Supporting Information

Heller et al. 10.1073/pnas.0910651106

SI Text

Participants. Because depression is a heterogeneous disorder (e.g., 1), we over-recruited the MDD group in an attempt to ensure sufficient power to address the underlying neural abnormalities subserving the binary category of MDD.

Task. Negative pictures were selected according to the IAPS norms to be both unpleasant (1, most unpleasant, to 9, most pleasant; M = 2.95; SD, 0.87) and arousing (1, least arousing, to 9, most arousing; M = 5.44; SD, 0.80), whereas positive images were pleasant (M = 7.13; SD, 0.62) and arousing (M = 5.28; SD, 0.58) Stimuli were presented using E-Prime software (Psychology Software Tools) via a fiber-optic goggle system (Avotec) with a screen resolution of 800 × 600 pixels.

Behavioral Measures. Reaction time to image onset, as well as pupil dilation measures were acquired. Assessing pupil dilation provides an unobtrusive measure of autonomic arousal (2) with pupil constriction driven primarily by the parasympathetic branch of the autonomic nervous system (ANS), and pupil dilation primarily reflecting activity of the sympathetic branch. Pupil dilation is thus an indicator of increased cognitive and attentional load during effortful top-down regulation (3–5). To assess autonomic arousal associated with effortful reappraisal, we measured the extent to which the pupil dilated during the active reappraisal period of each stimulus trial. Based on our previous research showing pupil dilation to be a sensitive index of the cognitive effort during reappraisal in healthy individuals (6, 7), we examined whether pupil dilation changed across the scan session for either of the groups.

Pupil Data Acquisition and Analysis. Horizontal pupil diameter data were acquired continuously at 60 Hz using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments), which was interfaced with the fiber optic goggle system. Pupil data from four controls and six depressed individuals were not usable because of technical problems. Pupil dilation data were processed using algorithms written by Siegle et al. (4) with MatLab software (MathWorks), modified in our laboratory. Blinks were identified and eliminated using local regression slopes and amplitude thresholds. Data were smoothed with a five-sample rolling average and linearly detrended over each scan run. For successive 500-ms bins in each trial, the proportion of time that the eye was open and mean pupil diameter were calculated. Pupil values were then range-corrected to standardize according to the pretrial maximally dilated pupil diameter and the maximally constricted pupil diameter in the 2 s after picture onset [(current pupil diameter − minimum pupil diameter)/(maximum pupil diameter − minimum pupil diameter)]. Data were averaged across a 5 s interval starting 1 s after instruction and continuing until picture offset (the reappraisal period). Data were then analyzed using mixed-model GLM (subject as a random factor nested within the fixed factor group, and reappraisal as a within subject fixed factor).

Image Acquisition. Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems) equipped with a standard clinical whole-head transmit-receive quadrature head coil. Functional images were acquired using a T2*-weighted gradient-echo, echo planar imaging (EPI) pulse sequence [33 sagittal slices, 4-mm thickness, 1-mm interslice gap; 64 × 64 matrix; 240 mm field of view (FOV); repetition time (TR)/echo time (TE)/Flip, 2,000 ms/30 ms/60°; 190 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 × 256 in-plane resolution; 240 mm FOV; 124 × 1.1-mm axial slices).

Image Analysis. Our single subject GLM included covariates intended to model each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction), and for both the early and late phases of the scanning session (early: runs 1–3; late: runs 4–6) as well as six motion estimate covariates. We also included a second-order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of five sine basis functions to produce separate estimated hemodynamic response functions (HRFs) for each trial type. The estimated HRFs were converted to percentage signal change values, and within-subjects contrasts were calculated between the enhance and suppress conditions for positive pictures (i.e., positive enhance – positive suppress; 1st Half, 2nd Half), averaged across time points corresponding to the peak hemodynamic response during the regulation period (8–14 s after stimulus onset). Contrasts were normalized to Talairach space and smoothed using a 5 mm full-width at half-maximum Gaussian filter.

