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Corticostriatothalamic Reward Prediction Error Signals and Executive Control in Late-Life Depression

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Abstract

Background—Altered corticostriatothalamic encoding of reinforcement is a core feature of depression. Here we examine reinforcement learning in late-life depression in the theoretical framework of the vascular depression hypothesis. This hypothesis attributes the co-occurrence of late-life depression and poor executive control to prefrontal/cingulate disconnection by vascular lesions.

Methods—Our fMRI study compared 31 patients with major depression aged 60+ to 16 controls. Using a computational model, we estimated neural and behavioral responses to reinforcement in an uncertain, changing environment (probabilistic reversal learning).

Results—Poor executive control and depression each explained distinct variance in corticostriatothalamic response to unexpected rewards. Depression, but not poor executive control, predicted disrupted functional connectivity between the striatum and prefrontal cortex. White-matter hyperintensities predicted diminished corticostriatothalamic responses to reinforcement, but did not mediate effects of depression or executive control. In two independent samples, poor executive control predicted a failure to persist with rewarded actions, an effect distinct from depressive oversensitivity to punishment. The findings were unchanged in a subsample of participants with vascular disease. Results were robust to effects of confounders including psychiatric comorbidities, physical illness, depressive severity, and psychotropic exposure.

Conclusions—Contrary to the predictions of the vascular depression hypothesis, altered encoding of rewards in late-life depression is dissociable from impaired contingency learning associated with poor executive control. Functional connectivity and behavioral analyses point to a disruption of ascending mesostriatocortical reward signals in late-life depression and a failure of cortical contingency encoding in elderly with poor executive control.

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helinski Declaration of 1975, revised in 2008.

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Keywords

prefrontal cortex; executive control; aged; reward; reinforcement; depression

Introduction

One cardinal feature of depression is weakened or distorted behavioral effectiveness of reinforcement (reviewed in (Eshel and Roiser, 2010)). Learning theory suggests that the problem may lie in representing unexpected rewards that normally drive appetitive behavior (Bush and Mosteller, 1951, Rescorla and Wagner, 1972). A reward's behavioral effectiveness depends not only on its magnitude, but also on the amount of surprise, since surprise results in learning. This surprise is quantified by the *reward prediction error*—the difference between the actually received and expected reward. In every episode of learning (trial, t), expected reward is updated from its previous value by the prediction error (Eq. 1, simplified for illustration):

$$\begin{aligned} \text{ExpectedReward}_t &= \text{ExpectedReward}_{t-1} + \alpha * \text{RewardPredictionError}_t \\ \text{RewardPredictionError}_t &= \text{ActualReward}_t - \text{ExpectedReward}_{t-1} \end{aligned} \quad \text{Eq. 1}$$

Reward expectancy, in turn, controls approach behavior. Variants of this simple learning rule underlie all reinforcement learning models (Sutton and Barto, 1998). Equation 1 helps understand the asymptotic learning curves observed in operant conditioning (Bush and Mosteller, 1951, Skinner, 1938). Early in learning, a rat rewarded for lever presses has low reward expectancy. Early rewards generate large prediction errors, driving a rapid increase in the response rate. Late in learning, reward expectancy becomes high, prediction errors wane, and the response rate stabilizes.

Neural reward prediction error signals are thought to originate in the mesostriatal dopamine pathway (Schultz *et al.*, 1997). They are believed to shape cognitive processes and behavior through synaptic modification of corticostriatothalamic circuits [see (Glimcher, 2011), (Chase *et al.*, 2015) for a theoretical review and meta-analysis of human imaging studies]. Specifically, trial-by-trial learning signals are thought to train sustained, multi-trial prefrontal representations of the reward contingency (Histed *et al.*, 2009, Pasupathy and Miller, 2005). In human imaging, the degree of co-variation between model-estimated reward prediction errors and BOLD is typically assumed to reflect individual differences in corticostriatothalamic prediction error signals (Dombrovski *et al.*, 2013, Gradin *et al.*, 2011, Kumar *et al.*, 2008). In depression, corticostriatothalamic circuits display altered responses to rewards and punishments in general (Eshel and Roiser, 2010) and diminished reward prediction error signals in particular (Gradin *et al.*, 2011, Kumar *et al.*, 2008). Using fMRI, we have recently extended these observations to late-life depression (Dombrovski *et al.*, 2013). We also observed that, in depressed individuals, oversensitivity to punishments (Murphy *et al.*, 2003) was inversely related to the strength of corticostriatothalamic reward prediction error signals (Dombrovski *et al.*, 2013).

