Can't Shake that Feeling: Event-related fMRI Assessment of Sustained Amygdala Activity in Response to Emotional Information in Depressed Individuals

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Abstract

Background. Previous research suggests depressed individuals engage in prolonged elaborative processing of emotional information. A computational neural network model of emotional information processing (Siegle 1999) suggests this process involves sustained amygdala activity in response to processing negative features information. This study examined whether brain activity in response to emotional stimuli was sustained in depressed individuals, even following subsequent distracting stimuli.

Methods. Seven depressed and 10 never-depressed individuals were studied using event-related fMRI during alternating 15 second emotional processing (valence identification) and non-emotional processing (Sternberg memory) trials. Amygdala regions were traced on high-resolution structural scans and co-registered to the functional data. The time course of activity in these areas during emotional and non-emotional processing trials was examined.

Results. During emotional processing trials, never-depressed individuals displayed amygdalar responses to all stimuli, which decayed within 10 seconds. In contrast, depressed individuals displayed sustained amygdala responses to negative words that lasted throughout the following non-emotional processing trials (25 seconds later). The difference in sustained amygdala activity to negative and positive words was moderately related to self-reported rumination.

Conclusions. Results suggest that depression is associated with sustained activity in brain areas responsible for coding emotional features.

Introduction

Some of the most troubling aspects of depression involve prolonged involuntary processing of emotional information, in the form of elaboration (e.g., MacLeod & Mathews 1991) or rumination (e.g., Nolen-Hoeksema 1998) on negative topics. Such sustained involuntary emotional processing has been hypothesized to result in information biases commonly observed in depression such as preferential memory for, and attention to negative information (e.g., Williams & Oaksford 1992), and has been implicated in the onset and maintenance of depression (e.g., Beck 1967; Ingram 1984, 1990; Ingram, Miranda, & Segal 1998; MacLeod & Matthews 1991; Teadsale 1988). This study examines brain mechanisms associated with sustained processing after briefly presented negative information in depressed and never-depressed individuals using BOLD contrast event-related functional magnetic resonance imaging (fMRI). The study also examined the extent to which sustained processing interfered with subsequent behavioral tasks and whether it was related to self-reported rumination.

Evidence for Sustained Processing in Depression

Sustained processing and elaboration of emotional information has been inferred from a variety of indirect behavioral measures. For example, depressed individuals tend to display enhanced memory for negative information (e.g., Matt et al, 1991), and to interpret events as negative (e.g., Norman et al, 1988). Similarly, Wenzlaff et al (1988) have shown dysphoric individuals display intrusive negative thoughts, even during thought-supression. Elaborative processing has also been advanced as an explanation for delays by depressed individuals in naming the color in which emotional words are written (e.g., Williams & Nulty, 1986), in the absense of early attentional effects (e.g., MacLeod et al, 1986).

A more sparse literature has used continuous peripheral physiological signals to demonstrate sustained recruitment of cognitive resources in the seconds following the presentation of emotional information, particularly in depressed individuals (e.g., Deldin et al, 2001; Christenfeld et al 2001; Siegle et al 2001a,c; Nyklicek et al 1997). For example, sustained processing of emotional information, indexed by sustained pupil dilation (a correlate of cognitive load), has been observed in depressed individuals up to 6 seconds after their responses to stimuli on an emotional valence identification task (Siegle et al 2001a). Such sustained pupil dilation was not present in response to non-emotional processing tasks, e.g., a cued reaction time task, suggesting that the phenomenon could reflect elaborative emotional processing. Similarly, Deldin (2001) has reported that depressed individuals display increased slow-wave activity up to 13 seconds following presentation of negative material, and Larson and Davidson (2001) have suggested that relative to controls, dysphoric individuals experience increased startle blink potentiation for up to six seconds following the presentation of negative pictures; particularly those displaying frontal EEG assymetry. No previous studies have examined brain mechanisms specifically associated with sustained processing using neuroimaging, potentially due to 1) a lack of hypotheses regarding brain mechanisms underlying sustained processing and 2) the difficulty, until recently, of examining sustained processing in an event-related context using neuroimaging. The following sections describe such a theoretical framework and an fMRI design for testing it.

Mechanisms Underlying Sustained Processing

Various cognitive mechanisms for sustained affective processing in depression have been advanced. Ingram (1984) suggests that if cognitive activity involves the spread of activation between nodes in a cognitive network representing semantic and affective information (e.g., Bower 1981), depressed individuals suffer from strongly activated connections between negative

affective nodes and multiple semantic nodes, creating feedback loops that propagate depressive affect and cognition. More biologically plausible neural models of emotional information processing are consistent with Ingram's (1984) cognitive theory. A great deal of evidence suggests that emotional information is processed in parallel by brain systems responsible for identifying emotional aspects of information (the amygdala system, e.g., Gallagher & Chiba 1996; LeDoux, 1993, 1996) and other brain areas primarily responsible for identifying non-emotional aspects of information (e.g, the hippocampal system, LeDoux, 1996). These systems are highly connected, and subject to feedback (e.g., Tucker & Derryberry 1992). Ingram's notion of increased feedback between structures responsible for processing primarily cognitive and emotional features could thus suggest increased feedback between the amygdala system and brain structures responsible for identification of non-emotional aspects of information including the hippocampus. Amygdala hyperactivation, in particular, has been demonstrated in depressed individuals (Abercrombie et al. 1998; Drevets 1999) and has been implicated in the maintenance of depression (Dougherty & Rauch 1997). Disruptions in both volume and activity of these structures have been noted in depressed individuals (e.g., Drevets et. al. 1992; Drevets 1999; Hornig, Mozley, & Amsterdam 1997; Sheline, Sanghavi, Mintun, & Gado 1999) and in animal models of depression (e.g., Zangen, Overstreet, & Yadid 1999).

Other research suggests depression involves disinhibition of the amygdala system. Such disinhibition of emotional-processing structures motivates interventions such as Cognitive Therapy, in which depressed individuals are taught to distance themselves from emotional reactivity through processes such as cognitive reappraisal of emotional situations. A potential candidate mechanism for such disinhibition involves decreased inhibition from integrative cortical brain structures such as the dorsolateral prefrontal cortex (DLPFC; e.g., Davidson,

2000). While such inhibitory pathways have not been empirically identified inverse relationships between DLPFC and amygdala activity have been shown through functional neuroimaging (e.g., Drevets 1999). Moreover, multiple studies have demonstrated decreased DLPFC activation in depressed individuals (e.g., Davidson 1994, 2000; Baxter et al 1989; Bench et al 1993). Similarly, non-depressed individuals have decreased DLPFC activation during induced sad moods (e.g., Baker et al 1997; Gemar et al. 1996; Liotti et al 2000a). Thus, the amygdala is suggested to be important in maintaining processing of emotional information in depressed individuals. The current research therefore focused on identifying sustained (~30 seconds after a stimulus) disruptions in amygdala activity in depressed individuals, as well as associated disruptions in areas directly connected to the amygdala such as orbitofrontal cortex, in which activity has been associated with amygdala activity in neuroimaging studies, (Zald et al, 1998) or areas such as DLPFC that may have inverse relationships to amygdala activity. The following sections outline methods used for assessing this sustained activity and predictions for depressed individuals.