Following single subject GLM analysis, we normalized and smoothed the maps and subsequently contrasted the "enhance" and "suppress", as well as the "enhance" vs. "attend" brain maps for each subject prior to performing random effects group analyses. We elected not to use the amplitude modulator for all analyses because the time course plots as well as the connectivity analyses required splitting the scan session into discrete sections. We also performed the same analysis for negative stimuli in order to compare the group differences in neural activity to positive vs. negative slides.

Connectivity Analysis. Connectivity analyses were performed using the beta series correlation method described in (8). Briefly, this approach requires that separate parameter estimates (beta values) be computed for each trial. Trials were modeled as having two components: one component occurring at the onset of the image presentation—before regulation instruction; the second component being placed 6 s after image onset, modeling the neural response to the regulation of emotion. BOLD responses during stimulus onset and regulation periods were modeled as brief epochs of neural activity convolved with an in-house canonical hemodynamic response function (HRF), obtained by averaging empirically derived HRFs (8). The onsets of temporally adjacent covariates were spaced at least 4 s apart (9) to minimize the contamination of the regulation period covariate by residual stimulus onset period activity. This approach has been used to successfully model separate components of a trial in numerous published studies (10–12). The least squares solution of the GLM yielded a set of 236 beta values of interest (2 trial components × 2 picture valences × 3 regulation instructions [24 enhance, suppress trials; 12 attend trials). Nuisance covariates included the second-order polynomial used to model the baseline and slow signal drift, as well as six motion estimate covariates. Beta values were sorted by trial type so that a series of betas exist for each component of each condition. The extent to which brain regions interact during a particular task stage is quantified by the extent to which their respective beta series from that condition are correlated.

Correction for Multiple Comparisons. With the AlphaSim clustering technique, the overall family-wise error rate (FWE) is controlled by simulating null data sets with the same spatial autocorrelation as

found in the residual images and creating a frequency distribution of different cluster sizes. Clusters with a size that exceeds the minimum cluster size corresponding to the a priori chosen FWE are retained for additional analysis. This cluster-based method of thresholding, analogous to cluster-based thresholding using Gaussian Random Field Theory (13), is an alternative to voxel-based correction and is often more sensitive to activation when one can reasonably expect multiple contiguous activated voxels (14, 15).

1. Drevets WC, Savitz J, Trimble M (2008) The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr* 13:663–681.
2. Loewenfeld IE (1993) *The Pupil: Anatomy, Physiology, and Clinical Applications* (Iowa State Univ Press, Ames, IA).
3. Kahneman D, Beatty J (1966) Pupil diameter and load on memory. *Science* 154:1583–1585.
4. Siegle GJ, Steinhauer SR, Stenger VA, Konecky R, Carter CS (2003) Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. *NeuroImage* 20:114–124.
5. Ohira H, et al. (2006) Association of neural and physiological responses during voluntary emotion suppression. *NeuroImage* 29:721–733.
6. Urry HL, et al. (2006) Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci* 26:4415–4425.
7. van Reekum CM, et al. (2007) Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *NeuroImage* 36:1041–1055.
8. Rissman J, Gazzaley A, D'Esposito M (2004) Measuring functional connectivity during distinct stages of a cognitive task. *NeuroImage* 23:752–763.
9. Zarahn E, Aguirre G, D'Esposito M (1997) A trial-based experimental design for fMRI. *Neuroimage* 6:122–138.
10. Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J Neurosci* 24:3944–3952.
11. Postle BR, Zarahn E, D'Esposito M (2000) Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. *Brain Res Brain Res Protoc* 5:57–66.
12. Ranganath C, Cohen MX, Dam C, D'Esposito M (2004) Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *J Neurosci* 24:3917–3925.
13. Friston KJ Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC (1993) Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp* 1:210–220.
14. Forman SD et al. (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn Reson Med* 33:636–647.
15. Petersson KM, Nichols TE, Poline JB, Holmes AP (1999) Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. *Philos Trans R Soc London Ser B* 354:1261–1281.

