Supplementary material for 'Impaired reward-related learning signals in remitted unmedicated patients with recurrent depression'

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Learning rate selection procedure

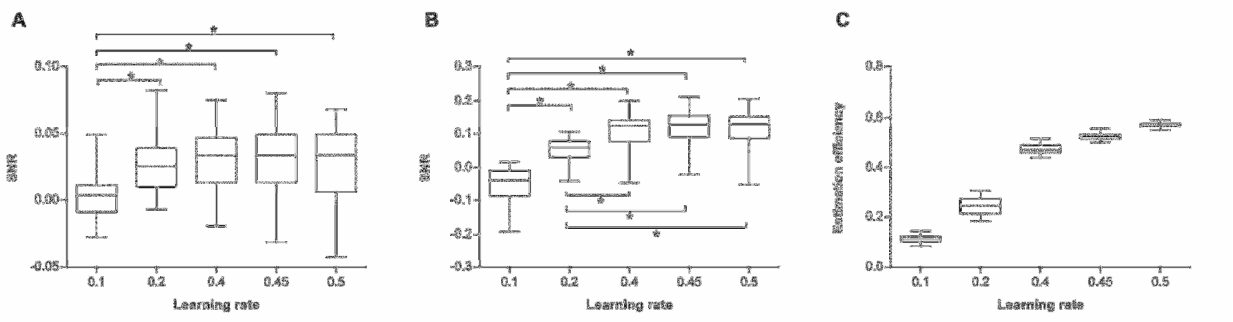
As recommended for model-based fMRI analysis (Wilson and Niv, 2015) we selected multiple plausible learning rates from literature (0.1 and 0.4 from Kumar *et al.* (2008) and O'Doherty *et al.* (2006); 0.2 from O'Doherty *et al.* (2003; 2004); 0.45 from Gradin *et al.* (2011); 0.5 from Lawson *et al.* (2017)) and explored which learning rate fitted our data best. For all learning rates we calculated signal-to-noise (SNR) values within our a priori VTA ROI, by dividing the contrast map from the CS*TD+US*TD contrast by the residual variance estimate map. For a complete overview, we calculated SNR values based on a one-group t-test contrast map across all subjects (Supplementary Fig. 1A), as well as on the two-group t-test contrast map (Supplementary Fig. 1B). Second, we also determined estimation efficiency values of SPM designs (Liu *et al.* (2001)) across all subjects (Supplementary Fig. 1C). Third, we compared TD-related VTA activation across the range of learning rates to ensure our results were robust.

Results learning rate selection procedure

When comparing the TD-related activation of alternative plausible learning rates, there was a significant difference between SNR for different learning rates, both when calculations were based on the one-group contrast map ($F_{4,135} = 7.30$, $P = 0.000$) as well as the two-group (group difference) contrast map ($F_{4,135} = 57.49$, $P = 0.000$). Both SNR analyses revealed the highest SNR when using $\alpha = 0.45$ (Supplementary Table 1, Supplementary Fig. 1A and 1B). In both SNR-analyses, Tukey HSD post-hoc tests confirmed a significant difference between $\alpha = 0.1$ and the other learning rates. The SNR-analysis based on the group difference contrast map furthermore revealed a significant difference between $\alpha = 0.2$ and the other learning rates. For the estimation efficiency calculations, there was a significant difference between all different learning rates (($F_{4,310} = 6787.49$, $P = 0.000$). Tukey HSD post-hoc tests confirmed significant differences between all learning rates, where the model with $\alpha = 0.5$ revealed the highest estimation efficiency (Supplementary Table 1, Supplementary Fig. 1C). When exploring TD-related VTA activation for all learning rates we found comparable results, with maximal responses for $\alpha = 0.4$, 0.45 and 0.5 (Supplementary Table 2). Wilson and Niv (2015) report that different learning rates have relatively little effect on neural results, however, sensitivity of the model-based analysis to learning rate can increase when the contrast-to-noise ratio is high. In line with this observation, we therefore chose to report results for the learning rate with the highest SNR ($\alpha = 0.45$).

