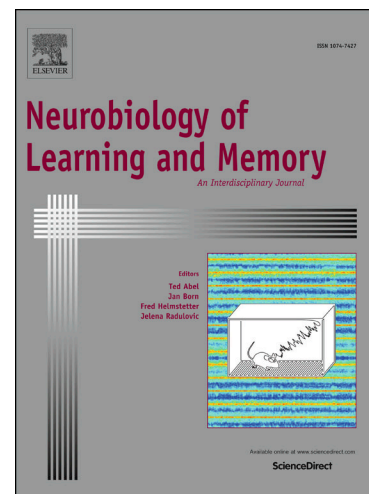
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## Learning and Memory is Modulated by Cannabidiol When Administered During Trace Fear-Conditioning

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### Abstract

Cannabidiol (CBD) is thought to have therapeutic potential for treating psychiatric conditions that affect cognitive aspects of learning and memory, including anxiety and post-traumatic stress disorder (PTSD). Studies have shown that CBD enhances extinction of fear memory when given after conditioning. This led us to hypothesize that CBD, if administered prior to fear conditioning, might modulate cognitive learning and memory processes in additional ways that would further guide its potential use for treating PTSD. Therefore, we designed a study to investigate effects of CBD on fear learning and memory when administered to mice prior to administering a trace fear conditioning protocol which imposes cognitive demands on the learning and memory process. We show that CBD-treated animals had increased levels of freezing during conditioning, enhanced generalized fear, inhibited cue-dependent memory extinction, slightly increased levels of freezing during an auditory-cued memory test, and increased contextual fear memory. Because synaptic plasticity is the fundamental mechanism of learning and memory, we also evaluated the impact of CBD on trace conditioning-dependent dendritic spine plasticity which occurred in the dorsal lateral amygdala and CA1 region of the ventral hippocampus. We showed that CBD mildly enhanced spine densities independent of conditioning, and inhibited conditioning-dependent spine increases in the hippocampi, but not the amygdala of fear conditioned animals. Overall, the memory-modulating effects of a single pre-conditioning dose of CBD, which we show here, demonstrate the need to more fully characterize its basic effects on memory, suggest caution when using it clinically as an anxiolytic, and point to a need for more research into its potential as a therapeutic for treating memory-loss disorders.

### 1. Introduction

Estimated at around 10%, the world-wide lifetime prevalence of post-traumatic stress disorder (PTSD) is very high (Atwoli et al., 2015). However, currently available pharmacotherapy is limited to selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and Monoamine Oxidase inhibitors, all of which elevate neurotransmitter levels, provide only small benefits, and can produce dangerous side effects (Hoskins et al., 2015; Jeffreys et al., 2012). This makes discovery of new therapeutics for PTSD and other anxiety disorders very important. In an attempt to address this deficiency, prescription of medical marijuana for treating stress disorders, including PTSD, has become legalized in about half of the states in the United States of America. However, major cannabinoids in marijuana include Tetrahydrocannabinol (THC), Cannabidiol (CBD), and also an entourage of over 100 compounds which have been poorly evaluated for their neuropsychiatric value (Turna et al., 2017; Mechoulam, 2016; Aizpurua-Olaizola et al., 2016; O'Neil et al., 2017; Rong et al., 2017). In addition, the use of THC for treating neuropsychiatric disorders is of concern due to its ability to induce psychosis (reviewed in Wilkinson et al., 2014), and variables in genetics, delivery systems, and dosing, make assessing positive and negative effects of medicinal marijuana difficult.

CBD, in contrast, is a major cannabinoid which is not thought to be psychotropic and exerts certain anxiolytic properties that suggest its potential as a therapeutic for treating psychiatric conditions including anxiety disorders and PTSD (Mechoulam and Hanus, 2002; Mechoulam et al., 2007; Iuvone et

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