Assessment of Sustained Affective Processing Using fMRI

fMRI provides a non-invasive central measure believed to correlate with brain activity on a trial-by-trial basis and was therefore chosen as a dependent measure for the current study. Potentially, the clinical relevance of sustained processing in response to affective stimuli would be enhanced if it interfered with subsequent tasks. For example, if an individual is criticized, elaboration on the criticism rather than working could result in poor job performance. To examine such interference effects, depressed and never-depressed individuals completed tasks in which trials alternately required emotional processing and non-emotional processing. A common approach to provoking emotional processing was used in which individuals are asked to name

the affective valence (positive, negative, or neutral) of presented stimuli (a "valence identification task," e.g., Hill & Kemp-Wheeler 1989; Mathews & Milroy 1994; Siegle et al 2001a,b,c). The common delayed match to sample, or "Sternberg memory" task was chosen as an appropriate non-emotional processing task. This task involves showing participants three numbers followed by a fourth number. Participants are asked whether the fourth number was in the set of the first three. The task was chosen because there is a wealth of behavioral and psychophysiological data on it, because it takes a few seconds to complete a trial in which stimuli are being continuously presented allowing detection of residual activity from the previous trial, and is easy enough that depressed individuals would not get frustrated by the task. "Affective interference" was operationalized as the degree to which the affective content of the emotional stimulus predicted brain activity on the subsequent non-emotional processing trials.

Our basic hypothesis was that depressed individuals would show more sustained activation in brain areas responsible for recognizing emotional information during the emotion-processing trial which would carry over into the subsequent non-emotional processing trial, leading to more affective interference for depressed than never-depressed individuals. Because the preceding theories involve complex interacting systems of disruptions (e.g., positive feedback between the hippocampal and amygdala systems, decreased inhibition of amygdala), it is difficult to predict 1) whether these systems are expected to interact non-linearly, 2) whether sustained processing is expected to occur for all stimuli or just some as a result of relevant disruptions, and 3) what the precise time course of relevant changes in information processing are expected to be. Computational simulation allows quantitative integration of assumptions about underlying cognitive and biological systems (Siegle & Hasselmo, 2001) and was therefore used to further specify hypotheses.

Using a Formal Model to Generate Predictions

Predictions for changes in MR signal in response to positive, negative, and neutral stimuli were made using a computational neural network model of emotional information processing disruptions in depression. A brief summary of the model, described more fully in other papers (Siegle 1999, Siegle & Hasselmo 2001, Siegle & Ingram, 1997) follows. In neural network models activation spreads between connected nodes that loosely represent populations of connected neurons. By systematically changing the strength of connections between these nodes, the model can be made to associate incoming activity with subsequent activity (or a response to a stimulus), and can thus be said to learn associations. Our network was constructed to identify emotional stimuli as positive, negative, or neutral, based on physiological models (e.g., LeDoux, 1996). As shown in Figure 1, stimuli (locally coded in the stimulus units) are processed in parallel by units responsible for identifying affective features (an analog of amygdala system functions) and non-affective features (an analog of hippocampal system functions). Feedback occurs between these layers as a simplified analog of feedback between these brain systems. These layers project to units responsible for making decisions about the information. Activity in the decision units inhibits the emotional processing units, as an analog of the idea that integrative cortical activity could inhibit amygdala processing. Emotionality is encoded (trained) by strengthening connections from input and non-affective feature units to affective feature units representing either a positive or negative valence. Personal relevance is encoded by the amount the network is exposed to stimuli. More exposure yields enhanced connections between the affective and non-affective processing systems, using a Hebb learning rule (pathways between simultaneously active features become strengthened). Importantly, model layers are not meant to represent detailed biological features of the involved structures but only their hypothesized

functional activity.

To reflect the idea that depression often follows a negative life event (e.g., Paykel 1979) that is thought about or well-learned, environmental aspects of depression are operationalized in the model as prolonged exposure to some negative information. Connections to representations of this negative information are thereby strengthened. To represent the decreased inhibition of emotional processing areas by cortex, the strength of activation of the decision units was decreased. Feedback between affective and non-affective feature detection units was also manipulated as an analog of Ingram's (1984) idea that depression involves diffusely increased connections to representations of sadness in a depressed person's semantic network. Manipulation of each of these parameters has been shown to reflect cognitive factors associated with depression (e.g., Siegle & Ingram 1997).

To represent alternation between emotional and non-emotional processing (Sternberg memory) trials the model was first presented with an emotional stimulus for valence identification for 300 epochs followed by three non-emotional cues that had no relationship to word stimuli (50 epochs each) and a non-emotional target to identify (300 epochs). A match was judged if activation in response to the target was above an arbitrary threshold, which decreased rapidly over time on a negative exponential function. The decreasing threshold was used to represent the idea that participants respond to nearly every stimulus; as time passes, they apply less strict criteria to making the correct decision. While this simulation does not represent many aspects of the Sternberg task, it does accomplish its primary mission: to allow examination of residual activation from the valence identification task during a period in which non-emotional stimuli are presented. Network parameters are listed in the Appendix.

The network's behavior was simulated in response to positive, negative, and neutral stimuli

on the valence identification task, before and after manipulation of variables related to depression. To make predictions regarding the time course of amygdala activity in response to emotional stimuli, activity in the network's valence units were summed and convolved with an expected hemodynamic response. The network, along with its behavior over time on a valence identification of non-personally-relevant negative information / Sternberg memory trial pair is depicted on the top of Figure 1. The left side of the figure displays the activity in the network's valence identification units. In the top graphs an analog of time is on the x-axis and activity is on the y-axis. The original network's representation of negative information becomes active and quickly drops off (top left Affective Feature Unit activity graph). In the network in which aspects of depression were simulated, the network's activity in response to negative information is more sustained (top right Affective & Non-affective Feature Unit activity graphs). To obtain a prediction for fMRI data the sum of the network's valence units was convolved with a gamma function representative of a hemodynamic response. As shown on the bottom graphs on the Affective Feature Unit activity panel, it is predicted that the depressed individuals will display a sustained response to negative words. The network's valence units, convolved with a gamma function in response to each type of stimulus is shown on the bottom. As shown in the figure, manipulating parameters analogous to aspects of depression in the network make its responses to negative words larger and more sustained.

More generally, systematic manipulation of the three parameters relevant to simulating depression (overtraining on negative information, feedback between affective and semantic processing units, and decreased inhibition from decision units) suggested that decreasing inhibition from decision units and increasing feedback within the network made the network's valence-unit responses to both positive and negative stimuli stronger and more sustained (bottom

middle panel of Figure 1); overtraining the network on negative information made its responses to negative words particularly strong (bottom right panel of Figure 1). With strong inhibition of the valence units, overtraining the network had little effect. These observations lead to the novel prediction that disinhibition of the amygdala alone would result in diffusely sustained activity, but not particularly high activity in response to negative information; a more specific additional mechanism such as overlearning of negative associations would be needed to engender particularly sustained amygdala activity in response to negative stimuli. These parameters interacted such that increasing all three parameters resulted in non-linearly higher responses to negative information than would be expected by any method alone.[1]

Insert Figure 1 about here

Analytic strategy: Translating network behaviors to hypotheses.

Based on the network's performance, the following analytic strategy was adopted. 1) behavioral data were examined to be sure that stimuli deemed negative and personally relevant were perceived that way by subjects, and that there were no gross differences in reaction times to stimuli among groups. Interference of emotional information processing with Sternberg reation times was predicted for depressed individuals. 2) In the imaging data, primary hypotheses regarded the detection of sustained amygdala activity in depressed individuals in response to negative information. If depression involves primarily disinhibition of the amygdala system (e.g.,

[1] Of note, the qualitative character of these behaviors were largely independent of other network parameters listed in the Appendix. For example, the number of nodes governed how many stimuli the network could code; decreasing this number increased the effects of overtraining, but did not change the fact that overtraining led to sustained processing.

as a consequence of deceased cortical activity or increased amygdala-hippocampal feedback) the network's performance suggested that depressed individuals would display sustained amygdala activity to all emotional stimuli, in comparison to controls. In contrast, if depression also involves strengthening of connections or representations specifically associated with negative information, depressed individuals would display particularly high and prolonged levels of sustained amygdala activity in response to negative information, even after being asked to respond to subsequent unrelated stimuli. 3) To examine whether other brain areas (those implicated by the model and other areas) also preserved sustained activity to negative information, a whole-brain analysis was performed. It was expected that hippocampal activity would covary with amygdala activity, and that activity in the dorsolateral-prefrontal-cortex would be diffusely decreased in response to all emotional stimuli in depressed individuals who displayed increased amygdala activity. 4) The clinical relevance of sustained amygdalar processing can be inferred by examining the extent to which it is related to clinically documented phenomena. Since the simulated mechanisms bear resemblance to mechanisms proposed for depressive rumination (e.g., Siegle & Ingram 1997; Siegle & Thayer, in press) we predicted that sustained amygdala activity to negative information, would be associated with self-reported rumination. Thus, self-report measures of rumination were also administered and sustained amygdala activity occurring in the seconds following emotional stimuli was examined in relation to self-reported rumination.

