

DEPRESSION AND COGNITIVE CONTROL IN THE FACE OF
NEGATIVE INFORMATION OR STRESSORS

by

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Depression and Cognitive Control in the Face of Negative Information or Stressors

Thesis directed by Professors Marie Banich and Sona Dimidjian

Previous research has indicated that people with depression exhibit altered cognitive control functioning when confronted by negative information or stress. However, identifying the factors that drive such altered functioning, or how to protect the ability to implement cognitive control, remain topics of debate. The current thesis explores these themes: *what* is it about the content of salient, distracting stimuli that *predicts* altered cognitive control in depression, *how* is such interference manifested on the level of brain activation, and *what protects* cognitive control functioning in the face of such stimuli. Study 1 investigated the relationship between depression and brain activation in response to ignoring negatively valenced words in a subclinical population. We found that higher depression predicted increased activity in brain regions implicated in self-referential thought and emotion processing, and increased recruitment of areas involved in the top-down control of attention. These patterns were specific to negative distractors, suggesting that altered brain response at higher levels of depression is in response to negative emotional information. Study 2 investigated whether having behavioral control over stressors would buffer women with clinical or subclinical depression from the negative effects of stress exposure on cognitive control. We found that people exposed to controllable stress performed better on a test of general executive functioning than those exposed to uncontrollable stress, but that more severe depressive symptoms predicted poorer performance within the controllable stress group. Notably, this increase in impairment at higher levels of depression was partially mediated by more extreme responses to stress. These results suggest that if individual

differences in stress sensitivity are taken into account, people with depression may also benefit from having behavioral control over stressors. The present studies support the theory that depression is related to changes in behavioral and neural functioning when exerting cognitive control over negative information or after stress exposure, but that behavioral strategies may help protect the ability to implement cognitive control.

CONTENTS

CHAPTER

I.	GENERAL INTRODUCTION.....	1
II.	STUDY 1	7
	Introduction.....	7
	Methods.....	12
	Results.....	24
	Discussion.....	34
III.	STUDY 2	44
	Introduction.....	44
	Methods.....	47
	Results.....	56
	Discussion.....	62
IV.	GENERAL DISCUSSION	66
	BIBLIOGRAPHY	68

TABLES

Table

1. Behavioral performance across the group (Study 1)	25
2. Brain regions recruited across the group when ignoring negative distractors (Study 1)	26
3. Specificity of brain response to negative distractors across the group (Study 1)	27
4. Anhedonic depression predicts activation in regions recruited across the group when ignoring negative distractors (Study 1).....	30
5. Anhedonic depression predicts activation in unique regions outside those recruited across the group in response to negative distractors (Study 1)	32
6. Specificity of correlations between anhedonic depression and activation in unique regions outside those recruited across the group (Study 1)	33
7. Demographic information (Study 2)	57

FIGURES

Figure

1. Anhedonic depression predicts increased activity in regions of default mode network in response to negative distractors (Study 1).....30
2. Anhedonic depression predicts increased activity in subcortical regions and areas of medial cortex in response to negative distractors (Study 1)32
3. Stress manipulation (Study 2).....51
4. Lower subjective response to controllable (but not uncontrollable) stress predicts improvement in color-word Stroop performance across varying levels of depression severity (Study 2)60

CHAPTER I

GENERAL INTRODUCTION

You are constantly told in depression that your judgment is compromised, but part of depression is that it touches cognition... Your mind is leached until you seem dim-witted even to yourself... I felt the logic disappearing right out from under me.

Andrew Soloman, *The Noonday Demon*

Now the standard cure for one who is sunk is to consider those in actual destitution or physical suffering—this is an all-weather beatitude for gloom in general and fairly salutary day-time advice for everyone. But at three o'clock in the morning, a forgotten package has the same tragic importance as a death sentence, and the cure doesn't work—and in a real dark night of the soul it is always three o'clock in the morning, day after day.

F. Scott Fitzgerald, *The Crack-Up*

Background

Depression is one of the most common and debilitating of the mental disorders, affecting one out of every five women and one out of every ten men in the United States (Kessler et al., 2005; 2007). At both clinical and subclinical levels of severity, depression predicts increased occupational disability (Judd et al., 2000), physical disability (Merikangas et al., 2007; Ustun & Kessler, 2002), relationship problems (Judd et al., 2000), impairments in daily functioning (Naismith, Longley, Scott & Hickie, 2007), and suicide (Borges et al., 2008). Depression is highly recurrent, with 78-85% of people who have had a major depressive episode experiencing recurrence within 15 years (Mueller et al., 1999). Given the prevalence and serious consequences of depression, important areas of clinical research include exploring the nature of depression and developing effective intervention and prevention strategies.

In the past several decades, cognitive models of depression have been central to such clinical research. These models propose that changes in cognition are core to the pathology of

depression, evident in both altered cognitive content (e.g. increased negative, self-referent thoughts) and process (e.g. changes in information processing), (Joormann, 2009). Some of these cognitive changes are recognized as cardinal symptoms of clinical depression, including problems with concentration, attention and decision-making (Diagnostic and Statistical Manual, 4th ed. Text Revised (DSM-IV TR), American Psychiatric Association, 2000).

Each of these cognitive symptoms of depression is related to a family of processes known as executive functions (EF) or cognitive control. Cognitive control includes abilities such as holding abstract goals in mind, using goals to provide “top-down” direction for attention, updating working memory, selecting responses, and inhibiting thoughts or actions that are irrelevant to or incompatible with goals (Banich et al., 2009; Miller, 2000). Impairments in cognitive control, specifically, may drive the deficits in attention and concentration that define depression (Levin, Heller, Mohanty, Herrington & Miller, 2007). A recent meta-analysis of research examining neuropsychological functioning in depression revealed broad impairments in cognitive control across multiple forms of goal-directed behavior (Snyder, 2012). Such impairments have been detected at both clinical and subclinical levels of severity (Austin, Mitchell & Goodwin, 2001; Levin et al., 2007), and may persist beyond the remission of a formal depressive episode (Paradiso, Lambert, Garvey & Robinson, 1996). Although we cannot determine from existing research whether such impairments are causes, consequences, or correlates of depression, this evidence suggests that changes in cognitive control characterize depression at varying levels of severity and across the course of the disease.

People with depression may be especially likely to exhibit altered cognitive functioning when they are confronted by particular types of salient stimuli. For example, depressed persons tend to show cognitive biases towards the processing of negative and self-referent information

(Gotlib & Joormann, 2010; Joormann, 2010), even when such information is irrelevant to task goals (Joormann & Gotlib, 2007; 2008). In addition, depressed persons are more sensitive than their non-depressed peers to the effects of stress exposure (Burke, Davis, Otte & Moore, 2005), and such increased reactivity to stressors predicts disrupted performance on tasks that place demands on executive functions (Rohleder, Wolf & Wolf, 2010). This pattern of cognitive impairment in the face of salient events is consistent with Beck's cognitive model (1967), which maintains that increased reactivity to stressful and negative events is caused by the match in emotional content between such events and the negative "schemata" of depressed persons (memory structures sculpted by past experiences which guide information processing and shape beliefs about the self, the world, and the future). Cognitive reactivity theory, founded on Beck's model, proposes that it is the interaction between cognitive vulnerability and activating events (e.g. negative information, negative mood, or stress) that results in persistent negative thinking and ultimately, increased risk of depression (Scher, Ingram & Segal, 2005). From this perspective, negative or stressful information may have uniquely disruptive effects on the cognitive functioning of vulnerable individuals. Even negative events that seem relatively minor to non-depressed people, such as Fitzgerald's forgotten package, may have devastating consequences for the mood and cognitive abilities of someone who is depressed or at risk for depression.

