Increased Amygdala and Decreased Dorsolateral Prefrontal BOLD Responses in Unipolar Depression: Related and Independent Features

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Background: *Major depressive disorder is characterized by increased and sustained emotional reactivity, which has been linked to sustained amygdala activity. It is also characterized by disruptions in executive control, linked to abnormal dorsolateral prefrontal cortex (DLPFC) function. These mechanisms have been hypothesized to interact in depression. This study explored relationships between amygdala and DLPFC activity during emotional and cognitive information processing in unipolar depression.*

Method: *Twenty-seven unmedicated patients with DSM-IV unipolar major depressive disorder and 25 never-depressed healthy control subjects completed tasks requiring executive control (digit sorting) and emotional information processing (personal relevance rating of words) during event-related functional magnetic resonance imaging (fMRI) assessment.*

Results: *Relative to control subjects, depressed subjects displayed sustained amygdala reactivity on the emotional tasks and decreased DLPFC activity on the digit-sorting task. Decreased relationships between the time-series of amygdala and DLPFC activity were observed within tasks in depression, but different depressed individuals showed each type of bias.*

Conclusions: *Depression is associated with increased limbic activity in response to emotional information processing and decreased DLPFC activity in response to cognitive tasks though these may reflect separate mechanisms. Depressed individuals also display decreased relationships between amygdala and DLPFC activity, potentially signifying decreased functional relationships among these structures.*

Key Words: Amygdala, DLPFC, emotion, executive control, fMRI, regulation

Relationships between two aspects of unipolar depression subserving cognitive and emotional information processing were examined in this study. The first is increased and sustained amygdala activity (Abercrombie et al 1998; Drevets 1999; Drevets et al 1992) especially in response to emotional information (Sheline et al 2001; Siegle et al 2002). Because the amygdala is important for recognition and generation of emotion (LeDoux 1996), this phenomenon may underlie involuntary elaboration on negative topics, which is linked to depressive severity and persistence (Ingram 1984; Nolen-Hoeksema et al 1993; Teasdale 1988). The second aspect involves disruptions of executive control (Goodwin 1997; Ottowitz et al 2002), associated with the dorsolateral prefrontal cortex (DLPFC). Disrupted DLPFC activity has been observed in depression (Baxter et al 1989; Bench et al 1993; Davidson et al 2000; Drevets 1999; Harvey et al 2005; Mayberg et al 1999). These mechanisms may interact: if executive control is necessary for emotion regulation (Metcalfe and Mischel 1999) and, specifically, if the DLPFC initiates a process of emotion regulation that results in inhibition of limbic regions such as the amygdala (Davidson 2000, 2003; Drevets and Raichle 1998; Mayberg et al 1999; Ochsner et al 2002; 2004), sustained emotional reactivity might result indirectly from decreased DLPFC function. Indeed, increased and sustained amygdala activity has been linked to decreased DLPFC activity in healthy (Dolcos and McCarthy 2006) and depressed individuals (Siegle et al 2002).

Yet relationships between DLPFC and amygdala function in depression have not yet been examined explicitly because the same depressed individuals have not been imaged during tasks requiring DLPFC function (executive control) but not emotional processing, as well as emotional information processing tasks. Although initial results support behavioral deficits in both emotional information processing and executive control in the same individuals (Langenecker et al 2005), these behavioral deficits were not correlated. Neuroimaging may provide a more sensitive measure of these task-related relationships.

Importantly, there are not direct connections from the DLPFC to the amygdala. Rather, the DLPFC's influence may be mediated by connections from the ventromedial prefrontal cortex (VMPFC), the rostral anterior cingulate gyrus, and the orbital frontal cortex to the amygdala (Ghashghaei and Barbas 2002; Ray and Price 1993). These regions have been proximally identified with emotion regulation. Inhibitory connections from the amygdala back to multiple prefrontal regions (Amaral et al 1992; Perez-Janaray and Vives 1991) could also allow excessive amygdala activity to contribute to decreased prefrontal activity (Moore and Grace 2000), even without endogenously disrupted DLPFC activity.

Thus, there are multiple possible roles for the DLPFC in increased amygdala activity in depression including 1) poor ability to mobilize DLPFC resources for executive functioning, including initiating emotion regulation. In this case, the same individuals with disruptions of DLPFC activity on cognitive tasks should display sustained amygdala activity during emotional information processing. 2) If increased amygdala activity leads to inhibition of the DLPFC, DLPFC impairment would be apparent primarily on emotional information processing tasks. 3) Potentially, DLPFC function is adequate in depression, but its regulatory communication with the amygdala is impaired, possibly through decreased communication between the DLPFC and proximally inhibitory regions such as the VMPFC. 4) Disruptions of emotional information processing and executive control could be independent. In this case, different individuals should display

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Table 1. Subject Demographics and Behavioral Data

Measure	Depressed	Control	Significant Difference
N	30[a]	28[a]	*ns*
Male, *n*	13	11	*ns*
Caucasian, *n*	20	18	*ns*
Age range	18–55	19–50	—
Age, M(SD)	38.0 (12.7)	31.5 (9.0)	$t(52.1) = -2.23$, $p = .03$
Years Education, M(SD)	14.6 (2.8)	15.8 (2.0)	*ns*
BDI, M(SD)	26.8 (13.3)	4.6 (7.6)	*ns*
Median No. Depressive Episodes	15 or more	0	—
NAART VIQ equivalent	107.2 (9.0)	107.4 (8.0)	*ns*
Post Scan Emotion Ratings of Employed Words (1 = very negative and 7 = very positive)			
Positive words, M(SD)	5.8 (.68)	6.1 (.41)	$t(46.4) = 2.2$, $p = .03$
Negative words, M(SD)	2.31 (.70)	2.00 (.49)	*ns*
Neutral words, M(SD)	4.06 (.29)	4.16 (.39)	*ns*
Reaction Times on the PRRT (msec)			
Positive words, M(SD)	954 (353)	1207 (618)	*ns*
Negative words, M(SD)	1014 (283)	1297 (557)	$t(40.7) = -2.33$, $p = .02$, Difference = 283 msec
Neutral Words M(SD)	1065 (352)	1147 (481)	*ns*
Digit-Sorting Percent Correct			
Three Digits, M(SD)	.91 (.18)	.86 (.23)	—
Four Digits, M(SD)	.89 (.22)	.93 (.11)	—
Five Digits, M(SD)	.87 (.23)	.89 (.17)	—

BDI, Beck Depression Inventory; NAART, North American Adult Reading Test; *ns*, not significant; VIQ, Verbal Intelligence Quotient.
[a]All participants completed the first task (digit sorting), but due to time constraints, other tasks were not administered to some participants. Reported demographics are for the digit-sorting task. The personal-relevance rating task was completed by a subset of participants including 21 control participants (9 male, 12 Caucasian, Mean age = 36, Mean BDI = 3.7) and 20 depressed participants (9 male, 13 Caucasian, Mean age = 38.8, Mean BDI = 27.3).

disruptions of amygdala activity during emotional information processing and DLPFC activity on cognitive tasks.

To examine these possibilities, unmedicated depressed and healthy participants completed tasks designed to provoke limbic reactivity to emotional stimuli and DLPFC activity during an executive-control/working memory task. Our questions included the following: 1) Do unmedicated depressed individuals display increased and sustained amygdala activity to negative words (our previous work Siegle et al 2002) had examined only unsuccessfully medicated depressed individuals)? 2) Do the same depressed individuals who display increased amygdala activity following emotional stimuli also display disruptions of DLPFC activity on a nonemotional working memory task? 3) Is there evidence of disruptions in the relationship of amygdala and DLPFC function during emotional information processing in depression?

This last question was addressed in two ways. First, we examined whether the entire amygdala and DLPFC time-series covaried. Similar research has used variants of zero-order correlation (e.g., Anand et al 2005); additionally, to capture lagged or delayed relationships (e.g., due to emotion regulation), we employed lagged cross-correlations. Second, relationships of task-related responses within individuals (i.e., are each participant's large amygdala responses to negative words associated with large DLPFC responses?) were examined. Similar research has used correlations of peak responses (Rissman et al 2004). To detect relationships of other features of the waveforms (e.g., relating sustained amygdala activity to peak DLPFC activity), we employed functional canonical correlation.