Methods and Materials

Participants.

Participants included 10 never depressed controls (4 Male, 8 Caucasian, 2 African American, ages 21-47, M(SD)age=36.1(6.7), M(SD)education = 14.3(2.1)) and 7 patients (4 Male, all

Caucasian, ages 24-46, M(SD)age=34.3(8.8), M(SD)education=15.4(.97)) diagnosed by clinicians with unipolar major depression using DSM-IV criteria (APA 1994). Patients were recruited through the University of Pittsburgh's Mental Health Interventions Research Center (MHIRC). Five depressed participants recived the Structured Clinical Interview for DSM-IV Diagnosis (SCID; Spitzer, Williams, Gibbon, & First 1992) which confirmed their diagnosis. Depressed participants reported previously having had 2-6 previous episodes of depression, M(SD) =4.0 (1.5) and having been depressed for between 7 and 70 weeks in their current episode, M(SD)=29.7 (24.4). Control participants endorsed no symptoms of depression, and had no current or historical Axis I disorder using the SCID interview. All participants had normal vision (20/30 using a hand-held Snellen chart), described no notable health or eye problems, and had not abused alcohol or psychoactive drugs within the past six months. No patients were prescribed tricyclics or Nefazadone, and participants with a previous history of psychosis or manic episodes were excluded. All participants had previously participated in another study using the same tasks in which fMRI data were not recorded, but pupil dilation data were recorded (Siegle et al 2001c).

fMRI Data Acquisition

Twenty-six coronal 3.8mm slices were acquired perpendicular to the AC-PC line using a 2-interleave spiral pulse sequence (T2*-weighted images depicting BOLD contrast; TR=2000ms, TE=35ms, FOV=24cm, flip=70 on a 1.5T GE scanner). This 2-shot pulse sequence allowed acquisition of an entire image, including the frontal, temporal, and parietal regions, every 4 seconds for a total of 8 whole-brain images per 32 second task/Sternberg trial pair.

Stimulus Presentation and Behavioral Data Collection Apparati

Stimuli for information processing tasks were displayed in white on a back projection screen.

Participants lay in the scanner approximately 65 cm from the bottom of the stimulus. Stimuli were lowercase letters approximately 1.6 cm high. Reaction times were recorded using a glove capable of reading reaction times with millisecond resolution. To account for differential response latencies to different buttons, the mapping of glove buttons to responses was counterbalanced across participants.

Target Stimulus Materials.

For an emotion-identification task, 10 positive, 10 negative, and 10 neutral words balanced for normed affect, word frequency, and word length were chosen using a computer program (Siegle 1994) designed to create affective word lists from the ANEW (Bradley & Lang 1997) master list. To obtain personally relevant stimuli, participants were asked to generate words between three and 11 letters long, before testing. Participants were instructed to generate "10 personally relevant negative words that best represent what you think about when you are upset, down, or depressed," as well as "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."

Procedure.

One appointment was scheduled with participants after their participation in the pupil dilation component of the experiment, during which they generated a word list and completed rumination measures. Participants were told about the experiment and signed consent forms. Participants completed the information processing measures during the scan followed by mood questionnaires. Participants underwent two emotion processing tasks (valence identification of words and personal relevance rating of sentences), and a control cued-reaction-time task; in each

task trials alternated with Sternberg memory trials. The order of administration of a sentence rating and emotional valence identification task was counterbalanced across participants.

Tasks.

In each of the three tasks, trials alternated between task-relevant trials and Sternberg memory trials. Before Sternberg memory trials the directions "Did you see it" appeared in the middle of the screen for one second to alert participants of the ensuing in trial-type. In Sternberg memory task trials, participants viewed a fixation mask (row of X's with vertical prongs over the center) for one second followed by three random two-digit numbers, followed by a mask (row of X's) for one second each. A target two-digit number then appeared for the following nine seconds. Participants were instructed to push a button for "Yes" if the target was in the previously presented set and another button for "No" if it was not. The order of these buttons was counterbalanced among participants.

For a valence identification task, the 60 positive, negative, and neutral words described previously were presented. The question "What's the emotion" was printed in the middle of the screen for one second followed by a fixation mask which remained on the screen for two seconds. The mask was replaced by the target word for 150 ms and was replaced by a mask (row of X's) for nine seconds. All masks and stimuli were drawn in white on a black background. Research participants were instructed to name the emotionality of each word by pushing buttons for "Positive", "Negative", or "Neutral" as quickly and accurately as they could after the word appeared. Labels for these responses were on screen in the participant's field of view. In an emotional sentence-rating task, the same procedure was used except that instead of viewing a word followed by a mask, participants viewed 15 positive and 15 negative sentences from the Automatic Thoughts Questionnaire (Hollon & Kendall 1980) for nine seconds. Participants were

asked to push a button reflecting whether the sentences were not personally relevant, somewhat relevant, or personally relevant. The order of the yes and no buttons was the same as for the Sternberg trials. A cued reaction-time task was the same as the valence identification task except that instead of a word, a row of "a"'s between three and five letters long was displayed. Participants were instructed to push the middle button as quickly as possible after they detected the change. The change from fixation square to the mask thus served as a cue, or two-second warning, for the stimulus.

Measures of Mood and Rumination.

To assess depressive severity at the time of testing the Beck Depression Inventory (BDI; Beck 1967) was administered. The BDI's concentration on cognitive aspects of depression makes it particularly appropriate for examining aspects of depressive symptomatology related to disruptions in information processing. A variety of self-report measures were used to assess rumination. These include the Response Styles Questionnaire (RSQ; a 71 item inventory with a rumination subscale assessing the frequency of thoughts about one's symptoms of depression (RSQ-rum); Nolen-Hoeksema, Morrow, & Fredrickson 1993), a multi-dimensional rumination questionnaire (MRQ; a 61 item questionnaire with subscales for thinking about depressive affect in relation to a negative event (MRQ-Emots), thinking about what can be done in response to it (MRQ-Inst), and searching for meaning in the event (MRQ-Srch); Fritz 1999), Revised Impact of Event Scale (R-IES; a 15 item inventory with a scale that measures the intrusiveness of thoughts; Horowitz, Wilner, & Alvarez 1979), the Thought Control Questionnaire (TCQ; a 30 item inventory that assesses how people cope with intrusive thoughts, containing a reappraisal scale (TCQ-Reapp), worry scale (TCQ-Worry) and self-punishment scale (TCQ-pun); Wells & Davies 1994) and the Emotion Control Questionnaire (ECQ; a personality inventory with a scale

measuring a tendency to rehearse thoughts (ECQ-reh), Roger & Najarian 1989). In addition, two event-related measures were given to assess the degree to which individuals found themselves engaging in rumination-like behaviors during the tasks (Rumination on a Negative Thought (RNT); Luminet, Rime, & Wagner, submitted; Rumination on a Negative Event (RNE); Papageorgiou & Wells 1999). For these two measures, factor analytically derived general rumination subscales (RNT-Gen, RNE-Gen) described by Siegle (2001) were used.