In contrast to cognitive reactivity to specific types of salient stimuli, other research suggests that cognitive dysfunction is evident among depressed people even in the absence of stress or negative emotional information. Evidence for impaired attention, working memory updating, and selection (amongst other abilities) with non-emotional information suggests that depression may be related to general deficits in cognitive control, regardless of the nature of the information

being processed (Snyder, 2012). Depressed individuals may be more sensitive to the disruptive influence of any type of distracting material, including emotional or stressful material, but also other information that is not personally salient. Revisions to cognitive models of depression suggest that both specific reactivity (to salient negative information or stressors) and general impairment (in cognitive control ability) may each play a role in the cognitive dysfunction that characterizes depression. However, the relative contribution of each of these factors, i.e. *what* is it about the nature of salient, distracting information that *predicts* altered cognitive functioning, remain ambiguous.

Relatedly, researchers are only beginning to clarify the underlying neural mechanisms of *how* cognitive control functions are altered in depression the face of negative information or stress, and the specificity of such brain responses. For example, previous research investigating brain functioning in depression has not typically compared patterns of activation in response to negative versus other highly distracting information, an omission that limits our ability to make conclusions about the role of negative emotionality. In order to tease apart questions of *what predicts* altered cognitive control functioning in depression, it is important to begin to explore *how* such changes in functioning manifest on a neurobiological level.

Finally, from a clinical perspective, the critical next step to such research is identifying *what protects* cognitive functioning from disruption and how such factors operate for people with elevated depression. For example, previous research has shown that having behavioral control over stressors can buffer non-depressed people from the negative effects of stress exposure on learning and problem-solving abilities (Hiroto, 1974; Hiroto & Seligman, 1975; Jones, Nation & Massad, 1977; DeVellis, McEvoy-DeVellis & McCauley, 1978; Hirt & Genshaft, 1981; Kofta & Sedek, 1989). However, studies investigating the protective effects of controllability on cognitive

functioning in people with elevated depression have yielded mixed results (e.g. Kilpatrick-Tabak & Roth, 1978 versus Klein & Seligman, 1976). In order to develop interventions for this population, researchers must further investigate how specific aspects of depression, such as altered response to stress or impairments in cognitive abilities, interact with the activities of therapy designed to improve daily functioning.

Current Studies

The broad questions that guide the present research thesis are: *what* is it about the content of salient, distracting stimuli that *predicts* altered cognitive control functioning in depression, *how* do such changes in cognitive functioning manifest on the level of brain activation, and *what protects* cognitive control in the face of such stimuli. The studies described here each target specific components of these themes.

In Study 1, we examined brain activation in response to distracting information in people with varying levels of subclinical depression. First, we investigated whether the severity of depressive symptoms was related to brain activation in the face of negative distractors in an emotion-word Stroop task. Second, to examine the specificity of such responses to negative valence, these patterns of neuroactivation were compared to brain responses to positive or incongruent distractors, in the emotion-word or a color-word Stroop task. Previous research has shown altered brain response to negative distracting information at higher levels of depression (e.g. Engels et al., 2010; Mitterschiffthaler et al., 2008). We extended this research to investigate whether such altered brain activation is specific to negative distractors, is detected in response to other types of emotional distractors, or is more broadly related to distracting information in general.

In Study 2, we tested the protective effects of stress controllability on cognitive control functioning in women with varying levels of clinical and subclinical depression, and examined whether these effects were moderated by symptom severity or by subjective responses to stress. To pursue this investigation, we compared performance on a color-word Stroop task between two groups of women who were exposed to controllable or uncontrollable stress. Next, we conducted analyses to determine whether the effects of such exposure on Stroop performance depended on either the intensity of the individual's self-reported response to stressors or on the severity of her depressive symptoms. Finally, we investigated the possibility that subjective responses to stress exposure mediated the relationship between depression severity and Stroop performance. These analyses explored the possibility that heightened stress sensitivity in individuals with depression may have obscured the protective effects of behavioral control.

CHAPTER II

STUDY 1

Introduction

People who are depressed show impairments in cognitive control in the face of negative emotional information (Dai, Feng & Koster, 2011; Goeleven, De Raedt, Baert & Koster, 2006; Gotlib, Krasnoperova, Yu & Joormann, 2004; Ingram, Bernet & McLaughlin, 1994; Joormann, 2004; Joormann & Gotlib, 2008; Joormann, Levens & Gotlib, 2011; Joormann, Nee, Berman, Jonidas & Gotlib, 2010; McCabe & Gotlib, 1993). Cognitive theories suggest that for depressed persons, attentional resources are more likely to be “hijacked” by negative information both because such information is more personally salient (i.e., increased bottom up reactivity) and because depression is often linked to general impairments in the ability to direct attention (i.e., decreased top down control).

This theme of increased cognitive reactivity and decreased cognitive control is also reflected on a neurobiological level in depression. Recent research shows that depression predicts increased activation in a set of brain regions commonly referred to as the default mode network (DMN) (reviews in Marchetti, Koster, Sonuga-Barke & De Raedt, 2012; Northoff, Wiebking, Feinberg & Panksepp, 2011; Whitfield-Gabrieli & Ford, 2012). The DMN consists of a constellation of brain structures, including core midline cortical regions that play an important role in self-referential and introspective thought (Andrews-Hanna, 2012; Gusnard Akbudak, Shulman & Raichle, 2001; Northoff, et al., 2006), and regions of the medial temporal lobe (MTL) that likely support autobiographical retrieval and prospection (Andrews-Hanna, 2012;

Andrews-Hanna, Reidler, et al., 2010; Buckner & Carroll, 2006; Schacter & Addis, 2007; Spreng, Mar & Kim, 2008). As such, activity in the DMN tends to decrease during externally-focused tasks, and increase during passive rest states when individuals often muse about self-relevant themes (Andrews-Hanna, 2010; Raichle, MacLeod et al., 2001). Hence, levels of activation in DMN are typically below resting baseline (i.e. “deactivated”) during the execution of tasks requiring attention to external stimuli, but may be above baseline (i.e. “activated”) for tasks requiring introspection or autobiographical thinking.

In comparison with healthy individuals, people with clinical depression exhibit increased activation of DMN regions during the performance of tasks that include emotional (Grimm, Boesinger, et al., 2009; Sheline et al., 2009) or self-referent information (Johnson, Nolen-Hoeksema, Mitchell & Levin, 2009). During states of rest, depression predicts increased DMN activity as well as greater temporal dominance of DMN compared to brain systems recruited for external attention (i.e. greater amount of time during rest in which activation of DMN exceeds activation of external attention network) (Marchetti et al., 2012; Whitfield-Gabrieli & Ford, 2012). These patterns of altered DMN functioning in depression have been interpreted to signify heightened reactivity to self-relevant or affective information and impaired ability to disengage from internally directed (e.g. ruminative) thinking (Marchetti et al., 2012). Together, this research evidence has spurred scientists to focus on the DMN as a key site of altered neural functioning that may be related to the cognitive symptoms of depression (Northoff et al., 2011).

