P.6.d.005 Anhedonia, depression, anxiety, and craving for opiates in opiate addicts stabilized on oral naltrexone and long acting naltrexone implant

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Background: Naltrexone is an opioid receptors antagonist that blocks the analgesic and euphoric effects of opioids. Opioid craving, depression, anxiety, and anhedonia are triggers for relapse, and concerns have been raised that naltrexone increases them due to its blockade of endogenous opioids. The purpose of this study was to assess the effects of long term (six months) blockade of the opiate receptors with naltrexone on opioid craving, depression, anxiety and anhedonia within a double blind double dummy placebo controlled randomized clinical trial of naltrexone implant vs. oral naltrexone and placebo.

Methods: Patients with opioid dependence were enrolled into a three cell randomized, double blind, double dummy, parallel, placebo-controlled 6-month trial comparing implantable naltrexone, oral naltrexone, and placebo. 306 recently detoxified opioid addicts were randomized to a 6 month course of biweekly drug counseling and one of three medication groups (102 patients in each one): Naltrexone implant (1000 mg, 3 times – every other month) + Oral placebo daily (NI+OP), Placebo implant + Oral naltrexone (PI+ON) (50 mg/day), and double placebo (implant and oral) (PI+OP). Medications were administered under double-dummy/double-blind conditions. Urine drug testing and brief psychiatric evaluations were done at each biweekly visit. Oral medication compliance was evaluated using a urine riboflavin marker. Monthly psychometric assessments were done using a Visual Analog Scale for opioid craving, and the Beck Depression Inventory, Spielberger State-Trait Anxiety Test, Chapman Scale of Physical and Social Anhedonia, and Ferguson Anhedonia Scale. Outcomes were analyzed using ANOVA with month of treatment and medication group as independent variables and psychomentric assessments as dependent ones (Tukey test for between group post hoc comparisons was used).

Results: The number of heroin negative urines revealed a clear advantage of the naltrexone implant group over the 2 others: The cumulative proportion of heroin negative urines in NI+OP group was 63.6% compared to 42.7% in PI+ON group and 34.1% in PI+OP group ($p < 0.0001$, Fisher Exact test). The percentage of patients that completed six months of treatment without relapse was 52.9% in the naltrexone-implant group, 15.7% in oral naltrexone, and 10.8% in the placebo group (survival analysis, Log Rank Mantel-Cox c2=68.4; $p < 0.001$ to naltrexone implant group) [1]. There was a significant decrease of craving over the course of treatment from 3–3.5 on a 10-point scale at baseline to 0.5–1.1 at six months among those who were retained in treatment and did not relapse (F5, 1095= 21.2; $p < 0.001$) with no between group differences. Depression, anxiety, and anhedonia were moderately elevated at baseline and decreased to normal levels within the first 1–2 months for patients who remained in treatment and did not relapse with no significant difference between groups.

Conclusion: The improvements in opioid craving, depression, anxiety, and anhedonia among those who remained in treatment and did not relapse are most likely an effect of treatment success and not specifically related to naltrexone since they occurred regardless of medication group (including a double placebo group). Long-term blockade of opiate receptors with naltrexone did not induce anhedonia or depression among these patients.

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P.6.d.006 I was gonna process rewards – but then I got high: the acute and chronic effects of cannabis and ketamine on reward processing

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Both the acute and chronic effects of dependence-forming drugs (e.g. cannabis and ketamine) have been associated with deficits in various aspects of reward-processing. Recently, two behavioural tasks have successfully been used to assess effort-related-decision-making and the development of a rewarded response-bias: namely, the Effort-Expenditure-for-Rewards-Task (EEfRT) [1] and the Probabilistic-Reward-Task (PRT) [2], respectively. However, the relationships between these aspects of reward-processing and cannabis and ketamine use have not been thoroughly investigated. We had two main aims: i) to investigate the acute effects of three types of cannabis (THC-only, THC+CBD and placebo) on effort-related-decision-making ii) to investigate the effects of cannabis and ketamine dependence on effort-related-decision-making and the development of a rewarded response-bias.

In experiment 1, using a repeated-measures design, participants ($n = 16$, 7 male) received one of three types of vaporized cannabis (containing: 8 mg of THC; 8 mg of THC + 10 mg CBD; or placebo) and subsequently completed the EEfRT. In experiment 2, using a between-subjects design, three groups were compared: people dependent upon cannabis ($n = 20$), people dependent upon ketamine ($n = 17$) and poly-drug using controls ($n = 20$) who were not dependent on any drug. Participants completed the EEfRT and PRT in a non-intoxicated state. During the EEfRT participants made a series of choices between exerting a large amount of physical effort in order to win a large amount of money and exerting a small amount of physical effort in order to win a small amount of money. The number of large-effort/large-reward choices was the outcome variable. During the PRT a face was presented on the screen for a short amount of time and the participants were asked to determine if the mouth was either short or long. One response was reinforced with money three times more frequently than the other so that a response-bias was acquired. The magnitude of the response-bias was the outcome variable.