Data Selection and Cleaning

Selection of Stimuli for Analysis. Valence identification and sentence rating trials with reaction times below 150 ms or outside 1.5 times the interquartile range from the median reaction time were discarded as outliers, because previous results suggest that reaction times in this range indicate that a response was made without regard for the stimulus (e.g., Matthews & Southall 1991; Siegle et al 2001a,b). This procedure eliminated little data (on average 5-6 trials per person, and never more than 11 trials for any person). Trials in which the valence rating was incongruent with the normed valence on the valence identification task were not removed from the data set, because it was assumed that essential cognitive processes leading to a decision were similar regardless of the eventual decision.

Aggregation of Reaction Times. Harmonic means of reaction times were used to reliably index the central tendency of an individual's reaction times within a condition (as recommended by Ratcliff 1993). To eliminate spurious skew due to outliers while preserving rank-ordering of data, outliers more than 1.5 times the interquartile range from the median harmonic mean on any variable were scaled to the closest obtained value below this cutoff plus the difference between this value and the next closest value as in Siegle et al (2001a). This technique was adopted

rather than other techniques (e.g., trimmed means) to preserve as much valid data as possible, while not decreasing statistical power due to inclusion of outliers.

Preparation of fMRI data for analysis. Statistical analyses were conducted in the Neuroimaging Software (NIS) data stream using software developed locally through the Human Brain Project. Data were prepared using methods described by Carter et al (2000). Following motion correction using the AIR algorithm (Woods, Cherry, & Mazzoitta 1992), linear trends in fMRI data, calculated over blocks of 40 trials (5.5 minutes) were removed to eliminate effects of slow drift in the fMRI signal that were not related to trial characteristics. fMRI data were then cross-registered to (i.e., warped to conform to the shape of) a standard reference brain using the 12 parameter AIR algorithm.

To examine a-priori hypotheses the amygdala was traced on the reference brain's high-resolution structural MRI (SPGR) using guidelines based largely on Honeycutt's (1998) recommendations. Specifically, the posterior boundary was defined axially as the alveus of the hippocampus. The anterior boundary was defined axially 2mm from the temporal horn of the lateral ventrical. The superior boundary was defined coronally as the ventral horn of the subarachnoid space and the inferior boundary was defined coronaly as the most dorsal finger of the white matter tract under the horn of the subarachnoid space. The lateral boundary was defined coronally at 2mm from the surrounding white matter and mesial boundary was defined coronally at 2mm from the subarachnoid space.

Reliability was calculated for each region of interest using interclass correlations between raters on the number of voxels identified in each slice in which either rater had drawn on an SPGR. GS's intra-rater reliability for tracing the amygdala using these guidelines was .85 and inter-rater reliability between GS and another experienced rater was .89. Activation in the traced

region, coregistered to the functional data, was averaged for each scan.

Results

Hypotheses generated using the computational model were evaluated. As hypotheses primarily regarded the valence identification task, these data are discussed below. Data from the cued reaction time task are also examined as a non-emotional-processing contrast. As expected, the depressed group scored as significantly more dysphoric on the BDI than the control group, depressed M(SD)=21.6(9.9), control M(SD)=2.4(1.8), $t(15)=-6.0$, $p<.0005$, Difference (D)=19 points. The groups also did not differ significantly on age, $t(15)=.3$, $p=.7$, education, $t(15)=-1.3$, $p=.2$, or gender, $t(15)=-1.1$, $p=.09$.

Behavioral stimulus ratings: Were negative words deemed negative, and were idiosyncratically generated words deemed personally relevant?

Emotional words were clearly separated in judgments of valence both during the valence identification task and in post-task ratings. During the task, words were generally rated as consistent with the valence under which they were normed or generated, $M_{\%agreement}=.74$, $SD=.18$. Similarly, ratings on the valence identification task generally agreed with post-test word ratings, on a scale on which 1 was very negative and 7 was very positive. Ratings were counted as in agreement if the word was rated 1-3 and considered negative during testing, rated 3-5 and considered neutral during testing, or rated 5-7 and considered positive during testing, $M_{\%agreement}=.75$, $SD=.14$. On a 5 point scale of "not relevant to me" to "very personally relevant", idiosyncratically generated words were reliably rated as more personally relevant than normed words $D=1.25$, $t(16)=10.71$, $p<.0005$.

Behavioral Data.

Group x valence x personal-relevance split-plot ANOVAs on mean harmonic mean valence-

identification and Sternberg task decision times revealed no main effects or interactions with group, $p>.4$ for all tests. The only significant test was a main effect of valence for the valence identification task, $F(2,14)=7.4$, $p=.007$, $\eta^2=.51$. All individuals responded more slowly to neutral words, M(SD)= 1312 (604) ms than to positive words, M(SD)= 1061(463) ms, $F(1,16)=17.3$, $p=.001$, or negative words, M(SD)= 1163(504) ms, $F(1,16)=6.09$, $p=.025$. With the possible exception of one subject, whose Sternberg accuracy data were lost, all subjects had uniformely excellent signal detection rates on the Sternberg task, $M_{d'}=4.33$, $M_{\%correct}=.95$, SD=.06. Fourteen subjects made two or fewer errors; on control made 16 errors and one depressed individual made 5 errors. There were no significant differences in signal detection rates between controls and depressed individuals, $p>.6$. T tests of reaction times on the cued-rt task also suggested that there were no global group differences, D=37ms, $t(15)=.53$, $p=.6$.

Planned contrasts using traced amygdala regions: Did depressed individuals display particularly sustained amygdala activity in response to negative information?

Were there group differences in sustained amygdala activity? Activation in the traced left and right amygdala regions over the eight scans per trial, expressed as a percentage difference from a pre-stimulus baseline (scan 1), is shown in Figure 2. To examine valence related sustained processing, left and right amygdala activity, summed over the last three scans, minus a pre-stimulus (scan 1) baseline, was subjected to hierarchical regressions in which activation to negative stimuli was the dependent variable. Activation to positive stimuli was entered on the first step, $R^2_{left}=.02$, $R^2_{right}=.13$, and group (depressed/never-depressed) was entered on the second step, $\Delta R^2_{left}=.31$, $\Delta F(1,14)=6.6$, $p=.022$, $\Delta R^2_{right}=.24$, $\Delta F(1,14)=5.1$, $p=.04$. Thus, analyses suggest depressed individuals show greater bilateral sustained amygdala activation for negative than positive words compared to healthy controls.

Was sustained amygdala activity stable? To evaluate the stability of the sustained response, amygdala activity for each subject, separately for each valence was fitted to an ex-gaussian waveform in which the height of the peak and slope of the tail were allowed to vary. An ex-gaussian is the sum of a gaussian (often used as an approximation for a hemodynamic response, e.g., Rajapakse et al 1998) and a negative exponential curve, which governs the slope of the right tail. The slope data were subjected to group x personal relevance x valence split plot ANOVAs. These revealed a three-way interaction for the left amygdala, Greenhouse Geisser $F(1.98,14) = 3.49$, $p=.04$, $\eta^2=.18$, driven by the depressed individuals' particularly flat slopes for negative normed words, $t(15)=3.2$, $p=.005$, and no significant effects for right amygdala.

Insert Figure 2 about here

Exploratory Analyses: Were there other areas reflecting sustained processing of negative information by depressed individuals?

Exploratory analyses consisted of whole-brain voxel-by-voxel ANOVAs (as in Carter et al 2000) using subject as a random factor, and group, scan, valence and personal relevance as fixed factors. Random effects analysis permits generalization of results at the population level and hence, is well suited to clinical studies. Voxels were identified in which effects were detectable at $p<.01$, corrected for multiple comparisons using a contiguity threshold, and in which the response in scans 4-7 for negative words versus positive and neutral words was different for depressed and control individuals (restriction at $p<.1$). Of particular interest, this analysis revealed bilateral amygdala ROIs and an amygdala/hippocampal ROI that had time-series similar to those presented above. These particles and associated time series are shown in Figure 3. Table

1 lists the Tailerach coordinates of all regions of interest (ROIs) detected in this analysis. As shown in the table, there were a number of other areas detected by the analysis that are not discussed because analogs for them were not included in the hypothesis-generating model. In addition, the ANOVA also detected a single ROI in which biases in sustained activity were negatively correlated with the left amygdala particle which was in the left DLPFC (BA8/9), Tailerach coordinates, -52,13,39. Activity in this ROI appeared to decrease for positive and negative words in depressed individuals and is included in Figure 3.

