References

[1] Bar M., 2009. A cognitive neuroscience hypothesis of mood and depression. Trends Cogn Sci. 13: 456–63.
[2] Gotlib I.H., Joormann J., 2010. Cognition and depression: current status and future directions. Annu Rev Clin Psychol. 6: 285–312.
[3] Koster E.H., De Lissnyder E., Derakshan N., De Raedt R., 2011. Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. Clin Psychol Rev. 31: 138–45.
[4] Nolen-Hoeksema S., Watkins E.R., 2011. A Heuristic for Developing Transdiagnostic Models of Psychopathology Explaining Multifinality and Divergent Trajectories. Perspect Psychol Sci. 6: 589–609.
[5] Piguet C., Desseilles M., Sterpenich V., Cojan Y., Bertschy G., Vuilleumier P., 2014. Neural substrates of rumination tendency in non-depressed individuals. Biol Psychol. 103: 195–202.

P.1.i.039 Acute effects of Δ9-tetrahydrocannabinol and cannabidiol on hippocampal glutamate and GABA levels

N. Solowij[1]*, H. Van Hell[1], S. Broyd[1], C. Suo[2], M. Yucel[2]
[1]University of Wollongong, School of Psychology and Illawarra Health and Medical Research Institute, Wollongong, Australia; [2]Monash University, Monash Clinical and Imaging Neuroscience and School of Psychological Sciences, Melbourne, Australia

Purpose of the study: Cannabis is increasingly proposed as a therapeutic agent for multiple indications and yet its recreational use in humans is associated with a range of adverse outcomes, including psychosocial and neurocognitive harms that implicate the hippocampus as a particular target. We have demonstrated dose-dependent reduction of hippocampal and amygdala volumes in long term heavy cannabis users, alongside elevated psychotic-like symptoms, poorer cognitive function and impaired brain electrophysiology (e.g. reduced mismatch negativity (MMN; thought to be underpinned by NMDAR functionality)) [1–3]. These phenotypes resemble schizophrenia outcomes and evidence continues to mount for an association between cannabis use and schizophrenia. While Δ9-tetrahydrocannabinol (THC) is thought to be psychotogenic and associated with worse outcomes, cannabidiol (CBD) may ameliorate the adverse effects of THC with intriguing therapeutic properties (e.g. anxiolytic, antipsychotic, antioxidant). We have evidence that prolonged exposure to CBD may protect against hippocampal volume loss in chronic users. The mechanisms of potential neuroprotection by CBD are currently not known. In this study we investigated the acute effects of THC and CBD on glutamate and GABA levels in the hippocampus.

Methods used: In a randomized double-blind placebo-controlled cross-over trial we administered THC (6 mg) and CBD (200 mg) alone, and in combination, to human volunteers (N = 20; frequent [n = 10] and infrequent [n = 10] cannabis users) by vaporisation, using previously described protocols [4]. We acquired magnetic resonance spectroscopic (MRS) data over a 30 minute period following drug administration to probe the acute effects of THC and CBD on glutamate and GABA levels using LCModel in a voxel positioned over the left hippocampus.

Results: Preliminary analyses indicate that each compound differentially modulates GABA and glutamate levels in the hippocampus. THC decreased while CBD increased hippocampal glutamate levels relative to placebo. Both compounds increased GABA levels. GABA and glutamate levels were inversely correlated after administration of THC ($r = -0.63$, $p = 0.009$). Frequent users had higher glutamate levels than infrequent under placebo and a greater reduction in glutamate following THC. They also showed a greater increase in GABA after THC and CBD. The results for combined THC and CBD were mixed. Hippocampal basal GABA levels strongly predicted MMN amplitude, under placebo (r2=0.50), as well as after THC (r2=0.80) and CBD (r2=0.55) administration. Hippocampal basal glutamate levels were associated MMN after administration of THC and CBD combined (r2=0.45).

Conclusions: This is the first such study in humans and clearly demonstrates modulation of hippocampal GABA and glutamate by these cannabinoids and their association with neurocognitive outcomes (MMN). The group differences between frequent and infrequent cannabis users may be due to an aberrant endocannabinoid system in regular users. The implications of these findings overall, and for potential CBD treatment for schizophrenia and/or cannabis dependence, will be discussed in light of the shifting policies toward legalisation of cannabis for medicinal and recreational use.

References

[1] Yücel, M., Solowij, N., Respondek, C., et al., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry, 65: 694–701.
[2] Solowij, N., Stephens, R.S., Roffman, R.A., et al., 2002. Cognitive functioning of long term heavy cannabis users seeking treatment. JAMA, 287: 1123–1131.
[3] Greenwood, LM., Broyd, S.J., Croft, R., et al., 2014. Chronic effects of cannabis use on the auditory mismatch negativity. Biol Psychiatry, 75: 449–458.
[4] Solowij, N., Broyd, S.J., Van Hell, H.H., et al., 2014. A protocol for the delivery of cannabidiol (CBD) and combined CBD and Δ9-tetrahydrocannabinol (THC) by vaporisation. BMC Pharmacol Toxicol, 15: 58.

P.1.i.040 Effects of intranasal oxytocin on reward anticipation in patients with post-traumatic stress disorder: an fMRI study

L. Nawijn[1]*, M. Van Zuiden[1], S.B.J. Koch[1], J.L. Frijling[1], D.J. Veltman[2], M. Olff[1,3] *[1]Academic Medical Center, Department of Psychiatry, Amsterdam, The Netherlands; [2]VU University Medical Center, Department of Psychiatry, Amsterdam, The Netherlands; [3]Arq, Psychotrauma Expert Group, Diemen, The Netherlands*

Rationale: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that may develop after a traumatic event. Anhedonia (or emotional numbing) is a key symptom of PTSD, next to re-experiencing, hyperarousal and avoidance. PTSD has recently been associated with reduced reward processing, including neural responses, which could underlie the frequently observed anhedonic symptoms in PTSD [1]. The neuropeptide oxytocin is a promising agent for targeting both fear- and reward-related neurobiological deficits in PTSD [2]. Besides its potential anxiolytic effects [3], intranasal oxytocin administration also has been found to enhance neural reward processing in healthy individuals [e.g. 4]. By enhancing reward processing, oxytocin could potentially help alleviate anhedonic symptoms in PTSD. In this study, we investigated whether a single intranasal oxytocin administration affects neural responses to reward and loss in PTSD patients and trauma-exposed healthy controls.

Methods: Trauma-exposed male and female police officers with (n = 35, 21 males) and without PTSD (n = 38, 19 males) were included in this functional magnetic resonance imaging (fMRI) study. A double-blind randomized placebo-controlled trial was conducted, using a cross-over design in which medication order