These observations reveal certain neural correlates of altered reward-guided behavior in depression, yet its specific neural mechanisms remain unclear. One particularly influential account of behavioral disturbance in depression emphasizes failures of top-down control, broadly linked to prefrontal dysfunction (Robbins, 2007). Executive control is impaired in depression (Snyder, 2013), and the co-occurrence of depression and poor executive control forms the basis for the *vascular depression hypothesis* (Alexopoulos *et al.*, 1997, Taylor *et al.*, 2013). It attributes depression and poor executive control in old age to prefrontal and cingulate disconnection from subcortical structures by ischemic white matter lesions (Aizenstein *et al.*, 2011, Alexopoulos, 2002, Alexopoulos *et al.*, 2012, Sneed *et al.*, 2007). This hypothesis is supported by findings of poor treatment response in patients with poor executive control and white matter hyperintensities (WMH) (Baldwin *et al.*, 2004, Barch *et al.*, 2012, Sneed *et al.*, 2007). Can the vascular depression hypothesis explain alterations in reward-guided behavior and reward signals seen in late-life depression? Our fMRI study of reward-guided behavior tested the prediction that *both depression and poor executive control are related to a disconnection of the prefrontal and cingulate cortices from the striatum and thalamus.*

To establish that we possess the appropriate index of corticostriatothalamic integrity for testing the predictions of the vascular depression hypothesis, we assessed whether individual variation in prediction error signals scaled with executive control ability in patients with late-life depression. We were then able to test whether depression and executive control accounted for shared variance in corticostriatothalamic integrity (indexed by prediction error signals), as would be the case if they were both caused by disconnection. Then, to obtain more direct evidence of functional striato-cortical disconnection, we tested the effects of depression and poor executive control on striato-cortical functional connectivity. Next, to examine the role of vascular lesions, we tested whether (i) WMH disrupted corticostriatothalamic responses and striato-cortical functional connectivity and (ii) whether they explained the relationship of these indices with depression and executive control. All analyses were repeated in a subsample with vascular conditions. Finally, we tested whether late-life depression and poor executive control had similar or distinct effects on reward- and punishment-guided behavior in two non-overlapping samples.

Methods

Participants and diagnosis of depression (Table 1)

Between January 1 of 2008 and August 31 of 2011, we recruited 47 participants aged 60 and older: 31 with major depressive disorder (MDD) and 16 psychiatrically healthy controls. MDD was diagnosed by Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders* (2000, First M, 1995) (SCID/DSM-IV). Participants with MDD had symptoms of varying severity (Table 1; examined in Sensitivity analyses). To exclude individuals with dementia, all were required to have a MMSE score of ≥ 24 . Our reported sample is exclusive of elderly with sensory disorders that precluded cognitive testing, limited English, mental retardation, delirium, neurologic disorders including strokes, bipolar disorder, schizophrenia, schizoaffective disorder, exposure to electroconvulsive therapy in the previous 6 months, and conditions precluding

an fMRI assessment. This is a subsample of participants described in our earlier report (Dombrovski *et al.*, 2013), exclusive of 6 participants missing assessments of executive control.

All participants provided written informed consent. The University of Pittsburgh Institutional Review Board approved the study.

Assessments

Cognitive and clinical characterization—Current global cognitive function was assessed with the Dementia Rating Scale (DRS) (Mattis, 1988). Depression severity was measured with the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Burden of physical illness was assessed with the Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G) (Miller *et al.*, 1992). We measured antidepressant exposure in the current episode of depression using the Antidepressant Treatment History Form (Sackeim, 2001), based on antidepressant trial duration, dose, and use of augmenting agents. We additionally assessed exposure to sedatives/hypnotics, anticholinergics, and opioids.

Executive control—We assessed executive control with the Executive Interview (EXIT; range 0–50) (Royall *et al.*, 1992). The 25 items are administered in rapid succession with minimal instructions to elicit automatic behaviors. Items include modifications of well-known “frontal lobe” tests (number/letter sequencing, Stroop, fluency, go/no-go, and Luria’s hand sequences). Higher EXIT scores indicate greater impairment. Crucially, unlike in the probabilistic reversal learning task, no external reinforcement is given.

Probabilistic reversal learning fMRI task (Fig. 1)—On each of 300 trials, participants choose between two stimuli using button presses. In the first 25-trial block, one stimulus has a high probability of reward when chosen (varied between 80% and 87%), and the other, a low probability of reward (13%–20%). Thus, even when correctly choosing the high-reward probability stimulus, participants receive occasional misleading or ‘probabilistic’ negative feedback. After every 25 trials, this contingency is reversed, such that the high-reward probability stimulus is assigned a low reward probability and vice versa. There are a total of 12 reversals. On this task, one needs to first learn the identity of the best stimulus and then trade off ‘staying’ with the previously reinforced stimulus despite occasional misleading feedback and ‘switching’ when a true reversal occurs. The tendency to ‘stay’ too long after reversal while ignoring negative feedback leads to perseverative errors. Conversely, the tendency to ‘switch’ after a single misleading punishment results in lose-switches (also known as probabilistic switches), previously linked to depression (Murphy *et al.*, 2003). Spontaneous or win-switch errors occur when the participant abandons a choice rewarded on a preceding trial.

Imaging—Thirty-two 3mm slices were acquired parallel to the AC-PC line using a reverse EPI pulse sequence (one of two 3T Siemens Trio magnets, T2*-weighted images depicting BOLD contrast [activity and connectivity indices did not vary between scanners: $t(51) < 0.73$, $p > .47$]; TR=1670ms, TE=29ms, FOV=20cm, flip=75), yielding 954 whole-brain volumes per participant. Following slice-time correction, motion correction (AFNI 3dVolReg) and

linear detrending to eliminate scanner drift, data were converted to percent-change, temporally smoothed, cross-registered to the Colin-27 Montreal Neurological Institute template (AIR's 32-parameter non-linear warp), and spatially smoothed (6mm FWHM).