Insert Table 1 & Figure 3 about here

Decomposition analyses were conducted on the sum of late activity (scans 4-7) in the four ROIs corresponding to modeled areas. Planned contrasts suggested that, as hypothesized, depressed individuals showed sustained responses for negative information vs. neutral information, in comparison to controls, in both amygdala particles, Left: $t(15)=3.1$, $p=.007$, $D=5.5\%$, Right: $t(15)=2.5$, $p=.02$, $D=3.9$, and the left hippocampal particle: $t(15)=2.9$, $p=.01$, $D=2.2\%$, but not the DLPFC particle, $t(15)=-.7$, $p=.51$, $D=-.23\%$. Simple effects analyses, Bonferroni corrected for 3 comparisons, yielded few significant differences between groups on any valence for the three particles. Specifically, only the following significant differences were observed: Left amygdala, negative words: $t(15)=3.7$, $p=.004$, $D=4.7\%$, left amygdala/hippocampus, negative words, $t(15)=2.9$, $p=.009$, $D=1.7\%$.

To be certain that these effects were unique to the processing of valence, and not just doing a cognitively demanding task, group differences in the same rois were examined for the cued-rt / Sternberg task. No group differences were statistically significant ($p>.05$).

Relationships between DLPFC and Amygdala Activity: Was DLPFC activity decreased in the same individuals who displayed increased amygdala activity?

Davidson's (2000) theory suggests that amygdala activity should be tempered by DLPFC activity in controls, but less so in depressed individuals. Were this phenomenon the result of decreased trial-by-trial moderation, within subject correlations would be expected to be strongly negative in controls but not in depressed individuals. Were this phenomenon the result of decreased overall DLPFC functioning, relationships between valence related DLPFC activity and amygdala activity would be expected to be negative, in general, and especially in depressed individuals.

Correlations were examined between activity in the empirically identified amygdala and DLPFC particles. Within subject correlations between amygdala and DLPFC activity were low (M_r<.04 for all comparisons) and in no case was the relationship statistically significantly different for depressed and never-depressed individuals. Yet, between subject correlations revealed a significant negative relationship between biases (activity in scans 4-7 to negative vs. positive words) in the empirically identified left DLPFC and left amygdala particles, r=-.63, p=.007, and the left hippocampal particle, r=-.68, p=.003, and a marginally significant negative correlation with the empirically identified right amygdala particle, r=-.41, p=.1. Similarly, when bias was computed as the difference in sustained activity (scan 4-7) on negative vs. neutral words, correlations were significant and negative between DLPFC activity and both left amygdala, r=-.50, p=.04, and the left amygdala/hippocampal particle, r=-.57, p=.02.

As expected, the magnitude of these relationships was especially strong in depressed individuals. For biases computed as the difference in sustained response to positive and negative words, $r_{DLPFC,left\ amygdala}$=-.74, $r_{DLPFC,right\ amygdala}$=-.69, $r_{DLPFC,left\ hippocampus}$=-.97. For biases

computed as the difference in sustained response to neutral and negative words, $r_{DLPFC,left\ amygdala}$=-.83, $r_{DLPFC,right\ amygdala}$=-.56, $r_{DLPFC,left\ hippocampus}$=-.87.

Relationships Between Sustained Amygdala Activity and Self-Reported Rumination

Self-reported rumination, as indexed by multiple measures, was moderately related to amygdala activity on scans 6-7. Table 1 shows correlations of the difference in activity to positive and negative information for left and right amygdala activity and each of the administered rumination measures. Some aggregate measures were also powerful predictors, but because so few individuals were tested, power is low to draw conclusions regarding these measures in the current sample. For example, in the individuals for whom fMRI assessment was performed, 7.5% of variation in the amygdala particle's response to negative versus positive words on scan 6 was accounted for by group (depressed / control). An additional 56% of variation (64% total) was accounted for by adding Fritz's (1999) multidimensional rumination measure.

Insert Table 2 about here

Discussion

The preceding data suggest that depressed individuals display sustained amygdala processing in response to negative information in comparison to controls. Specifically, when a negative word is presented briefly (150ms), depressed individuals appear to continue to process that information for up to 30 seconds, even when they are given a subsequent non-emotional distracting task, designed to provoke activation in brain areas hypothesized to be active in shutting off the amygdala. Moreover, sustained amygdalar processing of negative information

was related to self-reported rumination suggesting that the observed biases are clinically relevant.

Amygdala activity was inversely related to DLPFC activity, which is consistent with the idea that depression could involve, in part, decreased inhibition of the amygdala by cortex. As DLPFC activity was inversely correlated with amygdala activity to negative words on an inter-individual level, but not on a trial-by-trial level, there is some support for the idea that depression might be characterized by overall decreased DLPFC activity. Yet, this causality is difficult to infer from the data. Since the DLPFC particle's activity appeared to drop below its baseline activity in the late scans for depressed individuals when amygdala activity was high, and since there was no group difference on a non-affective processing task in which amygdala activity was low, these data are also potentially consistent with the notion that increased amygdala or hippocampal activity could have a causal role in modulating cortical activity (e.g., Moore & Grace 2000).

A number of other areas displayed increases in sustained reactivity to negative words in depressed individuals. Since they were not modeled, and their activity was not predicted, interpretation of their activity is necessarily speculative. Two of these areas, the posterior cingulate and inferior parietal cortex, have both been associated with autobiographical memory retrieval (Maddock et al, 2001). Activation due to autobiographical memory retrieval is consistent with the idea that depressed individuals engage in personally relevant elaboration on negative information. Alternatively, as posterior cingulate activity has been implicated in negative mood induction (e.g., Baker et al, 1997), its activity in depressed individuals could reflect sustained affective reactivity to negative stimuli. Strong connections from parahippocampal and frontal regions to the posterior cingulate could also be important to the

observed increased activity in the posterior cingulate. Increased activity of the superior frontal gyrus (BA6) in depressed individuals in response to negative words is more difficult to understand, though activity in this area has been observed to increase with elated mood (Baker et al, 1997), and decrease with depressive severity (Hirono et al, 1998), suggesting that its activity is related to affect. More specific examination of this structure's activity in response to emotional stimuli could help to further explain observed results.

Using a similar approach, sustained processing of emotional information, indexed by sustained pupil dilation (a correlate of cognitive load), has been observed in depressed individuals up to 6 seconds after their responses to emotional stimuli on a valence identification task (Siegle et al 2001a,c) The current data suggest relationships between sustained pupil dilation and sustained amygdala activity. Because all participants who went through this protocol had also gone through the same tasks during measurement of pupil dilation (Siegle et al 2001c), the current study can be used to help interpret the pupil dilation data. Yet, a hierarchical regression on sustained pupil dilation biases (negative vs. positive) suggested that analogous biases in the empirically derived left amygdala and DLPFC regions of interest accounted for an additional 52% of variation above and beyond group[2]. These relationships suggest that both sustained fMRI and pupil dilation signals may index some of the same phenomena, and that fMRI may be able to more specifically index valence effects, which are occluded by more peripheral measures.

A number of limitations to this study must be acknowledged. The samples were relatively small, and thus effects of personal relevance may not have been detected due to low power. Not all depressed participants were very dysphoric at the time of testing suggesting that results could be a function of aspects of depression that are not directly related to mood. The administered

[2] $F(2,12)=7.2$, $p=.008$. The areas accounted for separate and overlapping variance: left amygdala: $r=.61$, semipartial $r^2=.11$, $t(12)=1.7$, $p=.11$, DLPFC: $r=-.67$, semipartial $r^2=.15$, $t(12)=-2.0$, $p=.06$

rumination measures were highly correlated with depressive severity (most > .6) making it difficult to disentangle relationships between the observed information processing biases, rumination, and depressive severity.

