Neural correlates of idiographic goal priming in depression: goal-specific dysfunctions in the orbitofrontal cortex

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INTRODUCTION

Unipolar depression is an episodic disorder characterized by decreased hedonic and motivational responsiveness to events previously associated with positive outcomes (Akiskal and McKinney, 1973; Depue and Iacono, 1989). These symptoms implicate dysfunction of incentive motivation and positive affectivity (Watson et al., 1999) that involve alterations in cognition and neurophysiology via multiple brain pathways and circuits (Davidson et al., 2002; Mayberg, 2003). Although there is broad evidence that depression is associated with disruption of appetitive/approach motivation (Dickson and MacLeod, 2004; McFarland et al., 2006), most studies of motivational deficits in depression have focused on temperament-based mechanisms for approach and avoidance (Fowles, 1988; Gray, 1994). However, recent studies also suggest that dysfunction of self-regulation, defined as the psychological and neurophysiological processes that underlie personal goal pursuit (Carver, 2004), constitutes both a risk factor for and a consequence of depression (Kasch et al., 2002). The present study tested the hypothesis that depression would be associated with dysfunction in neural mechanisms underlying the representation and processing of two important classes of personal goals.

Regulatory focus theory (RFT) identifies two distinct classes of goals representing desired end-states toward which people self-regulate (Higgins, 1997). The two types of goals are associated with different cognitive, motivational and strategic inclinations. Promotion goals involve accomplishment, advancement or aspiration—that is, ‘making good things happen’. Prevention goals involve security, safety or responsibility—that is, ‘keeping bad things from happening’. Pursuit of promotion and prevention goals involves strategic rather than spatiotemporal approach and avoidance respectively and can be activated intentionally as well as automatically (e.g. when a stimulus ‘primes’ a goal representation). RFT predicts that perceived progress toward a promotion goal is associated with feelings of happiness while perceived failure is associated with sadness and dejection; in contrast, perceived progress toward a prevention goal leads to quiescence while perceived failure leads to agitation and anxiety (Higgins et al., 1997). Chronic perceived failure to attain promotion goals is associated with...
depressive symptoms, whereas failure to attain prevention goals is associated with symptoms of anxiety (Strauman, 1992). The psychological mechanisms that underlie pursuit of promotion and prevention goals emerge during development primarily as a function of socialization (Manian et al., 2006) and can be distinguished reliably from the temperament-based mechanisms described in biobehavioral theories of approach and avoidance (Strauman and Wilson, in press).

Although there is considerable evidence from behavioral studies supporting the predictions of RFT regarding promotion and prevention goal pursuit, data regarding the neural correlates of promotion/prevention goal activation are just beginning to appear. Using EEG, Amodio and colleagues (2004) found that chronic promotion focus was associated with greater left frontal activity while chronic prevention focus was associated with greater right frontal activity. Using functional magnetic resonance imaging (fMRI), Cunningham et al. (2005) found that individual differences in promotion/prevention focus were associated with patterns of neural activation in response to a valence judgment task. In a recent study, we used fMRI to identify brain regions activated during incidental priming of promotion and prevention goals (Eddington et al., 2007). Based on evidence of cortical asymmetry associated with individual differences in regulatory focus (Amodio et al., 2004), we predicted that promotion and prevention goal priming would be associated with activation in the left and right orbitofrontal cortices (OFC), respectively. Promotion goal priming discriminantly activated a region of left OFC (BA 11), and variability in activation of this region following promotion goal priming was correlated with individual differences in the strength of participants’ self-reported orientation to promotion goals.

To our knowledge, the Eddington et al. study was the first to use fMRI to link idiographically assessed personal goal representation and priming with changes in cerebral blood flow in the OFC—a region implicated in decision making, in performance monitoring and in representing the hedonic value of primary as well as abstract (secondary) reinforcers (Kringelbach, 2005). Furthermore, the left OFC activation following promotion goal priming was detected while participants were performing a task unrelated to personal goal pursuit, supporting the postulate of RFT that promotion and prevention goals, as highly accessible knowledge structures, can be activated implicitly. Other investigators have found evidence linking OFC with goal-pursuit-related cognitive and motivational processes such as integrating information regarding the current state of the organism with previously acquired social knowledge in order to guide behavioral choices and strategies (Furuyashiki and Gallagher, 2007; Petrides, 2007). Thus, the OFC may be an important component of a neural system that instantiates personal goal representations and, via interactions with other brain regions, determines incentive values and guides hierarchically organized goal-directed behaviors (Holland and Gallagher, 2004).

