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Opposite effects of THC and CBD on auditory mismatch negativity: a randomised controlled trial of acute cannabinoid

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Abstract
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P.1.g.022 Opposite effects of THC and CBD on auditory mismatch negativity: a randomised controlled trial of acute cannabinoid administration

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Background: The interplay between the main constituents of cannabis, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has gained interest in recent years. THC has generally been found to be anxiogenic, paranoia inducing, psychotogenic and cognitively impairing, while CBD has demonstrated anxiolytic and antipsychotic properties. There is evidence that THC and CBD have opposite effects on brain function and that CBD may ameliorate adverse effects of THC. The purpose of this study was to examine the acute effects of each compound alone and in combination on a candidate endophenotype for schizophrenia, the mismatch negativity (MMN), which is reduced in amplitude in patients and subserved by NMDA receptor function, to explore mechanisms by which THC may trigger and CBD may ameliorate psychotic-like brain phenomena.

Methods: In a double-blind placebo-controlled study, 36 healthy volunteers (31 male) comprising 18 experienced cannabis users and 18 non-naïve controls/irregular users (median lifetime occasions of use 307 versus 24, respectively), underwent 5 randomised drug sessions with a one week washout: 1. Placebo; 2. THC 8 mg; 3. CBD 400 mg; 4. CBD 4 mg + THC 8 mg [LoCBD+THC]; 5. CBD 400 mg + THC 12 mg [HiCBD+THC]. Drugs were dissolved in 100% ethanol (which served as placebo) and vaporised using a Volcano® Vaporiser. Participants completed a multifeature auditory oddball paradigm with duration and frequency deviants (6% each). MMN amplitude was analysed at Fz. A 5 (drug condition) x 2 (MMN type) repeated measures ANOVA with a between-subjects factor of group (users vs. controls), was followed by planned comparisons to determine (a) whether high dose CBD and THC alone affect MMN relative to placebo; (b) whether low and high doses of CBD combined with THC affect MMN relative to THC alone; and (c) whether effects differ according to lifetime cannabis exposure.

Results: There was a significant drug by MMN type interaction ($F = 6.12$, $p < 0.001$) and drug interacted with group ($F = 2.89$, $p < 0.025$). CBD reduced while THC enhanced frequency MMN, more so in users than controls, and CBD enhanced duration MMN in controls but not users. Frequency MMN was more consistently affected in the comparison of the three THC conditions, where a significant drug by group interaction indicated that HiCBD+THC significantly decreased frequency MMN amplitude relative to THC alone and LoCBD+THC in users in particular, while trend differences in controls indicated that LoCBD+THC tended to reduce both frequency and duration MMN compared to THC.

Conclusions: While CBD may have opposite effects to THC on frequency MMN, the pattern of results was less clear for duration MMN, suggesting that these two components may be subserved by differential underlying neurobiological interactions with the endogenous cannabinoid system. The effects of CBD were not typically in the direction expected with regard to potential antipsychotic properties and when combined with THC differed according to dose, prior exposure to cannabis and the nature of the MMN investigated. Associations with psychotic-like symptoms, cognitive function, endogenous cannabinoid levels and genotype will be further explored.