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Supplemental Data

Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation

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List of Supplemental Tables and Figures

Supplemental Text

Table S1

	Coordinates			Cluster size		a path		ab path		Num. voxels	
Name	**x**	**y**	**z**	**Vox**	**Vol**	**Z**	**p**	**Z**	**p**	**P<.001**	**P<.005**
Mediated by nuc. accumbens											
VStr/basal forebrain	28	7	-18	25	1329	3.46	0.0005	3.48	0.0005	4	25
VMPFC	17	31	-14	303	16112	3.58	0.0003	3.58	0.0003	40	303
L VLPFC	-48	28	-14	31	1648	3.57	0.0004	3.55	0.0004	4	31
R VLPFC	41	48	0	13	691	3.35	0.0008	3.18	0.0015	0	13
Rostral MPFC	3	58	9	136	7232	3.58	0.0003	3.58	0.0003	24	136
R aPFC	21	55	18	12	638	3.56	0.0004	3.58	0.0003	7	12
L DLPFC	-31	24	45	15	798	3.55	0.0004	3.28	0.001	0	15
DMPFC	10	28	45	58	3084	3.58	0.0003	3.52	0.0004	8	58
Mediated by left amygdala											
R VLPFC	48	31	-9	17	904	3.51	0.0004	-3.448	0.0006	1	17
R mid-lateral OFC	28	31	-14	3	160	3.54	0.0004	-3.581	0.0003	3	3

Figure S1

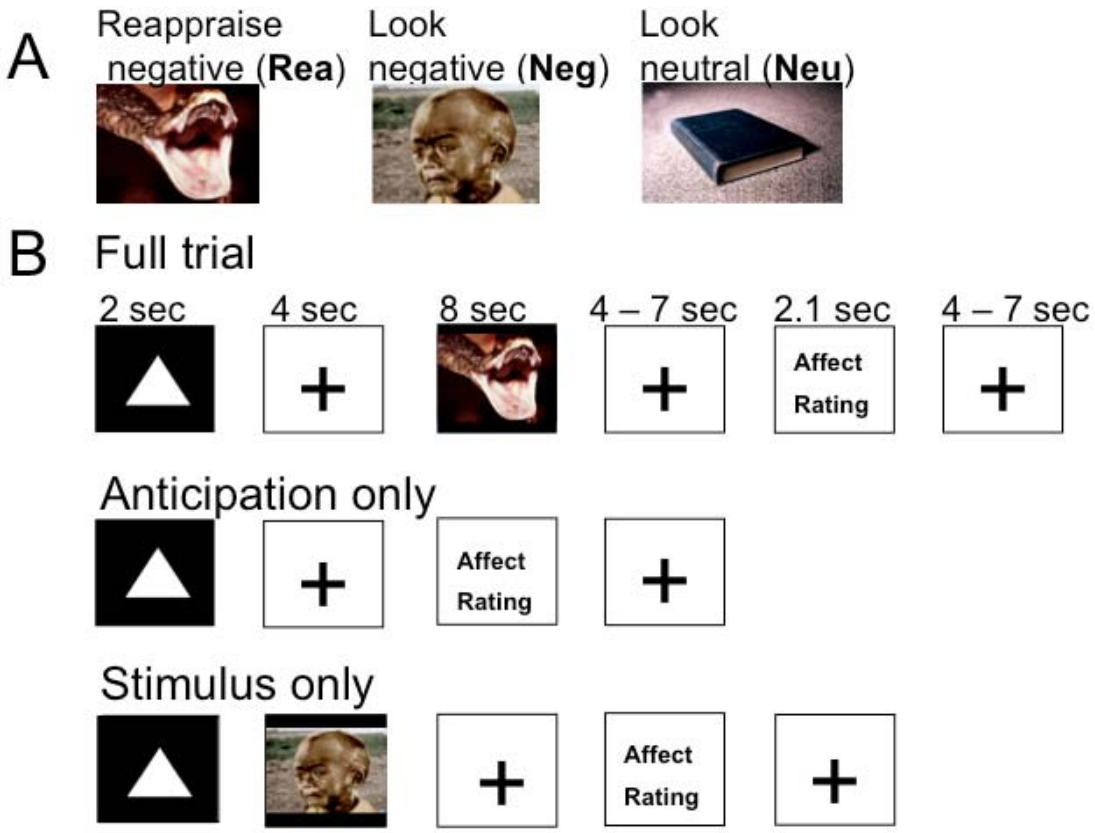

Figure S1. Task design. The design includes three trial types: Anticipation and stimulus trials, Anticipation only trials, and Stimulus only trials, for each of the 3 conditions (Reappraise Negative [ReappNeg], Experience Negative [LookNeg], and Experience Neutral [LookNeu]).