In addition to evidence for altered DMN functioning, several studies have shown either under- or over-recruitment of cognitive control systems in depression, specifically in regions of prefrontal cortex (PFC) (Clark, Chamberlain & Sahakian, 2009; Mayberg, 2003). Compared with healthy individuals, those with depression exhibit decreased activation in cognitive control

systems at rest (Mayberg, 2003) as well as when performing goal-directed tasks (Clark, Chamberlain, & Sahakian, 2009), the latter tending to co-occur with poor behavioral performance. In cases in which adequate performance is observed, people with depression often show greater activation in cognitive control regions than their non-depressed peers (but this may also be accompanied by decreased recruitment of other regions responsible for top-down control, e.g. Siltan et al., 2011). This evidence for both blunted recruitment and overactivation suggests that regions involved in cognitive control are not working as efficiently in depressed as compared with healthy individuals (see discussion in Clark, Chamberlain, & Sahakian, 2009; Engels et al., 2010; Herrington et al., 2010; Levin et al., 2007). Notably, problems with cognitive control have been observed not only when distracting information is negatively valenced (Elliott, Rubinstein, Sahakian, & Dolan 2002; Mitterschiffthaler et al., 2008), but also when it is non-emotional in nature (Fitzgerald et al., 2008; Harvey et al., 2005; Holmes & Pizzagalli, 2008; Kaiser et al., 2003; Matsuo et al., 2007; Siltan et al., 2011) suggesting a general disruption in the neural mechanisms involved in cognitive control.

In sum, depression has been linked to altered brain responses and performance impairments for tasks that include negative information, but also those that feature other types of distracting material. Therefore, it is not clear from prior research what it is about the nature of negative distracting information that contributes to the behavioral and neurobiological effects observed in depression. It makes theoretical sense for negative information to “hijack” attentional resources because the congruence between a depressed individual’s self-schema and negative emotional content makes such information especially salient. However, it could be that another aspect of the content of negative distractors, such as the generally arousing or distracting nature of such information, is driving altered responses in depression.

For example, people with depression may be more sensitive to emotional information, regardless of the valence of that information. Depression has been related to altered processing of both positive and negative affective stimuli (Epp, Dobson, Dozois, & Frewen, 2012; Forbes & Dahl, 2005; Shestyuk, Deldin, Brand, & Deveney 2005). Furthermore, overlapping brain systems show activation in response to positive or negative information, suggesting the presence of a common neural system recruited generally for processing affective material (Northoff et al., 2011; but see Davidson, 2003; 2004). From this perspective, altered brain responses to negative information may simply reflect differences in how depressed individuals respond to emotional content, rather than being specific to information with a negative valence. Previous research that investigated brain response to different types of affective stimuli in clinically or subclinically depressed populations is mixed (e.g. Engels et al., 2010; Herrington et al., 2010; versus Anand et al., 2005), suggesting that further investigation is warranted.

Even more generally, it may be that people with elevated depression are simply more sensitive to the challenge inherent to ignoring distracting information of any type. Supporting this idea are findings that increased depression predicts altered recruitment of cognitive control systems in response to emotionally-neutral, distracting information, as well as impaired performance on such tasks (Hammar & Ardal, 2009; Levin et al. 2007; McDermott & Ebermeier, 2009; Siltan et al.; 2011; Snyder, 2012). However, previous research has seldom directly compared brain systems recruited for cognitive control with negative versus other highly distracting information (Compton et al., 2003), and no such research has been conducted with a focus on depression. Therefore, it is not clear whether the pattern of altered brain response to negative information exhibited by people at higher levels of depression diverges from, or overlaps with, their brain responses to other types of distracting material.

Study Goals

The current research had the following goals: 1) to investigate the degree to which subclinical anhedonic depression is associated with altered patterns of brain activation when task-irrelevant negative information must be ignored; and 2) to clarify the specificity of such altered brain functioning to negative information versus other task-irrelevant information, i.e. other types of emotional (here, positively valenced) or non-emotional information.

We predicted that people with elevated depression would show similarly altered recruitment of brain systems implicated in cognitive control across various types of distractors, but uniquely altered activation in regions of DMN in response to negative distractors. Cognitive control systems are recruited for many different cognitively demanding tasks, and research revealing dysregulation in such systems in response to various types of information implicates these systems as a general source of dysfunction in depression. In contrast, studies relating depression to increased activation in DMN regions during task performance have typically shown these effects in response to emotional or self-referent stimuli, suggesting increased bottom-up reactivity to personally salient information. Because negative words constitute such salient information for depressed persons, we predicted that depression would be associated with activation in DMN regions in response to negative distractors, specifically.

To pursue our research goals, we administered two variants of the Stroop task, in which words are printed in different colors of ink and individuals are instructed to identify the ink color while ignoring the meaning of the word. In the emotion-word Stroop task (ew-Stroop), cognitive control must be exerted to ignore the meaning of positive or negative words that are distracting because their emotional nature captures attention (e.g., the word “suicide” in green ink). In the color-word Stroop task (cw-Stroop), cognitive control is exerted to ignore the meaning of

incongruent words that are distracting because they name an alternative ink color (e.g., the word “red” in blue ink). In both cases, we compared brain activation for each type of distractor (i.e. negative, positive, or incongruent) to the neural response to neutral (non-emotional and non-color) words.

The current study expands upon prior research in that we investigated depression from a dimensional perspective, and at subclinical levels of severity. Much of the previous research exploring depression and cognitive control has investigated such processes in clinical populations using categorical diagnoses (e.g. Joormann & Gotlib, 2007; 2008). However, researchers increasingly suggest that a dimensional view of depression may be most appropriate (Cuthbert & Insel, 2010; Hankin et al., 2005; Widiger & Samuel, 2005). Furthermore, studies show that altered functioning of brain networks such as DMN precedes, and persists after, a clinical episode (Marchetti et al., 2012) and impaired performance on tasks requiring cognitive control may endure after remission (Nakano et al., 2008). Therefore, investigation of brain functioning across the spectrum of subclinical severity provides an alternate perspective on the construct of depression that complements traditional diagnostic and categorical approaches. With these considerations, the present study explored the association between self-reported level of anhedonic depression and brain functioning in a subclinical population. To ensure that our sample included a broad range of depression severity, we recruited a moderately large sample of undergraduate student participants reporting high variance in anhedonic depression.

