Mistakes are meant for learning: dissociable roles for dopamine receptor subtypes in learning from positive and negative feedback in visual reversal learning

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Reversal learning implicates striatal dopamine

Reversal learning is impaired in a number of psychiatric disorders including schizophrenia and obsessive-compulsive disorder (Leeson et al. 2009; Remijnse et al. 2006), but such cognitive inflexibility is also observed in Parkinson's disease (Swainson et al. 2000). Notably, Parkinson's patients display impairments only after taking their dopaminergic medication, suggesting that a relative hyperdopaminergic state leads to inflexible behavior (Cools et al. 2001). Dopamine signaling in the caudate/dorsomedial striatum (DMS), in particular at the D2 receptor, seems to be critical for successful reversal learning (Clarke et al. 2011; Boulougouris et al. 2010; O'Neill & Brown 2007; Groman et al. 2013), although hyperdopaminergic states in the ventral striatum also causes inflexibility (Verharen et al. 2018).

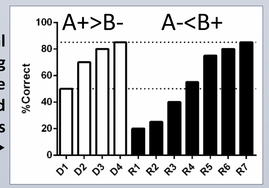
Objective

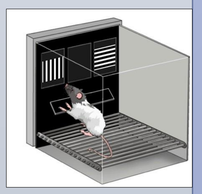
The aim of these experiments was to test whether dopamine D1- and D2-like receptors play dissociable roles in reversal learning.

◀ **Reversal learning in the wild.**

▼ **Reversal learning in the laboratory: human and rodent subjects.**

After initial learning (white), the stimulus-reward contingencies reverse. ▶





Acknowledgments

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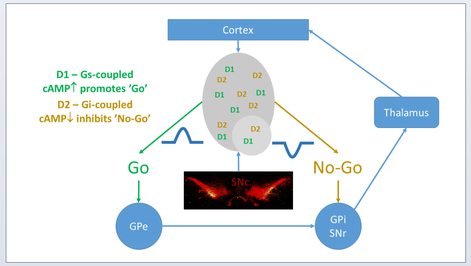
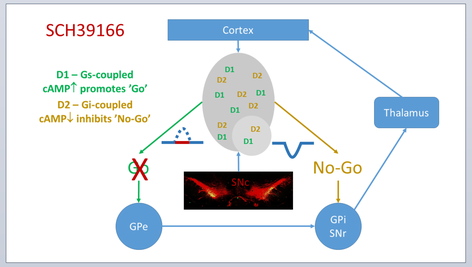
Dissociable components of reversal learning

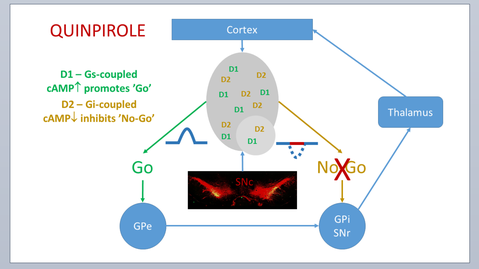
Successful reversal learning requires subjects to learn from both positive (stop avoiding, start approaching B+) and negative (stop approaching, start avoiding A-) feedback. Are these types of learning dissociable? Can we make any predictions based on the role of dopamine as a reward prediction error signal?



▲ **A theoretical framework for basal ganglia function in learning from positive and negative feedback (see Frank et al. 2004). Dopamine bursts in response to positive feedback drives the direct ("Go") pathway via D1 receptors; dopamine neurons pause after negative feedback, promoting "No-Go" learning via the disinhibition of the indirect pathway which express D2 receptors.**

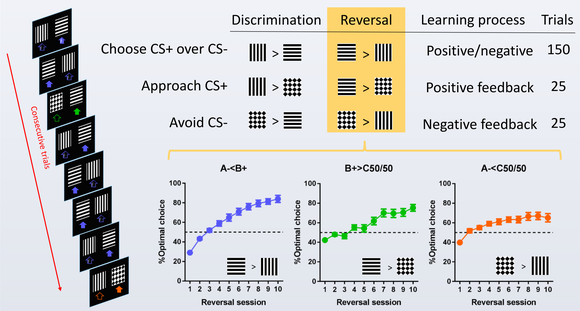


▲ **Hypothesis: Dopamine D1-receptor blockade should make the direct "Go" pathway unable to respond to increased dopamine levels. Learning from positive feedback will be selectively impaired.**

