

Major depressive disorder is associated with blunted learning signals in medial prefrontal cortex and putamen when seeking monetary reward

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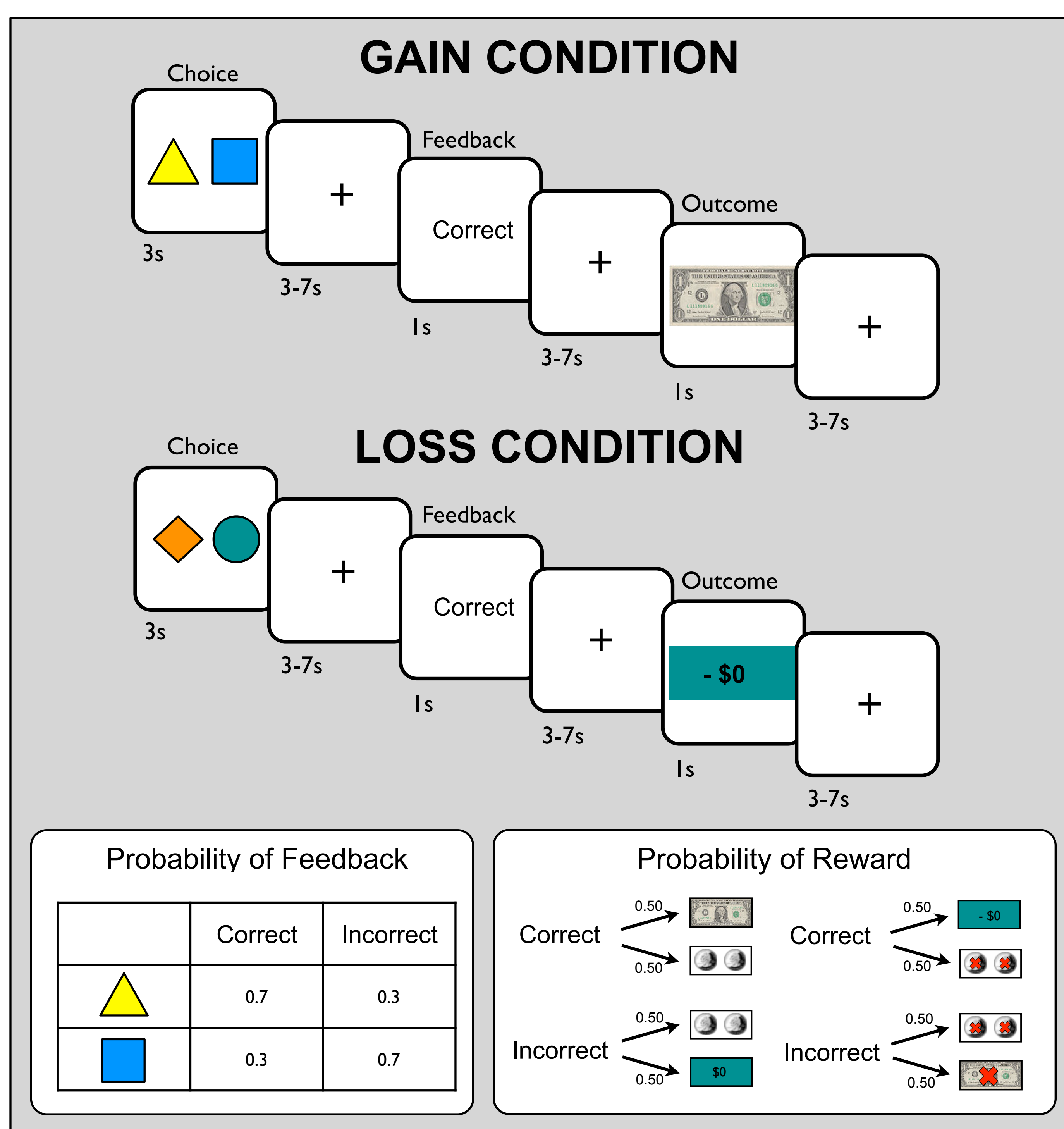
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Introduction

- Major depressive disorder (MDD) is characterized by debilitating motivational and affective symptoms, such as anhedonia and social withdrawal.
- Such motivational symptoms may be related to atypical learning processes that link predictive cues with reinforcing outcomes.
- There is debate over whether depression and these symptoms are associated with a striatal reward deficit, and during which temporal stage (anticipation v. experience of reinforcement) and context this may occur.
- To address this, we examined a dopamine-mediated learning signal (prediction error) using a multi-stage reinforcement learning task never before examined in depression.
- We hypothesized that blunted learning signal responses in the cortico-striatal pathway would be associated with MDD and motivation-related symptoms.**