Methods

Recruitment and Sample Characteristics

The sample (N=92) consisted of people aged 18-25 (M=19.03, SD=1.04) recruited from introductory psychology classes at the University of Illinois at Champaign-Urbana. Participants were pre-screened with the Mood and Anxiety Symptom Questionnaire (MASQ, measuring anhedonic depression (MASQAD8) and anxious arousal (MASQ-AA); Watson, Clark, et al., 1995; Watson, Weber, et al., 1995) and the Penn State Worry Questionnaire (PSWQ, measuring anxious apprehension; Meyer, Miller, Metzger & Borkovec, 1990) and selected for high variance in these measures. High variance in anhedonic depression across the current sample permitted us to investigate correlations between depression severity and brain response to distracting information. Other measures were included in prescreening to enable investigation of anxiety, as reported elsewhere (Engels, et al., 2010; Silton, et al., 2011). Participants (59% female, 80% European American) were native English speakers who were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were screened to ensure they did not meet the following exclusion criteria: a) use of psychoactive medications, b) abnormal color vision, c) previous loss of consciousness that exceeded 10 minutes, d) claustrophobia, e) recent drug or alcohol use, f) excessive caffeine intake, or g) recent lack of sleep.

Fourteen additional participants were excluded from the study for the following reasons: excessive motion in the scanner (N=6); equipment malfunction (N=7); or missing questionnaire data (N=1).

The analyses described here were performed on a subset of data from a larger research investigation incorporating an array of measures and methods; therefore, only the measures and procedures relevant to the current analysis are described here. Analyses performed on an overlapping data set, but which address research questions distinct from those of the current study, are reported elsewhere (Engels et al., 2010; Silton et al. 2011).

MR Data Acquisition

A 3T Siemens Allegra scanner with a quadrature headcoil was used for data acquisition. For functional scans, 370 functional images were acquired with the following echoplanar image (EPI) parameters: 2000ms TR, 25ms TE, flip angle 80°, FOV=22cm. Thirty-eight oblique axial slices (3.4375 x 3.4375mm in-plane resolution, 3mm slice thickness, 0.3mm gap between slices) were acquired parallel to the anterior and posterior commissures. These parameters were identical across functional runs. After the functional scans, a high resolution T1-weighted image with the same slice prescription was acquired to provide anatomical data to register each participant's functional data to standard space. For anatomical scans, a T1-weighted 160-slice MPRAGE sequence was acquired (1x1mm in-plane resolution, 1mm slice thickness, EPI parameters of 1700ms TR, 3.5ms TE). In addition, a multi-echo gradient-echo field map scan (TE's of 10 ms and 12.46 ms) was acquired prior to the EPI scans with a slice prescription identical to the functional slices for correction of geometric distortions.

Procedures

The experiment comprised two separate research sessions, with session 1 conducted approximately one week prior to session 2.

Assessment of anhedonic depression and related measures. At session 1, participants were given a laboratory tour, informed of study procedures, and provided written consent. At this session, participants completed the Mood and Anxiety Symptom Questionnaire. The measure of primary interest to the current study was the MASQ-AD8, an 8-item subscale designed to assess self-reported levels of anhedonic depression and which has been demonstrated as a predictor of current and lifetime clinical depression (Bredemeier et al., 2010). We focused on anhedonic depression because this scale has been shown to reflect depression more precisely, rather than

general negative affect (Bredemeier et al., 2010; Nitschke et al., 2001; however, see Buckby, Yung, Cosgrave, & Killackey, 2007). Additional measures included: the MASQ-AA, a 17-item subscale of the MASQ which assesses self-reported levels of anxious arousal; and the Penn State Worry Questionnaire, a 16-item questionnaire that measures anxious apprehension, i.e. the general tendency to worry.¹

In addition to these self-report measures, the Structured Clinical Interview for Axis I Disorders, Non-Patient edition (SCID-NP, First, Spitzer, Gibbon, & Williams, 1997) was administered by a graduate student in clinical psychology. This interview provides assessment of Axis I disorders. All interviewers had at least two years of experience administering and scoring the SCID. A consensus team that consisted of a second interviewer and a clinical faculty supervisor reviewed written case summaries detailing each criterion symptom and assessed lifetime DSM-IV TR diagnoses of depressive disorders (major depressive disorder, dysthymia, or depressive disorder not otherwise specified) on the scale: 1= absent, 2= features (at least two symptoms), 3= provisional (one short of full DSM-IV TR criteria), and 4= definite. Out of the participants included here, 24 met criteria for a history of provisional or definite depressive disorder. Sixty-eight participants were free of any lifetime depressive disorder, and none of the participants met criteria for any current depressive disorder.

Brain imaging data. At session 2, participants completed cognitive tasks in the magnetic resonance environment. Functional MRI data was collected from participants during two Stroop tasks requiring top-down attentional control: one with emotional distractors and one with non-

¹ Although anxiety was not the focus of the current study, collecting such measures allowed us to examine whether predictive effects of anhedonic depression persisted when controlling for specific forms of anxiety.

emotional distractors. The order of presentation of these tasks was counterbalanced across participants.

Emotion-word Stroop task (ew-Stroop) (Williams, Mathews & MacLeod, 1996). In the ew-Stroop, the participant must identify the ink color of emotional or neutral words while ignoring the irrelevant meaning of the word stimuli. Although this version of the ew-Stroop does not feature direct conflict at the response level (as in the color-word Stroop, below), it does feature attentional competition between processing word meaning versus ink color. Cognitive control is therefore required to direct attention to ink color only. Comparison of reaction times or brain functioning between trial types yields information about the subject's ability to exert top-down cognitive control in the face of emotional distractors (e.g. Engels et al., 2010; Gotlib & Cane, 1987; Gotlib & McCann, 1984; Mitterschiffthaler et al., 2008).

In the current study, the ew-Stroop consisted of blocks of positive or negative emotion words alternating with blocks of neutral (non-emotional) words. Positive and negative word blocks contained only valenced words; previous research has demonstrated that consistent presentation of emotional material is more likely to result in attentional interference (Holle, Neely, & Heimberg, 1997), making this design more likely to challenge cognitive control systems. The word stimuli, each presented one time only, were selected from the set of Affective Norms for English Words (ANEW; Bradley & Lang, 1999) on the basis of established norms for valence, arousal, and frequency of usage. Positive or negative words were selected and matched for high-arousal and length; neutral words were selected on the basis of both low arousal and neutral valence.

The ew-Stroop included 16 word blocks (4 positive, 4 negative and 8 neutral) each consisting of 16 trials for a total of one run of 256 trials. Also, four fixation blocks were included (one at

the beginning, one at the end, and two mid-session) in which a brightened fixation cross was presented for 1500ms followed by a dimmer fixation presented for 500ms. There were also several brief rest periods during the task (totaling 100 seconds), in which participants viewed written instructions telling them to relax with their eyes open. There were eight orders of stimulus presentation, optimized to control for stimulus order effects; each participant was randomly assigned to one of these orders. Each trial consisted of a word presented in one of four colors of ink (red, yellow, green, blue) for 1500ms followed by fixation cross for 275-725ms (onset-to-onset intertrial interval = 2000 +/- 225ms). Word presentation and recording of behavioral responses were controlled by STIM software (James Long Company, Caroga Lake, NY). Words were presented in capital letters with Tahoma 72-point font through back projection onto a screen outside the scanner bore and a mirror fixed to the head coil. Participants responded with the middle and index fingers of both hands, with a specific and unchanging response mapping of color to button (32 practice trials presented before the first Stroop task allowed the subject to acquire this stimulus-response mapping).