Based on previous data and computational modeling (Siegle 1999; Siegle et al 2002), we hypothesized that depression would be associated with increased and sustained amygdala activity to emotional stimuli and decreased DLPFC activity during the cognitive task. We further hypothesized that these mechanisms would be related; sustained amygdala activity would be explained by decreased DLPFC or decreased strength of coupling between DLPFC and amygdala activity within participants. We did not hypothesize that there would be a negative correlation between DLPFC and amygdala activity on tasks involving emotional stimuli; if the DLPFC is important for emotion regulation (e.g., Ochsner et al 2004), it could become active following amygdala activity, leading to a positive correlation. To examine mediating roles for a relevant region of the VMPFC in this process, activity in the rostral anterior cingulate cortex during emotional information processing and functional connectivity (i.e., within-task relationships) of the amygdala and DLPFC to the rostral anterior cingulate in regions showing group differences were also examined.

Methods and Materials

Participants

Thirty patients with major depressive disorder and 28 healthy control subjects (no current or historical Axis I disorder via SCID [First et al 1996] diagnoses; demographics in Table 1) participated. Participants described no health problems, eye problems, or psychoactive drug abuse in the past 6 months. Participants with a history of psychosis, manic, or hypomanic episodes, or antidepressant use within 2 weeks of testing (6 weeks for fluoxetine) were excluded. Participants reported no excessive use of alcohol in the past 6 months (one participant's data was ambiguous, and he could not be recontacted). All participants scored in the normal range on a cognitive screen, (Nelson and Willison 1991); verbal IQ-equivalent > 80. One control and one depressed participant's data were eliminated based on noncorrectable artifacts.

Procedure

Participants attended three appointments within three weeks: 1) signing internal review board–approved consent forms, com-

pleting a SCID, and taking a vision test; 2) tasks during psychophysiologic assessment; 3) the same tasks during functional magnetic resonance imaging (fMRI) assessment. A digit-sorting task was administered first to avoid confounding by previous emotional responsivity, followed by other tasks in counterbalanced order; only one of the other tasks is reported here.[1] The Beck Depression Inventory II (BDI; Beck et al 1996) was administered following fMRI assessment to assess depressive severity.

Apparatus

Either 34 or 30 3.2-mm slices were acquired parallel to the anterior–posterior commissure line using a reverse spiral pulse sequence (3-T GE scanner, T2*-weighted images depicting blood oxygen level–dependent contrast; repetition time = 1500 msec, echo time = 25 msec, field of view = 24 cm, flip angle = 60°), yielding 12 whole-brain images per 18-sec trial. The change from 34 slices (21 control subjects, 19 depressed) to 30 slices (7 control subjects, 11 depressed) was to reduce scanner overheating and had no discernable effects on the obtained signal.

Stimuli were displayed in black on a white background via a back-projection screen (.88° visual angle). Responses were recorded using a Psychology Software Tools glove. Mappings of glove buttons to responses were counterbalanced across participants and displayed throughout the tasks (e.g., "YN" representing "Yes" on the index finger and "No" on the ring finger).

Tasks During fMRI Assessment

Personal Relevance Rating Task (PRRT). In 60 slow-event related trials, participants viewed a fixation cue (1 sec) followed by a positive, negative, or neutral word (200 msec), followed by a mask (row of Xs; 10.8 sec). Participants pushed a button for whether the word was relevant, somewhat relevant, or not relevant to them or their lives, as quickly and accurately as they could. Participant-generated and normed words were used as in our previous studies of depression (Siegle et al 2001, 2002, 2003a, submitted). Ten positive, 10 negative, and 10 neutral words balanced for arousal, normed affect, word frequency, and word length were chosen using a computer program (Siegle 1994) that drew words from the ANEW (Bradley and Lang 1997) master list. Before the experiment, participants also generated "10 personally relevant negative words that best represent what you think about when you are upset, down, or depressed," "10 personally relevant positive words that best represent what you think about when you are happy or in a good mood," and "10 personally relevant neutral (i.e., not positive or negative) words that best represent what you think about when you are neither very happy nor very upset, down, or depressed."

Digit-Sorting. In 36 slow-event-related trials, participants viewed a fixation mask (1 sec) followed by a set of three, four, or five digits (2 sec), followed by another fixation mask (5 sec). Then, a "target" digit from the previously presented set appeared (10 sec). Participants were told that they should read the digits from left to right, put them in numerical order in memory, and remember the middle digit in the sorted list. With four digits, the higher of the middle digits was to be remembered. When the target appeared, they were to push a button indicating whether the target was the remembered middle digit, as quickly and accurately as they could. Participants were asked not to use strategies such as sorting the digits by moving their eyes on the screen because we were examining the process of sorting items in memory. This task selectively activated the DLPFC in a subset of the healthy individuals in this study (Siegle et al 2003b).

Data Selection and Cleaning

Data Preparation. Harmonic means of reaction times were calculated within subjects for each condition because harmonic means minimize biasing effects of long reaction times better than other measures of central tendency (Ratcliff 1993). Outliers outside 1.5 times the interquartile range from the median were rescaled to this threshold. fMRI analyses were conducted via locally developed NeuroImaging Software (NIS) and AFNI (Cox 1996). Following motion correction using the six-parameter AIR algorithm (Woods et al 1993), linear trends within runs were removed to eliminate effects of scanner drift. Outliers $>$ Md $\pm$ 2.2IQR were replaced with Md $\pm$ 2.2IQR. The fMRI data were temporally smoothed (five-point middle-peaked filter), cross-registered to a reference brain using the 12 parameter AIR algorithm, and spatially smoothed (6-mm full width at half maximum).

Anatomic Region Identification. The amygdala was identified anatomically in the functional data because it is small and boundaries with functionally distinct regions (e.g., the hippocampus) are hard to identify on functional scans. Anatomically identified DLPFC and cingulate regions were not used because they encompass large regions of potential functional heterogeneity and because relevant subregions are reliably differentiated on exploratory analyses of tasks involving cognitive control and emotional information processing.

Thus, the amygdala was traced on the reference brain's high-resolution structural MRI as in our previous studies in which we have established adequate intra- and interrater reliability (Siegle et al 2002; boundaries: posterior, the alveus of the hippocampus; anterior, 2 mm from the temporal horn of the lateral ventrical; superior, ventral horn of the subarachnoid space [SS]; inferior, most dorsal finger of the white matter tract under the horn of the SS; lateral, 2 mm from the surrounding white matter; mesial, 2 mm from the SS).

Exploratory Region Identification. Data were analyzed for trials with 50- to 5000-msec reaction times. For the digit-sorting task only, correct trials were used. Random-effects whole-brain voxelwise analyses of variance (ANOVAs) using subject as a random factor, and group, scan, and valence as fixed factors identified regions with significant group $\times$ scan or group $\times$ scan $\times$ condition interactions subject to empirically derived contiguity thresholding (Cox 1996) ($p < .001$ uncorrected; $p < .05$ corrected). To control for temporal autocorrelation, anatomic and empirically detected regions were further subjected to mixed-effects analyses of percent-change using scan and condition as repeated measures and subject as a random factor, assuming an AR1 covariance structure using restricted maximum likelihood estimation (REML). For the digit-sorting task regions were further restricted to those in which the depressed, the control, or both groups displayed higher activity in the five-digit than the three-digit condition to eliminate differences solely in negative-going responses.

Determination of Relationships Between Amygdala and DLPFC Activity. To determine whether emotion-related amygdala activity (9 sec following the onset of negative words on the PRRT) and cognition-related DLPFC activity (9 sec following the

[1]The full battery of tasks, to be reported on in separate publications, included a personal relevance rating task (described in the following sections), a Stroop task, a cued-reaction-time task, an emotional Stroop task (for a few participants), and an alternating digit-sorting/emotion-identification task. Each of these tasks used emotional words.

onset of five-digit trials on the digit-sorting task) explained unique variance in depression status, logistic regression was employed. This technique reveals unique and overlapping contributions of continuous independent variables to variance in a binary dependent variable.