A potential concern involves the absence of detectable behavioral (i.e., decision time or signal detection rate) differences between depressed and control individuals on the administered tasks. Since hypotheses for the valence identification involved sustained processing rather than early processing and since biases in early processing of emotional information in depression are notoriously difficult to detect (e.g., MacLeod & Mathews 1991), the absence of these differences is not surprising. The absence of group differences in Sternberg reaction times following negative v. positive words is not consistent with the idea of interference of the valence of a word on subsequent performance. Potentially, the low cognitive load entailed by a three-number Sternberg task allowed both emotional and non-emotional processing to occur; perhaps behavioral effects would be revealed in a more cognitively demanding task.

Another curiosity involves the apparently increased sustained amygdalar processing of neutral words by control participants, relative to depressed participants and relative to other valences. This phenomenon was not predicted by the model. One explanation involves the idea that when never-depressed individuals are asked to make emotional judgments about neutral words, the amygdala's emotion recognition functions could be recruited; having made no quick emotional association, amygdalar processing could continue. Since this study represents the first event-related fMRI study of emotional word valence identification, further empirical investigation of this phenomenon in a larger sample, along with computational modeling of possible substrates of the effect will be important before it is relied on.

A final possible concern involves the possibility that results relied on words that were not

perceived consistently by subjects with the valence under which they were categorized (e.g., a word categorized as positive that a subject perceived as negative). To rule out this possibility, the exploratory analyses were rerun restricted to words for which the normed or generated valence was consistent with the participant's ratings on a word-rating task given at the end of the experiment, using the criteria described above. The bilateral amygdala particles still displayed sensitivity to valence, and were also sensitive to personal relevance (controls displayed particularly high levels of sustained activity to neutral words and depressed individuals displayed low levels of sustained activity to normed positive words).

These limitations not withstanding, this study has a number of potentially important clinical implications. Depressed individuals are frequently observed to have difficulty in life situations not considered to be inherently emotional. This study suggests that a depressed person's experience of an emotional stimulus could persist well beyond that stimulus, and in fact, could persist into the time the are expected to be engaging in other activities. Such prolonged processing could lead to interference with the subsequent activity. Indeed, a number of participants reported that they made errors on non-emotional processing trials following particularly negative personally relevant words because they were still thinking about the presented word. Moreover, data are consistent with a model of both overall disinhibition of the amygdala in conjunction with specifically greater amygdala activity in response to negative information. Simulations suggested that the magnitude of differences in responses to positive and neutral stimuli could be dependent on the extent to which an individual has learned negative associations very well (in contrast to overall disinhibition of the amygdala).

To the extent that results support a relationship between sustained amygdala activity to negative information and self-reported rumination, there are more pervasive clinical

implications. Depressive rumination is often thought to happen on the course of minutes to hours. Potentially, the same mechanisms underlying sustained processing, which begin in the seconds following emotional information, are involved in the experience of depressive rumination. If these mechanisms involve amygdalar activity, it could be suggested that initial emotional reactions to stimuli serve as triggers or precursors for later rumination. Of particular note, the one scale that assessed adaptive cognitive reappraisal of emotional information (TCQ – reappraisal scale) was not well correlated with amygdala activity. These data could thus further suggest that rumination does not involve only dry cognitive reflection on emotional information; rather, sustained processing of negative information actively involving parts of the brain associated with emotional appraisal and expression.

At the very least, these observations suggest that understanding brain mechanisms underlying sustained processing of emotional information may be important to understanding the phenomenology of depression. They could also have implications for treatment of depression. For example, experiments with Siegle's (1999) model suggests that re-engaging inhibition from DLPFC could decrease sustained amygdalar activity. Therapies such as Wells' (2000) attentional control training may help depressed individuals to invoke such cortical control, even though they nominally do not require insight, reflection on emotions, or a therapeutic relationship. This model could provide a mechanism behind which the action of such therapies could be explained.

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Appendix – Network Parameters

Network Architecture

The network was comprised of the following populations of units:

65 input units, locally coded (representing 60 words, 5 numbers)

65 semantic units locally coded (representing 60 words, 5 numbers)

2 valence units (representing positivity and negativity)

3 task units (representing valence identification, stimulus identification, Sternberg memory)

68 output units (representing 60 words, 5 numbers, 3 valences (positive, negative, neutral))

Initial Training

Hebb training was used to strengthen the following connections. Input units were trained to activate unique semantic units. Semantic units were trained to activate unique output units. 20 semantic units were trained to activate the "positive" valence unit. 20 semantic units were trained to activate primarily the "negative" valence unit. Neutral words slightly activated both the positive and negative valence units. The valence units were trained to reciprocally activate the semantic units and to activate all decision units corresponding to the appropriate valences and, less strongly, semantic associations of the appropriate valence. Additional training was provided to make connections stronger for input, semantic, and valence units going from and to 10 "positive," 10 "negative," and 10 "neutral" personally relevant stimuli. Thus final connection strengths from non-personally relevant positive semantic units to the valence units were (.1432 -.0114), and from personally relevant semantic units (.2118 .0024). From non-personally-relevant negative semantic units to valence units strengths were (-.0114 .1432) and from personally relevant units (.0024 .2118). From non-personally relevant neutral semantic units to valence units strengths were (-.0114 -.0114) and from personally relevant neutral units to valence units

strengths were (.0024 .0024). From the Sternberg units connection strengths to valence units were (-.05 -.05). Connections from valence to semantic units were the transpose of the semantic to valence unit connections. Task units amplified semantic, valence, or Sternberg unit connections. Decision units inhibited valence units with constant strength. All weights were stored in a single square weight matrix.

Activation Rule

Activation propagated through the network to implement a cascaded recurrent associative network. A raw activation was computed as the "current_activation * weight_matrix + input + noise". Current activation was then computed as a cascaded function of the raw and previous activation: τ *raw_activation+(1-τ)*(previous_activation), as in Cohen, Dunbar, & McClelland (1990). Finally, the current activation was scaled using a trimmed logistic of the raw activation which limited its activation to between -.02 and 2:

$$\min(-.02, \frac{4.3279}{1+e^{-activation}} - 2.164)$$

Simulation of a Trial

Each phase of empirically administered trials was simulated for a number of epochs proportional to the time of each segment of the empirically administered trials. Task units were turned on to represent the valence identification task at the beginning of the trial. To simulate the pre-trial interval the network's input was set to a mask of noise. To simulate the presentation of a stimulus, input was set to a single input unit being on, plus noise. To simulate the backward mask interval, input was again set to noise. During the Sternberg portion of a trial task units were reset to represent the Sternberg task. For a pre-stimulus interval, a mask was presented. Next, input units were successively set to each Sternberg stimulus, plus noise, followed by a mask interval, and presentation of a final Sternberg stimulus, which remained active until the end of

the trial. Relevant parameters for simulation of depression are shown in table 3.

