

The effect of dopaminergic drugs on reward prediction error and novelty processing in ADHD

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TARGET AUDIENCE: Clinical and basic neuroscientists with an interest in reward processing, reinforced learning, and ADHD.

PURPOSE: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by inattention, hyperactivity and impulsivity. ADHD is conceptualised as a disorder of the dopaminergic system, based on the efficacy of dopamine enhancing medications as well as genetic associations with polymorphisms within dopamine receptors and reuptake proteins [1-4]. Accordingly, reward related processing has also been found to be dysregulated in ADHD [1, 2] and may play a role in its pathophysiology. Indeed, there has been considerable interest in imaging reward system function [3] and the genetics of dopaminergic molecules associated with reward systems [4, 5] in ADHD. However, computational approaches to reward related processing and the application of reinforcement learning models have currently been relatively under-explored. For example, though striatal reward prediction error signals occupy a central position in reinforcement learning models of reward-seeking behaviour in humans [6] these have not currently been characterised in ADHD. Further, reward prediction error signals and reward-seeking behaviour have been shown to be modulated by stimulus novelty [7]. This is particularly pertinent to ADHD, as ADHD is associated with novelty seeking personality traits, while drugs that enhance dopaminergic signalling used to treat ADHD are themselves linked to increased novelty seeking. As such stimulant medications are thought to confer their therapeutic effects by increasing dopaminergic signalling, one potential effect of these medications could be to further increase novelty processing in ADHD. We therefore aim to investigate the effect of dopaminergic medication on novelty processing and reward prediction in ADHD in the current study.

METHODS: We adopted a within-subject repeated measures, double-blind placebo controlled study design in which adults with ADHD are tested twice (once on and once off their typical stimulant medication). Thirty ADHD patients as well as 30 age, gender and IQ matched controls are being recruited and we present data here on the first six ADHD patients tested. During each session participants were familiarised with 32 unique landscape pictures then administered either placebo or their regular stimulant medication. Ninety minutes later they performed a ‘three-armed bandit’ task [7] during fMRI scanning (T2*-weighted EPI, TE=43 ms, TR=2.52s). On each trial participants selected one of three options (represented as a landscape picture). Each picture was associated with a fixed probability (mean: ~ 0.33) of a £1 reward and participants’ aim was to maximise their total reward. On every fourth trial one picture was randomly replaced by a new one that was either pre-familiarised or novel. Reward distributions were equal for both novel and pre-familiarised pictures. We next fitted a temporal-difference learning model with 4 free parameters to each participant’s data as in [7]. This model assumes that participants learn the value of each picture and adjust their choices accordingly. The value associated with each picture ($Q(p,t)$) is updated from experience according to the rule $Q(p,t,t+1)=Q(p,t,t)+v\delta(t)$, where v is the learning rate parameter, and $\delta(t)$ the prediction error. The probability of choosing a given picture is computed using a softmax selection strategy [8]. The ‘novelty bonus’ is determined by allowing different initial expected values for novel (Q_n) compared to familiar pictures (Q_f). fMRI data were analysed in SPM8. Pre-processing included realignment, normalisation and smoothing with an 8 mm³ FWHM Gaussian kernel. Four conditions were modelled at the first level: picture presentation and its parametric modulation by expected value of the chosen picture ($Q(p,t)$) and presentation of the outcome and its parametric modulation by reward prediction error $\delta(t)$. A second level paired sample t-test was performed to assess the effect of the drug compared to placebo on the correlation between BOLD signal and prediction error.

RESULTS: Average Q_f and Q_n values were, respectively, $Q_f=55.9(\pm 25.6)p$ and $Q_n=66.3(\pm 26.9)p$ after drug, and $Q_f=48.3(\pm 29.3)p$ and $Q_n=49.6(\pm 36.5)p$ after placebo, indicating a trend for a larger novelty bonus (Q_n-Q_f) after drug administration. Consistent with the existing literature, reward prediction error ($\delta(t)$) correlated ($p<0.001$, uncorrected) with fMRI activations in the ventral striatum (fig 1). Interestingly, these preliminary data suggest that though ventral striatum activity correlates strongly with reward prediction error off of medication, this relationship is disrupted by stimulant medication (fig 2).

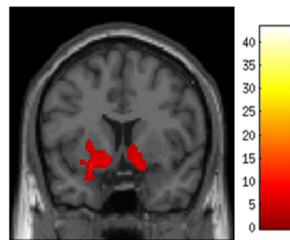


Fig 1. Striatal activation correlating with reward prediction error.

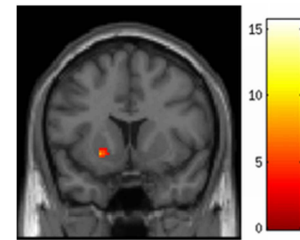


Fig 2. Changes in correlation with prediction error (Placebo>Drug).

DISCUSSION: Our preliminary data concord with and extend the published literature, demonstrating a strong association between reward prediction error and fMRI signal within the ventral striatum. Interestingly, this relationship was weakened following stimulant medication – a finding that has also been recently described in healthy volunteers following methamphetamine infusion [9]. Intriguingly, stimulant medication was also associated with an increase in novelty bonus – an effect that would be predicted to enhance novelty-seeking behaviour. These findings suggest that stimulant medication may impair brain representations of computational parameters that underpin learning even in patients with ADHD. How these preliminary findings relate to the general improvement in symptomatology reported by ADHD patients treated with stimulant medication remains to be clarified and will form part of the focus of this on-going study. Future work will also include modelling 2 discrete components of the reward prediction error (with and without a novelty bonus) as described in [7], and will investigate how these are modulated by stimulant medication.

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