To examine trial-independent relationships of DLPFC and amygdala activity during emotional information processing, lagged cross-correlations within the PRRT in which z′ transformed correlates were subjected to *t* tests for group differences at each lag were used.

To examine associations between amygdala and DLPFC responses to negative words, functional canonical correlation (e.g., He et al 2004; Ramsay and Silverman 2005) was used. Functional (i.e., interpolated) versions of each participant's amygdala and DLPFC trial-related responses were created, and a variant of the canonical correlation between these functional responses was computed (as in Ramsay and Silverman 2005). Functionalizing step: the amygdalar and DLPFC percent-change responses for each trial for each individual was fit separately to a b-spline with seven basis functions. Only scans 2–8 were used because the values of the relative responses were always zero on the initial scan. This step converted the vector of seven responses for the amygdala and DLPFC into a representation that smoothly varies from scan to scan. Canonical correlation step: to relate the functionalized versions of the amygdala and DLPFC time-series within individuals, a variation of canonical correlation was used in which the cost function penalizes the sum of the variance and squared curvature in the resulting weighting functions, as in equation 1, from (Ramsay and Silverman 2005, p. 206). Constraining the canonical correlation by curvature yields two smooth weighting functions, one for the amygdala and one for the DLPFC, consistent with the slowly varying nature of the hemodynamic response.

$$r(am_w, pfc_w) = \frac{\mathrm{cov}\left(\int am_w am_i, \int pfc_w pfc_i\right)^2}{\left\{\mathrm{var}\left(\int am_w am_i\right) + \lambda\|D^2 am_w\|^2\right\}\left\{\mathrm{var}\left(\int pfc_w pfc_i\right) + \lambda\|D^2 pfc_w\|^2\right\}} \quad (1)$$

Here, am_w is the weight vector for the amygdala. am_i refers to each amygdala waveform. Similarly, pfc_w is the weight vector for the DLPFC. pfc_i refers to each DLPFC waveform. λ is smoothing a parameter, chosen via cross-validation, that describes the extent to which curvature constraint is emphasized. $\|D^2 am_w\|^2$ and $\|D^2 pfc_w\|^2$ represent the roughness or integrated squared curvature of the amygdala and DLPFC response waveforms respectively.

Results

Behavioral Data

Participants rated words consistent with their assigned categories, $F(2,52) = 371.2$, $p < .005$, $\eta^2 = .94$, although depressed individuals rated positive words as less positive than control subjects, valence × group $F(2,52) = 3.08$, $p = .05$, $\eta^2 = .11$ (Table 1). There were no main effects or interactions with group or valence on PRRT reaction times ($p > .15$).

There were no group or condition-related effects on reaction time for digit sorting; these were not expected because responses were to targets occurring seconds after digit sorting was completed. There were also no main effects or interactions of group or condition on signal detection rates, which were high ($d' > 3.75$; Table 1). Depressed individuals incorrectly answered nonsignificantly more items as the conditions increased in difficulty, whereas errors were uniform for control subjects, digits × group linear contrast $F(1,58) = 2.9$, $p = .09$, $\eta^2 = .04$.

The fMRI analyses were organized around the questions described earlier.

1. Do unmedicated depressed individuals display increased and sustained amygdala activity to negative words?

In the anatomically defined amygdala regions, depressed participants displayed increased and sustained bilateral activity to negative words compared with healthy participants on the PRRT, group × scan: left: $F(7,110.4) = 2.27$, $p = .03$, $\eta^2 = .13$, right: $F(7,108.2) = 4.8$, $p < .0005$, $\eta^2 = .24$ (Figure 1; significant scans highlighted and listed in Table 2).

Figure 2 and Table 3 show multiple regions from the exploratory analyses that displayed significant group × scan or group × scan × valence effects on the PRRT. As shown in Figure 2, depressed individuals displayed increased sustained responses relative to control subjects in multiple regions associated with emotional and visual processing as well as depression. In particular, depressed individuals displayed increased and sustained left amygdala activity, compared with control participants, that were not moderated by valence, group × scan: left: $F(7,466.42) = 5.07$, $p < .0005$, $\eta^2 = .07$.

Depressed individuals displayed increased and sustained activity, particularly to negative versus neutral words com-

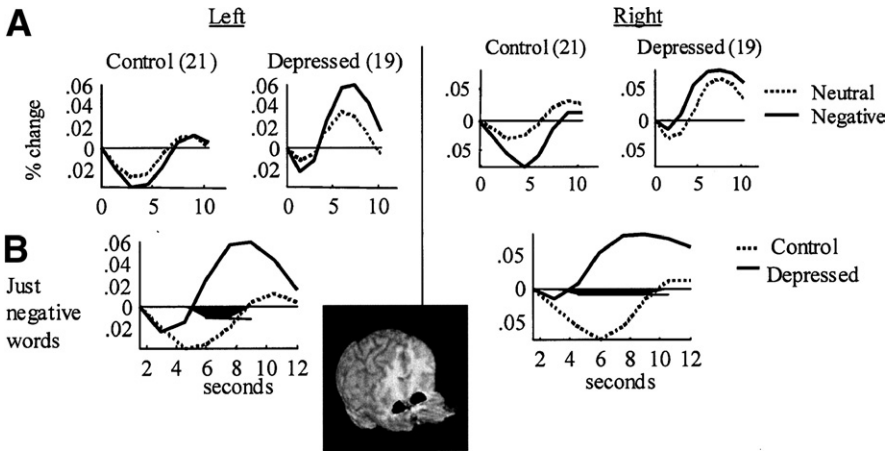


Figure 1. Personal relevance rating task: comparison of blood oxygen level–dependent signal in response to negative words in the traced amygdala in depressed and control participants. Highlighted regions represent significant differences, dark = $p < .05$, light = $p < .1$. The y axes represent % change from a prestimulus baseline (scan 1). The x axis is seconds, which varied between tasks. Depressed individuals displayed increased and sustained amygdala activity to negative words throughout trials. (Highlighted regions of significant differences shown on Table 2, rows 1 and 6.)

Table 2. Temporal Windows of Significant Effects Relative to Stimulus Onset

Task	Effect	Significant Differences: Amygdala	Significant Differences: DLPFC
PRRT	1. Group differences in negative words	Anatomically defined left: 6.00 to 9.00 sec: $t(38) = -2.18, p = .04, D = -.06, d = -.69$ Anatomically defined right: 4.50 to 10.50 sec: $t(38) = -2.73, p = .01, D = -.10, d = -.86$ Empirically detected left: 6.00 to 10.50 sec: $t(38) = -2.57, p = .01, D = -.11, d = -.81$	Empirically detected left from digit sorting task: **7.50 to 10.50 sec: t(38) = 1.95, p = .06, D = .06%, d = .62**
	2. Group difference in negative words, age-matched subsamples	Anatomically defined left: **nonsignificant effect shown for correspondence of effect size: 6.00 to 9.00 sec: t(31) = −1.44, p = .16, D = −.05, d = − .50** Anatomically defined right 4.50 to 12.00 sec: $t(31) = -2.35, p = .03, D = -.09, d = -.82$ Empirically detected left: 7.50 to 10.50 sec: $t(31) = -2.00, p = .05, D = -.11, d = -.70$	Empirically detected left from digit sorting task: **4.50 to 10.50 sec t(31) = 2.04, p = .05, D = .06, d = .71**
Digit Sorting	4. Group differences in five-digit condition	None	Empirically detected left: 4.50 to 18.00 sec: $t(54) = 3.44, p < .005, D = .11, d = .92$ Anatomically defined left: 4.50 to 18.00 sec: $t(54) = 3.65, p < .005, D = .11, d = .98$ Anatomically defined right: 4.50 to 9.00 sec: $t(54) = 2.18, p = .03, D = .07, d = .58$ 15.00 to 18.00 sec: $t(54) = 2.84, p = .01, D = .08, d = .76$
	5. Group differences in five-digit condition, age-matched, subsample	None	Empirically detected left: 3.00 to 18.00 sec: $t(47) = 3.72, p < .0005, D = .12, d = 1.07$ Anatomically defined left: 4.50 to 18.00 sec: $t(47) = 3.66, p < .005, D = .12, d = 1.05$ Anatomically defined right: 3.00 to 9.00 sec: $t(47) = 2.29, p = .03, D = .07, d = .66$ 15.00 to 18.00 sec: $t(47) = 2.52, p = .02, D = .07, d = .72$

D = difference in means (%); d = Cohen's effect size; PRRT, personal relevance rating task.
Not bold type: $p < .05$. Bold: $p < .1$ if present; bold: $p < .2$ examined as part of planned contrasts to illustrate relevant effects sizes.

pared to controls, in other regions associated with depression, particularly a rostral anterior cingulate region (BA24; circled in Figure 2; significant group differences 9–12 sec following stimulus onset, $t(38) = -2.2$, $p = .04$, D = 1.14%, $d = -.69$). As other detected regions were not directly addressed by our a priori questions, they are not analyzed further in this manuscript.