Supplementary Table 1. Descriptives for different learning rates

	α = 0.1		α = 0.2		α = 0.4		α = 0.45		α = 0.5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SNR based on one group (all subjects) map	0.003	0.016	0.029	0.023	0.031	0.023	0.032	0.027	0.027	0.029
SNR based on two-group (group difference) map	-0.049	0.050	0.052	0.038	0.111	0.055	0.121	0.053	0.118	0.057
Estimation efficiency	0.115	0.014	0.244	0.032	0.473	0.019	0.523	0.012	0.571	0.010



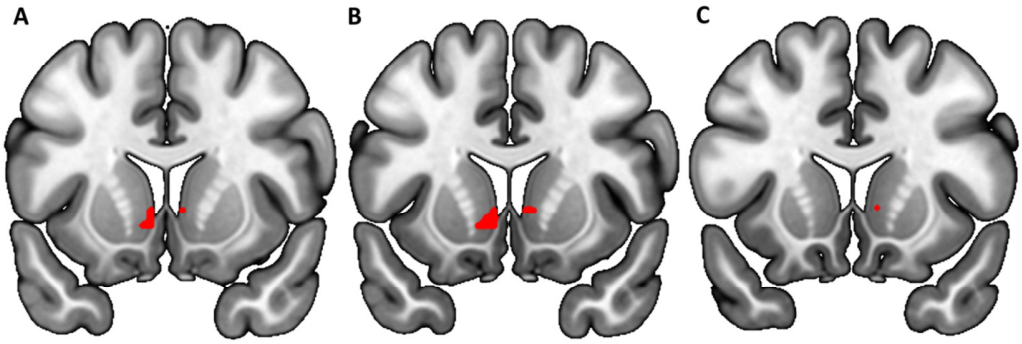
Supplementary Figure 1. Model efficacy for different learning rates. (A) SNR based on one-group (all subjects) contrast map **(B)** SNR based on two-group (group difference) contrast map **(C)** Estimation efficiency of SPM designs across all subjects.

Supplementary Table 2. TD-related VTA activation for different learning rates

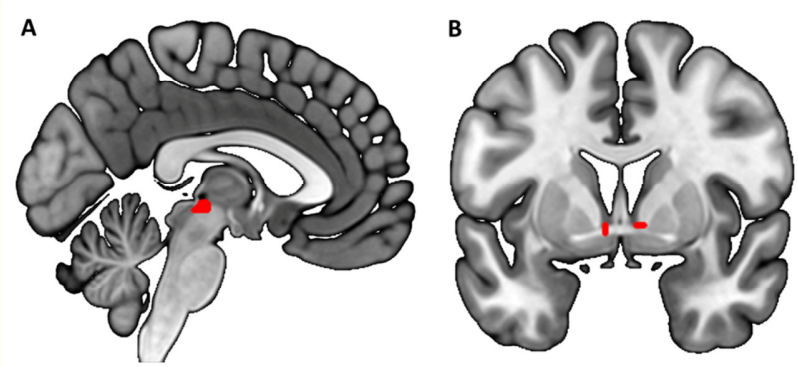
Learning rate	Contrast	Location	MNI coordinates	*z*	Significance*
α = 0.1	rrMDD>healthy controls	VTA	(0, -21, -3)	-	NS
α = 0.2	rrMDD>healthy controls	VTA	(0, -21, -3)	2.17	0.110
α = 0.4	rrMDD>healthy controls	VTA	(0, -21, -3)	2.84	0.024
α = 0.45	rrMDD> healthy controls	VTA	(0, -21, -3)	2.79	0.028
α = 0.5	rrMDD> healthy controls	VTA	(0, -21, -3)	2.60	0.045

CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, rrMDD=remitted recurrent major depressive disorder, VTA=Ventral Tegmental Area, *FWE small volume corrected, NS = difference not significant after SVC