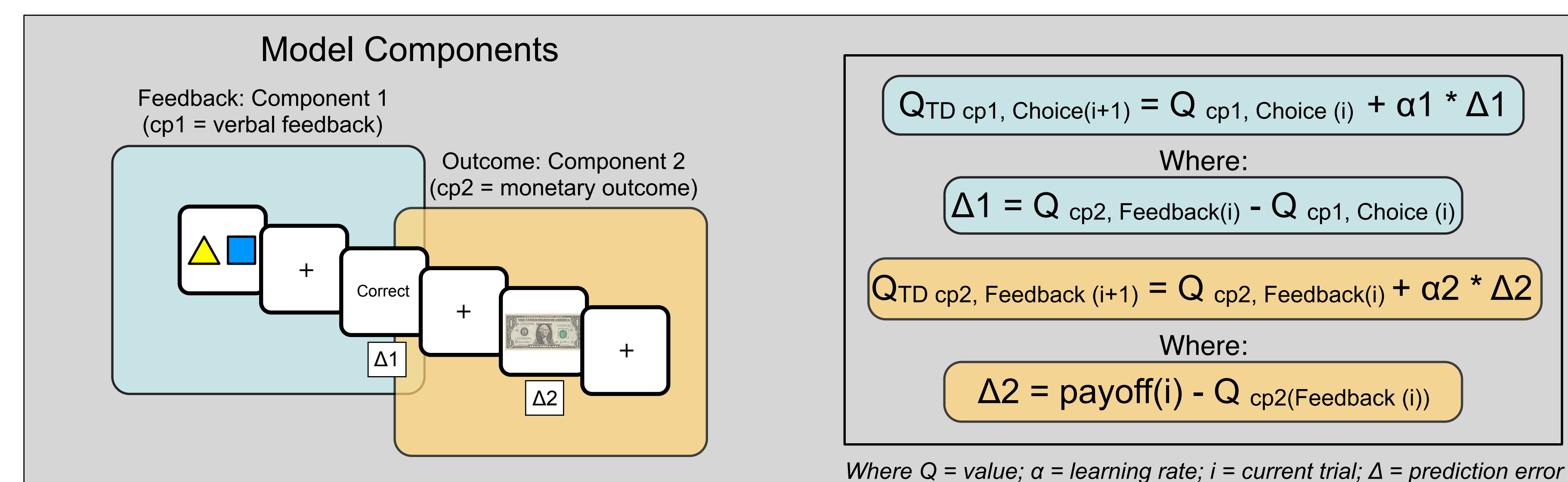
Methods



- 23 medication-naïve patients with MDD and 24 demographically matched comparison volunteers completed two phases of a probabilistic learning task (above) of 60 trials of **separate**, counterbalanced conditions during scanning:
 - In the **gain** condition (3 runs), subjects were instructed to earn as much money as possible; in the **loss** condition (3 runs), they avoided losing money from an endowment.
- Participants from this sample also participated in additional reward learning testing (see poster by Whitton et al- M83) and PET imaging related to predictors of response to pramipexole treatment (see poster by Schneier et al- W109).
- Scanning took place at the New York State Psychiatric Institute on a 3T scanner (**Functional: Whole brain, echo gradient, FOV 19.2, Slice thickness = 3, TR = 2000ms, TE = 28ms, 77 degree flip angle, 42 slices, 178 volumes**)

