Supplemental Information

Supplemental Data

Figure S1. Psychophysiological interaction analysis with the VMPFC region of interest as the seed region to examine VMPFC correlation with ventral striatum regions of interest for each setback condition (relates to Figure 3). A) Estimates of connectivity (arbitrary units) between VMPFC and ventral striatum for each type of setback ('*' denotes estimate significantly differs from zero, $p < .05$, error bars represent standard error). B) Individual participant VMPFC-ventral striatum connectivity estimates plotted against persistence (low alternative value condition). Connectivity estimates are not significantly related to persistence. UNC = Uncontrollable, CON = Controllable, L = left, R = right.

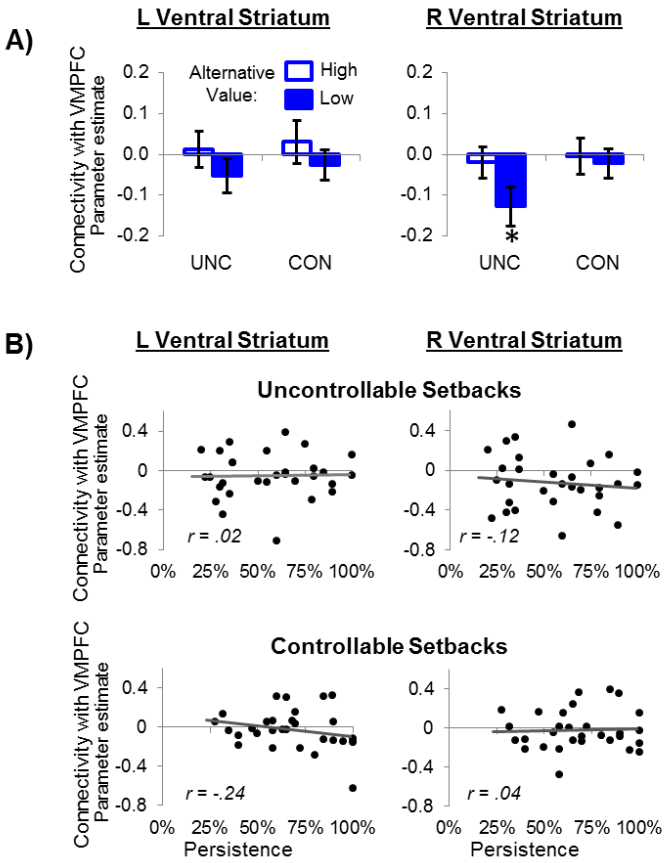
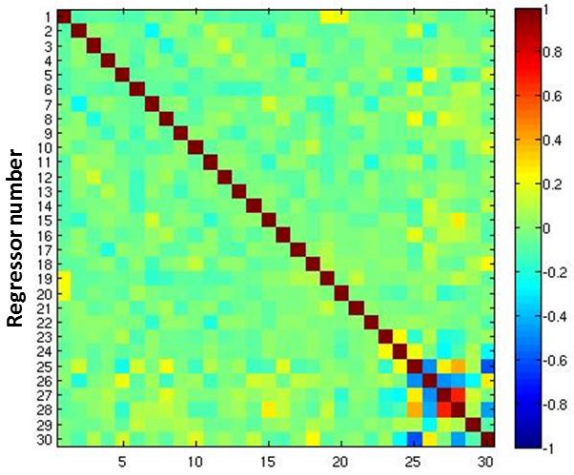


Figure S2. Correlation matrix (relates to Experimental Procedures). Correlation (pearson's r) between each regressor in the GLM.