Results main effects

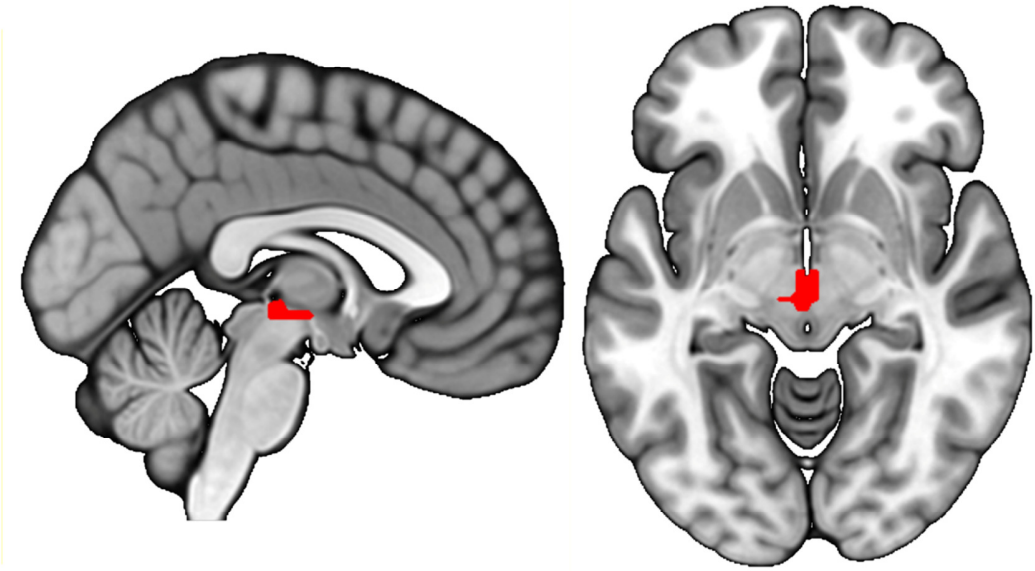


Supplementary Figure 2. Main effect of cue and reward delivery. **(A)** VS activation CSr+USr>Neutral contrast. **(B)** VS activation CSr>Neutral contrast. **(C)** VS activation USr>Neutral contrast.



Supplementary Figure 3. Main effect of PE. **(A)** VTA activation CS*TD+US*TD contrast. **(B)** VS activation CS*TD+US*TD.

TD-error results after HDRS correction



Supplementary Figure 4. TD-error related activation comparing rrMDD vs. HC after HDRS correction. MDD patients show more VTA activation compared to healthy controls (Z=2.57, P=0.048 FWE corrected on peak-level, SVC).

Results between group activation with SPSS test statistics

Based on the suggestions of anonymous reviewers we performed a sensitivity analysis by extracting the beta-weights from the *a-priori* ROIs and perform statistical analyses in SPSS.

Supplementary Table 3. Between group activation with SPSS test statistics

		Contrast	Location	MNI coordinates	Test-statistic	Significance[a]
Group differences	Total TD-signal (CS*TD+US*TD)	rrMDD>healthy controls	VTA	(0, -21, -3)	$t(61) = -2.94$	0.005
			VS	(9, 0, -3)	$t(61) = -3.12$	0.003
				(-6, 3, -6)		
		healthy controls>rrMDD		No clusters survived threshold		
	CS*TD	rrMDD>healthy controls	VTA	(0, -21, -3)	$t(61) = -2.26$	0.027
		healthy controls>rrMDD		No clusters survived threshold		
	US*TD	rrMDD>healthy controls	VTA	(0, -18, -15)	$t(61) = -3.04$	0.003
		healthy controls>rrMDD		No clusters survived threshold		

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

[a]two-sample t-test comparing beta weights from ROI voxels

Results analysis 6mm smoothing kernel

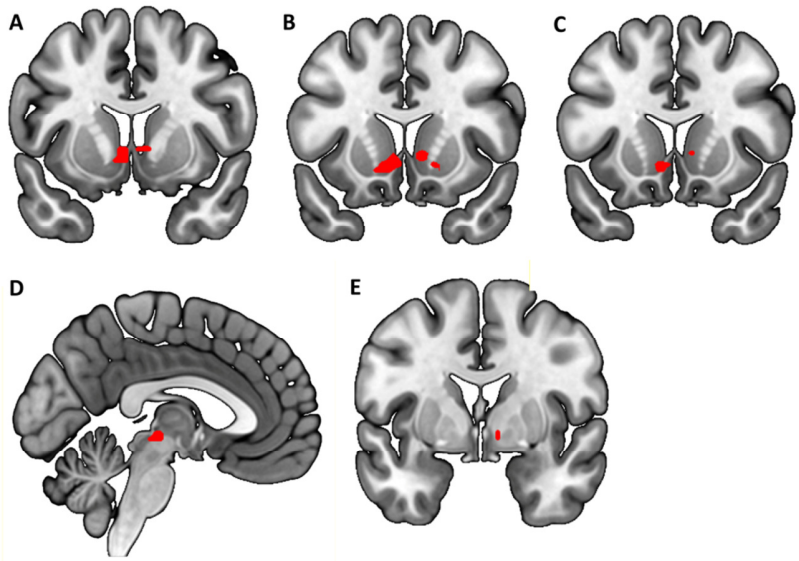
Based on the suggestions of anonymous reviewers we performed a sensitivity analysis with the kernel used for smoothing at 6mm (as this has been suggested to be required at at least 2 times the voxel size). We however initially chose a smaller kernel based on the small size of the VTA, because when it comes to small brain areas, meaningful activations might be attenuated when the smoothing kernel is too large.