Estimation of prediction error signals using reinforcement learning—We estimated prediction error signals from participants' reinforcement history and behavior on the probabilistic reversal learning task, using a modified Rescorla-Wagner reinforcement learning (RL) model (Dombrovski *et al.*, 2010, Dombrovski *et al.*, 2013)(Fig. 1).

Components of BOLD response tracking prediction errors—We estimated the empirical HRF in the control group using the independent switch vs. stay contrast in the vIPFC. It was then convolved with the positive prediction error estimates from the RL model for each subject. Voxelwise BOLD signal was regressed on these estimates using AFNI's 3dDeconvolve. We used AFNI's 3dTtest to map prediction error responses in the group of healthy controls. We applied a voxelwise threshold of $p < .001$ and a whole-brain cluster-size threshold (Cox, 1996, Forman *et al.*, 1995). The resulting thresholded group map served as a functional mask for extracting mean responses to positive prediction error in each region for each participant.

White-matter hyperintensities (WMH)—T2-weighted FLAIR data (TR=9002ms; TE_{effective}=56ms; TI=2200ms; N[excitations]=1) were obtained on 27/47 participants, demographically and clinically similar to the rest of the group ($p < .19$). WMH volumes were estimated with an automated localization and segmentation method (Wu *et al.*, 2006) and normalized to each participant's overall brain volume (Aizenstein *et al.*, 2011).

Replication of behavioral effects in a second sample—We used data from our earlier behavioral study of late-life depression (Dombrovski *et al.*, 2010), which used identical recruitment/assessment procedures and an 80-trial probabilistic reversal learning task with a single reversal. To ensure independence, we excluded participants who subsequently took part in the imaging protocol, leaving 39 with major depression and 12 non-psychiatric controls. The groups were similar in race (white: controls: 12/12, depressed: 32/39) and education (controls: mean[SD]=15.6[2.7]years, depressed: 14.1[3.0]), but the depressed participants were older (controls: 65.7[5.3]years, depressed: 70.9[8.1]years, $p = .045$) and more likely to be female (controls: 2/12, depressed: 23/39). Thus, in our analysis, we co-varied for age and gender as well as history of suicide attempts, which was previously shown to predict task performance (Dombrovski *et al.*, 2010).

Statistical analysis

We performed five separate families of tests: (1) magnitude of neural responses to unpredicted rewards—positive prediction errors—and effects of executive control and depression on these responses; (2) corticostriatal functional connectivity modulated by unexpected rewards for each participant and examined the effects of depression and executive control on connectivity indices; (3) effects of WMH on corticostriatal responses to

unpredicted rewards; (4) effects of executive control and depression on behavior in the present study; (5) replication of behavioral findings using data from our earlier study.

1. Effects of cognitive control and depression on BOLD response tracking

prediction errors—Applying positive prediction error group maps from non-psychiatric controls as a functional mask, we extracted BOLD responses to positive prediction error for each subject and region. Responses to positive prediction error were strongly inter-correlated across regions of the corticostriathalamic circuit, revealing a single underlying factor (Dombrovski *et al.*, 2013). Thus, to reduce dimensionality and control type I error, we examined summary activations across the entire network responsive to prediction error instead of activations in single regions. We followed up by examining separate clusters, to check whether the effects of executive dysfunction were spatially uniform. Our corticostriathalamic network mask was defined in healthy controls, and to preempt concerns about circularity, we first examined the effect of executive control on prediction error signals in the independent group of depressed patients. After independently establishing this effect, we examined effects of depression and executive control in the combined group. We included age, gender, and education as covariates in our main analyses in order to de-noise the relationship between the independent (executive dysfunction, depression) and dependent variables (BOLD). To ensure that this relationship was not an artifact of partialing out common variance between independent variables and covariates (Miller and Chapman, 2001), we verified that the results were similar without covariates.

2. Striatocortical functional connectivity in the context of unexpected rewards

—We aimed to test the effects of poor executive control and depression on the training of sustained prefrontal representations by trial-by-trial striatal signals (Pasupathy and Miller, 2005). We used the framework of generalized psychophysiological interaction analysis (McLaren *et al.*, 2012) to estimate striatocortical functional connectivity specifically associated with unexpected rewards as opposed to any surprising outcomes. We defined the striatal seed as the region responsive to positive prediction errors in the entire sample within the Talairach Daemon striatum ($p_{\text{voxelwise}} < .001$). Using AFNI, we extracted the time course for the striatal seed and deconvolved the HRF from it. We then computed an interaction between the z-scored “neural” striatal time course and the positive and negative prediction (PE+ and PE-) error regressors. The single-subject model, implemented using AFNI’s 3dDeconvolve included the PE+*striatum and PE-*striatum interactions, as well as the following nuisance regressors: main effects of PE+ and PE-, striatal seed time course, motor action (left or right), trial stages (choice, feedback, wait), and the six motion regressors. We then computed a map of the difference between the regression coefficients for the PE+*striatum and PE-*striatum interactions, which was taken to the group analyses.

3. Effects of WMH—We examined effects of WMH burden on BOLD responses and functional connectivity. We also tested whether WMH burden explained the effects of depression and executive control, as the vascular depression hypothesis would predict.