Color-word Stroop task (cw-Stroop) (Stroop, 1935). The cw-Stroop is the gold-standard assessment of selective attention (MacLeod, 1992). Latent variable analysis has demonstrated that the cw-Stroop loads strongly on a common executive function (EF) factor (Friedman et al., 2008), suggesting that this measure is suitable for examining general executive ability. In this task, subjects must identify as quickly as possible the ink color in which a word is printed while ignoring the meaning of the word. For incongruent words, the meaning of the written word and the ink hue are sources of conflicting color information (e.g. “red” written in blue ink), for congruent words they are sources of concordant color information (e.g. “red” written in red ink) and for neutral (non-color) words only the ink hue contains color information (e.g. “sum” written

in yellow ink). Comparison of reaction times and brain functioning between trial types yields information about the subject's ability to exert top-down cognitive control in the context of semantically conflicting, concordant, or unrelated distraction.

In the current study, the cw-Stroop consisted of blocks of congruent or incongruent words alternating with blocks of neutral words, for a total of 256 trials presented in 16 blocks (4 congruent; 4 incongruent; 8 neutral). Within congruent and incongruent blocks, 50% of trials were neutral to prevent reliance on word reading strategies. Because the present study investigated response to distracting information that interferes with task goals, we focus on responses to incongruent versus neutral words only. Block counterbalancing and stimulus presentation parameters were identical to that described above, as was color-response mapping.

Neuroimaging Data Analysis

Preprocessing. Image processing and analyses relied on tools from the FMRIB Software Library analysis package (<http://www.fmri-b.ox.ac.uk/fsl>) as well as tools from AFNI and Matlab. Each fMRI time series was first motion-corrected with FMRIB's Linear Image Registration Tool (Jenkinson, Bannister, Brady & Smith, 2002). Next, spikes (artifactual sudden intensity shifts) were corrected with the AFNI tool 3dDespike (<http://afni.nimh.nih.gov/afni>). Only participants demonstrating less than 3.3-mm absolute motion or 2-mm relative motion were included in the analysis (resulting in a study N=92). Each time series was corrected for geometric distortions caused by inhomogeneity in the magnetic field. The remaining preprocessing steps were conducted using FMRIB's Expert Analysis Toolbox and included the following. The first three volumes of each data set were discarded, retaining volumes collected when the magnetic resonance signal was at a steady state, yielding 367 images per task. Each time series was temporally filtered with a high-pass filter to remove drift in signal intensity

(212Hz), and spatially smoothed with a third-dimensional Gaussian kernel (full-width half maximum = 8mm).

Lower level single-subject analysis. Regression analyses were performed on each participant's time series within each Stroop task with FMRIB's Improved Linear Model, and statistical maps were created with a regression analysis performed at each intra-cerebral voxel (Woolrich, Ripley, Brady, & Smith, 2001). An explanatory variable (EV) was created for each trial block type (positive, negative, neutral, and rest within the ew-Stroop task; congruent, incongruent, neutral, and rest within the cw-Stroop task) with the fixation intervals within blocks left as the unmodeled baseline. Each EV was convolved with a double-gamma function to better approximate the blood-oxygen-level-dependent hemodynamic response (see Aguierre, Zarahn, & D'Esposito, 1998; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Thus each EV yielded a per-voxel effect-size parameter estimate (β) map representing the magnitude of activity associated with that condition compared with baseline. By creating contrasts between EVs, we assessed the activation associated with a particular trial (block) type, or in comparison to another trial (block) type. These contrasts provided per-voxel contrast parameter estimate maps for each subject. These functional activation maps, as well as the corresponding structural MRI map, were registered into Montreal Neurological Institute stereotaxic space with FMRIB's Linear Image Registration Tool with the default configuration file.

For the ew-Stroop, contrasts of interest included the following. The negative - neutral blocked contrast (Contrast 1) identified brain regions that exhibit cognitive control in the face of negative emotional distractors. The positive - neutral blocked contrast (Contrast 2) identified regions exhibiting cognitive control in the face of positive emotional distractors. A negative (-

neutral) – positive (-neutral) contrast (Contrast 3) identified differences in brain activation specific to negative as compared to positive distractors.

For the cw-Stroop, the contrast of interest was the incongruent - neutral blocked contrast (Contrast 4). This contrast investigated the neural correlates of cognitive control in the face of highly distracting conflicting information.

Fixed effects level single-subject analyses. To compare functional activation between Stroop tasks (i.e. brain responses for negative versus incongruent distractors), we conducted secondary within-subject fixed-effects analyses using FILM. In this analysis, the lower-level comparisons of parameter estimates (copes) generated with Contrast 1 (negative-neutral) and Contrast 4 (incongruent-neutral) were each used as inputs, yielding Contrast 5.

Group level analyses. Higher-level statistical analyses were carried out with FMRIB's Local Analysis of Mixed Effects. These analyses were accomplished with a one-sample t test, which yielded a three-dimensional functional z map image. Monte Carlo simulations via AFNI's AlphaSim program (Ward, 2000) estimated the overall significance level (i.e. the probability of a false positive) for thresholding, using a gray-matter mask to limit the number of voxels under consideration. These simulations provided a z value of 3.02 and cluster size of 73, a combination for thresholding that resulted in an overall familywise error rate less than 0.05 and significance of $p < 0.0025$. Clusters that survived this threshold were considered significant.

Regions recruited across the group for ignoring negative distractors. We took the following analytic approach. First, we identified brain regions that were commonly recruited across the entire group of participants for ignoring negative information as compared to neutral information (Contrast 1). These regions represent common neural functions required for cognitive control with negative information that are shared across people. At each of the peaks identified in the

group contrast, we created 5-voxel spheres, hence creating a set of group-defined regions of interest (ROIs).

Then, for each of these ROIs, we extracted parameters estimates for other contrasts to determine whether each ROI was specifically engaged in the face of negative emotional information, generally engaged in the face of emotional information, or generally engaged under any condition of cognitive demand. To do so, we determined whether these ROIs also show activation for the contrast of positive versus neutral distractors (Contrast 2), and more specifically whether they showed greater activation for the contrast of negative versus neutral than positive versus neutral distractors (Contrast 3). In addition, we examined activation for incongruent versus neutral distractors (Contrast 4) to investigate brain response to cognitive control demands with highly distracting but non-emotional information, and compared the response to negative versus incongruent distractors with an interaction analysis (Contrast 5). For regions engaged uniquely for negative distractors, but not other distractor types, we may interpret such specific engagement as evidence that neither emotionality nor the demand for cognitive control was driving neural responses. One-sample t-tests were conducted to examine the significance of these contrasts or interactions at each group-defined ROI.

Correlations with anhedonic depression within regions recruited across the group. We explored the relationship between anhedonic depression and brain activation in the face of negative distractors within the full set of ROIs defined above (i.e. all regions identified across the group in Contrast 1, including those that were specifically responsive to negative information as well as those showing general responsiveness to other types of distractors). To the degree that anhedonic depression predicts altered activation of regions recruited by the group as a whole, it

suggests that depressive symptomatology is acting by altering activity of the typical neural machinery required to perform the task.

Correlations were computed between brain activation for negative distractors (Contrast 1) and level of anhedonic depression, within each group-defined ROI. This was accomplished by converting depression scores into z-scores based on the scores of the group as a whole; these scores were then correlated with percent-signal change in the group level analysis.