2. Do the same depressed individuals who display increased amygdala activity following emotional stimuli also display decreased DLPFC control?

DLPFC Group Differences During the Digit-Sorting Task. Figure 3 and Table 3 show regions from the exploratory analyses that displayed significant group × scan or group × scan × condition effects on the digit-sorting task. As shown in the circled region, depressed individuals displayed decreased activity relative to control participants in a left DLPFC region (middle frontal gyrus touching Brodmann's area [BA] 9 and 46) that was not qualified by the number of digits, group × scan $F(11,874.5) = 5.49$, $p < .0005$, $\eta^2 = .06$; group × scan × condition $p = .87$. Yet the area under the curve in this region was particularly low in depressed individuals in the five-digit condition, group × condition $F(2,1858.6) = 13.2$, $p < .0005$, $\eta^2 = .01$. Both groups displayed inverse hemodynamic responses in the amygdala (e.g., Figure 3, right; scan main effect $F(11,1738.1) = 11.3$, $p < .0005$), consistent with cortical inhibition of the amygdala, but there were no main effects or interactions of group with scan or condition ($p > .2$).

DLPFC Activity During the PRRT. Activity in the empirically detected DLPFC region from the digit-sorting task was decreased across conditions during the PRRT in the depressed group, group × scan $F(7,397.121) = 4.04$, $p < .0005$, $\eta^2 = .06$ as shown in Figure 4 and Table 2. There were no main effects or interactions with condition, $p > .5$.

Relationship of Digit-Sorting DLPFC Activity to PRRT Amygdala Activity. Although the groups showed expected patterns on both tasks, indices of empirically identified amygdala function on the PRRT and DLPFC function on the five-digit condition of the digit-sorting task were weakly related across subjects: $r = -.05$, $p = .75$; Yet logistic regressions on group membership revealed independent contributions for each index. Wald tests were used to test partial regression coefficients (tests the ratio of beta to its standard error). For the empirically detected PRRT-left-amygdala region, B(SE) = 6.11(3.0), Wald(1) = 4.18, $p = .04$; digit sorting, left DLPFC: B(SE) = −3.94(2.03), Wald(1) = 3.77, $p = .05$. The variables explained group membership, $\chi^2(2) = 10.5$, $p = .005$, but did not interact, $p = .54$. As shown in Figure 5, compared with depressed participants, control subjects displayed higher DLPFC activity during digit sorting and lower amygdala activity during the PRRT; no depressed participants had amygdala activity in the sample's lower quartile and DLPFC activity in the upper quartile, $\chi^2(2) = 4.5$, $p = .03$. 17/18 depressed participants displayed DLPFC activity lower than the control subjects' median. Of these, 11/17 also displayed higher amygdala activity than control subjects' median.

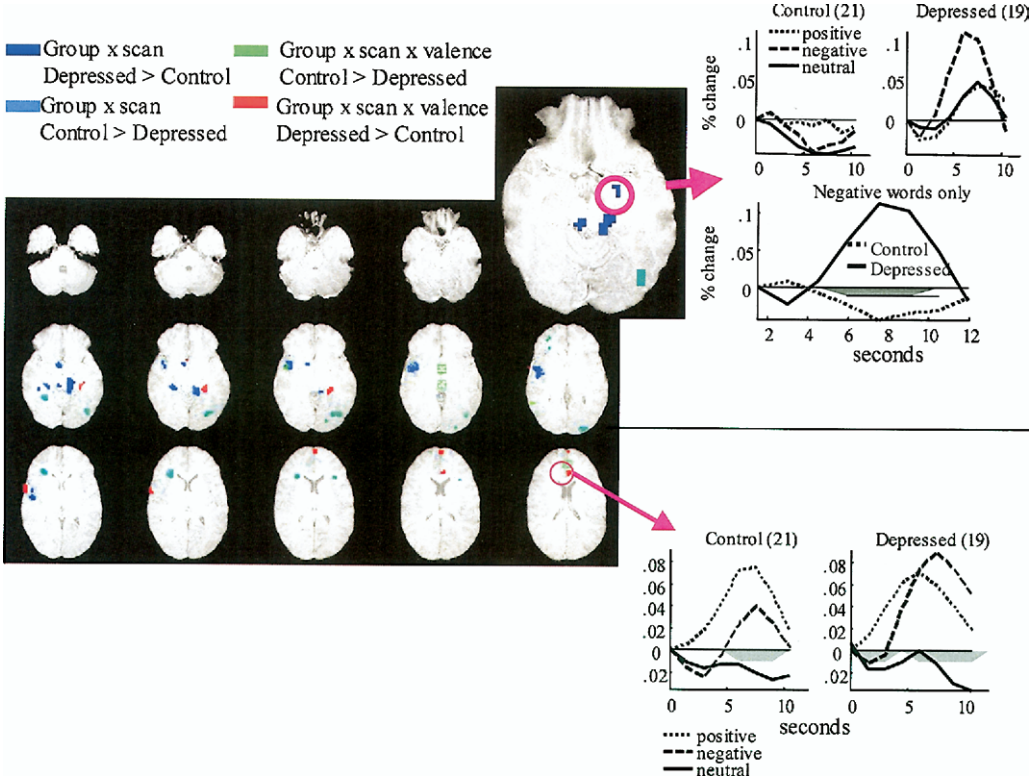


Figure 2. Personal relevance rating task: regions for which the time-course of responses for depressed and never-depressed individuals differed consistently, $p < .001$, contiguity = 14 voxels (group × scan) or 16 voxels (group × scan × valence). Contrasts to determine directionality were computed for negative words at the scan 9 sec following stimulus onset (reflecting sustained activity), and were restricted to those for which group differences were significant ($p < .05$).

This pattern is consistent with a model in which multiple impairments cluster.

3. Is there evidence of disruptions in the relationship of amygdala and DLPFC function during emotional information processing in depression?

For functional connectivity analyses, the empirically derived left DLPFC region from the digit-sorting task, and the anatomically defined left amygdala region were employed. We used the anatomically defined amygdala region because the empirically defined region was small and we did not wish to capitalize on characteristics of the sample from which it was derived. The BA24 region identified on the PRRT was examined as a potential mediator of observed effects.

Cross-Correlations on the PRRT. Left amygdala and left DLPFC activity generally had positive associations, though depressed participants had marginally attenuated correlations of DLPFC activity with amygdala activity 3 to 6 sec later, $t(37) = 1.74$, $p = .09$, $d = .56$ (Figure 6). Because stimulus-related amygdala activity was more sustained in the depressed group, less variance was attributable to DLPFC activity. As such, when lag-0 amygdala activity was accounted for, there were no group differences in the later lags.

Functional Canonical Correlation on the PRRT. Figure 7 shows the mean correlation between the functional canonical covariates for each condition and group, along with tests of group differences. Control subjects displayed moderately correlated variates suggesting that amygdala and DLPFC activity were related. Depressed participants displayed reduced correlations between the variates for positive and negative words, suggesting that amygdala and DLPFC activity were not as strongly related in emotional reactivity in depression. The same qualitative pattern was observed when the empirically derived amygdala region was used rather than the anatomically defined amygdala region, Negative: $r_{control} = .28$, $r_{depressed} = .19$, $t(38) = 1.07$, $p = .29$, Positive: $r_{control} = .37$, $r_{depressed} = .27$, $t(37) = 1.14$, $p = .26$, Neutral: $r_{control} = .18$, $r_{depressed} = .11$, $t(38) = .65$, $p = .52$.