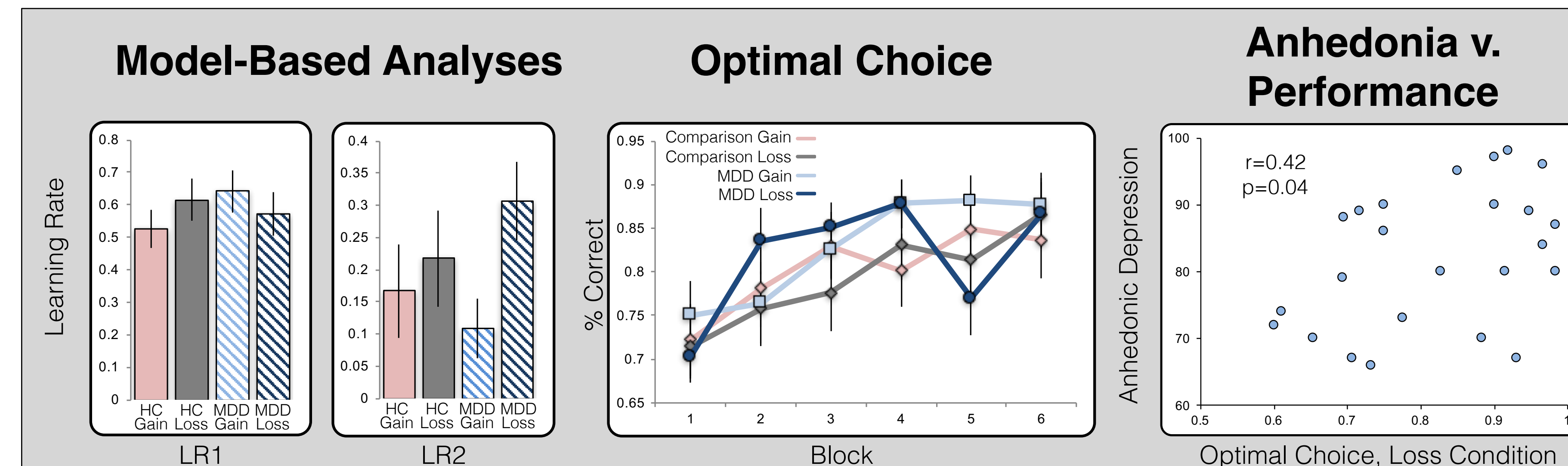
Participant Demographics	Healthy Comparisons	MDD Patients
Age	26.86 (5.62)	26.71 (6.52)
IQ	111.32 (8.49)	111.6 (8.28)
Number of Males	11	12
MASQ Anhedonic Depression*	37.48 (9.88)	82.04 (10.46)
MASQ Anxious Arousal*	19 (2.65)	25.67 (7.91)

Reinforcement Learning Model



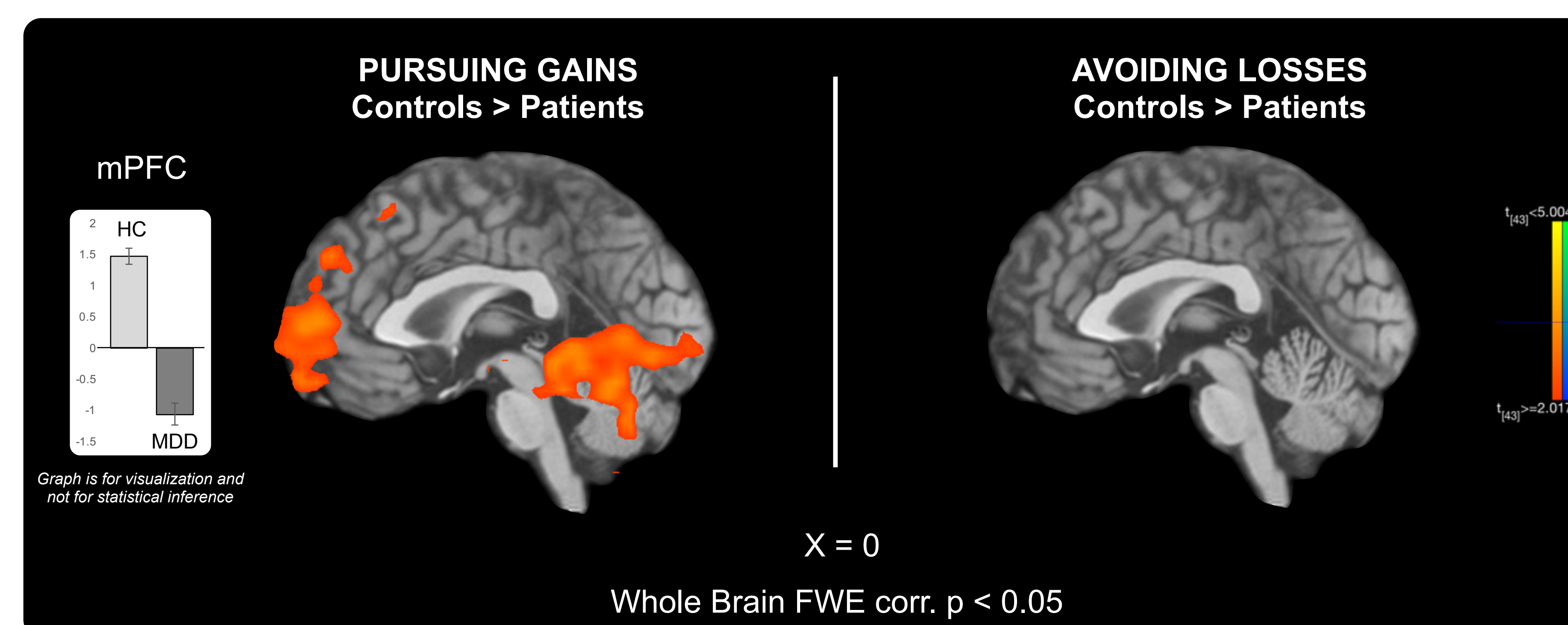
- Learning rates were estimated separately for verbal feedback (cp1) and monetary outcome (cp2).
- Prediction errors (Δ_1 , Δ_2) were calculated at verbal feedback (cp1) and at monetary outcome (cp2), and used as parametric regressors for the imaging data.