Next we investigated the specificity of the relationships between anhedonic depression and brain response to negative distractors. Specifically, within the subset of group-defined ROIs in which depression correlated with brain activation for Contrast 1, we investigated correlations between depression and brain response to positive distractors (Contrast 2) or incongruent distractors (Contrast 4). We then compared the correlations between anhedonic depression and Contrast 1 with the correlations detected between depression and Contrast 2, or depression and Contrast 4. All statistical comparisons of correlations also controlled for relationships between Contrasts (e.g. when comparing the correlations between depression and Contrast 1 versus depression and Contrast 2, we also controlled for variance shared between Contrasts 1 and 2). To the extent that the patterns of correlation detected for negative distractors fail to emerge, we may conclude that altered responses to emotional information, or to general demands for cognitive control, are not driving relationships between anhedonic depression and brain response to ignoring negative information within these group-defined regions.

Correlations with anhedonic depression outside of regions recruited across the group: whole-brain analysis. Finally, to ensure that our analytic strategy based on ROIs was not overly restrictive, we conducted a whole-brain analysis to identify brain responses to negative distractors that are uniquely related to depression but fall outside of the group-defined ROIs. To

the degree that anhedonic depression predicts activation in regions that fall outside the network recruited by the group as a whole, it suggests either compensatory or counterproductive brain activity.

We conducted a whole-brain correlation analysis to identify such regions, specifically predicting activation in response to negative distractors (Contrast 1) by level of anhedonic depression. Cluster correction and thresholding were identical to that described for group mean analyses. At each of the peaks identified in the whole-brain correlation, we created 5-voxel spheres, hence constructing a set of correlation-defined ROIs.

Next, we examined the specificity of the relationships between depression and brain response to negative distractors in these regions. Within the ROIs identified above, we compared correlations between anhedonic depression and brain response to negative distractors with correlations detected for positive (Contrast 2) or incongruent (Contrast 4) distractors. If patterns of correlation similar to those detected for negative distractors fail to emerge, it would provide evidence that altered response to emotional or generally distracting information is not driving the relationship between anhedonic depression and brain response to ignoring negative information.

Note that because the focus of the current study is on the broad predictive effects of depression we report the simple correlations between anhedonic depression and brain activation as our main findings. However, for all ROIs in which activation to negative (versus neutral) distractors correlated with depression, we also conducted correlations controlling for self-reported anxiety (anxious arousal and anxious apprehension). Unless noted, controlling for measures of anxiety did not affect the pattern or significance of results.

Behavioral Analysis

Average RTs were computed for each condition of interest, within each Stroop task (negative, positive, or neutral within the ew-Stroop; incongruent or neutral within the cw-Stroop). Within the ew-Stroop, interference scores were computed for negative and positive words with the equations: $((\text{negative RT} - \text{neutral RT}) / \text{neutral RT})$; $((\text{positive RT} - \text{neutral RT}) / \text{neutral RT})$. Within the cw-Stroop, interference scores were computed for incongruent words with the equation: $((\text{incongruent RT} - \text{neutral RT}) / \text{neutral RT})$. This method of calculating Stroop interference (as a percentage of neutral trial RT) controls for scaling effects in RT measures, in which reaction time differences tend to scale with the magnitude of reaction time latency (Lansbergen, Kenemans, & van Engeland, 2007).

We conducted analyses to examine relationships between anhedonic depression and performance by correlating level of depression with each type of interference, or with number of errors in each condition.

In addition, we performed all group-level analyses examining brain activation, and correlations between anhedonic depression and brain activation, also including performance measures as covariates. Because the inclusion of performance measures failed to affect the pattern or significance of any effects, we report simple analyses only.

Results

Behavioral Results

Performance across the group. In the ew-Stroop, accuracy was higher for neutral distractors than for negative, $t(91)=2.99, p<0.01$, or positive distractors, $t(91)=3.34, p<0.01$, but accuracy for the latter word types did not differ, $t(91)=-0.53, p=0.60$, (Table 1). RT interference for negative versus positive distractors was comparable, $t(91)=0.28, p=0.78$.

Table 1. Behavioral performance across the group

	emotion word Stroop			color word Stroop	
	Negative	Positive	Neutral	Incongruent	Neutral
% accuracy					
M	94.62	94.41	95.61	87.30	97.00
(SD)	(0.03)	(0.04)	(0.04)	(0.11)	(0.03)
RT interference					
M	0.010	0.007		0.164	
(SD)	(0.068)	(0.068)	(N/A)	(0.099)	(N/A)

In the cw-Stroop, accuracy was significantly lower for incongruent distractors than for neutral distractors, $t(91)=9.68, p<0.01$. Comparing performance between tasks, participants were less accurate and

showed greater RT interference for incongruent distractors than for negative (accuracy: $t(91)=6.62, p<0.01$; interference: $t(91)=11.62, p<0.01$) or positive distractors (accuracy: $t(91)=6.82, p<0.01$; interference: $t(91)=13.46, p<0.01$).

Relationships between anhedonic depression and performance. In correlation analysis, there was no relationship between depression and RT interference for negative distractors, $r(91)=0.08, p=0.46$. Level of depression was negatively correlated with percent accuracy responding to negative distractors, $r(91)=-0.30, p<0.01$. However, when controlling for neutral word error rate (i.e. negative %accuracy – neutral %accuracy) this predictive relationship was no longer significant, $r(91)=-0.11, p=0.28$.

Including RT interference or accuracy as covariates in correlation analyses investigating relationships between depression and brain responses to each distractor type failed to alter the significance or pattern of results. Therefore we report simple correlations only.

Neuroimaging Results

Brain regions recruited across the group when ignoring negative distractors. Table 2 lists the regions that showed significant activation or deactivation to negative distractors (compared with brain response to neutral distractors). Significant deactivation was detected within a number of midline regions associated with the default network, including left and right

posterior cingulate cortex (PCC) and right anterior cingulate extending into medial prefrontal cortex (mPFC). Deactivation was also detected in left fusiform gyrus extending into the left parahippocampal gyrus (PHG), and in right parahippocampal gyrus. In all cases, these relationships were driven by greater deactivation in these brain regions in response to negative distractors than neutral distractors (each compared to fixation).

Table 2. Brain regions recruited across the group when ignoring negative distractors

Region	Cluster Size	Max z	COI Location		
			x	y	z
Negative < Neutral					
left fusiform gyrus/parahippocampal gyrus	1348	-5.82	-28	-42	-18
right parahippocampal gyrus	1497	-5.36	26	-34	-20
left insula	4061	-5.10	-46	-4	4
right posterior cingulate cortex	566	-4.85	18	-52	12
right superior temporal gyrus/insula	2952	-4.71	46	-4	-4
right middle frontal gyrus	672	-4.68	22	14	48
right angular gyrus	185	-4.54	40	-76	30
left posterior cingulate cortex	492	-4.31	-12	-54	8
right anterior cingulate cortex/medial prefrontal cortex	552	-4.16	10	40	0
right postcentral gyrus	852	-4.12	12	-36	66
right inferior parietal lobule	92	-3.60	30	-42	58
Negative > Neutral					
right inferior frontal gyrus	91	3.85	58	32	8
left medial frontal gyrus	996	4.71	-6	48	44
left middle temporal gyrus	670	5.41	-58	-38	-4
left inferior frontal gyrus	2523	7.08	-48	26	-4

Note. Clusters defined by significance level of $p < 0.0025$, family-wise error rate < 0.05

In contrast, significant activation was detected in several prefrontal regions, such as left and right inferior frontal gyrus (IFG) and a region of left medial frontal gyrus extending into dorsal medial prefrontal cortex (dmPFC). Activation was also detected in an area of left middle temporal gyrus. Activation in these regions was driven by the greater activation in response to negative distractors than neutral distractors (each compared to fixation).