If promotion goal priming is associated with left OFC activation, and individuals experiencing chronic failure to attain promotion goals are vulnerable to depressive symptoms, then depression might be characterized by a dysfunction in left OFC activation following promotion goal priming. Such a deficit would be consistent with behavioral findings linking chronic perceived failure in promotion goal pursuit with vulnerability to depression (Strauman, 2002), as well as with the observation that compared with nondepressed controls, depressed individuals manifest decreased left OFC activation in response to affectively salient visual stimuli (Tremblay et al., 2005). In addition, recent clinical data indicated that a self-regulation-based treatment was differentially efficacious for patients diagnosed with primary major depressive disorder or dysthymic disorder characterized by chronically poor promotion goal pursuit (Strauman et al., 2006).

In the current study, we hypothesized that incidental priming of promotion goals during a social judgment task would reliably induce left OFC activation among individuals with no history of depression (replicating the findings of Eddington et al.), but that depressed patients would show an attenuated left OFC response to promotion goal priming. We also hypothesized, consistent with previous studies showing frontal asymmetry related to negative/positive affectivity (Allen and Kline, 2004; Davidson, 2004) and with recent perspectives on depressive/anxious comorbidity (Strauman, 2002; Watson, 2005), that priming prevention goals would lead to increased activation in the right PFC in depressed patients, reflecting compensatory hypersensitivity to prevention goals due to hypoactivation of promotion goals (Strauman, 2002). Finally, we predicted that despite these differences in response to personal goal priming, the two participant groups would show similar patterns of cortical activation in response to the judgment task itself.

**METHODS AND MATERIALS**

**Participants**

Participants were 24 adults (mean age, 36 years; 62% female) with current major depressive disorder who were part of a larger study, and 16 adults (mean age, 35.6 years; 63% female) with no personal or family history of any affective disorder. Participants in both groups met the following criteria: right-handed, as assessed by the Edinburgh Handedness Scale (Oldfield, 1971); no history of neurological disorder or head trauma; no cognitive impairment; not currently taking any medications for depression (including herbal remedies or anti-depressants used for other indications); not pregnant; and no implanted metal or other medical devices/conditions that were contraindicated with MRI.

Depressed patients met DSM-IV criteria for current major depressive disorder (and scored above 19 on the Hamilton Rating Scale for Depression) with no history of mania, psychosis or borderline or anti-social personality disorders.
Comorbid Axis I diagnoses were acceptable as long as the current depressive episode was primary. Depression severity was moderate on average, with a mean Hamilton score of 26.8.

Participants were recruited primarily through referrals (for the depressed group) and advertisements. The participants in the non-depressed control group were matched on age and gender to the first 16 depressed participants who enrolled in the study. Participants received monetary compensation for all assessments. After a complete description of the study was provided, written informed consent was obtained. Data from four subjects (two in each group) were discarded due to artifacts or technical problems during the fMRI scanning session. Therefore, the results reported below were based on a final sample of 22 depressed patients and 14 non-depressed controls.

**Pre-scan assessments**

**Structured Clinical Interview for the DSM-IV (SCID).** Participants were interviewed by an advanced clinical psychology trainee using the SCID-I (First et al., 1995). Family history of affective disorders was also assessed in the non-depressed group via participant self-report. Two potential non-depressed group participants were excluded due to a report history of maternal depression.

**Selves Questionnaire—Interview format.** An interview version of the Selves Questionnaire (SQ), a free-response measure that asks participants to describe attributes in three domains of self-beliefs (actual, ideal and ought; Higgins et al., 1986), was administered individually. Ideal self-beliefs represent promotion goals, whereas ought self-beliefs represent prevention goals. The interview included both the participant’s own beliefs as well as beliefs concerning the standpoint of significant others. For example, the question, ‘What are the attributes of the type of person you ideally would like to be?’ is intended to elicit the participant’s own-standpoint promotion goals.