Figure S2

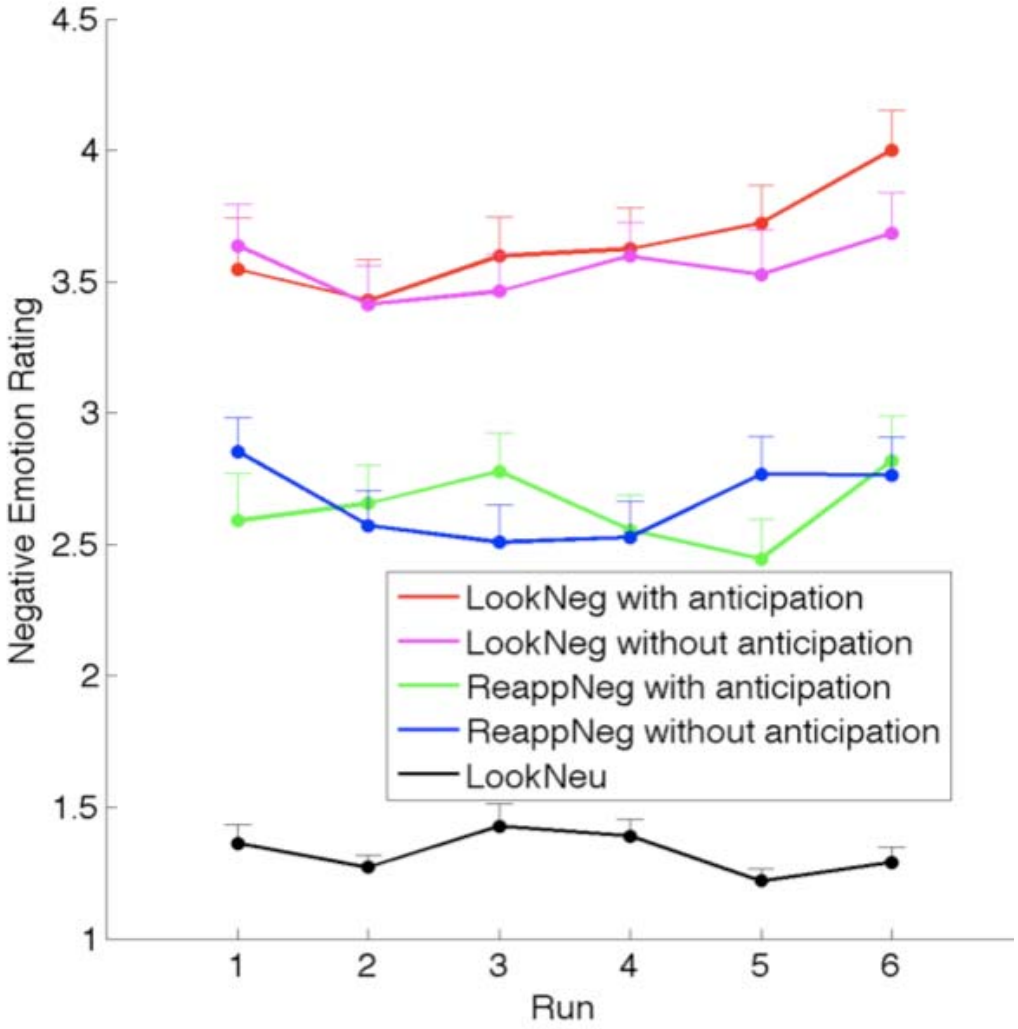

Figure S2. Emotion rating data. Group average ratings (y-axis) as a function of scanning run (x-axis) and task condition (lines). There was a robust effect of viewing negative vs. neutral images and a robust effect of reappraisal, both of which were sustained across runs. Neither interacted with whether the trial included a 4 sec anticipation period.

Figure S3

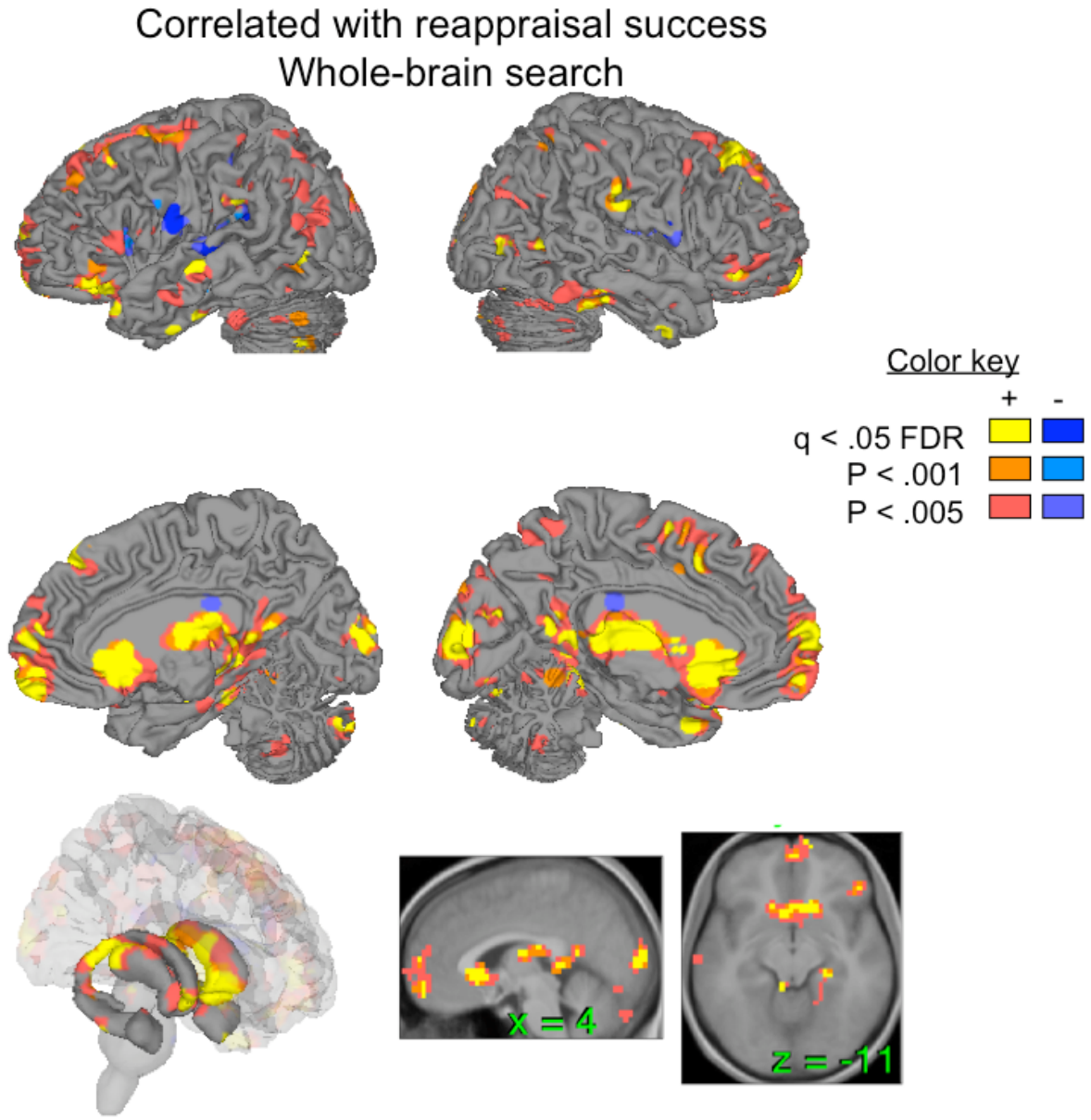

Figure S3. Whole-brain correlations between reappraisal activation [ReappNeg - LookNeg] and reappraisal success in reported experience [LookNeg – ReappNeg]. Positive correlations are shown in red/yellow, and negative correlations are shown in blue. Positive correlations indicate a greater relative increase in activity for participants who report more successful reappraisal , and negative correlations indicate a greater relative decrease in activity (LookNeg - ReappNeg) for participants who report more successful reappraisal. Thresholds are shown in the color key on the figure.