Regressors

1. Initial path choice of a round
2. Path choice after uncontrollable setback, high alternative condition
3. Path choice after controllable setback, high alternative condition
4. Path choice after uncontrollable setback, low alternative condition
5. Path choice after controllable setback, low alternative condition
6. Positive cue (class meeting)
7. Uncontrollable obstacle, high alternative condition
8. Controllable obstacle, high alternative condition
9. Uncontrollable obstacle, low alternative condition
10. Controllable obstacle, low alternative condition
11. Uncontrollable setback, high alternative condition
12. Controllable setback, high alternative condition
13. Uncontrollable setback, low alternative condition
14. Controllable setback, low alternative condition
15. Uncontrollable setback avoided, high alternative condition
16. Controllable setback avoided, high alternative condition
17. Uncontrollable setback avoided, low alternative condition
18. Controllable setback avoided, low alternative condition
19. Goal reached
20. Goal not reached
21. Missed Path choice
22. Missed positive cue
23. Missed obstacle
24. Feedback after missed obstacle
25. Head motion parameter, translation (x)
26. Head motion parameter, translation (y)
27. Head motion parameter, translation (z)
28. Head motion parameter, rotation (roll)
29. Head motion parameter, rotation (pitch)
30. Head motion parameter, rotation (yaw)

Table S1. Choices to persist after setbacks and response times for decisions following controllable and uncontrollable setbacks in the low and high alternative value conditions (relates to Figure 1). S.D. in parentheses. A marginal influence of the alternative value condition was observed on response times for the decision to persist with a path ($F(1,29) = 3.50$, $p = .07$), such that participants took longer to decide when alternative paths were low value. Setback controllability ($F(1,29) = .58$, $p=.45$) and its interaction with alternative value ($F(1,29) = 1.36$, $p=.25$) did not significantly influence response times.

	Low Alternative Value	High Alternative Value
Controllable Setback		
Persistence	68.29% (21.92)	68.02% (24.26)
Response Time	713ms (178)	706ms (180)
Uncontrollable Setback		
Persistence	56.19% (24.86)	55.11% (26.02)
Response Time	718ms (173)	682ms (166)

Table S2. Persistence (s.d.) and choices for High, Intermediate, and Low Value paths over the course of the experiment (relates to Figure 1). Time periods T1 through T4 refer to first through fourth quarter of the experiment. The effect of setback controllability on persistence is consistent over the course of the experiment (a 2 (controllability) X 2 (alternative value) X 4 (time period) ANOVA shows a main effect of controllability, $F(1,29) = 19.52$, $p < .001$, and no significant effects of alternative value or time, or interactions, all $Fs < 1$).

Condition	Time period	Persistence	High Value	Intermediate Value	Low Value
Controllable, Low Alternative	T1	66.94% (29.05)	62.89% (34.34)	24.89% (27.46)	14.44% (24.39)
	T2	65.33% (27.63)	56.33% (27.57)	28.33% (26.5)	17.83% (19.28)
	T3	69.00% (28.42)	72.89% (35.45)	19.00% (22.03)	12.00% (18.64)
	T4	69.33% (30.95)	67.28% (33.54)	16.83% (22.57)	22.28% (26.68)
Controllable, High Alternative	T1	72.00% (30.89)	67.17% (31.61)	15.44% (21.9)	15.67% (21.57)
	T2	65.67% (25.59)	51.17% (35.37)	27.67% (23.7)	22.83% (24.48)
	T3	70.50% (30.92)	62.83% (31.7)	27.00% (25.18)	13.50% (17.92)
	T4	64.67% (33.16)	64.83% (31.69)	14.00% (14.04)	22.00% (26.44)
Uncontrollable, Low Alternative	T1	56.11% (30.82)	53.06% (35.77)	26.50% (24.88)	26.00% (29.78)
	T2	53.50% (34.37)	55.67% (33.9)	23.83% (25.59)	23.83% (22.65)
	T3	56.83% (27.62)	55.33% (32.98)	28.00% (24.27)	18.33% (16.99)
	T4	58.17% (32.34)	56.67% (28.32)	24.61% (20.65)	21.78% (22.35)
Uncontrollable, High Alternative	T1	55.89% (28.43)	55.11% (38.82)	30.50% (29.78)	18.28% (22.75)
	T2	55.67% (32.64)	50.67% (35.13)	31.50% (25.5)	19.50% (24.93)
	T3	57.50 (33.34)	50.50% (31.19)	32.67% (26.9)	18.50% (18.25)
	T4	52.28% (31.70)	60.67% (35.64)	23.67% (24.42)	17.33% (22.73)

Table S3. Neural regions exhibiting a main effect of setback controllability (relates to Figure 2; $z > 2.57$; $p < .05$, cluster corrected).