**Depression measure.** The Hamilton Rating Scale for Depression (HRSD) is a clinician rating scale for depression (Hamilton, 1967) that was completed following the SCID interview by an advanced clinical psychology trainee.

**Goal priming task**

The priming task was conducted ~3 weeks after the pre-scan assessment. Unknown to the participants, the priming task used an idio grammatically generated set of stimuli based in part on participants’ unique responses to the SQ. Promotion and prevention goal primes were selected from among the ideal and ought attributes, respectively (a total of four selected from across own and other standpoint for each goal type). Single-word attributes with 2–5 syllables were chosen to be unique to the goal domain and to include as many self-discrepant attributes as possible. Yoked-control primes were selected from the ideal and ought attributes of other participants (and so were positively valenced as well) and were semantically unrelated to any attribute generated by the target participant.

Stimuli were presented in an event-related design in the context of a judgment task used in previous studies (Craik et al., 1999; Kelley et al., 2002). Four judgment conditions were presented in four blocks in the following order: (1) ‘Rate how well the adjective describes you’, (2) ‘Rate how well the adjective describes Oprah Winfrey’, (3) ‘Rate how socially desirable the adjective is’ and (4) ‘Indicate how many syllables the word has’. Responses were recorded on a 4-button box with four buttons corresponding to the following ratings for the first three blocks: almost always, most of the time, rarely, and never. For the syllables task, the buttons corresponded to 2, 3, 4 or 5 syllables. Participants were told that the purpose of the task was to find out how people make different judgments about attributes.

At the beginning of each block, participants had five practice words (not used in any of the analyses) which were the same for every participant and were semantically unrelated to any of the goal priming words. Following the practice words, the participants’ four promotion and four prevention goal priming words, as well as the eight control words, were presented in random order in each block. Thus, following the practice trials, these 16 words were repeated in random order for each block. Each word was presented for 2 s, with a jittered interstimulus interval (fixation cross) of 10, 12 or 14 s. Stimuli were presented using CIGAL, an in-house software program (Voyvodic, 1999).

**Neuroimaging protocol**

Images were acquired on a GE Signa 1.5T scanner (Waukesha, Wisconsin). Functional images were acquired using blood-oxygenation level-dependent (BOLD) contrast T2*-weighted spiral MRI (TR = 2000 ms, TE = 40 ms, flip angle = 90°, matrix = 64²; in-plane resolution 3.9² mm), and consisted of volumes of 28 contiguous 4-mm (interleaved) slices, acquired parallel to the line connecting the anterior and posterior commissures. Prior to the functional acquisition, a T1-weighted structural set including a 28-slice image (image dimensions 256 × 256 × 28; voxel size 0.975 × 0.975 × 2) coplanar with the functionals was acquired for purposes of coregistration.

Head motion was minimized by cushioning the subject’s head and placing a strip of tape attached to the table across the subject’s forehead. Stimuli were projected on a screen directly behind the subject’s head within the scanner bore, which subjects viewed with mirrored glasses. Responses were recorded using a 4-button response box placed under the subject’s right hand.

**fMRI data analysis**

MRI data were preprocessed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm/) and analyzed using in-house scripts programmed in MATLAB. Preprocessing consisted of typical steps: correction for slight differences in slice acquisition
timing, realignment of images to the first functional image to correct for motion artifacts, co-registration of the first functional image with the high-resolution anatomical image, normalization of the anatomical and functional images to a standard stereotactic space (Montreal Neurological Institute or MNI), and smoothing of the functional images using an 8 mm FWHM Gaussian kernel.

A selective averaging approach was used to identify areas of activation associated with goal priming, and with the judgment task, in the two samples. This approach allowed for a finer dissociation of the signal on a timepoint-by-timepoint basis in the context of our event-related design, which involved long interstimulus intervals. Two main analyses were performed, the first testing our hypotheses regarding the goal priming conditions, and the second examining cortical areas activated by the judgment task that were common to the two participant groups. Both sets of analyses used custom software from the Duke-UNC Brain Imaging and Analysis Center to selectively average the fMRI signal in each subject for each of eight time points (one pre-stimulus, one at stimulus onset, and six post-stimulus, with each equal to 2 s). These individual-level analyses produced whole-brain t maps, which subsequently were combined in group-level random-effects analyses.