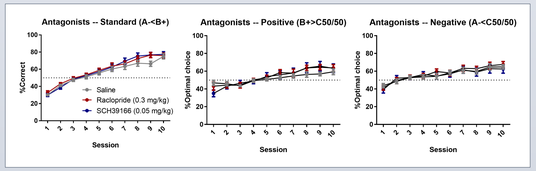


▲ **Hypothesis: Dopamine D2-receptor stimulation should make the indirect "No-Go" pathway unable to respond to decreased dopamine levels. Learning from negative feedback will be selectively impaired.**

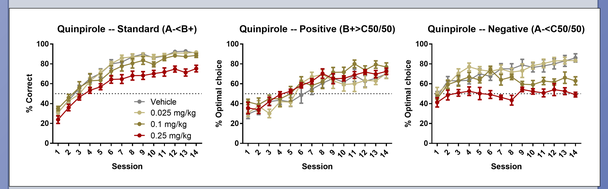
Psychopharmacology of reversal learning



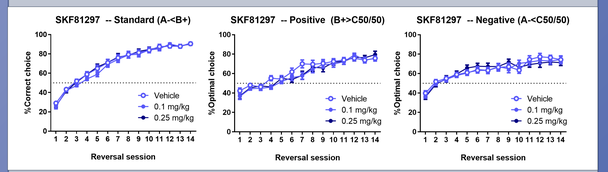
▲ **Visual discrimination and reversal task with interleaved probe trials to investigate learning from positive and negative feedback.**



▲ **No significant Main effect or Drug x Session interaction after dopamine D1 and D2-receptor antagonism on reversal learning. The D1-receptor antagonist SCH39166, however, impaired performance on positive probe trials during initial session (p=0.01).**



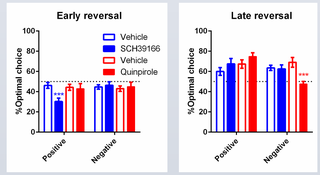
▲ **The D2/3-receptor agonist quinpirole impairs reversal learning overall (standard trials) at higher doses (Dose x Session, p=0.0043). Whereas no effect was observed on positive probe trials, performance on negative probe trials failed to improve above chance even after extended testing (Dose x Session, p<0.0001.)**



▲ **The D1-like receptor agonist SKF81297 did not significantly affect reversal learning in any trial type.**

Conclusions

- Dopamine D2/3 agonism impairs reversal learning by selectively blocking the learning from "mistakes". Even after two weeks of testing, quinpirole-treated rats were unable to learn to avoid the CS-, despite being as good as controls in choosing the CS+ over a neutral stimulus.
- Effects of quinpirole support predictions based on a "Go/No-Go" account of the direct and indirect pathways in the basal ganglia.
- Dopamine D1/5 antagonism transiently impairs learning from positive feedback, but does not affect performance on negative probe trials or indeed overall reversal learning.
- Effects of SCH39166 offers some support for the "Go/No-Go" model of reinforcement learning.
- No impact was observed of either the D2 antagonist or the D1 agonist SKF82197 on any trial types.



◀ **Dissociable effects of quinpirole and SCH39166 on the probe trials in the valence-probe visual discrimination task.**

Limitations

- Systemic injections do not inform us about the circuits being affected by the pharmacological agents. We are currently exploring striatal mechanisms. (See poster by J. Sala Bayo et al.)
- Probe trials introduce a probabilistic element (C50/50) and the way animals perceive this stimulus may affect performance. (See poster by Dr. B.U. Phillips et al. for task comparisons.)
- Added complexity of the task might recruit different neural circuits or be more sensitive to collateral drug effects on e.g. motivation. Whereas quinpirole does increase reward collection latency in this set of data, no effects on response latency were observed. Antagonist doses were chosen not to affect latencies.

References

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