To suggest whether obtained results could reflect disruptions in rostral anterior cingulate activity, functional canonical correlations of amygdala and DLPFC activity with the empirically detected BA24 region (in Figure 2) were examined. Functional canonical correlations between the amygdala and rostral cingulate following negative words were moderately strong and were marginally reduced in the depressed group, $r_{control} = .46$, $r_{depressed} = .36$, $Z = 1.54$, $p = .12$. Connectivity of the DLPFC to the rostral cingulate was quite strong and sharply reduced in the depressed group $r_{control} = .67$, $r_{depressed} = .52$, $Z = 3.1$, $p = .002$.

Potential Mediation of Amygdala–DLPFC Relationships by Rostral Cingulate Function on the PRRT. We examined variance in the amygdala/DLPFC relationship explained by BA24 activity on the PRRT using a mixed model. Mean sustained (last three scans per trial) DLPFC activity in response to negative words on the PRRT was the dependent variable and mean sustained (last three scans per trial) amygdala and BA 24 activity were independent variables. Trials were nested within subjects (random factors). Amygdala activity explained significant variation in DLPFC activity when it was the only explanatory variable in both depressed participants, $t = 2.42$, $p = .02$, $R^2 = .10$, and control participants, $t = 5.37$, $p < .01$, $R^2 = .25$. When BA 24 activity was included, in depressed participants, amygdala activity no longer explained significant independent variation in DLPFC activity, $t = .90$, $p = .37$, $sr^2 = .01$; BA 24 activity did

Table 3. Regions Displaying Significant Group × Scan Differences in the 9-sec poststimulus-Onset Range on the PRRT and Digit-Sorting Tasks

Effect	Depressed > Control	Control > Depressed
PRRT Group × Scan	Subcallosal gyrus 126: 10,5,−12 BA 25 6: 6,4,−12 Insula 285: 45,5,−3; 23: 46,−5,2 BA 13 189: 45,5,−4; 8: 44,−5,2 Parahippocampal gyrus 86: −22,−5,−15; 313:−16,−32,−7; 209: 28,−31,−7 Superior temporal gyrus 1246: 53,1,−1, BA 22 655: 52,1,0 BA 38 72: 47,7,−8 Culmen 516: −11,−36,−10; 8: 12,−31,−14 Lentiform nucleus 41: 15,7,−6 Hippocampus 119: 32,−29,−7 **Amygdala 84: −22,−5,−15** Substantia nigra 55: −10,−20,−10 Lateral globus palidus 17: 14,7,−6 Nucleus accumbens 32: 13,7,−8 Putamen 19: 16,7,−6 BA 6 6: 52,−7,6 BA 19 14: −16,−42,−5 BA 21 58,−2,−2 BA 27 6: 27,−30,−5; 10:−11,−36,−1 BA 28 5: −20,−24,−10 BA 30 129: −15,−36,−5 BA 34 70: 10,4,−12 BA 35 57: −19,−25,−13; 19: −17,−30,−9	Fusiform gyrus 13: −44,−66,−11; 174: 34,−49,−8 BA 37 50 32,−46,−8 Inferior occipital gyrus 74: −40,−71,−5 Inferior temporal gyrus 65: −42,−71,1 Insula 10: −34,24,11 Parahippocampal gyrus 51: 33,−48,−7 Lingual gyrus 9: −20,−84,2 BA 18 18: −44,−76,−9; 98: −28,−94,8 BA 19 108: −43,−71,−8; 11: 33,−46,−6; 9: −33,−92,8 Middle occipital gyrus 376: −44,−71,−8; 134: −41,−74,2; 202:−27,−94,8 Inferior frontal gyrus 155: 36,30,4; 31: −36,26,8 Middle frontal gyrus 10 34,50,−2; 13: 37,47,−2 BA 10 4: 34,50,−1; 38,47,−1 BA 45 5 33,25,5
PRRT Group × Scan × Valence	Anterior cingulate 10: 6,13,−10; 253: −3,36,13 **BA 24 49: −2,33,14** BA 25 8: 6,13,−10 BA 27 4: −26,−30,−4; 6: −22,−33,−2 BA 32 144: −3,37,13 Parahippocampal gyrus 247: −26,−34,−5 Superior temporal gyrus 36: 66,2,5 Middle frontal gyrus 52: −33,7,49; 27: −22,14,54; 517: −23,−5,58 Postcentral gyrus 756: −24,−31,59 BA 2 59: −29,−35,60 BA 3 334: −24,−30,59 BA 5 33: −28,−37,60 Precentral gyrus 27: 66,3,6; 536: −23,−23,59; 4: 21,−21,60 BA 4 276: −22,−26,59 BA 4 8: −8,−12,54 Superior frontal gyrus 64: −9,32,44; 260: −19,13,54 BA 6 7: 64,2,6; 573 −22,0,56; 43: −33,6,49 BA 6 15: 13,−10,56 BA 8 5: −11,31,42 BA 9 8: −4,54,15; 21: 5,49,18 Medial frontal gyrus 7: −2,66,7; 10: −5,54,15; 29: 5,49,18; 82: −10,34,40; 129: −9,−15,55; 24: 13,−10,56 Hippocampus 268: −29,−32,−5; BA 36 4: − 31,−32,−10	Middle temporal gyrus 30: 64,−51,5 BA 21 19: 65,−51,5 Superior occipital gyrus 10: 34,−84,28 BA 19 2: 34,−84,28 Cuneus 2: 33,−85,28
Digit Sorting Group × Scan	Middle frontal gyrus 15: 30,−16,44 Postcentral Gyrus 5: 52,−10,48; 9: 51,−15,51 BA 43 2:59, −7,22 Precentral gyrus 409: 62,−5,26; 8: −53,0,22; 10:−57,0,24; 8: 81,−16,44; 257: 50,−7,48; 5: 51,−15,51 BA 4,109: 62,−5,23; 4: 31,−17,44; 121: 51,−8,48 BA 6 6: −53,0,22; 94: 65,−5,28; 8: −57, 1,24; 6: 58,−4,30; 14: 51,−4,48	Inferior frontal Gyrus 60: −46,16,24; 155: −46,8,31 Precuneus 336: −17,−61,40 BA 7: 46; −18,−65,34; 9: −18,−60,44 **Middle frontal gyrus 1063: −40,20,28** **BA 9: 380: −45,11,32** **BA 46: 66: −45,20,24** BA 6: 22: −42,4,35 Precentral gyrus 101: −41,6,35

Table 3. (continued)

Effect	Depressed > Control	Control > Depressed
Digit Sorting Group × Scan × Condition	Superior frontal gyrus 9: −5,45,46 BA 8 7: −4,45,46 Lentiform, nucleus 10: −16,7,−2 Putamen 10: −16,7,−2	Anterior cingulate 7: 17,34,22 BA 32 5: 16,34,22 Middle temporal gyrus 80: −65, −19, −10 BA 21 60: −65,−19,−10 Inferior frontal gyrus 9: −57,10,32; 8: −53,7,32 Cingulate gyrus 6: 13,−39,30; 49: −5,−26,37 Inferior parietal lobule 8: 30,−37,55 Middle frontal gyrus 30: 46,49,18; 9: −50,10,35; 27: −38,9,38; 9: −42,8,41 BA 9 9: −57,10,32; 8 −53,7,32; 4: −50,10,35 BA 6 46: 8,−28,55 BA 10 4: −8,51,10; 22: 47,49,18 Paracentral Lobule 30: 10,−36,52; 61: 8,−28,55; 9: 13,−34,55 Medial Frontal Gyrus 7: −8,51,9; 7: 17,32,36; 10: 10,−27,55 BA 5 6: 10,−36,52 BA 31 27: −5,−26,39 BA 40 7: 31,−37,55

For the digit-sorting task, regions are constrained to those in which at least one group displayed greater activity in the five- than three-digit condition. All regions are specified as Name, Size (mm): Centroid Talairach x,y,z.