Analyses of neural activity associated with goal priming combined the trials for each condition across the four task blocks. For individual-level analyses, the fMRI signal was selectively averaged in each subject for each of the eight time points separately, as a function of trial type (i.e. promotion goal, prevention goal and yoked control). The promotion and prevention conditions were then directly compared, to ensure that the resulting activation patterns reflect only the differences between promotion and prevention goals and not differences in self-relevance or stimulus source (i.e. as with the yoked control words).

For group analyses, voxel- and region-of-interest (ROI)-based random-effects analyses were performed for both the promotion (vs prevention) and prevention (vs promotion) contrasts. The results of these group analyses were masked with the main effect of interest to ensure that the results were attributable to an increase in activation in one group as opposed to a decrease in activation in the comparison group. Statistical results from the peak voxel (the voxel showing the strongest effect) and time point (defined in the range of 8–10 s following stimulus onset) from each analysis are reported. The analyses testing the a priori hypotheses regarding left and right OFC activity used a threshold of \( P<0.05 \) to determine statistical significance (threshold for masking also was \( P<0.05 \)). Subsequent exploratory analyses outside the hypothesized brain regions used a more conservative threshold of \( P<0.001 \).

Analyses of cortical activation associated with the judgment task in the two groups combined across all three priming conditions (promotion, prevention and yoked control) and task blocks. Independent group analyses determined voxels where activity in response to the task was significantly greater than baseline \( (P<0.01) \) at the peak, defined as 8 s after stimulus onset, separately in each group. To determine areas of common activation, the output of these separate analyses was then used as input for a subsequent conjunction analysis. The statistical significance of the resulting combined t maps was computed using Fisher’s method of estimating the conjoint significance of independent tests (Fisher, 1950; Lazar et al., 2002), such that the conjoint significance threshold was \( P<0.001 \). Finally, an extent threshold of five contiguous voxels was used in all analyses, and the results from the peak voxels and time points (i.e. the time point following stimulus onset where the maximum effects in the contrasts of interest were observed: 8–10 s) are reported.

**RESULTS**

**Promotion and prevention goal priming: OFC results**

As predicted, for the promotion (vs prevention) goal priming condition comparison, the control group showed significant activation in an area of the left OFC (peak voxel \( x=16, y=27, z=11, \text{BA 11} \)), whereas the depressed patients showed attenuated magnitude of activation in this region (Figure 1). The difference between the two groups was statistically significant, \( t(34)=2.53, P<0.05 \). Moreover, consistent with our prediction for the prevention (vs promotion) goal priming condition comparison, the depressed group showed significant activation in an area of the right OFC (peak voxel \( x=16, y=38, z=5, \text{BA 10/11} \); Figure 1), whereas the control group did not. The difference between the two groups was statistically significant, \( t(34)=3.47, P<0.01 \). A group \( \times \) hemisphere \( \times \) condition repeated measures ANOVA also was conducted using the percent signal change data extracted from the peak time point and voxel in the left and right OFC areas; the three-way interaction approached statistical significance \( F(1, 34)=1.97, P<0.10 \).

We conducted additional analyses to determine whether severity of depressive symptoms was related to magnitude of activation in the identified left or right OFC site. Our hypotheses would predict that depression severity would be negatively correlated with left OFC activation in response to promotion goal priming and positively correlated with right OFC activation in response to prevention goal priming. Among the depressed patients, HRSD scores were significantly correlated with magnitude of activation at the peak time point from the peak right OFC voxel \( (r=0.50; P<0.05) \) but were not correlated with left OFC activation.