Figure S4

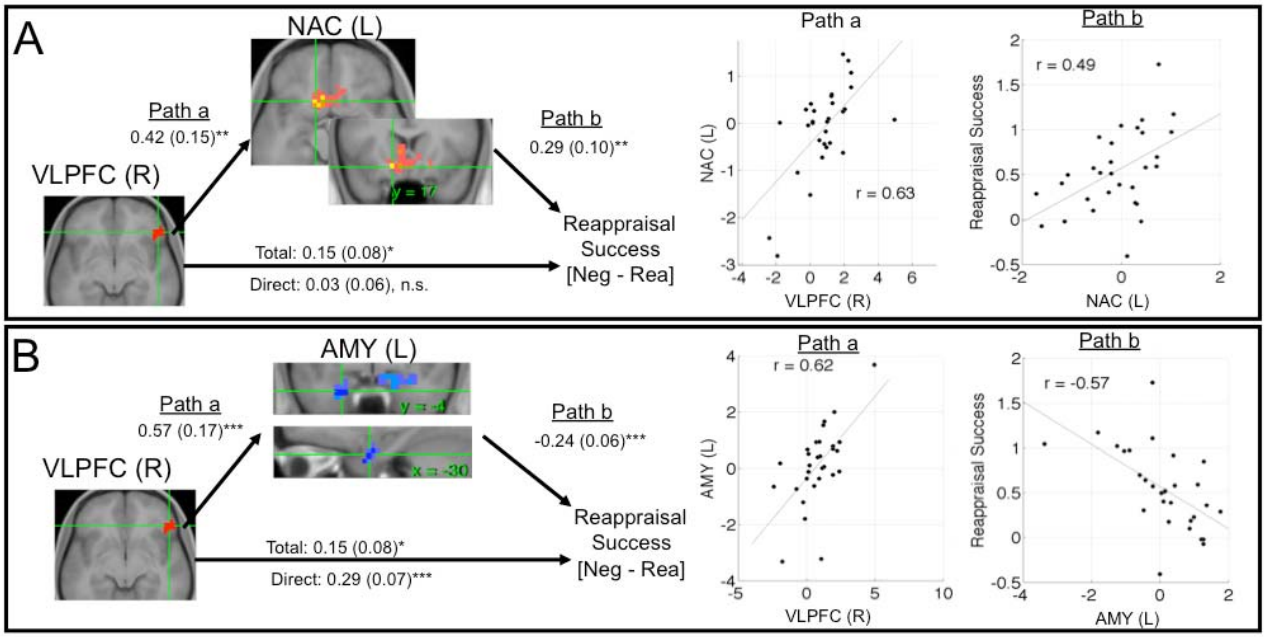

Figure S4. Mediation analyses for amygdala and nucleus accumbens regions of interest. The mediation effect parametric mapping identified regions that were mediators of the relationship between right ventrolateral prefrontal cortex (vlPFC) and reappraisal success by searching over voxels and performing mediation tests one voxel at a time. This figure shows statistics for the path models, averaging over voxels in each mediating region, for significant left nucleus accumbens/ventral striatal and left amygdala regions. These results differ slightly from the ones presented in Figure 3 because here each region is subjected to a separate mediation analysis, whereas in the analysis shown in Figure 3, they were included in the same mediation model.

Figure S5

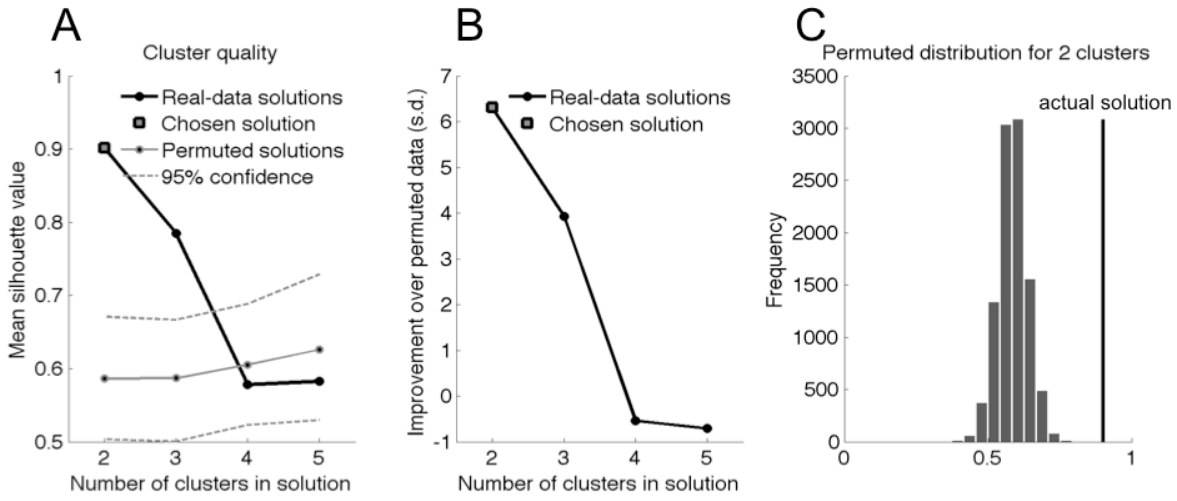

Figure S5. Results for cluster analysis examining grouping of mediators into functional networks. A) Cluster quality (y-axis, see Experimental Procedures) as a function of number of clusters in the candidate solution. Clusters in this context refer to interconnected networks of brain rgions. Higher values indicate tighter clustering of the data. The solid black line shows the actual data, with the chosen solution (2-cluster solution) marked with a gray square. The thin black line shows the average quality for permuted data, with 95% confidence intervals marked by dashed lines. Permutation disrupted the relationships among variables, so that there was no true grouping of the data into clusters, so that cluster quality under the null hypothesis of no grouping could be assessed. B) Z-scores (y-axis) for the real-data cluster quality relative to the cluster quality of permuted data. C) Distribution of null-hypothesis cluster quality (x-axis; frequency on y-axis) for the chosen 2-cluster solution. The real-data solution is marked with a vertical line.

Supplemental Discussion

Interpreting suppression effects in path models

A suppression effect occurs when the indirect pathway and the direct pathway have opposite signs—that is, when two variables independently influence an outcome variable (Y), but with effects of opposite signs. It might be best illustrated with an example from another domain. For example, increased use of technology may have both positive and negative effects on life satisfaction (Y), for different reasons. These effects tend to cancel each other out, resulting in a weak overall technology -> satisfaction relationship, unless the mediating variables with opposite signs can be identified: One might discover a positive pathway from technology -> connect with family and friends -> increased satisfaction, and a negative pathway from technology -> reachable by boss at home -> decreased satisfaction. Controlling for the suppressor variable (reachable by boss) would allow other positive relationships and any positive direct technology -> satisfaction effect to emerge.