Insert Table 3 about here

Table 1: Tailerach coordinates for ROIs displaying a group x scan x valence effect from a group x scan x valence x personal-relevance ANOVA, p<.01, in which the response to negative words vs. positive and neutral words was at least marginally different for depressed and never-depressed individuals (thresholded at p=.1). The p1 column represents significance for a test of a difference between depressed and control individuals on a negative v. positive valence contrast for the mean of scans 4-7. The p2 column represents the analogous test for a negative v. neutral valence contrast. Tailerach coordinates were determined using the most significant voxel in an ROI from the ANOVA.

location (x (R),y (A),z (S))	p1	p2	location
-23, 31, 18	**	*	middle frontal gyrus BA46
1, 8, 61	*	*	superior frontal gyrus, BA6
19, 5, -12	~	*	Subcallosal gyrus BA34 / amygdala
-15, -4, -6	*	**	amygdala
-21, -10, -8	~	*	amygdala / hippocampus
54, -23, 32	~	*	inferior parietal lobule, BA40
4, -31, 18	~	*	posterior cingulate gyrus, BA23

~p<.1, *p<.05, **p<.01

Table 2: Correlations between sustained biases in fMRI amygdala activity (positive-negative, scans 4-7) and self-reported rumination scales

	Traced Left	Traced Right	Empirical Left
Group	.356	.520*	.535*
RSQ-Rum	.637**	.461	.588*
RNT-Gen	.421	.334	.572*
RNE-Gen	.581*	.491	.731**
MRQ-Emots	.511*	.638**	.678**
MRQ-Inst	.624*	.602*	.682**
MRQ-Srch	.292	.484	.742**
RIES-Int	.373	.323	.359
TCQ-Worry	.176	.214	.350
TCQ-Pun	.303	.196	.205
TCQ-Reapp	-.048	-.135	.088
ECQ-Reh	-.521*	-.517*	-.469

*p<.05, ** p<.01, ***p<.001

Table 3: Parameters for neural network simulations, as described in the Appendix

Parameter	Value
Network construction	
Number of input nodes	65 (30 personally relevant, 30 non-personally relevant, 5 numbers)
Number of semantic nodes	65
Number of Valence nodes	2
Number of Output / Decision nodes	68
Activation parameters	
τ (input diffusion / cascade rate throughout the network)	0.04
TaskPriority	.5
maximum network activation	2 (via logistic)
minimum network activation	-.02
noise magnitude	0.01
Task parameters	
stimulus duration	10 epochs
total measured duration	1080 epochs
accumulation noise	0.0
valence determination accumulation threshold	starts at .9 and shrinks on negative exponential in time
Training parameters	
learning Rate	.3

preservation of old learning during new learning (i.e., forgetting rate)	.89
Parameters for simulation of depression	
additional epochs of training on negative stimuli	3
rate at which new training exemplars were assimilated	.05
preservation of old learning during new learning (i.e., forgetting rate)	.89
additional semantic-affective unit feedback	.007
decrease in inhibition of valence units by decision units	.015
Number of negative stimuli representing depressogenic loss	10

Figure 1 Caption

A computational neural network model of emotional information processing in depression, and associated predictions for amygdala activity. The model and depicted time-series are described in the text.

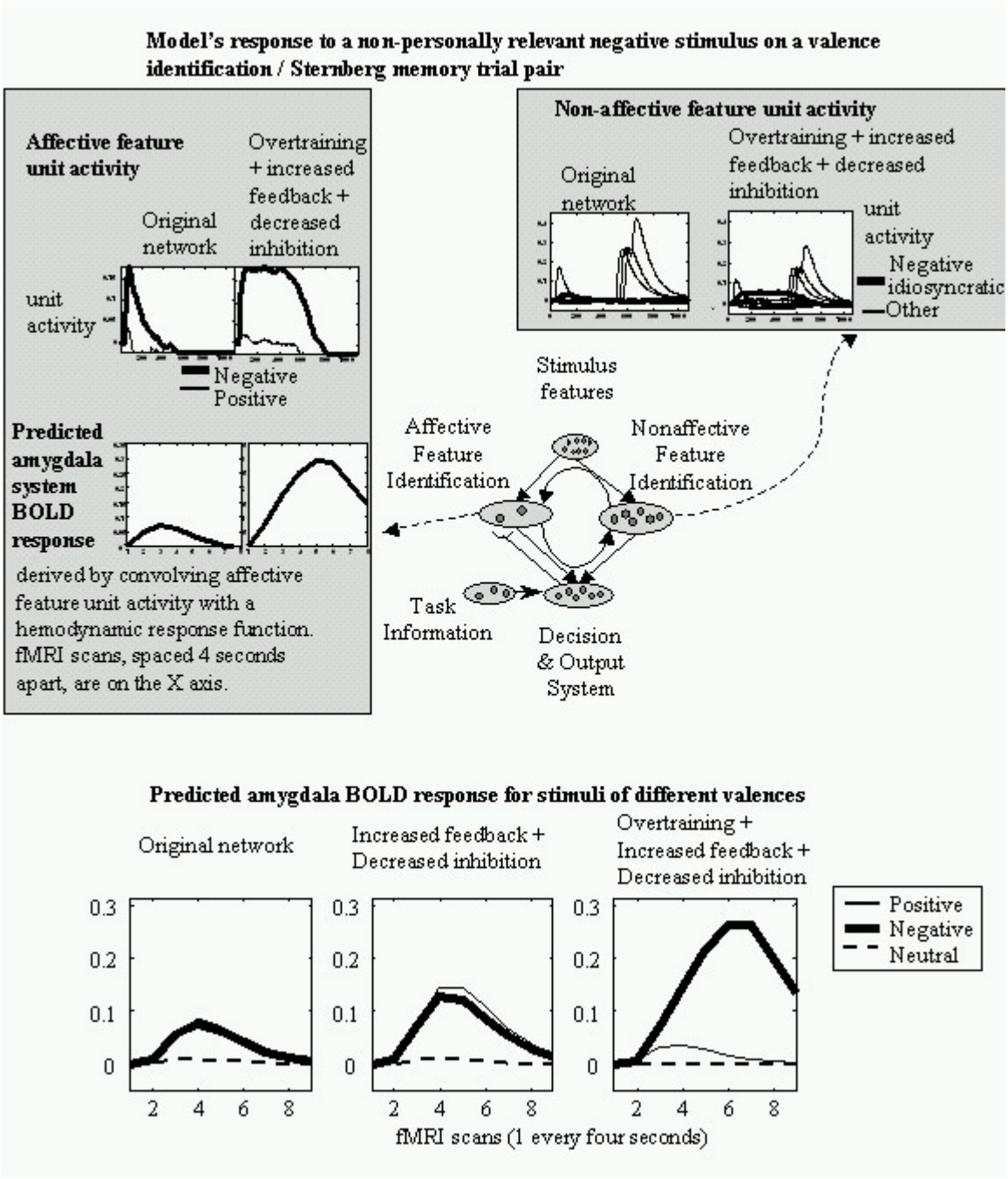

Model's response to a non-personally relevant negative stimulus on a valence identification / Sternberg memory trial pair
Affective feature unit activity
Original network
Overtraining + increased feedback + decreased inhibition
unit activity
Negative
Positive
Predicted amygdala system BOLD response
derived by convolving affective feature unit activity with a hemodynamic response function. fMRI scans, spaced 4 seconds apart, are on the X axis.
Non-affective feature unit activity
Original network
Overtraining + increased feedback + decreased inhibition
unit activity
Negative
idiosyncratic
Other
Stimulus features
Affective Feature Identification
Nonaffective Feature Identification
Task Information
Decision & Output System
Predicted amygdala BOLD response for stimuli of different valences
Original network
Increased feedback + Decreased inhibition
Overtraining + Increased feedback + Decreased inhibition
0.3
0.2
0.1
0
2
4
6
8
fMRI scans (1 every four seconds)
Positive
Negative
Neutral

Figure 2 Caption

Time courses for traced right and left amygdala regions of interest. The x-axis in all graphs represents scan which occurred 4 seconds apart, for a total of 32 seconds. The first 4 scans occurred during an affective valence-identification trial. The last 4 scans occurred during a Sternberg memory trial. The y axis represents mean the percent MR signal activity change from a scan 1 baseline.