4. Effects of cognitive control and depression on behavior—We used linear models with EXIT scores and depression group status as independent variables, age, gender

and education as covariates, and the following behavioral indices as dependent variables: lose-switches, spontaneous switches, and perseverative errors. When necessary, we tested the robustness of results to deviations from normality using a generalized linear model.

5. Replication of behavioral effects—We tested the effect of executive control on reversal learning performance, including depression, gender, and history of suicide attempt as factors and age and education as covariates.

Results

Executive control and neural response to unpredicted rewards (Fig. 2)

In depressed patients, poor executive control predicted blunted responses to unpredicted rewards in the network independently identified in controls, encompassing a frontoparietal circuit, a cinguloopercular circuit, dorsomedial prefrontal cortex, thalamus, and striatum ($F[1,26]=13.4$, $p=.001$, $\eta_p^2=.34$, controlling for age, gender, and education). In the combined group of patients and controls, lower neural response to unexpected rewards in this network was predicted by poorer executive control ($F[1,41]=15.7$, $p<.001$, $\eta_p^2=.29$) and depression ($F[1,42]=17.4$, $p<.001$, $\eta_p^2=.31$), controlling for age ($\eta_p^2=.02$), gender ($\eta_p^2=.08$), and education ($\eta_p^2<.01$). Contrary to the prediction of the vascular hypothesis, effects of executive control and depression were not shared, but rather were simply additive (model including depression [$\eta_p^2=.34$], age, gender, education: $R^2=.35$; model including executive control [$\eta_p^2=.29$], depression [$\eta_p^2=.31$], age, gender, education: $R^2=.57$). Results were similar without covariates (Fig. 1). The disruptive effects of depression and poor executive control on responses to unpredicted rewards were not anatomically selective, with no significant differences between prefrontal, thalamo-striatal, paralimbic (precuneus), parietal, and temporal regions ($p>.33$, $\eta_p^2=.11$).

Effects on striatocortical connectivity modulated by unpredicted rewards (Fig. 3)

In healthy controls, unpredicted rewards, contrasted with unpredicted punishments, triggered an increase in functional connectivity between striatum and left operculoinsular cortex, right vIPFC, bilateral superior temporal gyrus (STG), bilateral thalamus, and posterior cingulate cortex (Fig. 2a). In a ROI analysis, functional connectivity in this circuit was less strongly modulated by unpredicted rewards in patients with depression than in controls ($F[1,42]=10.4$, $p=.002$, $\eta_p^2=.20$), but was not affected by poor executive control ($p=.85$, $\eta_p^2<.01$; Fig. 2b). Since the ROIs were identified in controls, we also performed an unbiased whole-brain group contrast. Similarly, an effect of depression was seen for striatal connectivity with the left operculoinsular cortex (Fig. 2c), with no significant effects of poor executive control.

Effects of depression and executive control in a subsample with vascular conditions

To test the predictions of the vascular depression hypothesis in a group at highest risk for neurovascular injury, we limited the sample to those with clinically significant vascular disease. These 37 participants (25 depressed, 12 controls; 22 female; mean[SD] age: 68[7]) scored ≥ 2 on the Cumulative Illness Rating Scale adapted for Geriatrics, Vascular subscale [examples: one symptom of atherosclerotic disease (angina, claudication, bruit, amaurosis

fugax, absent pedal pulses) or need for daily antihypertensives or aortic aneurysm < 4 cm (Miller *et al.*, 1992)]. The results remained qualitatively unchanged. Weaker corticostriathalamic response to unexpected rewards was predicted by poorer executive control ($F[1,30]=20.6$, $p<.001$, $\eta_p^2=.41$) and depression ($F[1,30]=14.3$, $p<.001$, $\eta_p^2=.32$; age: $\eta_p^2=.04$, gender: $\eta_p^2=.08$, education: $\eta_p^2=.08$). Further, striato-cortical functional connectivity was weaker in patients with depression than in controls ($F[1,30]=5.8$, $p=.022$, $\eta_p^2=.16$), but was unaffected by poor executive control ($p=.61$, $\eta_p^2<.01$).

WMH

WMH burden predicted blunted corticostriatal responses to unpredicted rewards ($F[1,22]=8.7$, $p=.007$, $\eta_p^2=.28$), after controlling for predictors reported above. WMH burden failed to explain the effects of depression (effect of depression controlling for WMH: $\eta_p^2=.51$, without WMH: $\eta_p^2=.40$) or poor executive control (controlling for WMH: $\eta_p^2=.35$, without WMH: $\eta_p^2=.40$). WMH burden explained no significant variance in striatocortical connectivity ($p>.29$, $\eta_p^2<.05$). Finally, in the sub-sample of participants with vascular disease, white-matter hyperintensity (WMH) burden predicted a weaker neuro-hemodynamic response to unexpected rewards ($F[1,19]=5.5$, $p=.030$, $\eta_p^2=.23$), but did not explain the effects of executive control ($F[1,19]=10.0$, $p=.005$, $\eta_p^2=.35$) or depression ($F[1,19]=11.0$, $p=.004$, $\eta_p^2=.37$).