There are many examples of suppression effects in published literature, and they can often uncover strong direct relationships that are masked by confounding suppressor variables or explain results that are initially counter-intuitive. As an example of the first case, Goldberg (Goldberg et al., 1996) found that a steroid use-prevention program reduced intentions to use steroids. They also found that greater reason for using steroids was related to increased intentions to use. Both of these effects are intuitive. However, as MacKinnon et al. (MacKinnon et al., 2000) describe in their re-analysis of these data, those who had greater reason to use steroids tended to enroll in the program, creating a positive link between reasons for using steroids and program enrollment. Thus, the indirect pathway connecting program enrollment, more reasons for using steroids, and increased intentions to use partially canceled out the beneficial direct effects of the program. After controlling for the confounding suppressor (reasons to use), the beneficial effects of the program grow stronger.

As an example of the second case, Guber (1999) describes a dataset drawn from the 1997 Digest of Education Statistics on the relationship between state spending on public schools and SAT scores. Surprisingly, the original relationship between spending and SAT scores across U.S. states was negative: More spending predicted significantly lower scores. However, a likely cause is that a third variable was acting as a confounding suppressor variable. High-spending

states tended to require all students to take the SAT, even the academically poor ones; thus, percentage of students taking the test is a strong negative predictor of average SAT. When percent taking the test was included as a mediator, the direct relationship between spending and SAT became significantly positive, in line with what one might expect.

In the present study, the amygdala may appear to be a complete mediator of the PFC-reappraisal success correlation (in the sense that the direct relationship is not significant) when it is the only mediator in the model, but that is partially because there is still much unexplained variance in this model that masks the direct effect. Including the nuc. accumbens (NAC) in the model explains additional variance, allowing the direct effect to reach statistical significance.

Additional implications of dual routes for reappraisal effects on emotion: how we measure changes in emotional responding

The finding that fMRI responses in both the amygdala and NAC/VS were meaningfully related to emotional experience has implications for both understanding amygdala and striatal function and the use of self-reported emotion in neuroscience research more generally. Consider first that although the amygdala has been broadly implicated in negative emotional responses, ranging from the acquisition of conditioned fear (Phelps, 2006) to hyperactivity in a range of anxiety disorders (Etkin and Wager, 2007), there has been reason to doubt that amygdala activation reflects experiential changes in all situations in which it has been activated (Anderson and Phelps, 2002; Barrett and Wager, 2006; Wager et al., in press). In part this may be due to the fact that the amgydala is a complex, heterogeneous group of structures, only some of which have been linked to emotional experience in some situations. Several meta-analyses from our group have shown that although the superior amygdala is activated both by stimuli that do (e.g. a small child crying hysterically) and stimuli that do not (e.g. a fearful facial expression) generate negative emotional experiences, it is more consistently activated by the stimuli that *do not* elicit experience (Phan et al., 2002; Phan et al., 2004; Wager et al., in press). This finding, and the individuals results on which it is based, have been taken to suggest that the amygdala may play a role in the perceptual detection and encoding of affectively relevant stimuli, which may or may not have a direct impact on affective experience (Anderson and Phelps, 2001, 2002; Barret et al., 2007; Wager et al., in press; Whalen, 1998). Therefore, the finding that amygdala activity mediates negative emotional experience *in this task context* is a significant finding, and it

provides support for the notion that prefrontal-amygdala correlations in other reappraisal studies that use the amygdala as an outcome variable – but did not measure emotional experience (or any other behavioral index of emotional response) (Johnstone et al., 2007; Urry et al., 2006; van Reekum et al., 2007) – may in fact be relevant to shaping emotional experience.

This argument leads to the broader implication of the amygdala-experience relationship observed here. One reason some of the aforementioned papers have not measured emotional experience is because of concerns that it may not be a wholly reliable or valid index of emotional responding. As noted at the outset, we recognized the necessity of behavioral measures for constraining functional interpretations of neural indicators (Poldrack, 2006), and selected self-reports as our behavioral measure because it can be reliably collected in the scanner environment, provides clear valence information (unlike most autonomic measures), and has been shown to predict mental and physical health outcomes (Brosschot et al., 2006; Gross and Munoz, 1995; Moskowitz, 2003; Scheier and Carver, 1992; Tugade et al., 2004). The fact that changes in self-reported negative emotion were mediated by activity in brain systems thought – on indepedent *a priori* grounds – to be important for emotional appraisals provides additional support for self-report as a useful measure for studies of emotion and its regulation.

Additional implications for the role of prefrontal cortex in emotional appraisal: the nature of correlations between PFC and amygdala

An interesting difference between this study and some previous studies of reappraisal is that we found positive correlations between vlPFC and amygdala, whereas several studies mentioned above found negative correlations. One reason for these differences may have to do with the structure of the reappraisal task as used by different investigators. In the Urry et al. and Johnstone et al. papers, the appraisal process was permitted to evolve for 4 s before presenting a reappraisal cue, perhaps separating in time an negative initial appraisal process that involves positive vlPFC-amgydala connectivity and a subsequent positive reappraisal process that involves negative vlPFC-activity. However, it is also possible that amygdala activity can be related in complex ways to appraisal. Kim et al., for example, found amygdala increases when participants increased positive emotional responses (Kim and Hamann, 2007), and studies of autobiographical memory retrieval have found co-activation of amygdala and vlPFC (Greenberg et al., 2005; Maguire and Frith, 2003). This raises the possibility that reappraisal cues presented

in advance of pictures in our paradigm may have strengthened participants' ability to engage in meaning-based reinterpretations, shifting frontal-amygdala connectivity positively. The present data cannot disentangle these and other potential explanations, but it opens the way for a more detailed mapping of effective connectivity as a function of specific strategies and stimulus types.