In experiment 1, relative to placebo, both types of cannabis reduced the likelihood of participants making a large-effort/large-reward choice ($p < 0.001$ THC-only; $p = 0.028$ THC+CBD). However, THC-only cannabis, compared to placebo, led to a greater sensitivity to probability ($p = 0.029$) and expected-value ($p = 0.014$). In experiment 2, compared to poly-drug using controls, the cannabis-dependent group demonstrated a weaker

overall response-bias ($p = 0.032$) while the ketamine-dependent group demonstrated a marginally weaker overall response-bias ($p = 0.060$). Moreover, only the poly-drug using controls' response-bias improved from block 1 to block 2 ($p < 0.001$). Exploratory analyses indicated that these group differences might be associated with depression and tobacco use. However, compared to poly-drug using controls, neither dependent group demonstrated differences in effort-related-decision-making.

Experiment 1 suggests that both types of active cannabis acutely led to an inclination to exert less effort despite the opportunity for larger rewards. This supports the lay notion that being intoxicated on cannabis leads to increased laziness. However, results from experiment 2 suggests neither cannabis nor ketamine dependence was associated with impaired effort-related-decision-making. On the other hand, both cannabis and ketamine dependence were associated with an impaired ability to acquire a rewarded response-bias, but this may be explained by comorbid depression and tobacco use.

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P.6.d.008 Functional connectivity patterns between putamen and anterior cingulate cortex during response inhibition in smokers and non-smokers

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Both the anterior cingulate cortex (ACC) and putamen have been strongly implicated in response inhibition networks [1]. Literature on motor learning suggests a division in function of the anterior and posterior parts of the putamen, with the anterior part being specialized in response selection and displaying strong synchronization with the ACC and the posterior part being specialized in response repetition [2]. Our first aim was to confirm this functional division in a response inhibition task and demonstrate that the anterior putamen and ACC show unique functional connectivity during response inhibition. Our second aim was to compare smokers to non-smokers on functional connectivity of the anterior putamen during response inhibition. We hypothesized that smokers, who are thought to be more impulsive, would display diminished synchronization between the anterior putamen and ACC.

In a previously published fMRI GO/NOGO study [3], smokers exhibited reduced activation of the ACC during successful inhibition compared to non-smokers, in the absence of performance differences. We conducted functional connectivity analyses on this dataset of 25 smokers (mean age=22.56 years, $SD = 2.84$, 18 male) and 23 non-smokers (mean age=21.74 years, $SD = 1.82$, 14 male). Smokers all smoked at least 15 cigarettes per day for at least three years, whereas non-smokers had smoked ten cigarettes or less during their lifetime. There were no significant differences between the groups in mean age and education level. Notably, smokers had a significantly higher total score ($M = 65.5$ versus $M = 59$ in non-smokers) on the Barratt Impulsiveness Scale (BIS-11); $t(46) = -2.72$, $p = 0.009$. Subject specific anatomical seed regions were created with a split at the level of the anterior commissure. Functional connectivity analyses were performed using the generalized form of psychophysiological interaction (gPPI).

A whole brain analysis of connectivity strength from the anterior putamen seed during successful inhibition revealed a strong significant cluster in the ACC in all participants together (123 voxels, $p < 0.05$ FWE corrected). Performing the same analysis with the posterior seed yielded no significant cluster in the ACC, supporting our hypothesis of unique functional connectivity between the anterior putamen and the ACC during response inhibition. Interestingly, contrasting successful inhibition with failed inhibition for the anterior putamen also resulted in a significant ACC cluster (45 voxels, $p < 0.001$ uncorrected), suggesting that crosstalk between the anterior putamen and ACC may be crucial for successful inhibition.

To examine differences between smokers and non-smokers we conducted independent-sample T-tests on the successful inhibition contrast for the two seed regions. No activation peaks survived whole brain FWE correction. However, for the anterior putamen, two clusters were significant at cluster level ($p < 0.05$ FWE corrected), localized in the right insula and the cuneus. Smokers displayed increased connectivity with these regions. Over the whole group, connectivity with the right insula was positively correlated with the BIS-11 total score ($r = 0.326$, $p = 0.024$). The insula is seen as an important hub for attentional control [4] and is also thought to play a role in nicotine dependence [5]. Our results may indicate that smokers, who are on average more impulsive, have more difficulties allocating attentional resources during or after successful inhibition.

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P.6.d.009 Polyabuse and diversion of drugs: methylphenidate/cannabis-induced manic like-symptoms

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Introduction: The significant increase in methylphenidate (MPH) prescription rates over the last 15 years have led to controversy