**Task-related activation**

To ensure that any group differences observed in response to promotion vs prevention goal priming were not attributable to differences in response to the task itself, we examined patterns of cortical activation related to the judgment task, combining across all priming trials and task blocks. As in previous studies, this analysis revealed a network of...
activation common to both groups that included frontal, parietal, temporal and occipital regions (Table 1). The frontal regions included both lateral (i.e. dorsolateral PFC—BA 4/6/9 and ventrolateral PFC—BA 44/45/47, extending into insula—BA 13) and medial areas (i.e. anterior cingulate—BA 24/32, extending into the premotor cortex—BA 4/6/8). In the parietal lobe, there was bilateral activation in the somatosensory areas (i.e. BA 1, 2, 3 and 5), which was stronger and more widespread in the left hemisphere, and in more posterior areas (i.e. BA 7 and 40). The temporal lobe activation included posterior areas of the superior temporal gyrus (BA 22). Finally, in the occipital cortex, common activation was observed in both medial (BA 17/18) and lateral (BA 18/19/37) visual areas.

Promotion and prevention goal priming: exploratory analyses

Finally, we conducted an exploratory whole-brain two-group analysis of the two promotion/prevention contrasts to identify other areas of activation associated with goal priming that distinguished the participant groups. This analysis yielded several areas showing dissociative responses to the priming conditions in the depressed vs non-depressed groups which had not been predicted a priori (Table 2).

DISCUSSION

Although depression has long been conceptualized as a disorder of motivation, the nature of that deficit has been
understood primarily in terms of temperament-based mechanisms for spatiotemporal approach behaviors in response to appetitive cues. Research in social cognition provides a complementary perspective on depression, specifically on the potential impact of dysfunctions in personal goal pursuit. In this study, we used fMRI to examine responses of depressed and non-depressed adults to incidental priming of idio graphically assessed promotion (‘making good things happen’) and prevention (‘keeping bad things from happening’) goals. Based on behavioral findings as well as recent studies in social cognitive neuroscience, we hypothesized that major depressive disorder would be associated with an attenuated left OFC response to incidental promotion goal priming, as well as an exaggerated right OFC response to prevention goal priming.

The results supported our predictions. Whereas non-depressed adults manifested robust left OFC activation following exposure to their own promotion (vs prevention) goals (replicating previous findings), depressed individuals showed significantly less activation at that location. Conversely, compared to non-depressed participants, depressed patients showed significantly greater activation than controls in an area in right OFC following exposure to their own prevention (vs promotion) goals. Furthermore, among the depressed participants, severity of depressive symptoms was positively correlated with magnitude of activation in the right OFC. That is, more severely depressed participants showed stronger activation in the right OFC when exposed to their own prevention goals. Combining these observations, we postulate that depression is associated at both behavioral and neurobiological levels with down-regulation of promotion goal pursuit and simultaneous (and possibly compensatory) hyperresponsivity to prevention goals, consistent with a self-regulation-based model of depression (Strauman, 2002). These findings are also consistent with the notion of regulatory fit, that is, people tend to use goal pursuit strategies that fit with their motivational orientation, and they will experience stronger motivation when fit is higher (Higgins, 2000). Thus, the patterns of neural activation in response to goal priming may reflect depressed individuals’ stronger orientation toward prevention goals and non-depressed individuals’ stronger orientation toward promotion goals.

The observed differences in response to goal priming were discernable even as the participants were actively engaged in a judgment task that was unrelated to goal pursuit. Analysis of the task-related activation showed remarkably similar cortical responses in the two groups, including activity in...
executive, sensorimotor and visual areas, which are consistently associated with visual/verbal tasks requiring a motor response. Thus, the group differences in responses to goal priming could not be attributed to differences in task-related activation per se.

These findings highlight both similarities and distinctions between social–cognitive and biobehavioral perspectives on motivation. Regulatory focus theory emphasizes the role of personal goal representations and social–cognitive processes underlying strategic pursuit of such goals, whereas biobehavioral models emphasize spatiotemporal approach/avoidance in response to more concrete, evolutionarily shaped cues for reward or punishment. A novel aspect of the current study is the use of idiothetically selected goal priming materials. Just as previous research has suggested that certain dysfunctional cognitive processes in depression, like attention, are best probed using self-relevant stimuli (Mogg and Bradley, 2005), our findings suggest that standard laboratory stimuli intended to manipulate motivational states may not optimally probe dysfunctional personal goal pursuit. Furthermore, the current study showed that priming promotion or prevention goals induced activation in orbitofrontal regions previously implicated in representing critical aspects of goal pursuit, including the hedonic value of reinforcers, decision making, and performance monitoring (Kringelbach, 2005; Rolls, 2000). Thus, our findings also are consistent with recent theorizing about the role of the orbitofrontal cortex in depression (Drevets, 2007).

