Dopamine Receptor Modulation of Risky Decision-making

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Introduction

➢Many psychopathological disorders are characterized by abnormal risky decision-making as well as alterations in dopamine receptor expression.

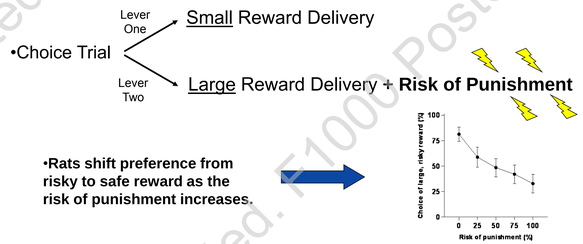
➢Determining the involvement of specific brain regions and dopamine receptor subtypes in risky decision-making may provide a better understanding of the biological basis of risky behavior. Additionally, these data may provide information about the neurobiological underpinnings of disorders associated with abnormal risk-taking.

- We tested the effects of acute systemic administration of drugs specific to D1-like and D2 –like receptors on risky decision-making in rats.
- To determine if risk preference is related to dopamine receptor expression, *in situ* hybridization was used to quantify region-specific D1 and D2 receptor mRNA in drug-naïve rats characterized on the risky decision-making task.

The Risky Decision-making Task

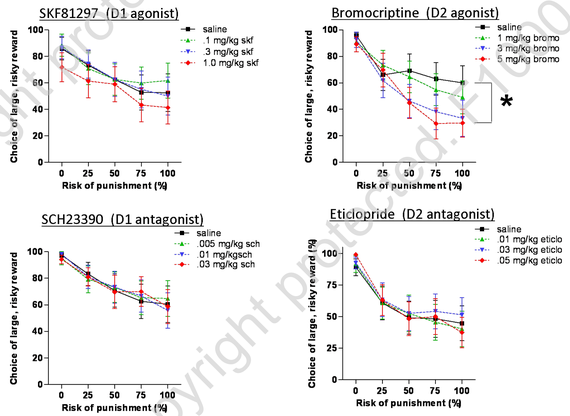
•Male Long-Evans rats were given choices between a small, "safe" food reward (one food pellet) and a large food reward (three food pellets) associated with varying risks (probabilities) of punishment (0.3 mA footshock). (Simon et al., 2009, Neuropsychopharmacol).

•Each 60 minute session consisted of 5 blocks of 8 forced choice trials with only one lever available, and 10 choice trials, with punishment risk increasing with each consecutive block (0, 25, 50, 75, 100%).



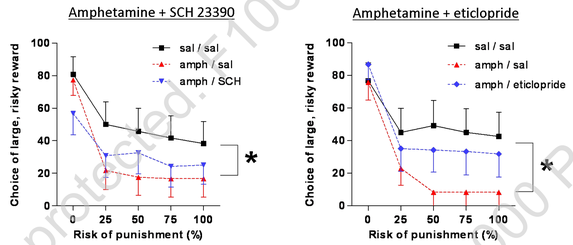
•Rats shift preference from risky to safe reward as the risk of punishment increases.

D2- but not D1-like Receptor Activation Reduces Risk



The D2-like agonist bromocriptine decreased preference for the risky reward in a dose-dependent fashion. Blockade of D2-like receptors did not affect risky decision-making. D1-like receptor activation or blockade did not affect risky decision-making.

D2-like Receptor Blockade Abolishes the Effects of Amphetamine

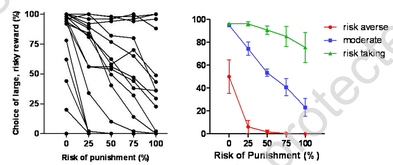


•Amphetamine attenuated risky decision-making.

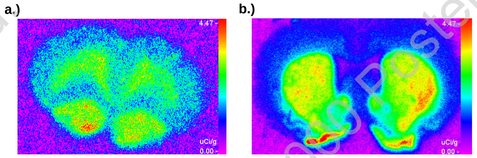
•Amphetamine coadministered with SCH 23390 attenuated risky choice in the same fashion as amphetamine. This indicated that **D1 activation is not necessary for amphetamine's effects on risky choice.**

•Amphetamine with eticlopride did not affect risky decision-making. **D2 receptor activation is necessary for amphetamine's effects on risk.**

Risky Decision-making Characterization & D1 and D2 Receptor *In Situ* Hybridization



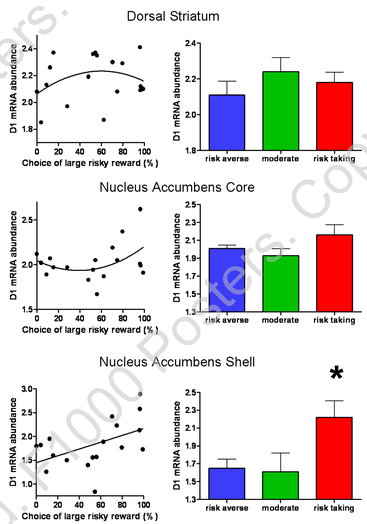
Rats decreased preference for the large reward as risk of punishment increased. For analysis, rats were divided into groups based on risk preference (n=6/group).