Behavioral Results



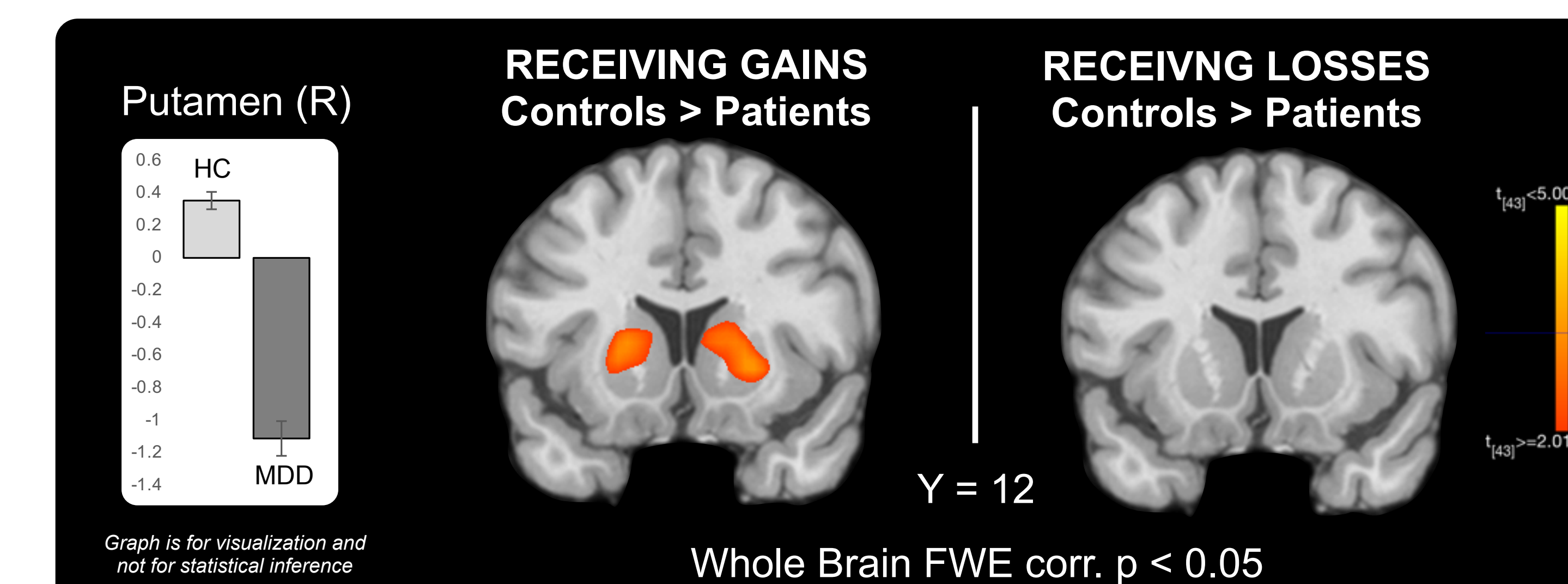
- Participants did learn successfully as indicated by improvement in optimal choice performance and decreased reaction time (RT) across blocks (Effect of block: $F_{\text{optimal choice}} = 6.74$, $p < 0.01$, $F_{\text{RT}} = 12.3$, $p < 0.001$).
- Analyses identified no significant group, condition, or interaction effects for reaction time, model-based analyses, or optimal choice.
- We identified a positive relationship between anhedonic depression scores as measured by the MASQ and optimal choice performance in the loss, but not gain, condition ($r = 0.42$, $p = 0.04$). This indicates that participants with more severe anhedonic symptoms performed better when motivated by loss.

