**Title:** Dopaminergic modulation of reinforcement learning in stimulant drug addiction

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**Background:** Chronic stimulant use has been associated with disruptions in fronto-striatal systems implicated in associative learning [1]. Experimental studies have also shown that individuals with stimulant drug addiction experience difficulties in selecting the appropriate action following feedback [2]. However, the precise impairments in feedback learning in stimulant-addicted individuals are still unclear. A possible explanation might lie in an abnormal prediction error mechanism, as stimulant drugs directly target striatal dopaminergic neurons [3].

**Objectives and hypotheses:** We sought to examine the learning impairments in stimulant-addicted individuals by using a reinforcement learning paradigm [4], which critically depends on error prediction. Since reinforcement learning is a dopamine-dependent mechanism, we decided to pharmacologically manipulate dopamine transmission in order to further probe the substrates of reinforcement learning in stimulant drug addiction. We used the dopamine D2/3 agonist pramiepxole and the D2/3 antagonist amisulpride. Given the downregulation in striatal dopamine D2 receptors in stimulant drug addiction [5], we hypothesise that stimulant addicted individuals show impairments in learning from reward and punishment. A dopamine D2/3 receptor blockade in healthy volunteers would thus mimic the impairments seen in stimulant drug addiction. Acute pramipexole administration, on the other hand, would ameliorate reinforcement learning in stimulant-addicted individuals by boosting synaptic levels of dopamine.

**Methods:** In this randomised, double-blind, placebo-controlled, crossover study, we recruited 18 healthy volunteers and 18 individuals who meet the DSM-IV criteria for stimulant drug dependence. Recent drug use was verified before participants receive either a single dose of placebo, pramipexole (0.5mg) or amisulpride (400mg). All participants completed a probabilistic reinforcement learning task where they were instructed to earn as much money as possible by learning, through trial-and-error, from positive and negative feedback. Trial-by-trial performance was then extracted and fitted to a reinforcement learning model within a Hierarchical Bayesian framework. The model included parameters that estimate the rates of learning from reward (reward learning rate), punishment (punishment learning rate), and non-reinforced trials (extinction rate), as well as general sensitivity to feedback (reinforcement sensitivity).

**Results:** Computational modelling revealed that on placebo, stimulant-addicted individuals show impaired learning from punishment (group mean difference, d=-0.433, 95% highest density intervals (HDI)=-0.672,-0.192,p<.001). This performance profile was mimicked in healthy volunteers in response to amisulpride (d=-0.382, 95% HDI=-0.536,-0.240, p<.001), and additionally revealed marked reductions in learning from reward (d=-0.133, 95% HDI =-0.244,-0.024, p=.008). However, amisulpride showed the opposite effect in the stimulant group i.e. improved learning from punishment (d=0.198, 95% HDI=0.014,0.393, p=.029). The only group difference observed on pramipexole was an increase in reinforcement sensitivity in stimulant-addicted individuals (d=2.28,95% HDI=0.691,3.86,p=.004).

**Conclusion:** We showed that stimulant-addicted individuals exhibit a selective deficit in learning from punishment during reinforcement learning. While dopamine D2/3 receptor blockade ameliorated the learning deficits in stimulant-addicted individuals, possibly due to auto-receptor effects, it impaired learning performance in healthy volunteers. The results confirmed altered dopamine receptor function in stimulant-addicted individuals.

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