Additional implications of network analyses for understanding cognition-emotion interactions

The first network involved the NAC/VS (Figure 5B) and included three additional regions that have been implicated in action selection and memory. However, we also note that the NAC/VS region we identified extended into the subgenual cingulate, which has recently been shown to play an important role in the modulation of depression and mood (Drevets, 2001; Johansen-Berg et al., 2007; Mayberg et al., 1999); high-resolution studies are needed to dissociate the contributions of NAC and subgenual cingulate to the pathways reported here. One additional region in this network was the pre-SMA, which has been implicated in multiple cognitive control processes (van Snellenberg and Wager, in press; Wager et al., 2004a; Wager and Smith, 2003) and in the energization of internally driven processes that lead to effective intentional response selection (Alexander et al., 2007; Cunnington et al., 2005; Isoda and Hikosaka, 2007; Sumner et al., 2007) (Lau et al., 2004). A second region was the precuneus, which has been implicated in the control and switching of attention among objects and object features (Barber and Carter, 2005; Wager et al., 2004a) and in monitoring of the internal environment and "self" (Cavanna and Trimble, 2006; Gusnard and Raichle, 2001) and episodic memory retrieval (Lundstrom et al., 2005). Finally, a third region encompassed the retrosplenial cingulate cortex and cingulate isthmus, which have been implicated in autobiographical memory (Maddock, 1999) and may provide an anatomical bridge from the precuneus to medial temporal lobe structures that have well-known roles in the formation of declarative memories (Davachi, 2006). The positive association of vlPFC with activity in this network suggests that the selection of reappraisal-appropriate information from memory may be used to construct a positive construal of the situations depicted in negative images (Ochsner, 2004), and that this can mediate reappraisal success. Although speculative, this interpretation is consistent with what is known about the regions involved in this network and is consistent with the connectivity pattern we observed, which indicated a pathway from vlPFC to pre-SMA, which served as a network "hub" that is connected to the precuneus and retrosplenial cortex/cingulate isthmus, which in turn

connected to the NAC/VS. In this network context, one way of reappraising an aversive event can be seen to involve the interactions of vlPFC with a network of regions that together represent a positive, approach motivated appraisal of the event.

Here it should be noted that our search for frontal "mediated" regions suggested that the medial PFC (including dorsal, ventral, and rostral divisions) was functionally connected to this network. Though we found strong correlations between rostral MPFC and reappraisal success, it was not a primary focus here because we did not find overall reappraisal-related activation in our group of participants. However, its focus in previous papers (Johnstone et al., 2007; Urry et al., 2006) suggests that it may play an important role in reappraisal, and in our study it seemed to be related to the enhancement of NAC/VS activity that, in turn, predicted reappraisal success.

The second network involved the amgydala and included three additional anatomically interconnected areas that have been commonly associated with negative appraisals and negative emotion more generally (Figure 5B). The first region was the right lateral orbitofrontal cortex (lOFC), which has been associated with diverse forms of valenced affective experience (Berridge and Kringelbach, 2008; Wager et al., in press) and related motivational processes such as updating behavior on the basis of negative feedback (O'Doherty, 2003; O'Doherty et al., 2003) and negative (aversive) prediction errors (Seymour et al., 2005). The second was the anterior insula (AI), which is activated by aversive stimuli of various kinds and is most commonly associated with negative emotional experience in normal emotion (Wager et al., in press) and increased emotional activation across several kinds of anxiety disorders (Etkin and Wager, 2007). This region has been called primary "interoceptive" cortex (Craig, 2003), though it appears to be activated by aversive social experiences as well (Sanfey et al., 2003). The third was the rostral dorsal cingulate (rdACC), a region often activated when cognitive expectancies modulate affective processes. For example, hypnosis (Faymonville et al., 2000; Rainville et al., 1997) and placebo treatments (Lieberman et al., 2004; Price et al., 2007; Wager et al., 2004b) that lead to reduced pain have consistently reduced rdACC activity. A fourth region in the subthalamus was also included in this network, but we do not speculate on its interpretation here. The positive association of vlPFC activity with activity in this network is consistent with the idea that reappraisal success can also hinge on limiting activity in a network of structures important for representing negative affective states.

Supplemental Experimental Procedures

Reappraisal training procedures

Prior to scanning, participants completed a training session on the reappraisal strategy. Previous work on the reappraisal process has established that an effective means of down-regulating negative emotion is by re-interpreting the affects, dispositions, outcomes or contexts for the actors and actions shown in less negative ways. Prior to scanning, participants were trained in the use of this strategy, which is known as reinterpretation (Ochsner and Gross, 2008). For example, if participants viewed an image of a crying baby in a barren landscape, they might imagine that the mother has simply gone to do an errand and will return soon. Different specific reappraisals – all of the same basic kind – were generated for each image. As described previously (Ochsner et al., 2002; Ochsner et al., 2004), this method is meant to capture the fact that in everyday no single type of reinterpretation is expected to be applicable to all life events – or here, all photos.

The training session consisted of two parts. In the first part, participants were asked to memorize the cue-task condition associations (e.g., circle with LookNeu, etc.). Participants were subsequently quizzed until they achieved 100% accuracy on 10 consecutive trials of each type. In part two, participants completed 7 sample trials with the experimenter present (1 Look Neutral, 2 Look Negative, 4 Reappraise Negative). On reappraisal trials they were given feedback on the appropriateness of their reappraisals for each image. During this time participants also were reminded not to look away from images or distract themselves with irrelevant and/or positive thoughts unrelated to the context of the image. After appropriate coaching to ensure that participants could reinterpret images quickly and effectively, the training ended with the completion of 18 practice trials (6 Look Neutral, 6 Look Negative, 6 Reappraise Negative) on their own. Images used during training were different from those used during the subsequent test. Eye position was monitored during scanning by viewing an image of the right eye projected onto a screen in the scanner control room (I-SCAN, Inc.). No subjects closed their eyes or averted their gaze during image viewing.

fMRI task design

Previous studies of reappraisal have not separated brain activity related to anticipation

and instruction processing, stimulus viewing, and picture rating, and a goal of our task design was to provide the ability to estimate separately brain activation magnitude related to each of these three phases of the image viewing and rating process. To accomplish this, a partial trial design was employed (Ollinger et al., 2001; Stern et al., 2007). Within each task condition, LookNeu, LookNeg, and ReappNeg, three different trial types were used: full trials, anticipation-only trials, and stimulus-only trials (see Supplementary Figure 1).

On full trials, a 2 sec condition cue was followed by a 4 sec anticipatory interval during which a fixation cross was presented on the screen. The image was subsequently presented for 8-sec. Following image presentation, a fixation cross was presented during a 4 or 7 sec jittered inter-stimulus interval (ISI; uniform distribution of 4 and 7 sec intervals). Following the ISI period, the words "how negative do you feel?" appeared on-screen for 2.1 sec, and participants were asked to rate negative affect on a five-point scale by pressing a button with one of five fingers on a button-response unit (1 = "not at all negative," indicated by a thumb button press, up to 5 = "extremely negative," indicated by a fifth-finger button press). Following the rating, a 4 or 7 sec jittered ISI concluded the trial.

The trial was identical to the full trial through the anticipation interval. Instead of an image presentation, participants were asked to rate the negative feelings experienced during anticipation on the same five-point scale. The stimulus only trials were identical to the full trials, except that the 4 sec anticipation interval was omitted. This design allowed us to construct predictors for Cue-, Anticipation-, and Image-related brain activity related to each task condition in the General Linear Model (GLM) that were uncorrelated enough to provide efficient estimates of activation in each task condition x trial phase combination (see below). In addition, responses during picture or anticipation rating could be estimated separately, thus permitting the parsing of brain activity during trial phases of interest from brain activity related to the reporting and button-press processes.