For each of the clusters of significant activation or deactivation in response to negative distractors, we created an ROI centered at the peak, for a total of 15 group-defined ROIs.

Specificity of brain response to negative distractors across the group. In seven of the 15 brain regions in which significant neural responses were detected for negative distractors across the group, exposure to neither positive nor incongruent distractors predicted comparable effects. This pattern suggests that neural responses (here, deactivations) to negative distractors in these regions were not driven by general effects of emotion or difficulty (Table 3).

Table 3. Specificity of brain response to negative distractors across the group

Region of Interest	emotion word Stroop		color word Stroop	Interactions	
	Negative - Neutral t	Positive - Neutral t	Incongruent - Neutral t	(Negative-Neutral) - (Positive-Neutral) t	(Negative-Neutral) - (Incongruent-Neutral) t
Brain activity specific to negative distractors					
left insula	-5.96 *	-1.62	-1.95	-3.24 *	-2.30 *
right posterior cingulate cortex	-5.57 *	-1.89	-1.88	-2.11 *	-2.14 *
right angular gyrus	-4.96 *	-0.87	4.21 *	-2.93 *	-6.60 *
right middle frontal gyrus	-4.42 *	-0.21	5.11 *	-3.01 *	-7.20 *
right parahippocampal gyrus	-4.41 *	-1.89	-1.65	-1.70	-2.07 *
right anterior cingulate cortex	-4.07 *	-0.87	1.48	-2.84 *	-3.48 *
right inferior parietal lobule	-3.14 *	-1.38	0.84	-1.45	-3.12 *
Brain activity specific to emotional distractors					
left fusiform gyrus/ parahippocampal gyrus	-5.74 *	-2.43 *	-1.37	-2.19 *	-3.00 *
left medial frontal gyrus	2.31 *	4.54 *	1.97	-1.08	0.64
right inferior frontal gyrus	3.15 *	2.47 *	0.57	0.28	0.48
left inferior frontal gyrus	5.57 *	6.29 *	-0.23	-0.60	4.20 *
Brain activity common across valence and task demands for cognitive control					
right superior temporal gyrus/ insula	-5.00 *	-2.14 *	-3.33 *	-2.10 *	-0.85
left posterior cingulate cortex	-4.33 *	-2.21 *	-4.56 *	-1.78	-0.28
right postcentral gyrus	-3.94 *	-2.11 *	-2.34 *	-1.00	-0.37
left Middle Temporal Gyrus	4.62 *	3.62 *	4.54 *	0.34	-0.12

$p < 0.05$ *

Specifically, within ROIs centered in right PCC, right PHG, right ACC/MPFC, left insula and right inferior parietal cortex, analyses failed to detect activation or deactivation in response to positive or incongruent distractors. Within the right angular gyrus and right middle frontal gyrus, no significant brain response was detected for positive distractors, and in contrast, these regions were activated in response to incongruent distractors. For the majority of these regions, levels of deactivation associated with negative distractors were significantly greater in magnitude than the brain responses associated with positive or incongruent distractors. (Note the exceptions of right PHG and right inferior parietal lobule, in which deactivation for negative distractors failed to exceed the (non-significant) deactivation for positive distractors).

In four of the 15 ROIs recruited to ignore negative distractors, similar and significant brain responses were also detected for ignoring positive distractors (also Table 3).

Deactivation was detected in left fusiform/PHG when ignoring positive distractors, although the degree of this deactivation was significantly weaker than that detected for negative distractors. In the same region, the level of deactivation observed for negative distractors significantly exceeded the (non-significant) brain response to incongruent distractors. This pattern suggests that this area of left fusiform/PHG is deactivated in response to emotional distractors, and especially when such distractors are negatively valenced.

In contrast, activation was detected in left and right IFG and left medial frontal gyrus for positive distractors, and to a similar extent as for negative distractors. The comparable, and significant, activation of these brain systems for positive and negative distractors suggests that they are recruited for cognitive control with emotional information in general.

Finally, in the remaining four of the 15 ROIS regions that were recruited when ignoring negative distractors, similar and significant brain responses were detected for positive and incongruent distractors (also Table 3).

Deactivation was detected in right superior temporal gyrus/insula, left PCC, and right postcentral gyrus for all distractors. In contrast, activation was detected in left middle temporal gyrus for all distractors. Across these ROIs, levels of activation or deactivation were comparable for all distractor types (with the exception of right superior temporal gyrus/insula, which showed less deactivation for positive than negative distractors). These similarities in brain responses suggest that these regions respond to the cognitive control demands of ignoring distracting information, in general.

Anhedonic depression predicts activation in regions deactivated across the group when ignoring negative distractors. Within two group-defined brain regions, activation in response to negative distractors compared to neutral distractors (Contrast 1) was correlated with anhedonic depression (Figure 1 and Table 4).² Specifically, higher levels of depression predicted less deactivation in right PCC, and marginally less deactivation in left fusiform gyrus/PHG, in response to negative distractors.

² In post-hoc analyses controlling for anxiety, these correlations with anhedonic depression were no longer significant ($p=0.12$ and $p=0.13$). However, neither anxious arousal nor anxious apprehension, alone, was significantly correlated with activation in these ROIs in response to negative distractors (p 's >0.52). Together, this suggests that factors shared across depression and anxiety may contribute to the correlations between depressive symptoms and brain response to negative distractors, but the effects are unlikely to be driven by anxiety.

Figure 1. Anhedonic depression predicts increased activity in regions of default mode network in response to negative distractors