Reinforcement Feedback PE



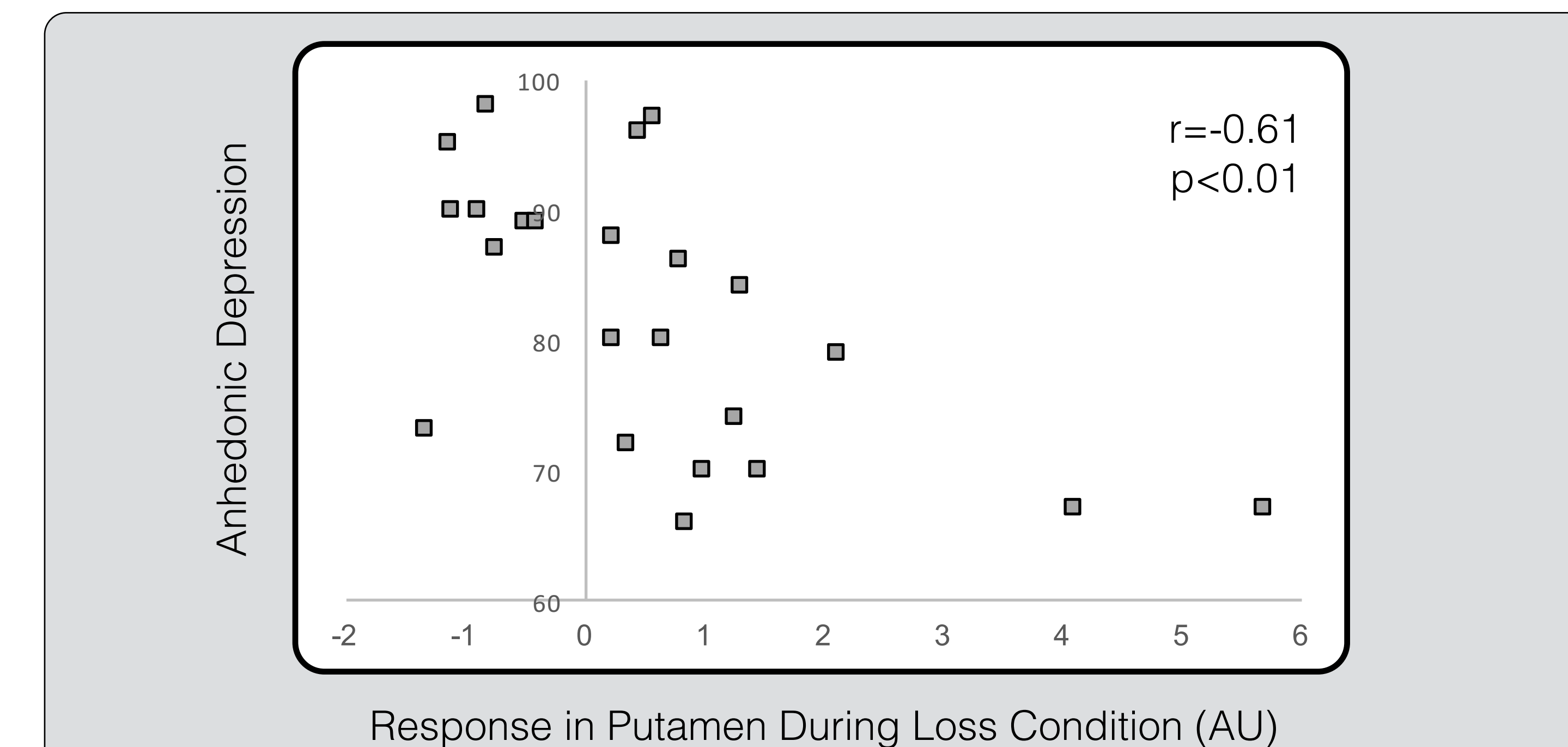
- Whole-brain corrected analyses showed feedback PE-related group differences in mPFC, striatum (not shown), and cerebellum when participants sought to earn money, but not when avoiding loss.
- Individual group maps suggest that this was driven by an increased response to PE during feedback in controls, and a decrease in the patient group.

Reinforcement Outcome PE



- Whole brain corrected results for reinforcement outcome PE revealed bilateral group differences in the putamen for gain but not loss.
- Examination of group responses in striatum revealed that patients showed a negative response to reinforcement outcome PE in bilateral putamen.

Relationship to Symptoms



- Analyses showed an inverse relationship between response in the putamen while learning from losses and anhedonic depression scales.

Summary

- Patients with MDD showed blunted learning signals in medial PFC during reward feedback, and in bilateral putamen during reward outcome.
- Most group differences were specific to learning when participants were pursuing gains and not when avoiding losses
- Anhedonic symptoms were associated with better loss-related performance and decreased putamen response in the loss condition. Ongoing analyses and future work may be able to identify whether any mediating or compensatory mechanisms underlie these relationships.
- This work implicates a functional role of the striatum and mPFC across temporal learning stages in depression, and supports a link between learning, cortico-striatal response, and the motivational symptoms of MDD.

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