Subjects completed 6 functional runs of 18 trials each for a total of 108 trials. Each run included 6 trials of each condition (Reapp Neg, Look Neg, Look Neutral) and trial type (full trial, ant only trial, stim only trial).

In this report, we compared brain responses during the viewing of aversive images in the ReappNeg vs. LookNeg conditions, as estimated controlling for activity during other phases of the trial (Cue, Anticipation, and Report). Negative emotion ratings did not differ significantly

based whether the anticipation period was included or not in either Look or Reappraise conditions (see Supplementary Figure 2). For LookNeg, the average rating difference for full trial vs. stimulus only trials was 0.10, paired $t(35) = 1.58$, $p > 0.10$. For ReappNeg, the difference was -0.02, paired $t(35) = -0.29$, $p > 0.7$. Subsequent analyses of behavioral and brain data were conducted on averages across full trials and stimulus-only trials. Likewise, reported reappraisal success (LookNeg – ReappNeg) was stable across time (Success x Run interaction $F(5, 172) = 1.02$, $p = .41$), and ratings for all image types were likewise stable across time. Thus, subsequent analyses were also conducted on averages across runs.

Image processing and data analysis

Preprocessing. Functional images were slice-time and motion corrected using FSL (FMRIB Centre, University of Oxford). Structural T1-weighted images were coregistered to the first functional image for each subject using an iterative procedure of automated registration using mutual information coregistration in SPM2 and manual adjustment of the automated algorithm's starting point by a trained analyst until the automated procedure provided satisfactory alignment. Structural images were normalized (spatially warped) to a standard template brain (the MNI avg152T1.img) using SPM2 software (Wellcome Department of Cognitive Neurology, UCL) using default options (7 x 8 x 7 nonlinear basis functions), and the warping parameters were applied to functional images for each subject. Normalized functional images were interpolated to 2 x 2 x 2 mm voxels and spatially smoothed with a 6-mm Gaussian filter.

First-level GLM model. First-level GLM analysis for each participant was performed using SPM2 (Friston, Jezzard, & Turner, 2004). Effects were modeled as a boxcar regressor convolved with a canonical hemodynamic response function (double-gamma) for the 2 sec cue period, 4 sec anticipation period, 8 sec stimulus viewing period during which subjects either attend or reappraise, and 2.1 sec rating period separately. Twelve regressors were specified, for cue-related responses, anticipation-related responses, image-viewing related responses, and rating-related responses in each of the three task conditions (LookNeu, LookNeg, and ReappNeg). Separate sets of regressors were specified for each of the 6 scanning runs for each subject. In addition, regressors specifiying a high-pass filter with a 120 sec cutoff were included

to model low-frequency drift. Since our primary concern was group statistics, no autoregressive (AR) model was used, which are unbiased and valid even without AR modeling.

Importantly, the trial design resulted in regressors that were essentially uncorrelated across conditions of interest. The critical feature of the design for the results we present here is that the regressors related to Image Viewing for each task condition are not collinear with combinations of other regressors, so that their estimates are stable and efficient. The average correlations between each Image-Viewing related regressor and other regressors (across other regressors and subjects) were r = 0.067, r = 0.063, and r = 0.062 for LookNeu, LookNeg, and ReappNeg. The correlations were very similar across both regressors and subjects as well: The maximum correlations with any other regressor for any subject were r = 0.074, r = 0.067, and r = 0.070, for each task condition, and the minimum correlations were r = -0.17, r = -0.18, and r = -0.17. Variance inflation factors reflect the overall multicolinearlity in a design matrix for each regressor and were low (< 2) for all twelve regressors and for all subjects, indicating that the task design was effective in providing stable and efficient estimates of brain activity related to each task phase (cue, anticipation, image viewing, and rating) and task condition.

Contrasts. Activation estimates were obtained for each subject using SPM2, and contrasts across conditions were estimated and analyzed in a second-level group analysis treating subject as a random effect. The contrast of interest in this report was [ReappNeg image viewing – LookNeg image viewing]. Positive contrast values indicate greater relative activity during reappraisal vs. natural experience of aversive images, and negative values indicate greater relative activity during experience (i.e., the reverse subtraction). Both effects were analyzed and reported here. As our main *a priori* hypotheses concerned changes during image viewing, contrasts related to other phases of the trial (Cue, Anticipation, and Report) will be addressed in subsequent papers. This choice serves to avoid undue complexity and preserve clarity in the present report.

Group analysis (Analysis steps 1-2). The second level random-effects analysis was performed using robust regression, a technique that both increases statistical power and decreases false positive rates in the presence of outliers (Wager, Keller, Lacey, & Jonides, 2005). Reported reappraisal success was calculated for each subject as the average difference in negative affect reports for [LookNeg – ReappNeg]. The second-level design matrix included two regressors: one corresponding to reappraisal success, and the other an intercept term.

Reappraisal success scores were centered by subtracting the mean, allowing the intercept term to be interpreted as the population estimate for reappraisal-induced activation ([ReappNeg – LookNeg]) for a subject who shows average reappraisal success. The interpretation of the reappraisal success regressor is the change in reappraisal-induced activation as a function of reappraisal success, i.e. the activation-reappraisal success relationship. The advantage of including reappraisal-induced activation ([ReappNeg – LookNeg]) in the model is that it accounts for known sources of individual variation when testing the significance of average activation contrast values. Thus, for voxels that do show a brain activity-reappraisal success relationship, this model has greater sensitivity to detect overall activation compared with an intercept-only model (which is what is typically performed, e.g., in SPM software).

An anatomically defined gray matter mask was created based on the Montreal Neurologic Institute (MNI) avg152T1 template (smoothed with an 8 mm FWHM filter and thresholded at a value of 0.5) and explicitly specified during analysis.

Localization of results. Normalized structural T1 images were averaged across participants to create an anatomical underlay for visualizing significant regions of activation, and for visually assessing normalization quality. In our experience, this is advantageous because the quality of nonlinear warping can vary across brain regions, resulting in greater differences between the standard brain and participants' actual T1 images in ventral subcortical regions in particular. We assessed activation locations based on identified structural landmarks in our participants (e.g., amygdala gray matter, striatal gray matter) using several brain atlases (Haines, 2000; Mai et al., 2004; Martin, 1996), rather than relying on standardized Talairach or MNI coordinates, which can be misleading in some brain regions depending on warping quality. However, we provide MNI coordinates for reference and use in future studies and meta-analyses.