Region (Right/Left)	peak z-statistic	center of mass (x, y, z)	volume (mm^3)
Medial Prefrontal, Striatum (L,R)	5.08	-2, 51, -18	24584
VMPFC (L) peak: -10, 44, -6*	4.53		
Ventral Striatum (L) peak: -6, 14, -6*	2.98		
Ventral Striatum (R) peak: 12, 10, -8*	3.38		
Lateral Orbitofrontal, Temporal Pole (R)	4.00	52, 26, 3	2096
Lateral Orbitofrontal, Temporal Pole (L)	4.91	-50, 17, -9	12384
Dorsolateral Prefrontal (R)	4.64	30, 9, 59	1976
Dorsolateral Prefrontal (L)	4.08	-27, 6, 59	1808
Mid-Cingulate (L,R)	4.51	1, -17, 48	4224
Precentral Gyrus, Postcentral Gyrus	4.47	44, -17, 57	3992
Superior Parietal Lobule, Supramarginal Gyrus (R)	4.24	44, -44, 47	3912
Superior Parietal Lobule, Supramarginal Gyrus (L)	4.30	-40, -44, 44	4840
Posterior Cingulate, Precuneus (L,R)	5.48	-3, -52, 24	8824
Angular Gyrus, Lateral Occipital	4.11	-52, -62, 22	2304
Lateral Occipital (L)	3.65	-28, -88, 19	1968
Lateral Occipital (R)	4.07	33, -83, 25	4712

*sub-cluster peaks (from voxel-wise TFCE procedure (Smith and Nichols, 2009), $p < .05$ corrected) are shown for clusters that span multiple regions of interest.

Supplemental Experimental Procedures

Persistence After Setback (PAS) task structure and affect ratings. Participants received 40 controllable and 40 uncontrollable setbacks across the entire experiment, making decisions to persist or not after each trial. Half of these events occurred in the high alternative value condition and half occurred in the low alternative value condition. Participants also avoided 24 controllable (passed exams) and 24 uncontrollable (non-cancelled courses) setbacks, and encountered 64 class meetings. The distribution of controllable and uncontrollable setbacks was predetermined to ensure that every participant had the same amount of trials and chances to persist. A post-experimental probe showed that no participants suspected that the setbacks were predetermined. Path choice screens, obstacle cues, setbacks and class meetings were pseudo-randomly ordered and separated in time by a fixation screen with randomized duration of 2 (50%), 4 (25%), or 6 (25%) seconds. Ordering of received and avoided setbacks was restricted such that once a setback was avoided, all subsequent setbacks in the round were also avoided if the participant correctly responded. After completing the task and exiting the scanner, participants rated their affective responses (valence and intensity) to each type of setback. Valence ratings were on a 5-point scale with anchors endpoints labeled "very negative" and "very positive," and the midpoint labeled "neutral". Intensity ratings were on a 5-point scale with endpoints labeled "not at all intense" and "extremely intense". Valence and intensity ratings were scored such that higher numbers indicated greater negative valence and greater intensity.

Neuroimaging data acquisition and preprocessing. Images were collected on a 3.0-T Siemens TRIO scanner, and preprocessed and analyzed with FMRIB's Software Library version 5.0 (FSL, http://www.fmrib.ox.ac.uk/fsl/), Woolrich et al., 2009). Structural images were acquired

with a T1-weighted MPRAGE sequence (256x256 matrix, FOV 256mm, 176 1-mm sagittal slices). Blood oxygen level dependent functional images were acquired with an echo-planar imaging sequence (TR=2000ms, TE=30 ms, FOV=192mm, flip angle 90°, bandwidth 2232 Hz/Px, echo spacing = 0.51, 35 oblique-axial slices aligned to the anterior commissure-posterior commissure line, voxel size 3 x 3 x 3mm). A field map sequence was acquired prior to functional imaging and used to correct for geometrical distortion in the functional images (using FSL-FUGUE (Jenkinson et al., 2012). Functional images were collected in four 10min 30s consecutive scans, corrected for geometrical distortion, head motion and slice-timing skew, and then high-pass filtered (cutoff period 100s). Data was resampled to 2mm cubic resolution and spatially smoothed with a 5mm FWHM isotropic Gaussian kernel. Images were spatially normalized into the Montreal Neurological Institute (MNI) standard.