WMH location—We verified that WMH located in tracts terminating in prefrontal and cingulate cortex (cingulum bundle, superior longitudinal fasciculus, uncinate fasciculus, and anterior thalamic radiation) exerted similar effects on corticostriathalamic prediction error signals as the total WMH burden. WMH in each of these tracts had disruptive effects on prediction error signals, but did not account for effects of depression and executive dysfunction, which remained undiminished (data available upon request).

Behavioral signatures of poor executive control and depression

Individuals with poor executive control failed to persist with rewarded actions. Meanwhile, participants with depression over-reacted to single misleading punishments. Specifically, poor executive control predicted spontaneous switches (EXIT: $F[1,41]=10.1$, $p=.003$, $\eta_p^2=.20$; depression: $F[1,41]=0.5$, $p=.50$, $\eta_p^2=.01$; controlling for age, gender, and education). Meanwhile, depression predicted lose-switches (depression: $F[1,41]=6.5$, $p=.014$, $\eta_p^2=.14$; EXIT: $F[1,41]=1.8$, $p=.19$, $\eta_p^2=.04$; controlling for age, gender, and education). Neither executive control nor depression affected perseverative errors ($p>.31$, $\eta_p^2<.03$). A repeated-measures analysis confirmed a double dissociation of these effects: poor executive control was selectively associated with spontaneous switches (EXIT*error type: $F[1,41]=7.9$, $p=.007$, $\eta_p^2=.16$) and depression was selectively associated with lose-switches (depression*error type: $F[1,41]=4.2$, $p=.048$, $\eta_p^2=.09$, both controlling for age, gender, and education). Only executive control ($F[1,40]=4.4$, $p=.043$, $\eta_p^2=.10$) but not depression ($F[1,41]=1.8$, $p=.18$, $\eta_p^2=.04$) explained significant variance in the overall number of correct responses. Finally, WMH burden did not explain any additional variance in behavioral indices ($p>.24$, $\eta_p^2<.06$).

Replication of behavioral effects

In the replication sample, participants with poor cognitive control similarly failed to persist with rewarded actions on a single-reversal task. Poor executive control predicted spontaneous switches during acquisition ($F[1,40]=6.5$, $p=.014$, $\eta_p^2=.14$; controlling for the effects of age, gender, education, and history of depression and attempted suicide), but not lose-switches or perseverative errors ($p>.39$, $\eta_p^2<.02$). There were not enough spontaneous switches in the post-reversal phase for analysis. As we have reported, depression was not reliably related to lose-switches in that study (Dombrovski *et al.*, 2010). As in the fMRI study, poor executive control selectively predicted the encoding of rewards (spontaneous switches) rather than sensitivity to single misleading punishments (lose-switches; EXIT*error type: $F[1,47]=6.2$, $p=.016$, $\eta_p^2=.12$).

Sensitivity analyses

Comorbid conditions—Depressed participants with lifetime history of substance use disorders tended to display blunted corticostriathalamic positive prediction error responses ($F[1,20]=4.1$, $p=.058$, $\eta_p^2=.17$). This effect was additive and did not modify that of executive dysfunction ($F[1,20]=7.4$, $p=.013$, $\eta_p^2=.27$). Lifetime history of anxiety disorders had no significant impact ($F[1,20]=0.2$, $p=.69$; all controlling for depression, age, gender, and education).

Burden of physical illness—While depressed participants suffered from a higher burden of physical illness (Table 1), it had no effect on corticostriathalamic positive prediction error responses ($F[1,39]=0.3$, $p=.57$, $\eta_p^2<.01$), while the effects of executive control ($F[1,39]=21.9$, $p<.001$, $\eta_p^2=.36$) and depression remained unchanged ($F[1,39]=22.0$, $p<.001$, $\eta_p^2=.36$).

Age at first episode of depression—One might argue that prefrontal disconnection associated with poor executive control better accounts for cases of late-onset depression. However, later age of onset was not associated with poorer executive control in our sample ($r=.05$, $p=.78$) and did not modify the effects of executive control on prediction error signals (EXIT: $F[1,24]=13.0$, $p=.001$, $\eta_p^2=.35$; age at first episode: $p=.81$, $\eta_p^2<.01$) or on spontaneous switch errors (EXIT: $F[1,24]=5.1$, $p=.034$, $\eta_p^2=.17$; age at first episode: $p=.72$, $\eta_p^2<.01$). At the same time, patients with earlier onset of depression demonstrated a greater sensitivity to single misleading punishments indexed by lose-switches, while there were still no significant effects of executive control (age at first episode: $F[1,24]=5.0$, $p=.035$, $\eta_p^2=.17$; EXIT: $p=.27$, $\eta_p^2=.05$).

Medication exposure—The relationship between executive dysfunction and corticostriathalamic positive prediction error responses was unaffected by exposure to opioids, sedatives or anticholinergics (EXIT: $F[1,23]=12.1$, $p=.002$, $\eta_p^2=.35$; exposure to any medication class: $p>.58$, $\eta_p^2<.02$). The same was true for the cumulative strength of antidepressant exposure measured by the Antidepressant Treatment History Form (EXIT: $F[1,17]=9.0$, $p=.008$, $\eta_p^2=.35$; ATHF: $p=.73$, $\eta_p^2<.01$).