Mediation Effect Parametric Maps (Analysis steps 3, 4a). The Mediation Effect Parametric Map (MEPM) analysis is based on a standard 3-variable path model (Baron and Kenny, 1986) with a bootstrap test for statistical significance (Efron and Tibshirani, 1993; Shrout and Bolger, 2002). A test for mediation tests whether a covariance between two variables (X and Y) can be explained by a third variable (M). A significant mediator is one whose inclusion as an intermediate variable in a path model of the effects of X on Y significantly affects the slope of the X – Y relationship; that is, the difference ($c - c'$) is statistically significant (see Results for nomenclature). The test of mediation is fundamentally different from a moderation or "psycho-

physiological interaction" (PPI) effect, in which the *level* of a moderating variable M predicts the strength of the X –Y relationship. A moderator interacts with the X –Y relationship, whereas a mediator explains it. Thus, the mediation test (not the moderation test) is critical for localizing and testing functional pathways that span more than two regions. Brain regions that are *mediators* are candidates for links in functional pathways that relate brain activity in multiple regions to behavior and other outcomes.

In the current application, we used right VLPFC activity in the [ReappNeg – LookNeg] contrast as the X variable and reappraisal success as the Y variable. Thus, the X-Y relationship (and the *c* path) is the linear association between prefrontal increases during reappraisal and reported emotion decreases. Thus, the association is the correlation in contrast estimates across subjects in this case, rather than within-subject time series values. The MEPM strategy is to search for voxels in the brain that mediate that relationship, so that X and Y are specified as in Figure 1, but the mediator (M) is unknown. In this case, we first searched for voxels whose [ReappNeg – LookNeg] contrast values mediate the VLPFC – reappraisal success relationship within amygdala and NAC, and then conducted a whole-brain search to test for additional mediating brain regions that may form functional networks with our *a priori* target regions.

More formally, the mediation test can be captured in a system of three equations:

$$y = cx + e_y$$

$$m = ax + e_m$$

$$y = bm + c'x + e'_y$$

where *y*, *x*, and *m* are *n* (participants) x 1 data vectors containing the outcome (y, reappraisal success), the predictor (x, VLPFC), and data from a candidate mediating voxel (m, [ReappNeg – LookNeg] contrast values). e_y , e_m, and $e`_y$ vectors denote residual error for the outcome and mediator controlling for *x* and the outcome controlling for *x* and *m*, respectively. The *a* path is the estimated linear change in *m* per unit change in *x* (e.g., the slope of the VLPFC-mediator relationship). The *b* path is the slope of the mediator-outcome relationship controlling for *x* (mediator to reappraisal success, controlling for VLPFC). The *c* and *c'* paths are as described above.

Statistical tests on *a* and *b* path coefficients assess the significance of each relationship. In addition, a statistical test of (*c* – *c'*) can be performed by testing the significance of the product of the path coefficients *a***b*. A positive mediator is one involved in a pathway that has a

net positive effect on the outcome (e.g., *a*b* is positive, greater reappraisal success in this case). A negative mediator has a net negative effect (lower reappraisal success). We test the significance of *a*b* using the accelerated, bias-corrected bootstrap test (Efron and Tibshirani, 1993) with 10,000 bootstrap samples to test each of the *a*, *b*, and *a*b* path coefficients at each voxel, saving maps of path coefficients and bootstrapped P-values for each effect. Custom Matlab code (Mathworks, Natick, MA, R2007b) was written to perform these tests and optimize them for speed, so that the whole-brain MEPM maps could be accomplished in ~12 hours on a 4-processor Intel Macintosh computer with 2 dual-core Intel Xeon processors (see Author Note for software download information).

If multiple regions are included as mediators (as in analyses with amygdala and NAacc as independent mediators), then additional equations specifying *a* paths for each additional mediator are added, e.g., $m_2 = a_2 x + e_{m2}$ for a second mediator, and the equation that assesses the direct effects of the mediators is modified to include the additional mediators, e.g., $y = bm + b_2 m_2 + c' \quad x + e' \quad _y$ for a 2-mediator model. Thus, the *b* path for each mediator tests whether it is significantly related to the outcome controlling for all other variables.

Though only a significant *a*b* product is required to provide evidence for a mediation effect, for significance in both ROIs and in the whole-brain analysis, we required that each of the paths *a*, *b*, and *a*b* be significant at $p < .005$, two-tailed, with three contiguous voxels. The conjunction across the three effects locates regions with the strongest evidence for both individual pathway links and the total mediation effect. Our choice of threshold was motivated by 1) the desire to use a standard threshold for comparability with other published results ($p < .005$ is one of the most common (Wager et al., 2007a)); 2) Control of false positives; and 3) Sensitivity, or the ability to detect many of the regions that show true mediation effects. The latter is important because using a threshold low enough to afford relatively high sensitivity enhances the ability to make inferences based on the pattern of results across the brain, and to meaningfully aggregate positive and negative findings across studies.

Mediation analysis is a tool for testing particular pathway relationships, but complementary tools are necessary for identifying functional networks of broadly interconnected regions. Principal components analysis (PCA), independent components analysis, and related tools provide complementary perspectives on neuroimaging data by identifying broadly interconnected networks. Though the MEPM analysis searches for mediating regions, we do not

conceptualize these regions as each constituting a separate functional path; rather, these individual networks are likely to be grouped into distributed functional networks that operate as a unit to mediate prefrontal-experience relationships. The analyses described below address this second point.

Region of interest (ROI) analyses and multiple comparisons correction. Four ROIs were drawn on the group-averaged, normalized T1-weighted images from our sample using custom software (SCAN Lab tools, T.D.W.), using several brain atlases for reference (Haines, 2000; Mai et al., 2004; Martin, 1996). The ROIs were in left and right amygdala (108 and 79 [3.5 x 3.5 x 4.5] mm voxels, respectivley) and left and right NAC/VS (52 and 53 voxels, respectively).