GLM specification. The GLM consisted of four regressors of interest and 26 regressors of non-interest (see Supplemental Information for complete GLM specification). The four regressors of interest modeled the setback events in each of the four conditions (controllable/uncontrollable setback received in the high/low alternative value condition, 2s duration). 20 regressors of non-interest modeled the remaining events in the task (Initial Choice, 2s; Post-setback Choice in each condition, 2s; class meeting cue and feedback, 4s; Obstacle cue in each condition, 2s, avoided setback events in each condition, 2s; round end with end of path reached/not reached, 2s, missed responses on path choice screens, obstacle cues, and setback events, 2s. These regressors were convolved with a canonical double-gamma response function in FSL's FEAT first-level analysis package. Six regressors modeled participant head movement during the scan.

Analysis of setback-specific connectivity with VMPFC seed region. Based on prior research demonstrating that inverse correlations between VMPFC and subcortical activity are predictive of negative emotion processing (Pezawas et al., 2005; Kim at al., 2011), we conducted a seed-based psychophysiological interaction (PPI) analysis with the VMPFC ROI as the seed region (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). This analysis was aimed at testing whether activity in the ventral striatum ROIs significantly correlated with VMPFC activity, specifically during the occurrence of each type of setback. For this purpose, a GLM was specified (for each functional scan for each participant) with the same regressors as described in the primary analysis, with five additional regressors: (1) the time course of activity in the VMPFC region (for the appropriate scan), (2-5) the interaction of the VMPFC time course with the setback regressor for each condition. Parameter estimates for the interaction regressors for each setback condition were computed for the ventral striatum ROIs.

Mediation analysis. In the case that a neural region was associated with affect and behavioral persistence, the region was tested as a mediator of the relationship between affect and behavioral persistence. This mediation model was tested with the method described and implemented by Preacher and Hayes (2004), using regression-based estimates of the total effect of setback-related negative affect on behavioral persistence as well as the direct effect of negative affect on persistence (controlling for neural responses), and using bootstrapping to estimate the 95% confidence interval for the indirect effect of negative affect on persistence through neural responses (a confidence interval not crossing zero indicates a significant effect).

Additional Statistical Analyses: supplementary behavioral measure of persistence. In accordance with the definition of persistence as the continuance of a course of action despite setbacks, the primary behavioral operationalization of persistence does not include choices to switch to a higher value path after a setback. However, abandoning a low value goal for a higher value goal might in some cases indicate increased ambition as much as a failure to persist with a goal. For this reason, we repeated the analyses with an alternative behavioral measure in which choices switch to a higher value goal are also scored as persistence choices. Importantly, using the behavioral measure of persistence choices plus instances where participants chose to switch to a higher value path did not change the main results reported in the paper.

A 2 (setback controllability: controllable or uncontrollable) x 2 (alternative value: high or low) ANOVA revealed that this alternative behavioral measure was influenced by a main effect of setback controllability ($F(1,29) = 23.85$, $p < .001$). The alternative behavioral measure was higher after controllable compared to uncontrollable setbacks in both the low ($t(29) = 3.21$, $p = .003$) and high ($t(29) = 4.94$, $p < .001$) alternative value conditions. The alternative behavioral measure was not significantly influenced by the value of alternatives (main effect and interaction $Fs < 1$). Further, the alternative behavioral measure correlated with ventral striatum responses to controllable (low alternative value condition) setbacks (left: $r = -.35$, $p = .06$; right: $r = -.47$, $p = .01$), but not ventral striatum responses to uncontrollable setbacks (left: $r = .13$, $p = .51$; right: $r = .22$, $p = .24$). VMPFC responses to uncontrollable setbacks (low alternative value condition) correlated with the alternative behavioral measure ($r = -.50$, $p < .005$) and significantly mediated the relationship between uncontrollable setback-related negative affect and the alternative behavioral measure in the low alternative value condition. That is, greater negative affective intensity predicted a higher score on the alternative behavioral measure (total effect: $B = 5.61$,

t(27) = 2.61, p = .01), but the relation was no longer significant when controlling for VMPFC responses (direct effect: B = 3.60, t(27) = 1.62, p = .12). The path from negative affective intensity, through VMPFC responses, to the alternative behavioral measure was significant (indirect effect: B = 2.08, bias corrected 95% confidence interval (CI) = .02 to 5.57). The same result was true using affective valence ratings as a measure of negative affect (total effect: B = 7.05, t(27) = 2.41, p = .02; direct effect: B = 3.98, t(27) = 1.17, p = .25; indirect effect: B = 3.24, CI = .10 to 10.18).