Potential experimental and analytic confounds—It was important to verify that the relationship between executive control and corticostriothalamic prediction error signals was not driven by participants who were not on task or whose behavior could not be fit with the reinforcement learning model. Neither the median response time nor its variation coefficient had an impact on corticostriothalamic positive prediction error signals ($p > .12$, $\eta_p^2 < .06$) and did not diminish the effect of executive control. Participants with poor executive control had significantly poorer fits of the reinforcement learning model ($F[1,40]=7.8$, $p=.008$, $\eta_p^2=.16$). However, controlling for model fits ($F[1,39]=1.0$, $p=.33$, $\eta_p^2=.03$) did not diminish the effect of executive control ($F[1,39]=13.7$, $p=.001$, $\eta_p^2=.26$).

Distribution of spontaneous switch errors—The distribution of spontaneous switch errors was zero-inflated. However, an analysis using a generalized linear model with a negative binomial log-link confirmed that the relationship between poor executive control and spontaneous switch errors was robust to this violation of normality (EXIT: Wald $\chi^2=8.1$, $p=.005$). Distributions of other dependent variables did not significantly deviate from the Gaussian.

Conclusions

We tested a prediction of the vascular depression hypothesis that prefrontal/cingulate disconnection from subcortical nuclei would account for neural correlates of depression and poor executive control during reward-guided behavior. Overall, this prediction was not confirmed. First, poor executive control was associated with disrupted corticostriothalamic responses to unpredicted rewards independently of the effects of depression. Second, depression, but not poor executive control, was associated with disrupted striatocortical differential connectivity to unpredicted rewards vs. unpredicted punishments. Third, while white-matter hyperintensities predicted blunted corticostriothalamic responses, they failed to account for the effects of depression or executive control. Fourth, poor executive control and depression had distinct behavioral signatures. Poor executive control predicted spontaneous switches, presumably reflecting a basic disruption in contingency encoding. Depression predicted oversensitivity to misleading punishments, presumably because preceding rewards were not robustly encoded. Below, we briefly explicate the neurobiological framework for interpreting the results. We then discuss implications for the vascular depression hypothesis and alternative models of depression.

Corticostriothalamic mechanisms of reward learning and the vascular depression hypothesis

Reward prediction errors were theoretically predicted (Montague *et al.*, 1996) and empirically shown (Schultz *et al.*, 1997) to originate in the mesostriatal dopaminergic pathway. Prediction errors are thought to influence behavior through synaptic modification of corticostriothalamic circuits. Prediction error signals during Pavlovian learning were first described in the human ventral striatum (O'Doherty *et al.*, 2003), which forms reentrant loops with the medial orbitofrontal and anterior cingulate cortices (Middleton and Strick, 2000) classically implicated in reward-guided behavior. During the learning of action-

reward (instrumental) contingencies, prediction error signals are found in the dorsal striatum connected to associative prefrontal cortices (O'Doherty *et al.*, 2004).

In this study, we used the strength of instrumental prediction error signals in the striatum, thalamus, cinguloopercular and frontoparietal networks as an indicator of their functional integrity. Based on what we know about the corticostriatothalamic reward systems from lesion, electrophysiological, and imaging studies, our functional connectivity and behavioral findings suggest that the two syndromes are paralleled by disruptions at different levels of corticostriatothalamic circuits. Alterations in reward signals associated with executive dysfunction, not surprisingly, fit the pattern of prefrontal dysfunction and, possibly, disconnection. The behavior of individuals with impaired executive control bears a close resemblance to that of patients with bilateral prefrontal lesions (Hornak *et al.*, 2004) and, interestingly, to that of primates with lesions to white-matter prefrontal connections (Rudebeck *et al.*, 2013). Our findings parallel those of a study showing that fluid intelligence (a proxy for executive control) was correlated with striatal prediction error signals independently of dopamine synthesis capacity (Schlagenhauf *et al.*, 2012). Both executive control and fluid intelligence depend on the functional integrity and intact outputs of the frontoparietal network (Cole *et al.*, 2012). Meanwhile, in depression, it is the ascending transmission of mesostriatal reward prediction errors that appears to be affected. This is indicated by diminished functional striatocortical connectivity in response to positive vs. negative prediction errors. These data are consistent with a disruption of the mesostriatal output through the pallidum and thalamus to the associative prefrontal neocortex. This interpretation is in agreement with electrophysiological evidence that, as contingencies are encoded, striatal responses to reinforcement emerge and asymptote before the prefrontal responses, which mediate behavioral improvement (Pasupathy and Miller, 2005). Thus, reduced functional striatocortical connectivity in depression presumably reflects disrupted training of tonic prefrontal representations by phasic striatal signals. Supporting this idea, the oversensitivity of depressed patients to misleading punishments resembles the behavior of individuals with a genetically reduced expression of striatal D₂ receptors, which conceivably attenuates mesostriatal prediction error signals (Jocham *et al.*, 2009). The notion that ascending dopaminergic signals are deficient in depression is further supported by the recent finding of an increased burden of brainstem Lewy bodies and tangles and lower density of ventral tegmental area dopaminergic neurons in older people with depressive symptoms (Wilson *et al.*, 2013).

