Dose-dependent effects of citalopram on visual reversal learning in the rat: impact on learning from positive and negative feedback

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Obsessive-compulsive disorder (OCD) implicates impaired cognitive flexibility and an elevated sensitivity to negative outcomes. Selective serotonin reuptake inhibitors (SSRIs) are the primary pharmacological treatment for OCD, yet these drugs paradoxically increase negative feedback sensitivity in both humans and experimental animals. We here sought to explore further the impact of citalopram on behavioural flexibility and positive and negative learning bias using a novel visual reversal learning paradigm. Male Sprague-Dawley rats were trained to approach a rewarded stimulus and avoid a non-rewarded stimulus in a two-choice touchscreen task (A+/B-). During interleaved probe trials, either stimulus was presented with a neutral stimulus, rewarded 50% of the time; analysis of performance on these probe trials allowed the tracking of learning from positive and negative feedback. Rats were matched for baseline learning bias and received intraperitoneal vehicle (saline) or citalopram hydrobromide injections at either 1 or 10 mg/kg during reversal sessions, when initial stimulus-reward contingencies were changed (A-/B+). We found that high-dose citalopram (10 mg/kg) robustly facilitated reversal performance in all phases, an effect driven by improved learning from both positive and negative feedback. In contrast, low-dose citalopram (1 mg/kg) transiently impaired reversal learning in the early phase, when behaviour is guided by the previous stimulus contingencies, but improved later learning when new associations are formed. This late improvement was primarily due to improved learning from negative feedback. These results suggest that citalopram can improve both learning from positive and negative feedback depending on the dose regimen, which could be relevant both for SSRI pharmacotherapy and potential adverse effects of such treatment in OCD and other psychiatric disorders.