PAS fMRI Task Instructions. The following instructions were given to each participant.

"In this game, you are a student trying to earn a degree. You'll choose a course of study, then try to progress toward your degree. You'll play several rounds of the game. Each degree you earn will add to your total points. Try to get as many points as you can.

"You start by choosing a program of study. Each of the choices (A, B, or C) leads to a degree that has a certain value, which is shown on the right side of the screen. To choose program A, press 1. To choose program B, press 2. To choose program C, press 3. Try it out on the next screen. {Choice Screen}.

"After you choose a program of study, you'll get chances to progress towards your degree. You can make progress in three ways: 1) by going to class, 2) by passing exams, 3) by getting past course cancellations.

"1) Going to class (green triangles). When you see a green triangle, it means you can make progress by going to class. Press a key to go class when you see a green triangle. It doesn't matter which key you press, any of the 1, 2, 3, or 4 keys will work. Try it on the next screen. {Class

meeting Screen} As long as you press a key when you see a green triangle, you will always make progress.

“2) Passing exams (orange triangles). Orange triangles mean you have an exam. When you see an orange triangle, you need to press the correct key to pass the exam and make progress. You have to use trial and error to figure out the correct key to pass exams. Once you figure out the correct key, you can use the same key to pass every exam until a new round starts. Try it now on the next screen. Just press the 1, 2, 3, or 4 key to try to pass the exam. {Exam Screen, Positive Outcome Screen} You won't always pass on your first try. You'll need to try different keys to figure out which one works. When you don't press the correct key, you fail the exam and lose the progress you made in the program. On the next screen, you'll see what happens if you press the wrong key. {Negative Outcome Screen} As you just saw, you lose your progress if you fail an exam. When you lose your progress you go back to the starting point and choose a program of study again. Again, to pass exams (orange triangles) you have to figure out the correct key. Once you find the correct key, you can use it to pass exams for the rest of the round.

“3) Course cancellations (purple triangles). Purple triangles signify that the school is cancelling courses in your program. When you see a purple triangle, press any key to find out if your course is cancelled. If it's cancelled you lose your progress and have to start over. Even if your course gets cancelled, you can still choose the same program of study on your next turn (there are lots of courses in each program). It doesn't matter what key you press when you see a purple triangle - you don't have any control over course cancellations. But you do need to press a key even though it doesn't matter which one. Try it out on the next screen. First you'll see what happens when your course is cancelled. {Course Cancellations Screen, Negative Outcome Screen}. Now you'll

see what happens when your course is not cancelled. {Course Cancellations Screen, Positive Outcome Screen}.

“Here are the things you need to know to play this game:

* First, choose your course of study

* Make progress as you encounter Green, Orange, and Purple triangles

* Green triangles = go to class by pressing ANY key

* Orange triangles = pass exam by pressing the CORRECT key

* Purple triangles = see if course is cancelled by pressing ANY key

More things you need to know to play this game:

*If you fail an exam or your course is cancelled, you start over and get a new chance to choose which degree to pursue (A, B, or C). You can always choose any degree even if you tried it before.

*In each round you have limited chances to earn your degree- if you reach the degree in time you get the points- if you don't reach the degree you get no points.

*Degrees that are worth more are not necessarily harder to earn-some high value degrees may be easy to earn and some low value degrees may be difficult to earn.”

Supplemental References

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Fsl. NeuroImage, 62(2), 782–90.

O’Reilly, J. X., Woolrich, M. W., Behrens, T. E. J., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. Social Cognitive and Affective Neuroscience, 7(5), 604–9.