The high co-occurrence of depression and poor cognitive control nevertheless demands an alternative explanation. We would argue that impaired executive control prevents people from finding and exploiting reward contingencies in their environment. This inability to learn reward contingencies is depressogenic: a potentially controllable environment becomes uncontrollable, akin to that found in learned helplessness experiments (Seligman and Maier, 1967). Support for this account is provided by evidence that cognitive decline rather than lesion location predicts depressive symptoms after a stroke (Nys *et al.*, 2006) and that cardiovascular risk factors predict depressive symptoms only if executive control is impaired (Mast *et al.*, 2004).

Limitations

The cross-sectional, case-control design of our study precludes causal inferences. It also raises questions about possible confounders, although many were ruled out in our sensitivity analyses. The fact that many patients were partially recovered from depression can be seen as a limitation. Another limitation is the availability of FLAIR data on only a subsample (58%), albeit large enough to detect a strong relationship between the WMH burden and BOLD response. The EXIT is a broad screening measure of executive control, and it is possible that its specific domains would show a stronger overlap with effects of depression. However, a recent meta-analysis demonstrated a broad, non-selective impairment across executive function domains in depression (Snyder, 2013). Further, our results are strengthened by absence of external reinforcement on the EXIT. Finally, a modest sample size warrants caution.

In summary, in a sample of older adults, depression and impaired executive control were linked to dissociable disruptions in the corticostriathalamic encoding of reinforcement. Neither of these disruptions was explained by WMH. We conclude that ascending striatocortical reward signals appear to be disrupted in late-life depression, while deficits associated with poor executive control more closely resemble effects of lateral prefrontal lesions or prefrontal disconnection.

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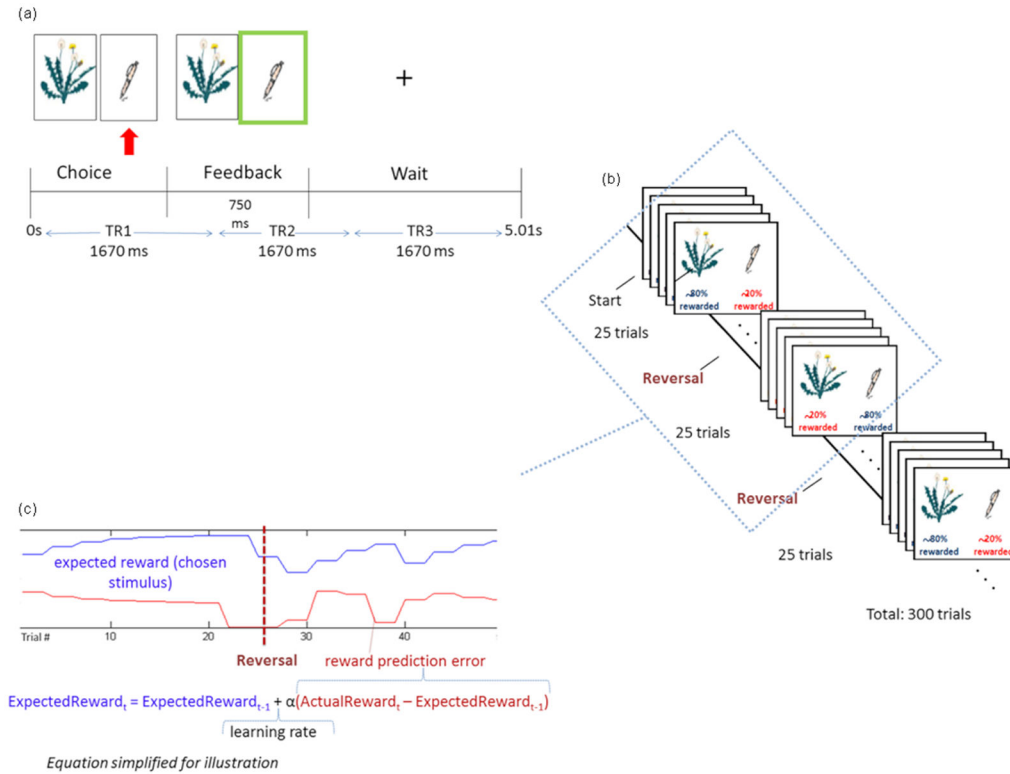


Fig. 1. Probabilistic Learning Task. (A) On each trial, the participant chooses between two stimuli. Following the choice, feedback is displayed: green frame for reward (as shown), red frame for reward omission. A fixation screen follows. Scanning is synchronized with trial onset. (B) One stimulus initially has a high probability of reward and the other, a low probability of reward. This contingency is reversed unbeknownst to the participant every 25 trials, a total of 12 reversals. (C) The reinforcement learning model estimates expected reward and reward prediction error for each trial (shown for 50 trials), using the participant’s reinforcement history and choices. [Simplified learning rule provided for illustration; the model is described in full in Dombrovski et al., JAMA Psychiatry, 2013.]