BA, Brodmann's area; PRRT, personal relevance rating task.

explain significant variation, $t = 3.21$, $p < .01$, $sr^2 = .09$, suggesting that BA 24 activity mediated the functional relationship between amygdala and DLPFC. Similarly, for control participants, although the amygdala explained 25% of the variation in sustained DLPFC activity when it was entered alone, it explained only 3% of the independent variation once BA 24 was entered, $t = 3.72$, $p < .01$; BA 24 again explained independent variance $t = 2.39$, $p = .02$, $sr^2 = .12$.

Sensitivity Analysis: Age-Matched Subsamples and Anatomic DLPFC Region

To understand whether the obtained results were a function of age differences between the groups, age-matched subsamples were examined by removing the four youngest control subjects and three oldest depressed participants from the sample. This technique yielded a nonsignificant age difference between groups of under 3 years (PRRT: $t(27.3) = -.71$, $p = .48$, $D = -2.5$ years; digit sorting: $t(46.5) = -1.0$, $p = .31$, $D = -2.9$ years). The graphs for all explored contrasts were virtually identical to those made for the full sample, and similar effect sizes were observed (Table 2). For a comparison not tuned to this sample, an anatomically defined DLPFC region was examined using AFNI's Talairach Atlas middle frontal gyrus mask from $5 < z < 37$, including lateral BA 9 and BA 46; decreased DLPFC activity was again observed on the digit-sorting task.

Discussion

Unmedicated depressed and healthy individuals completed cognitive (digit sorting), and emotional (personal relevance rating of words) tasks. As in our previous study (Siegle et al 2002), depressed individuals displayed increased and sustained amygdala activity for up to 15 sec in response to briefly presented (250 msec) negative words compared with control sub-

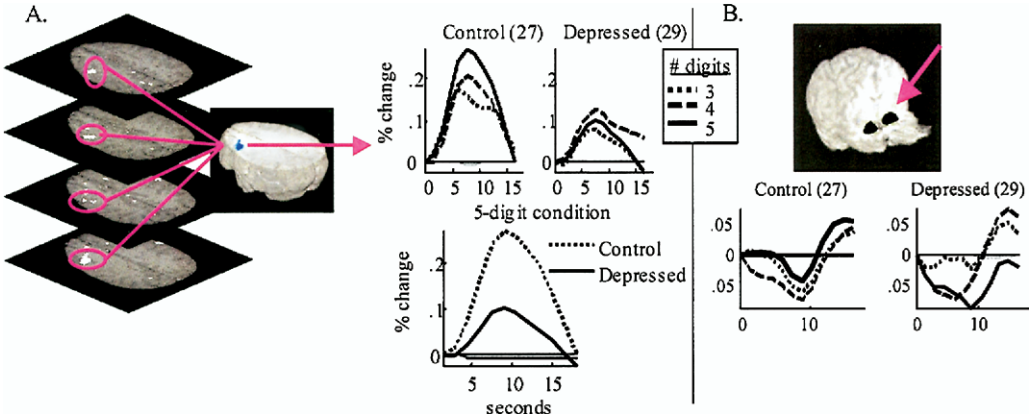


Figure 3. Digit-sorting task: **(A)** regions for which the time course of responses for depressed and never-depressed individuals differed consistently on the digit sorting task, $p < .001$, contiguity = 12 voxels (group × scan) or 15 voxels (group × scan × condition). Contrasts to determine directionality were computed for five digits at the scan 9 sec following stimulus onset (reflecting peak activity) and were restricted to those for which group differences were significant, $p < .05$. The time series for an empirically derived left DLPFC region is shown. **(B)** Time-series in the traced amygdala region.

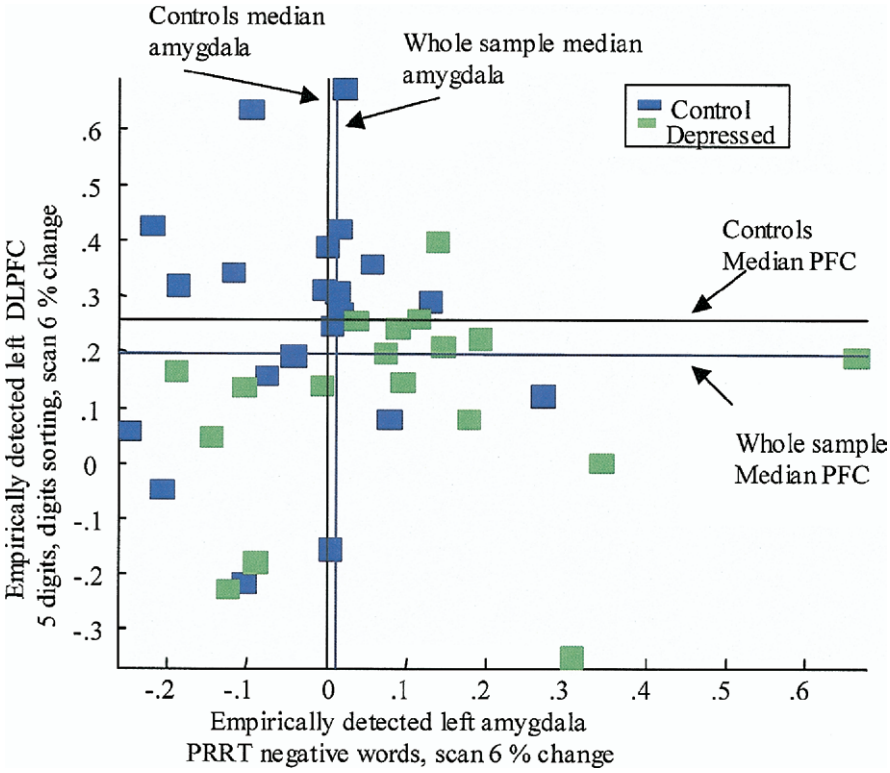


Figure 4. Scatterplot of the relationship between cognitive function (left dorsolateral prefrontal cortex [DLPFC] recruitment during digit sorting) and emotional reactivity (amygdala activity on the personal relevance rating task [PRRT]) . Each point represents a participant. Control participants clustered at the top left suggest high levels of DLPFC and low levels of amygdala activity relative to depressed participants.

jects, who displayed little amygdala activity on the task. Depressed participants also displayed decreased DLPFC activity on both tasks. These data support our primary hypotheses that depression involves increased and sustained amygdala activity, which could be associated with increased emotional reactivity, as well as decreased function in brain regions subserving executive control and potentially initiating emotion regulation.

Most depressed individuals displayed decreased DLPFC activity; sustained amygdala reactivity was present for just a subset. These data suggest that abnormal DLPFC function does not, alone, lead to dysregulation of amygdala reactivity in depression. Yet the majority of depressed individuals displayed both abnormalities, potentially suggesting they interact. For example, increased tonic amygdalar activity may lead to decreased DLPFC function in some depressed individuals. Other depressed individuals may not effectively recruit their DLPFC, independent of emotional reactivity.

Amygdala activity decreased during digit sorting consistent with the idea that cognitive processing, including DLPFC engagement, regulates substrates of emotions. The positive relationship between DLPFC and amygdala activity during the PRRT, along with the fact that there was a hemodynamic response to emotional words in the DLPFC but not the amygdala in control subjects, could further support involvement of the DLPFC in emotion regulation. As expected, DLPFC activity was less strongly coupled with amygdala activity in depressed than control participants, potentially because of increased tonic amygdala activity in the depressed group.

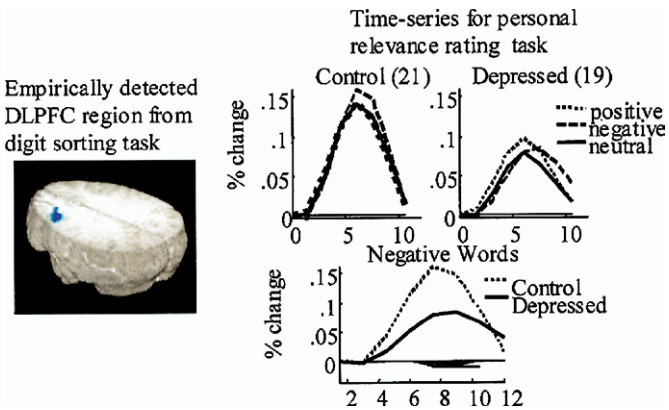


Figure 5. Blood oxygen level-dependent responses on the personal relevance task in the empirically detected dorsolateral prefrontal cortex (DLPFC) region from the digit-sorting task. Depressed individuals displayed decreased DLPFC activity compared with control subjects. (Regions of significant group differences are described in Table 2, row 4.)