We assessed the family-wise error rate (FWER) for the mediation search analyses in each ROI by using a permutation test ((Nichols and Hayasaka, 2003)), which provides estimates of the chances of obtaining a false positive result anywhere in the ROI, accounting for the observed correlations among voxels. We permuted the rows of the 30 (subjects) x *k* (voxels) matrix of subject contrast values, preserving spatial structure, and re-computed the mediation test (including the significance of *a, b,* and *a*b* effects, and their conjunction) for each of 2000 permutations. The primary chosen threshold of $p < .005$ controlled the false positive rate below $p < .05$ in each ROI. That is, under the null hypothesis of no true relationships among X, M, and Y variables, the chances of a false positive conjunction result (significant *a, b,* and *a*b*) anywhere within a given ROI were less than 5%. Based on the permutation test, corrected p-values were $p < 0.03$ and 0.02 for the L/R amygdalae, and $p < .008$ and .002 for the L/R NAC/VS, respectively. This threshold also provided adequate correction for multiple comparisons for each of the *a* and *b* pathways independently. For the left and right amygdala, *a*: $p < .075$, *b*: $p < .06$ (one-tailed, corrected). For the left and right NAC/VS, *a*: $p < .055$, *b*: $p < .04$.

Clustering of mediators and functional networks (Analysis step 4b).

An advantage of the clustering procedure is that a nonparametric permutation test can be used to assess whether there is significant grouping of regions into clusters (networks), and the null hypothesis that regions are operating either independently or as a single large network can be rejected. Secondly, clustering (as opposed to PCA/ICA alone) provides a way of identifying networks that is stable with respect to rotation of the data in multidimensional space. Rotational indeterminacy and instability have plagued PCA/ICA-based and factor analytic approaches.

Briefly, we first defined mediating regions as sets of contiguous voxels that survived the conjunction test (*a*, *b*, and *a*b,* each at $p < .005$, with a 3-voxel extent threshold) as described above. We extended the regions to include contiguous voxels at $p < .05$ in the conjunction, and calculated the average contrast activity for each subject within each region. We then removed linear effects of right VLPFC activity from each region using robust regression, so that the networks captured relationships among regions with respect to their direct relationship with reappraisal success.

In order to achieve stable clustering in a high-dimensional dataset, it is typical to use a data-reduction algorithm (e.g. PCA) prior to clustering in order to remove dimensions with near-zero variance from the dataset. Here we used non-metric multidimensional scaling (NMDS), which makes fewer assumptions than PCA, as the dissimilarities are not assumed to reflect distances in a Euclidean space (Shepard, 1980). NMDS involves an initial decision about the number of dimensions, c, to retain. Thereafter the NMDS algorithm returns a set of component scores in c-dimensional space, which are then clustered. To choose the appropriate dimensionality, we performed PCA on the covariance matrix of contrast values for each of 12 mediating regions identified in the MEPM analysis and used a scree (eigenvalue) plot to determine the appropriate number of dimensions to retain. The plot showed that 86% of the covariance in the dataset was contained in the first four dimensions, and additional dimensions explained little additional variance. We then calculated the 12 x 12 matrix of correlations among these regions and converted the correlations to dissimilarity values using the formula $(1-r)/2$, so that 0 indicated zero distance and 2 indicated the maximum possible difference. We applied nonmetric multidimensional scaling (NMDS) analysis to the resulting dissimilarity matrix using stress as the error metric (details in (Wager et al., 2007b)), retaining four dimensions. The result was a 12 region x 4 component matrix of scores, which were subjected to cluster analysis.

We used hierarchical clustering with average linkage (clusterdata.m in Matlab R2007b) to identify networks, as in (Kober et al., in press; Wager et al., 2007b). We used a permutation test to choose the number of clusters and to provide inferences on whether the distances between regions were distributed multimodally (as opposed to a single-mode, single-cluster distribution expected if there were no systematic groups of interconnected regions). For each possible solution between 2 and 5 clusters (networks), we first computed a measure of clustering quality, as defined in (Struyf et al., 1996):

$$q = \sum_k \sum_i \frac{d_{i_o} - d_{i_{nn}}}{\max(d_{i_o}, d_{i_{nn}})}$$

where d denotes Euclidean distance, and d_{i_o} is the distance from region i to the center of its own class, $d_{i_{nn}}$ is the distance to the nearest neighboring class, and k indexes over clusters. We then permuted the columns of the dimension scores, re-applied the clustering algorithm, and calculated *q* based on the permuted data. The permutation procedure disrupts clusters of nearby regions by exchanging their locations in each dimension with those of other regions, while conditionalizing on the marginal distribution of regions in each dimension. This process was repeated 10,000 times to develop a null-hypothesis distribution of *q*. Estimating the distribution of q for each candidate number of clusters k allowed us to assess Z-scores observed-data clustering solution, defined as:

$$Z_k = \frac{q_{obs} - \overline{q}_{null}}{\sqrt{\frac{\sum_1^I (q_{null} - \overline{q}_{null})^2}{I}}}$$

where q_{obs} is the quality for the observed solution, q_{null} is the quality for the permuted-data solution for one iteration, and I is the number of iterations (10,000). Fig. S5B shows Z_k on the y-axis plotted against candidate choices for k on the x-axis. The highest Z-value was found for 2 clusters, which we used as our estimate of k. The permuted-data distribution of q is shown for the 2-cluster solution in Fig. S5C, and q for the observed-data solution is shown by the vertical black line. The significance of the results ($p < .0001$, $Z = 6.24$) indicates that there were at least two separable networks of interconnected mediators. However, we did not test the significance of the difference between 2 and other numbers of clusters; other choices of k (e.g., 3 networks) may be reasonable candidates as well, though we note that the 4 and 5 cluster solutions provided poor fits.

Identification of additional mediated regions in the frontal cortex (Analysis step 5).

Though the choice of right VLPFC as a predictor was motivated by theoretical considerations, it is not likely to be unique in its relationship with subcortical affective pathways, given that activity in multiple frontal regions predicted reappraisal success. In a final analysis, we used the MEPM approach to localize frontal regions whose relationship with reappraisal success was mediated by subcortical activity. Two separate analyses were conducted with reappraisal

success as the outcome. In this analysis, both left NAC and amygdala were specified as mediators, and reappraisal success was specified as the outcome. Average activity values in each region from the previous analysis were used for the mediators. We performed a voxel-wise search for frontal regions whose [ReappNeg – LookNeg] contrast values were mediated (significant *a*b* effect) by each subcortical region.

To constrain the search to frontal regions, we created a mask of frontal regions labeled as "frontal" in the International Consortium for Brain Imaging (ICBM) single-subject atlas ((Mazziotta et al., 2001); http://www.loni.ucla.edu/ICBM/; an average of 27 T1-weighted images of a single subject registered to MNI space and manually labeled) and included the gyrus rectus and cingulate gyrus as labeled for more complete coverage. We smoothed the resulting mask with a 3 mm kernel thresholded at a value of 0, and searched for regions with a significant mediation (*a*b*) effect within this mask. For this exploratory analysis, we report results significant at $p < .001$ with a 3-contiguous-voxel extent or $p < .005$ with a 10-voxel extent.

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