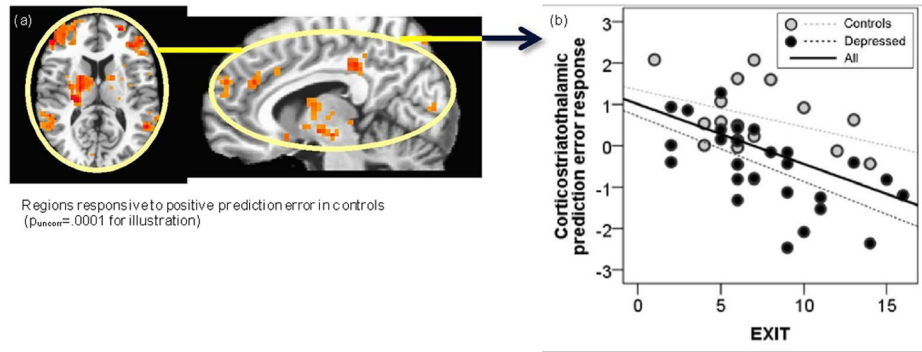


Fig. 2. Corticostriathalamic responses to positive prediction error and executive control. (a) Positive prediction error functional network masks were independently derived in controls. (b) In depressed participants, weak corticostriathalamic response to prediction errors was related to poor executive control as captured by the Executive Interview.

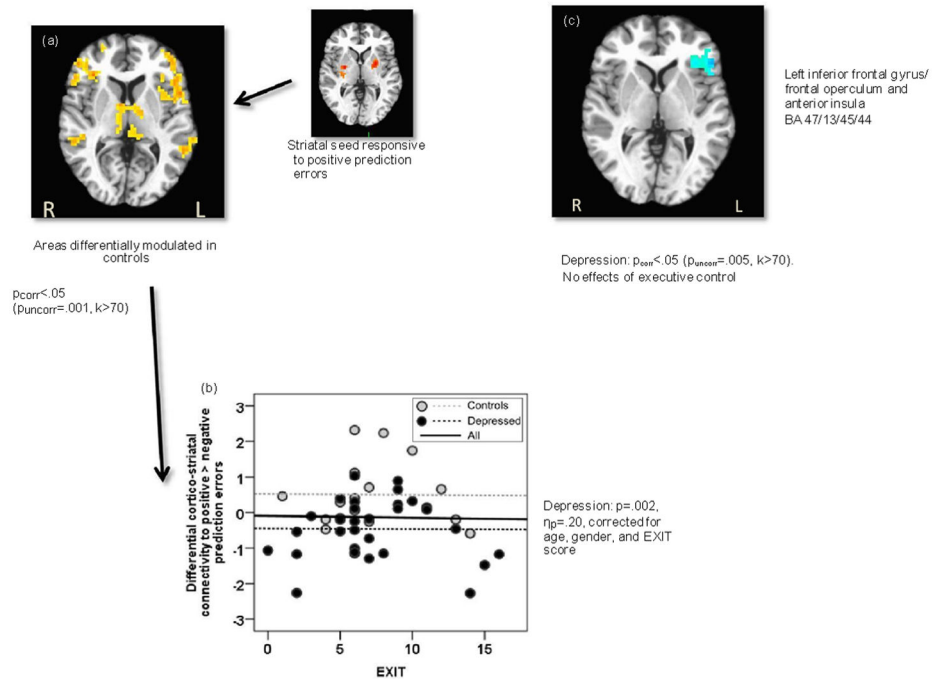


Fig. 3. Corticostriatal functional connectivity in the context of unexpected rewards. (a) Positive vs. negative prediction errors differentially enhanced functional connectivity between the striatum and left operculoinsular, right ventrolateral prefrontal cortex, bilateral superior temporal gyrus, and bilateral thalamus. (b) In a region-of-interest analysis, this cortico-thalamic network was less strongly modulated in depressed patients compared to controls. There were no effects of executive control. (c) An independent whole- brain contrast mapped the effect of depression to the left operculoinsular cortex. There were no significant effects of executive control.

Demographic, clinical and cognitive characteristics

Table 1

Characteristics	Non-psychiatric controls (n = 16)	Depressed (n = 31)	F	χ^2	P value
Male, No. (%)	6 (38)	12 (40)	-	1.13	0.57
Age, mean (SD), y	71 (8.0)	66 (5.4)	5.91		0.02
White, mean (SD), y	14 (88)	22 (73)	-	4.38	0.36
Education, mean (SD), y	13.8 (1.9)	14.5 (3.0)	0.92	-	0.34
Prenorbid IQ estimate, ¹ mean (SD)	103 (9)	105 (16)	0.31	-	0.58
Dementia rating scale, mean (SD)	138 (3.0)	136 (5.8)	2.03	-	0.16
Executive interview, mean (SD)	7 (4)	8 (4)	0.16	-	0.70
Physical illness burden, ² mean (SD)	6.5 (2.5)	9.3 (3.8)	6.41	-	0.02
Hamilton depression scale, ³ mean (SD)	2.9 (3.5)	12.3 (7.3)	23.0	-	<0.001
Beck hopelessness scale, mean (SD)	0.8 (0.9)	7.2 (6.2)	17.2	-	<0.001
Antidepressant exposure, ⁴ mean (SD)	-	3.3 (1.9)	-	-	-
Lifetime substance use, No.	-	8	-	-	-
Lifetime anxiety, No.	-	14	-	-	-

¹ Wechsler Test of Adult Reading, standard score

² Cumulative Illness Rating Scale, adapted for geriatrics

³ Hamilton Rating Scale for Depression

⁴ Antidepressant Treatment History Form, cumulative score