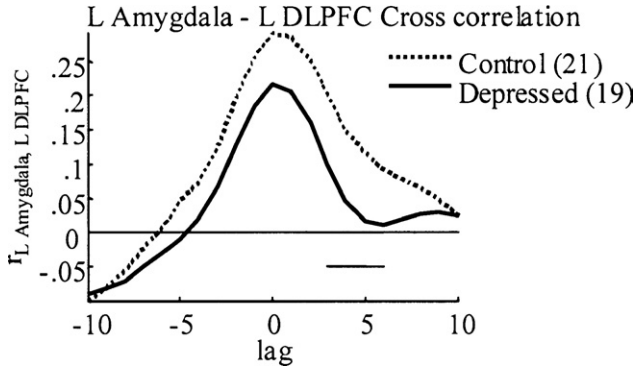
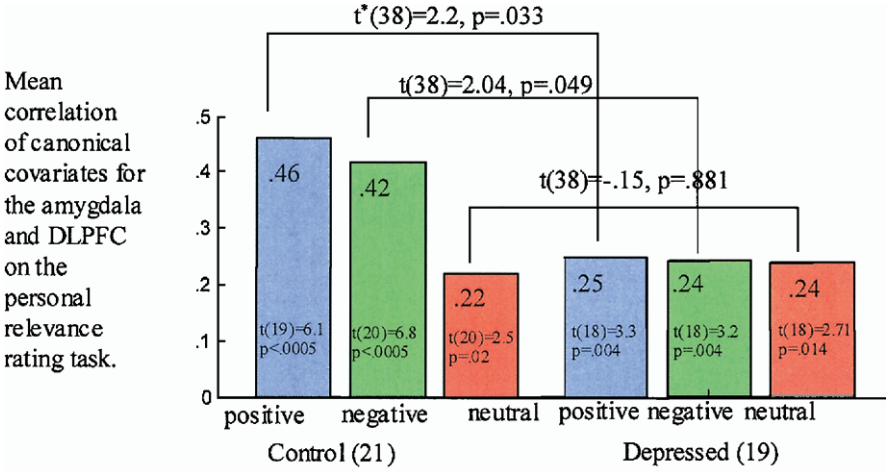


Figure 6. Cross-correlation of time series extracted from the traced left amygdala and left dorsolateral prefrontal cortex (DLPFC) region (empirically derived from the digit-sorting task), computed on the personal relevance rating task (PRRT). Lags represent scans. Negative lags indicate relationships between amygdala activity and subsequent DLPFC activity. Positive lags represent relationships between DLPFC activity and subsequent amygdala activity.



*T-tests of condition-related correlations and group-differences were computed using the Fisher-z' transformed correlation values.

Figure 7. Mean correlation among functional canonical covariates for amygdala and dorsolateral prefrontal cortex (DLPFC) activity for each condition, for each group, on the personal relevance rating task (computed as the inverse Fisher *z′* transform of the mean of the *z′*-transformed correlations). Relationships were significantly reduced for negative and positive words in the depressed group compared with control subjects.

Despite displaying decreased DLPFC activity, depressed participants did not display performance deficits in digit sorting. Potentially, depressed individuals can recruit enough executive control to accomplish explicit easy cognitive tasks but not enough for concurrent emotion regulation, yielding an overall decrease in task related activity. Similar explanations have been advanced for decreased performance in "unfocused" memory tasks but not tasks in which attention is explicitly focused in depression (Hertel and Rude 1991). It is also consistent with findings of increased emotional biases and rumination during cognitive dual tasks in depression (Wenzlaff et al 1988; Wenzlaff and Luxton 2003). Similarly, fMRI may be a more powerful detector for problems in executive control than behavior on this task, supported by the marginal group × condition behavioral effect. Future research with more difficult cognitive tasks or requiring explicit emotion regulation to complete cognitive tasks could test this hypothesis.

Another explanation is that depressed individuals' task vigilance decreased during the long interstimulus intervals (ISIs). Depressed individuals have displayed similar or increased DLPFC activity to that of control subjects in continuously demanding cognitive tasks (Barch et al 2003; Harvey et al 2005; Holmes et al 2005), whereas in the current task, involving longer ISIs, PFC deficits were observed. This explanation is consistent with decreased sustained physiological reactivity in an overlapping subset of these depressed participants during a different long-ISI cognitive task, which we attributed to a similar mechanism (Siegle et al 2004). Future research varying ISIs on a cognitive task within an experiment could test this hypothesis.

Other explanations for depressed participants' adequate performance but low PFC activity seem less plausible. For example, depressed participants could have increased processing efficiency, yielding decreased DLPFC activity. Neither literature nor other data in this experiment support this explanation. Alternatively, depressed individuals might use other brain regions to compensate for decreased DLPFC function. No brain regions displaying activity parametric with difficulty in depressed individuals had greater activity in depressed than control participants, although regions of the middle frontal gyrus superior and posterior to the DLPFC and areas of the precentral gyrus, primarily BA 6 and BA 4, were more active for depressed than control participants during digit sorting, possibly signifying compensatory activity.

Exploratory analyses revealed a network of brain structures associated with cognitive and emotional information processing other than the amygdala and DLPFC. In particular, activity in BA 24 increased in response to negative words in depressed individuals (who also display decreased BA 24 activity during the five-digit condition; $F = 6.7$, $p = .01$). Brodmann's area 24 has been implicated in emotion regulation and accounted for the majority of variance in the observed relationships between sustained amygdala and DLPFC activity. Thus, abnormal BA 24 activity could reflect a greater need for emotion regulation in depression, consistent with the low level of amygdala reactivity in the control subjects during the PRRT. Indices of functional connectivity between BA 24 and both the amygdala and DLPFC were reduced in depression, potentially reflecting inefficient communication between these structures. Potentially then, apparent deficits in emotion regulation stem from impaired functional relationships between the DLPFC and structures more proximally responsible for regulating the amygdala. In this sense, decreased DLPFC activity during digit sorting and decreased PRRT BA 24–DLPFC functional connectivity may reflect multiple convergent mechanisms for disrupted emotion regulation.

This study had multiple limitations. The groups differed in age, although subsamples that were better age matched yielded comparable effects. The PRRT always followed the digit-sorting task, and because of time limitations, not all participants completed each task. These features could have led to biased results or task-order effects, although such effects are unlikely because observed task-related effects were somewhat independent (Figure 4). In addition, the PRRT was administered among other emotional and cognitive information processing tasks employing emotional words, which could have affected responses during the PRRT. Participants had completed these tasks previously, which could have reduced novelty and introduced practice effects. Finally, because the PRRT did not elicit amygdala activity in the healthy participants, this task may be appropriate for demonstrating group differences but may not be appropriate for examining aspects of emotional reactivity mediated by the amygdala in healthy individuals.

Although our previous similar study of primarily medicated patients (Siegle et al 2002) showed specificity of sustained amygdala activity to negative information, this study of unmedicated patients found sustained amygdala activity to positive,

negative, and neutral words. Our peripheral physiologic studies suggest similar differences between medicated (Siegle et al 2003a) and unmedicated depressed patients (Siegle et al 2001, submitted). Potentially, both groups engage in elaborative processing of negative information; unmedicated depressed individuals also make negative elaborative associations with a broader set of stimuli (as in Hamilton and Abramson 1983). Thus, as suggested by our computational models (Siegle 1999, 2002), an unmedicated depressed participant confronted with the word "pen" might initially judge it as neutral but then consider personal associations with pens (e.g., "a pen once leaked in my pocket during an interview, and I wasn't hired. I'm a failure."). The tasks' long interstimulus interval could encourage such elaborative rumination.

