Optimal dopaminergic tone for reward learning and executive control in humans

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Motivation

1) Learning is supported by interactions between the prefrontal cortex and striatum. The PFC supports learning by using executive control to direct attention to the task and by learning explicit rules to guide behavior

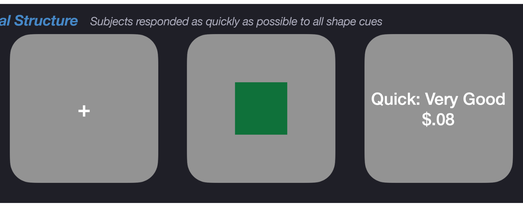
2) Dopamine has distinct effects in the striatum and the PFC and striatum, and has a powerful influence on learning

3) We sought to determine the effect of individual variability in prefrontal and striatal dopamine systems on learning, using genetic and PET assays as well as dopaminergic drug administration

Task

Key Idea: Speeded reaction time task with implicit feature-reward associations

Trial Structure *Subjects responded as quickly as possible to all shape cues*



Possible Cues

One of two dimensions (color or shape) had higher reward probability

85% probability of reward

15% probability of reward

**Faster responses, relative to participant baseline, led to larger rewards*

Drug conditions

- Placebo
- Bromocriptine (D2 receptor agonist)
- Tolcapone (COMT inhibitor)

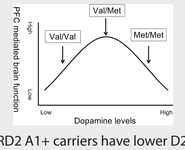
*double blind

PET measures **Separate sessions*

- FMT (dopamine synthesis capacity)
- Raclopride (D2 receptor density)
- Raclopride + methylphenidate (baseline dopamine release)

*52 of 72 subjects

Genotypes



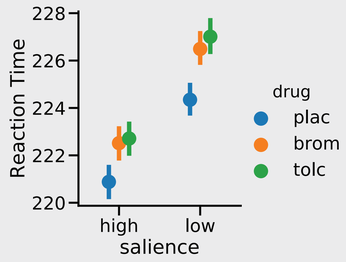
	DRD2 A1+	DRD2 A1-
COMT Val/Val	17	19
COMT Met/Met	20	21

DRD2 A1+ carriers have lower D2 receptor density and worse clinical outcomes

Behavioral Results

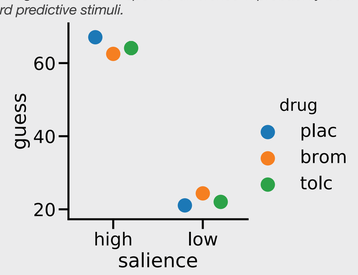
Reward speeds reaction times

Subjects responded more quickly to stimuli with higher reward probability
Both drugs slowed responses and reduced the reward probability effect



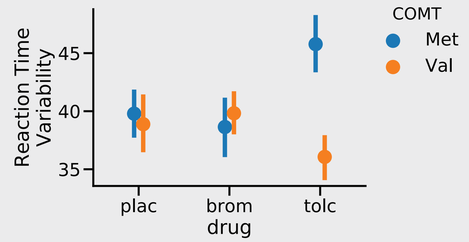
Subjects explictly learned reward probabilities

Subjects guessed the reward probabilities of each stimulus after each run.
Both drugs reduced the reported difference in probability between high and low reward predictive stimuli.

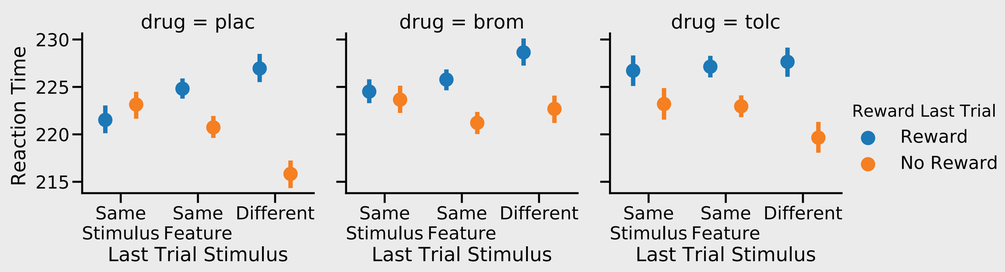


High PFC dopamine subjects are more variable on tolcapone

Consistent with a model in which dopamine overdose in PFC impairs executive control



Bromocriptine blunts learning from reward omissions



Modeling Results

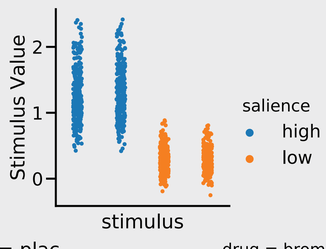
Rescorla-Wagner regression model fit to reaction times

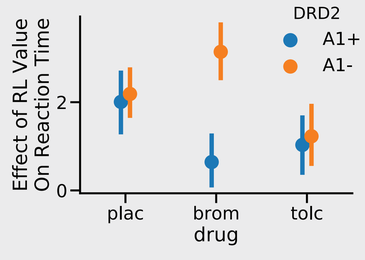
*RT ~ 1 + β*Value + ε*

Value is a vector of values V^t

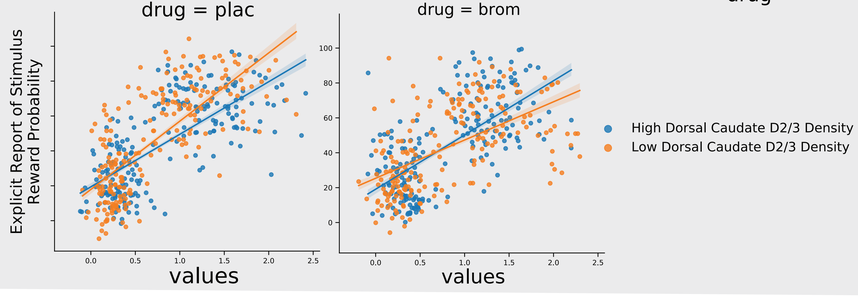
$V^t = V^{t-1} + \alpha (V^{t-1} - R^{t-1})$

β is the strength of the influence of learning on reaction times, whereas α is the learning rate





Higher caudate D2/3 receptor availability is associated with a reduced effect of RL Value on explicit reports of stimulus reward probability



Conclusions

1) Drugs affecting dopamine impair implicit and explicit learning

2) Tolcapone, which increases prefrontal dopamine, impairs executive control in our task (i.e., response variability) for COMT Met homozygotes who have higher prefrontal dopamine at baseline

3) D2 receptor activation impairs learning from negative outcomes, but this effect does not appear to vary as a function of striatal D2 receptor density

4) Bromocriptine enhances the effect of implicit learning on RTs for DRD2 A1-, while impairing it for DRD2 A+ subjects

5) Subjects with lower dorsal caudate D2/D3 receptor availability are better are reporting the value of stimuli, but these subjects take the hardest hit in performance on the D2/3 selective drug bromocriptine

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