Table S1. LNAcc connectivity; weighted Group × Time effect for "enhance" condition

Location	Cluster maximum			No. of voxels	Cluster volume, mm^3	*F* value	*P* value
	x	*y*	*z*				
L middle frontal gyrus (8)	−37	13	59	24	192	11.95	8.4×10^{-4}

$k > 15$ voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

Table S2. Group × Time effect for ''attend'' vs. baseline

Location	Cluster maximum			No. of voxels	Cluster volume, mm³	*F* value	*P* value
	x	*y*	*z*				
Medial frontal gyrus (8/32)	3	27	40	446	3,568	19.59	2.7×10^{-5}
Posterior cingulate (30)	−3	−49	20	272	2,176	15.61	1.5×10^{-4}
L putamen	−19	7	8	223	1,784	22.22	8.8×10^{-6}
R middle frontal Gyrus (44/48)	45	15	26	192	1,536	19.68	2.6×10^{-5}
R thalamus	7	−17	6	143	1,144	19.03	3.4×10^{-5}
R lingual gyrus	21	−53	0	121	968	14.21	2.9×10^{-4}
R paracentaral gyrus	3	−23	46	113	904	18.96	3.5×10^{-5}
R anterior insula	31	25	10	76	608	18.24	4.8×10^{-5}
L precentral gyrus (6)	−45	−1	48	70	560	17.84	5.7×10^{-5}
Medial frontal gyrus (10/32)	−3	49	18	63	504	21.41	1.2×10^{-5}
R superior frontal gyrus (6)	5	11	62	63	504	17.00	8.3×10^{-5}
R precentral gyrus (4)	45	−11	44	60	480	13.80	3.5×10^{-4}
L hippocampus	−23	−15	−12	59	472	23.53	5.1×10^{-6}
L inferior frontal gyrus (47)	−33	31	2	58	464	19.10	3.3×10^{-5}
R middle temporal gyrus (21)	63	−21	−6	54	432	16.82	9.0×10^{-5}

$k > 50$ voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

Table S3. Group × Time effect for ''enhance'' vs. ''attend'' condition

Location	Cluster maximum			No. of voxels	Cluster volume, mm^3	*F* value	*P* value
	x	*y*	*z*				
Lingual gyrus (18)	15	−85	−8	45	360	13.51	4.0×10^{-4}
Inferior lingual gyrus (17)	−1	−81	−12	20	160	12.29	7.1×10^{-4}
L postcentral gyrus (48)	−53	−15	14	18	144	11.97	8.3×10^{-4}

$k > 15$ voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

Table S4. Group Test for ''enhance'' vs. ''suppress'' condition. (Aggregated across time)

Location	Cluster maximum			No. of voxels	Cluster volume, mm^3	*t* value	*P* value
	x	*y*	*z*				
L superior temporal gyurs (22, 42)	−57	−25	12	126	1,008	4.01	2.4×10^{-4}
L cingulate gyrus (23)	−13	−27	36	110	880	4.08	2.0×10^{-4}
R precuneus (7)	7	−61	52	69	552	3.76	5.2×10^{-4}
L insula (13)	−31	5	14	67	536	4.09	1.9×10^{-4}
R precuneus (7)	11	−73	44	63	504	4.33	9.1×10^{-5}

All clusters correspond to Controls > Depressed. No voxels were significant for Depressed > Controls. $k > 50$ voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *t* and *P* values correspond to the peak.

Table S5. Group Test for ''enhance'' vs. ''attend'' condition. (Aggregated across time)

	Cluster maximum						
Location	*x*	*y*	*z*	No. of voxels	Cluster volume, mm^3	*t* value	*P* value
L post central gyrus	−54	−22	20	65	520	3.87	3.8×10^{-4}

All clusters correspond to Controls > Depressed. No voxels were significant for Depressed > Controls. k > 50 voxels. L, left; R, right; the *x*, *y*, *z* coordinates use the Talaraich system. *t* and *P* values correspond to the peak.