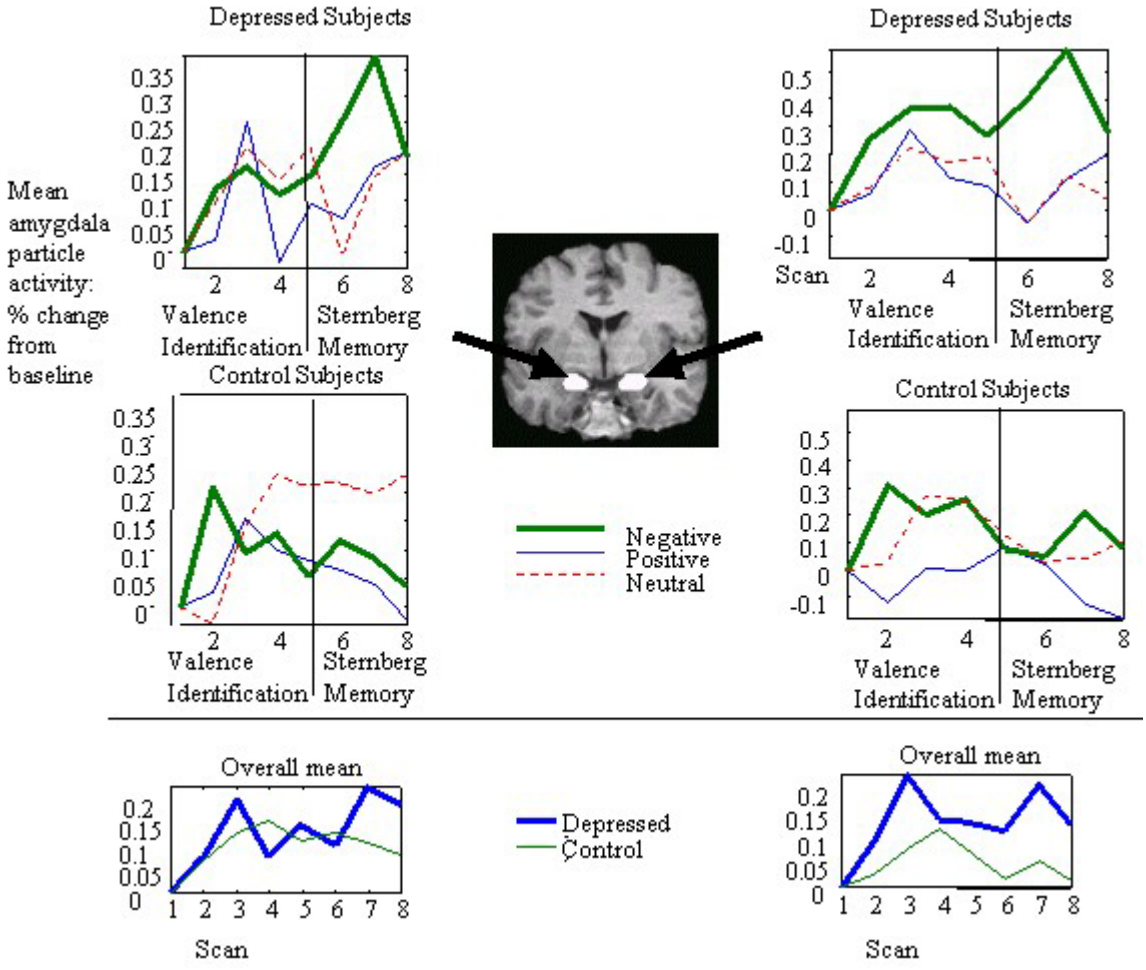
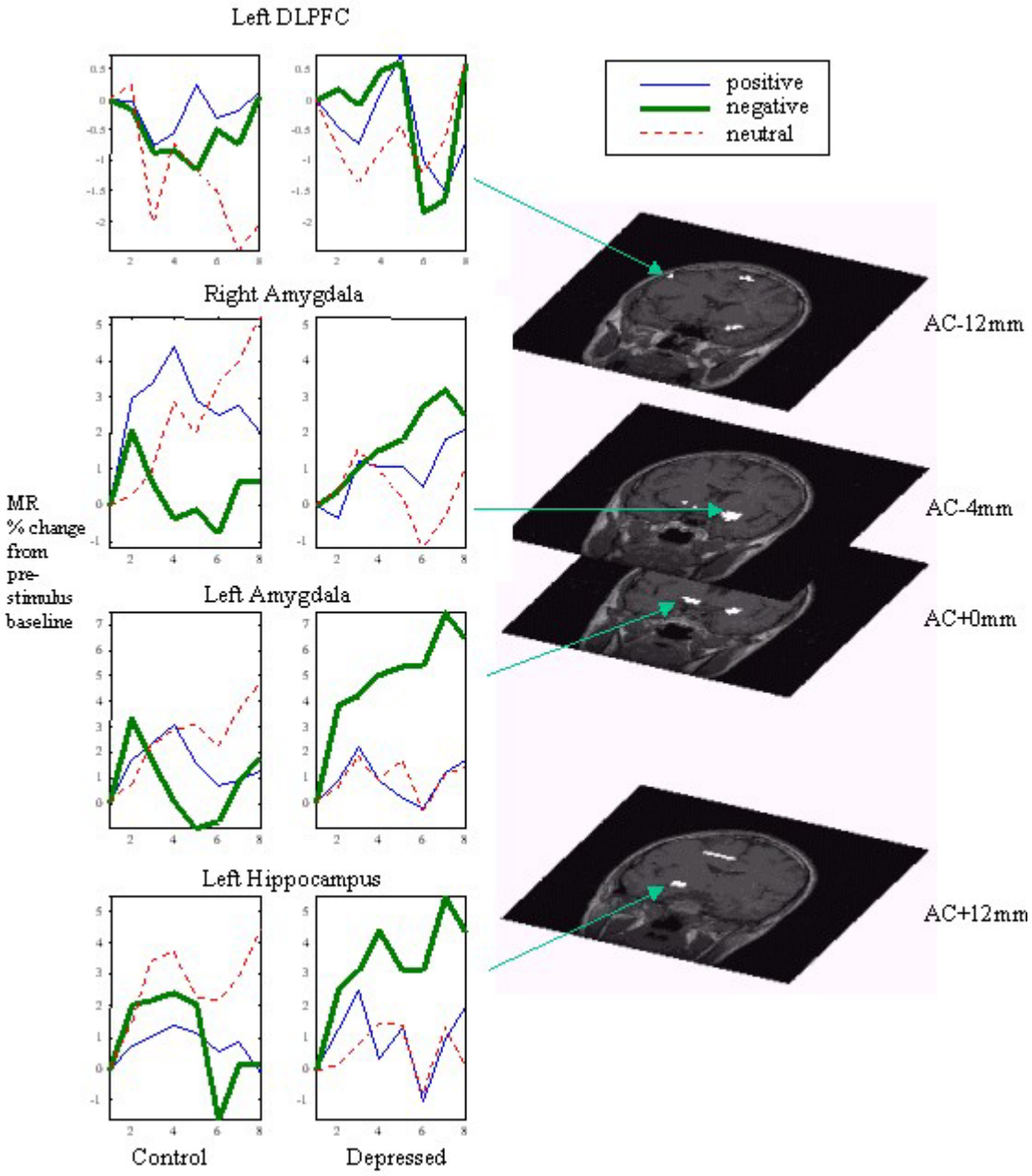

Depressed Subjects
Mean amygdala particle activity: % change from baseline
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
2 4 6 8
Valence Identification
Sternberg Memory
Control Subjects
Depressed Subjects
0.5
0.4
0.3
0.2
0.1
0
-0.1
Scan
Control Subjects
Negative
Positive
Neutral
Overall mean
Depressed
Control
1 2 3 4 5 6 7 8
Scan

Figure 3 Caption

Location and time courses for ANOVA derived dorsolateral prefrontal cortex (DLPFC), amygdala and amygdala/hippocampal regions of interest.


Left DLPFC
positive
negative
neutral
Right Amygdala
AC-12mm
MR
% change
from
pre-
stimulus
baseline
AC-4mm
Left Amygdala
AC+0mm
Left Hippocampus
AC+12mm
Control
Depressed