D1 or D2 mRNA hybridization was quantified in a.) medial prefrontal cortex, orbitofrontal cortex, and insular cortex, and b.) dorsal striatum, nucleus accumbens core and shell.

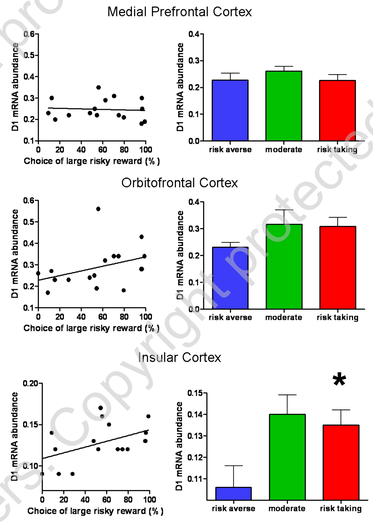
D1 Receptor mRNA Abundance in Nucleus Accumbens Shell and Insular Cortex Predicts Risky Decision-making

D1 mRNA Hybridization in Striatum



There were no significant relationships between risky decision-making and D1 mRNA in dorsal striatum or nucleus accumbens core. There was a positive correlation between risk and D1 in nucleus accumbens shell, such that **high D1 mRNA predicted high levels of risk-taking**.

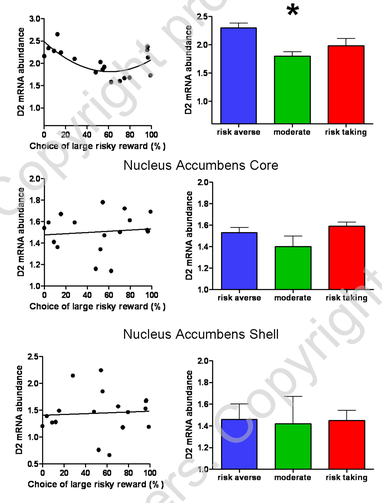
D1 mRNA Hybridization in Prefrontal Cortex



There was no significant relationship between risky decision-making and D1 mRNA in medial prefrontal cortex or orbitofrontal cortex. There was a positive correlation between risk and D1 in insular cortex, such that **high D1 mRNA predicted high risk taking.**

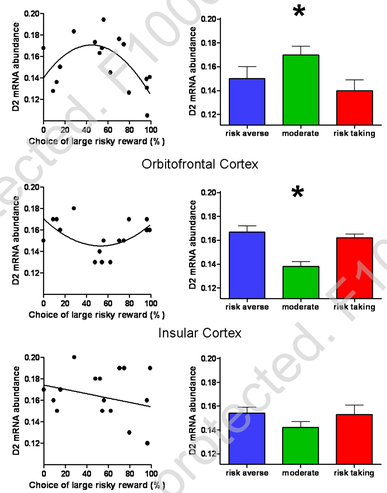
D2 Receptor mRNA Abundance Predicts Risk in Non-Linear Fashion

D2 mRNA Hybridization in Striatum



D2 mRNA in dorsal striatum negatively predicted risky decision-making: **higher levels of hybridization predicted risk aversion**. There was no relationship between risk and D2 in either region of nucleus accumbens.

D2 mRNA Hybridization in Prefrontal Cortex



D2 mRNA in medial prefrontal cortex predicted risk as an inverted U function: **low levels of D2 predicted either high or low risk**. The opposite relationship was evident in orbitofrontal cortex, with **high D2 predicting high or low risk.** High and low risk may both reflect inflexible decision-making.

Conclusions

•D2-like (but not D1-like) receptor activation reduces risk-taking. D2-like receptor modulation of risky decision-making is non-linear, as D2-like blockade does not affect risky decision-making.

•D1 receptor mRNA abundance in both shell & insular cortex predicts risk-taking. This suggests that D1 receptor abundance within this circuitry may be critical for the valuation of risky vs. safe outcomes.

•In dorsal striatum, rats characterized as risk-averse had greater D2 mRNA abundance than both risk-taking and moderate rats. This indicated that increased D2 receptor expression in this region is related to decreased risk preference (risk aversion). Of the relationships observed between D2 receptors and risk-taking, this most resembled the acute effects of D2-like receptor activation

•Nonlinear relationships were observed between risk-taking and D2 mRNA abundance in prefrontal cortex. Interestingly, opposite trends were observed in orbitofrontal cortex (U-shaped) and medial prefrontal cortex (inverted U-shaped).

•In summary, risky decision-making can be directly affected (reduced) by acute D2-like receptor activation, but trait risky decision-making appears to be a function of distinct patterns of both D1 and D2 receptor mRNA expression in various brain regions.

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