Supplementary Table 4. Within group activation with alternative smoothing kernel of 6mm

	Contrast	Location	MNI coordinates	*z*	Significance[a]
Cue+reward delivery (CS+US>Neutral)	rrMDD+healthy controls	VS	(-6, 12, -6)	2.98	0.002
			(6, 12, 0)	2.93	0.002
Cue delivery alone (CS>Neutral)	rrMDD+healthy controls	VS	(-9, 12, -6)	3.50	0.000
			(6, 9, 0)	3.36	0.000
Reward delivery alone (US>Neutral)	rrMDD+healthy controls	VS	(-6, 18, -9)	2.61	0.004
			(6, 12, 0)	2.26	0.012
Total TD signal (CS*TD+US*TD)	rrMDD+healthy controls	VTA	(0, -21, -3)	2.34	0.010
		VS	(-9, -3, -3)	2.04	0.021
			(9, 0, -6)	1.87	0.031

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

[a] $P_{\text{uncorrected}}$ to display extent of signal



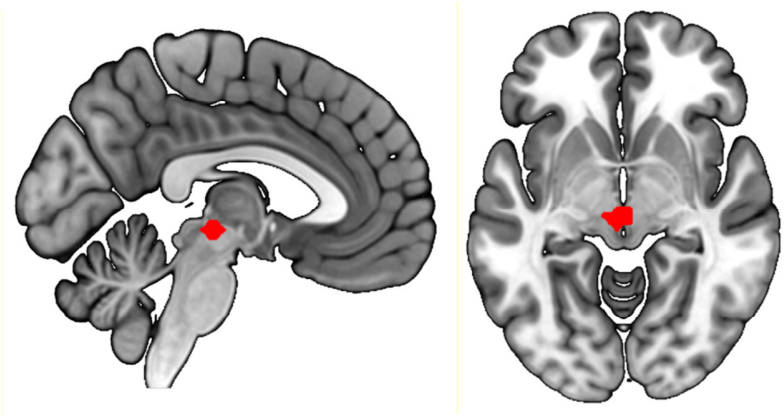
Supplementary Figure 5. Main effects after 6mm smoothing. **(A)** VS activation CSr+USr> Neutral. **(B)** VS activation CSr>Neutral. **(C)** VS activation USr>Neutral. **(D)** Main effect of PE in VTA (CS*TD+US*TD). **(E)** Main effect of PE in VS (CS*TD+US*TD).

Supplementary Table 5. Between group activation for analysis with alternative smoothing kernel of 6mm and SPM test statistics

	Contrast	Location	MNI coordinates	*z*	Significance[a]
Total TD-signal (CS*TD+US*TD)	rrMDD>healthy controls	VTA	(0, -21, -6)	2.41	0.049
		VS	(-9, -3, -3)	2.77	0.195
			(9, 0, -6)	2.59	0.279
	healthy controls>rrMDD	No clusters survived threshold			
CS*TD	rrMDD>healthy controls	VTA	(0, -21, -6)	1.93	0.124
	healthy controls>rrMDD	No clusters survived threshold			
US*TD	rrMDD>healthy controls	VTA	(3, -18, -6)	1.81	0.149
	healthy controls>rrMDD	No clusters survived threshold			

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

[a]FWE peak level corrected + SVC



Supplementary Figure 6. TD-error related activation comparing rrMDD vs. HC after 6mm smoothing. MDD patients show more VTA activation compared to healthy controls (Z=2.41, P=0.049 FWE corrected on peak-level, SVC).

Supplementary Table 6. Between group activation for analysis with alternative smoothing kernel of 6mm and SPSS test-statistics

		Contrast	Location	MNI coordinates	Test-statistic	Significance[a]
Group differences	Total TD-signal (CS*TD+US*TD)	rrMDD>healthy controls	VTA	(0, -21, -6)	$t(61) = -2.44$	0.018
			VS	(-9, -3, -3)	$t(61) = -2.55$	0.014
				(9, 0, -6)		
		healthy controls>rrMDD	No clusters survived threshold			
	CS*TD	rrMDD>healthy controls	VTA	(0, -21, -6)	$t(61) = -1.98$	0.052
		healthy controls>rrMDD	No clusters survived threshold			
	US*TD	rrMDD>healthy controls	VTA	(3, -18, -6)	$t(61) = -2.41$	0.019
		healthy controls>rrMDD	No clusters survived threshold			

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

[a]two-sample t-test comparing beta weights from ROI voxels

Results analysis without noise correction

Based on the suggestions of anonymous reviewers we performed a sensitivity analysis without excluding 18 patients and 8 controls because of missing data for cardiac and respiratory noise. We initially decided to exclude these subjects because correction for cardiac and respiratory noise appeared obligatory due to its location close to major arteries and adjacent pulsatile cerebrospinal fluid filled spaces. These physiological sources of noise generate time varying signals in fMRI data, which if left uncorrected can obscure signals of interest (Beissner and Baudrexel 2014; D'Ardenne et al, 2007).