Together these results suggest that disruptions in cognitive and emotional information processing are integral to the experience of depression. In particular, depression is characterized by decreased engagement in slowly presented executive control tasks and sustained processing of emotional information. The idea that these mechanisms may interact during emotional processing but that emotional information processing biases are not present in all depressed individuals may be important for future research geared toward understanding subtypes of unipolar depression. Each mechanism may be amenable to different targeted interventions.

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fMRI data from a subset of control participants on the digit-sorting task was published in an fMRI methods article (Siegle et al 2003b). fMRI data from a subset of control subjects and depressed participants on the personal relevance rating task, examined only in relation to recovery in cognitive therapy, has been also been published (Siegle et al 2006).

Abercrombie HC, Schaefer SM, Larson CL, Oakes TR, Lindgren KA, Holden JE, et al (1998): Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport* 9:3301–3307.

Amaral DG, Price JL, Pitkanen A, Carmichael ST (1992): Anatomical organization of the primate amygdaloid complex. In: Aggleton JP, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. New York: Wiley-Liss, 1–66.

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al (2005): Antidepressant effect on connectivity of the mood-regulating circuit: An fMRI study. *Neuropsychopharmacology* 30:1334–1344.

Barch DM, Sheline YI, Csernansky JG, Snyder AZ (2003): Working memory and prefrontal cortex dysfunction: Specificity to schizophrenia compared with major depression. *Biol Psychiatry* 53:376–384.

Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al (1989): Reduction of prefrontal glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 46:243–250.

Beck AT, Steer RA, Brown G (1996): *Beck Depression Inventory, Second Edition*. San Antonio, TX: Psychological Corporation.

Bench CJ, Friston KJ, Brown RG, Frackowiak RS, Dolan RJ (1993): Regional cerebral blood flow in depression measured by positron emission tomography the relationship with clinical dimensions. *Psychol Med* 23: 579–590.

Bradley MM, Lang PJ (1997): *Affective Norms for English Words ANEW Technical Manual and Affective Ratings*. Gainesville, FL: Center for Research in Psychophysiology University of Florida.

Cox R (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.

Davidson RJ (2000): Affective style psychopathology and resilience: Brain mechanisms and plasticity. *Am Psychol* 55:1196–1214.

Davidson RJ (2003): Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology* 40:655–665.

Davidson RJ, Jackson DC, Kalin NH (2000): Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychol Bull* 126: 890–909.

Dolcos F, McCarthy G (2006): Brain systems mediating cognitive interference by emotional distraction. *J Neurosci* 26:2072–2079.

Drevets WC (1999): Prefrontal cortical amygdalar metabolism in major depression. *Ann N Y Acad Sci* 877:614–637.

Drevets WC, Raichle M (1998): Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. *Cogn Emotion* 12:353–385.

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992): A functional anatomical study of unipolar depression. *J Neurosci* 12:3628–3641.

First MB, Spitzer RL, Gibbon M, Williams JB (1996): *Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition*. New York: Biometrics Research Department New York State Psychiatric Institute.

Ghashghaei HT, Barbas H (2002): Pathways for emotion: Interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* 115:1261–1279.

Goodwin GM (1997): Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in depression. *J Psychopharmacol* 11:115–122.

Hamilton EW, Abramson LY (1983): Cognitive patterns and major depressive disorder: A longitudinal study in a hospital setting. *J Abnorm Psychol* 92:173–184.

Harvey PO, Fossati P, Pochon JB, Levy R, Lebastard G, Lehericy S, et al (2005): Cognitive control and brain resources in major depression: An fMRI study using the n-back task. *Neuroimage* 26:860–869.

He G, Muller HG, Wang JL (2004): Methods of canonical analysis for functional data. *J Statist Plann Inf* 122:141–159.

Hertel PT, Rude SS (1991): Depressive deficits in memory: Focusing attention improves subsequent recall. *J Exp Psychol Gen* 120:301–309.

Holmes AJ, MacDonald A 3rd, Carter CS, Barch DM, Andrew Stenger V, Cohen JD (2005): Prefrontal functioning during context processing in schizophrenia and major depression: An event-related fMRI study. *Schizophr Res* 76:199–206.

Ingram RE (1984): Toward an information processing analysis of depression *Cogn Ther Res* 8:443–478.

Langenecker SA, Bieliauskas LA, Rapport LJ, Zubieta JK, Wilde EA, Berent S (2005): Face emotion perception and executive functioning deficits in depression. *J Clin Exp Neuropsychol* 27:320–333.

LeDoux J (1996): *The Emotional Brain*. New York: Simon & Schuster.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al (1999): Reciprocal limbic cortical function and negative mood Converging PET findings in depression and normal sadness. *Am J Psychiatry* 156:675–682.

Metcalfe J, Mischel W (1999): A hot/cool-system analysis of delay of gratification: Dynamics of willpower. *Psychol Rev* 106:3–19.

Nelson HE, Willison J (1991): *The National Adult Reading Test*. Berkshire, England: Nfer-Nelson.

Nolen-Hoeksema S, Morrow J, Fredrickson BL (1993): Response styles and the duration of episodes of depressed mood. *J Abnorm Psychol* 102: 20–28.

Ochsner KN, Bunge SA, Gross JJ, Gabrieli JDE (2002): Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14: 1215–1229.

Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ (2004): For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23:483–499.

Ottowitz WE, Dougherty DD, Savage CR (2002): The neural network basis for abnormalities of attention and executive function in major depressive disorder: Implications for application of the medical disease model to psychiatric disorders. *Harv Rev Psychiatry* 10:86–99.

Perez-Janaray M, Vives F (1991): Electrophysiological study of the response of medial prefrontal cortex neurons to stimulation of the basolateral nucleus of the amygdala in the rat. *Brain Res* 565:97–101.
Ramsay JO, Silverman BW (2005): *Functional Data Analysis*. New York: Springer.
Ratcliff R (1993): Methods for dealing with reaction time outliers. *Psychol Bull* 114:510–532.
Ray JP, Price JL (1993): The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 337:1–31.
Rissman J, Gazzaley A, D'Esposito M (2004): Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage* 23:752–763.
Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA (2001): Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biol Psychiatry* 50:651–658.
Siegle GJ (1994): The Balanced Affective Word List Creation Program. Available: http://www.sci.sdsu.edu/CAL/wordlist/ (accessed July 12, 2006).
Siegle GJ (1999): A neural network model of attention biases in depression. *Prog Brain Res* 121:415–441.
Siegle GJ, Carter CS, Thase ME (2006): fMRI predicts recovery in cognitive behavior therapy for unipolar depression. *Am J Psychiatry* 163:735–738.
Siegle GJ, Granholm E, Ingram RE, Matt GE (2001): Pupillary response and reaction time measures of sustained processing of negative information in depression. *Biol Psychiatry* 49:624–636.
Siegle GJ, Steinhauer SR, Carter CS, Ramel W, Thase ME (2003a): Do the seconds turn into hours? Relationships between sustained pupil dilation in response to emotional information and self reported rumination. *Cogn Ther Res* 27:365–383.
Siegle GJ, Steinhauer SR, Carter CS, Thase ME (submitted): Is sustained processing specific to emotional information in depression? Evidence from pupil dilation.
Siegle GJ, Steinhauer SR, Stenger V, Konecky R, Carter CS (2003b): Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. *Neuroimage* 20:114–124.
Siegle GJ, Steinhauer SR, Thase ME (2004): Pupillary Assessment and Computational Modeling of the Stroop Task in Depression. *Int J Psychophysiol* 52:63–76.
Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS (2002): Can't shake that feeling: fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51: 693–707.
Teasdale JD (1988): Cognitive vulnerability to persistent depression. *Cogn Emotion* 2:247–274.
Wenzlaff R, Wegner D, Roper D (1988): Depression and mental control the resurgence of unwanted negative thoughts. *J Pers Soc Psychol* 55:882–892.
Wenzlaff RM, Luxton DD (2003): The role of thought suppression in depressive rumination. *Cogn Ther Res* 27:293–308.
Woods RP, Mazziotta JC, Cherry SR (1993): MRI PET registration with automated algorithm. *J Comput Assist Tomogr* 17:536–546.