Similar to Eddington et al. (2007), there was only a minimal increase in right OFC activation following prevention goal priming among the non-depressed participants. In contrast, the depressed patients showed a significant increase in right OFC activation when exposed to their own prevention goals. Furthermore, the magnitude of activation in the peak voxel from this cluster was correlated with severity of depressive symptoms, as indicated by HRSD scores, among the depressed patients.1 These findings parallel current theorizing regarding dysfunction of approach/avoidance mutual inhibition in unipolar depression (Watson, 2005) and suggest that depression also may be characterized by hyper-responsivity to prevention goals, a motivational state potentially associated with hypervigilance, worry and anxiety symptoms.

This study highlights the importance of integrating theoretical perspectives in an effort to gain a better understanding of motivational deficits associated with depression. Our findings indicate that motivational dysfunction in depression needs to be conceptualized at multiple levels of analysis and as involving multiple brain systems. Given the evidence underscoring the importance of cognitive processes in major depression, for example, it is surprising that few neuroimaging studies have compared predictions derived from cognitive ('top-down') vs motivational ('bottom-up') models of depression. Neuroimaging methods are particularly useful for identifying both the unique and shared neural substrates underlying the dysfunctional systems defined by different etiological models. Such methods also enable researchers to test predictions about mechanisms of treatment-related change beyond traditional symptom measures.

Several limitations of the current study suggest the need for further testing of our primary hypotheses in future research. First, although the pairwise group comparisons of promotion/prevention priming supported our hypotheses, the three-way interaction did not reach conventional levels of statistical significance. Therefore, replication of our findings in a larger sample is needed. Second, while the use of idiographic, motivationally significant stimuli is one of the strengths of the current study, it also represents a limitation in that the SQ interview procedure prohibited the generation of large pools of goal words for each participant. In addition, the stimulus words for the current study were drawn from both the ‘own’ and the ‘significant other’ self-belief lists. There may be important differences in the cognitive, affective and motivational characteristics of goals that are strongly tied to others’ expectations for us compared to our expectations for ourselves, and differences in the sources used for the ‘other’ perspective may mediate the effects of goal priming (Burton et al., 2006; Shah, 2003). In future studies, an alternative method that combines idiographic and nomothetic approaches may yield a larger pool of stimuli that provides increased statistical power to detect priming-related differences and enables direct comparison between ‘self-standpoint’ vs ‘other-standpoint’ goals.

We note several possible implications of our findings for the etiology and treatment of depression. Whether the observed deficit in left OFC activation following promotion goal priming is a cause or a consequence of depression, the mechanisms by which such a deficit is linked to affective and motivational processes in other brain areas need to be identified. Computational and neuroanatomical models of dopamine function in the PFC offer one possible set of mechanisms (Miller and Cohen, 2001; Ramnani and Owen, 2004; Dunlop and Nemeroff, 2007). Likewise, regardless of the causal status of this observed functional deficit, there is evidence that dysfunction of self-regulation is more clinically prominent in a subset of depressed patients. In a recent randomized trial, depressed patients manifesting chronic difficulties pursuing promotion goals showed significantly greater improvement in response to a psychotherapy targeting self-regulatory cognition than to standard cognitive therapy (Strauman et al., 2006). Additional studies examining changes in self-regulatory cognition and patterns of neural activation in response to goal priming after different treatments for depression will be useful in determining whether the attenuated priming response to promotion goals reported here may represent a biomarker for treatment selection (Roffman et al., 2005).

1 Note that the correlation between activation in the right OFC voxel and severity of anxiety symptoms, as measured with the Beck Anxiety Inventory (Beck et al., 1988) was positive but non-significant (r = 0.20, n.s.).
REFERENCES