Supplementary Table 7. Within group activation for analysis without noise correction

		Contrast	Location	MNI coordinates	*z*	Significance[a]
Main effect	Cue+reward delivery (CS+US>Neutral)	rrMDD+healthy controls	VS	(6, 12, 0)	3.31	0.000
	Cue delivery alone (CS>Neutral)	rrMDD+healthy controls	VS	(6, 12, 0)	3.34	0.000
				(-3, 6, -3)	3.02	0.001
	Reward delivery alone (US>Neutral)	rrMDD+healthy controls	VS	(-6, 3, -3)	3.07	0.001
				(6, 12, 0)	2.93	0.002
	Total TD signal (CS*TD+US*TD)	rrMDD+healthy controls	VTA	(-6, -24, -6)	2.39	0.008
			VS	No main effect voxels in the VS		

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

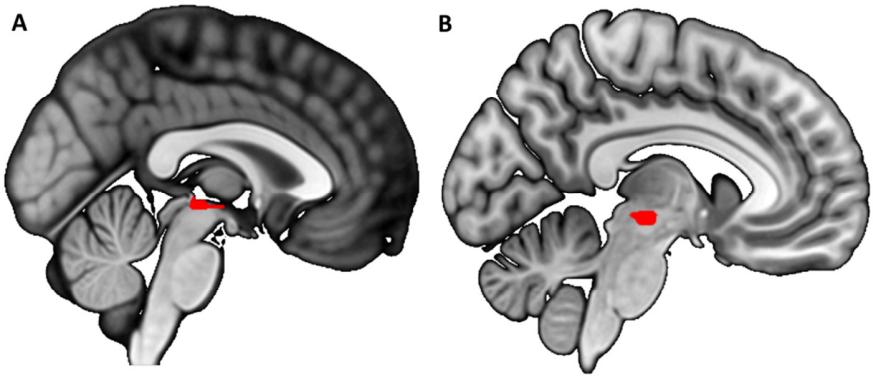
[a] $P_{\text{uncorrected}}$ in order to display the extent of the signal

Supplementary Table 8. Between group activation for analysis without noise correction

		Contrast	Location	MNI coordinates	*z*	Significance[a]
Group differences	Total TD-signal (CS*TD+US*TD)	rrMDD>healthy controls	VTA	(-6, -21, -6)	1.77	0.158
			VS	(-9, -3, -6)	1.95	0.644
				(9, -6, -6)	1.84	0.688
		healthy controls>rrMDD	No clusters survived threshold			
	CS*TD	rrMDD>healthy controls	VTA	No voxels survived SVC		
		healthy controls>rrMDD	No clusters survived threshold			
	US*TD	rrMDD>healthy controls	VTA	No voxels survived SVC		
		healthy controls>rrMDD	No clusters survived threshold			

rrMDD=remitted recurrent major depressive disorder, HC=Healthy Controls, CS=conditioned stimuli, US=unconditioned stimuli, TD=temporal difference signal, VS=Ventral Striatum, VTA=Ventral Tegmental Area.

[a]FWE peak level corrected + small volume corrected



Supplementary Figure 7. Difference main effect of PE with and without noise correction.

(A) Main effect VTA activation (CS*TD+US*TD) with noise correction. **(B)** Main effect VTA activation (CS*TD+US*TD) without noise correction.

References

Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, et al. Expected value and prediction error abnormalities in depression and schizophrenia. Brain 2011; 134: 1751-64.

Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. Brain 2008; 131: 2084-93.

Lawson RP, Nord CL, Seymour B, Thomas DL, Dayan P, Pilling S, et al. Disrupted habenula function in major depression. Mol Psychiatry 2017; 22: 202-8.

Liu TT, Frank LR, Wong EC, Buxton RB. Detection power, estimation efficiency, and predictability in event-related fMRI. Neuroimage 2001; 13: 759-73.

O'Doherty JP, Buchanan TW, Seymour B, Dolan RJ. Predictive neural coding of reward preference involves dissociable responses in human ventral midbrain and ventral striatum. Neuron 2006; 49: 157-66.

O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ. Temporal difference models and reward-related learning in the human brain. Neuron 2003; 38: 329-37.

O'Doherty JP, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 2004; 304: 452-4.

Wilson RC, Niv Y. Is Model Fitting Necessary for Model-Based fMRI? PLoS Comput Biol 2015; 11: e1004237.