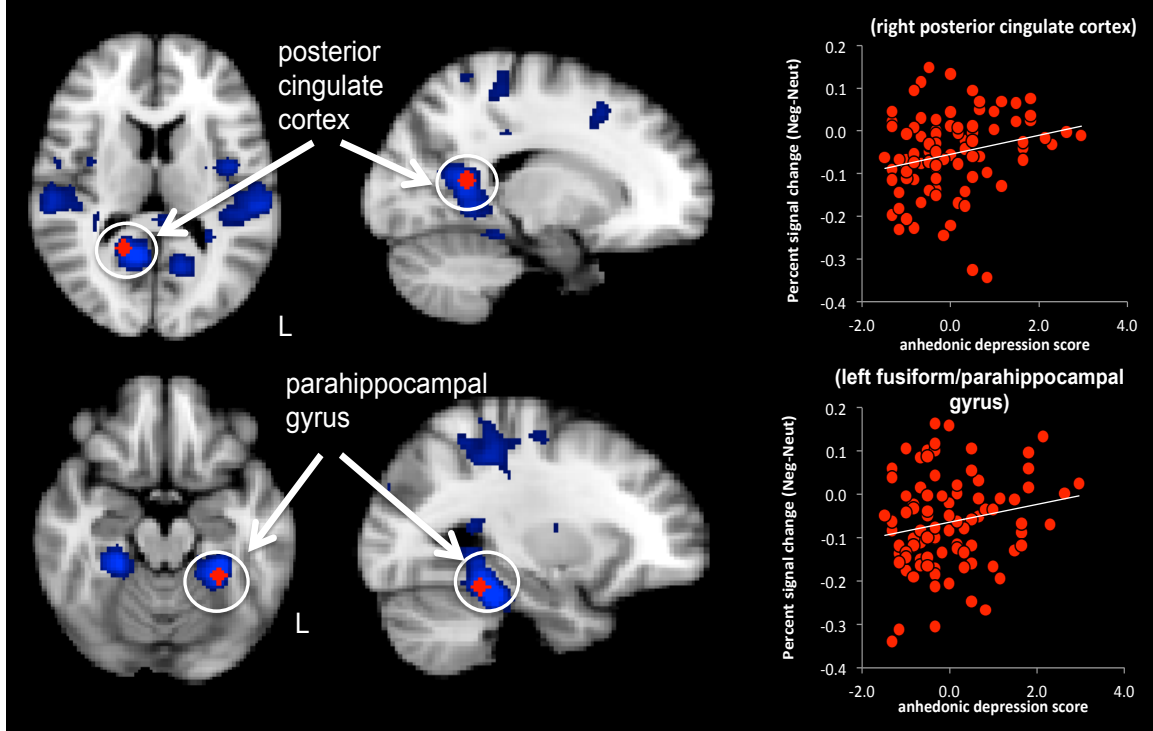


Figure 1. Anhedonic depression is positively correlated with increased activation in regions of posterior cingulate cortex and parahippocampal gyrus in response to negative distracting information (contrast: negative–neutral). These regions are deactivated across the group in response to negative distractors.

Table 4. Anhedonic depression predicts activation in regions recruited across the group when ignoring negative distractors

Region of Interest	emotion word Stroop				color word Stroop		Interactions			
	Negative - Neutral		Positive-Neutral		Incongruent - Neutral		(Negative-Neutral) vs. (Positive-Neutral) difference in correlations		(Negative-Neutral) vs. (Incongruent-Neutral) difference in correlations	
	r	p	r	p	r	p	t	p	t	p
Brain activity specific to negative distractors										
right posterior cingulate cortex	0.24	0.02	0.02	0.86	-0.17	0.10	1.61	0.05	2.72	<0.01
left fusiform gyrus/ parahippocampal gyrus	0.19	0.06	0.01	0.95	-0.22	0.03	1.34	0.09	2.85	<0.01

The pattern of positive correlations between anhedonic depression and brain response to negative distractors failed to emerge for either positive or incongruent distractors in either of these areas. Furthermore, the correlations between depression and brain response to negative distractors were marginally or significantly more positive than brain responses to other distractor types. Taken together, these results suggest that the predictive relationships between depression and brain response to negative distractors in these regions are not driven by emotionality or general demands for cognitive control.

Anhedonic depression predicts activation in unique regions outside those recruited across the group in response to negative distractors. In whole-brain analysis, level of anhedonic depression was positively correlated with activation for the negative-neutral contrast in five unique regions outside the group-defined ROIs described above (Figure 2 and Table 5). These included a region in left postcentral gyrus/PCC, left and right caudate, left medial frontal gyrus extending into dorsal anterior cingulate cortex (dACC) and a region of brain stem including dorsal areas of the pons and midbrain. Notably, higher levels of depression predicted both increased activation in these regions to negative distractors (compared with fixation), and slightly decreased activation to neutral distractors (compared with fixation), although neither correlation alone emerged as significant.

Figure 2. Anhedonic depression predicts increased activity in subcortical regions and areas of medial cortex in response to negative distractors

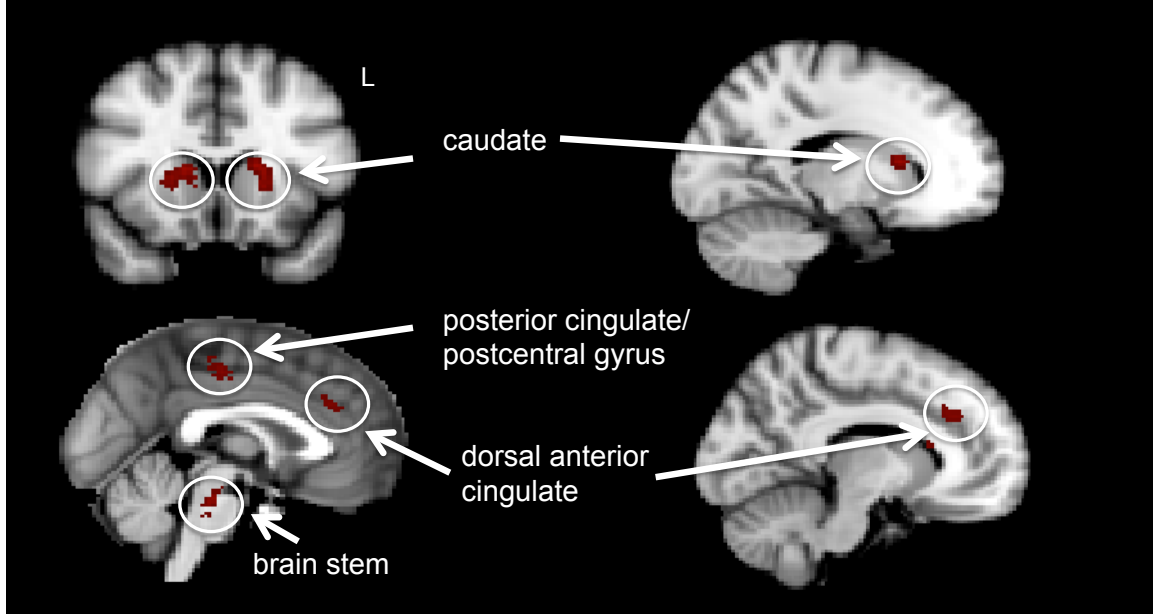


Figure 2. Anhedonic depression is positively correlated with activation in bilateral caudate; posterior cingulate extending into postcentral gyrus; an area of brain stem; and dorsal anterior cingulate when ignoring negative distractors (contrast: negative-neutral). Activation in these regions varies uniquely by depression

Table 5. Anhedonic depression predicts activation in unique regions outside those recruited across the group in response to negative distractors

Region	Cluster Size	Max z	COI Location		
			x	y	z
Negative > Neutral					
left medial frontal gyrus	126	3.31	-12	32	30
left postcentral gyrus/ posterior cingulate cortex	126	3.33	0	-22	46
brain stem	107	3.54	-2	-26	-24
left caudate	95	3.63	-16	16	12
right caudate	117	3.68	14	18	10

Note. Clusters defined by significance level of $p < 0.0025$, family-wise error rate < 0.05

Using the coordinates of the peak correlations for each of these regions, we created a set of ROIs that represent areas in which activation for the contrast of negative versus neutral distractors is predicted by level of anhedonic depression. Within this set of ROIs, there were no significant correlations between anhedonic depression and the contrast of positive versus neutral distractors (Table 6). However, a marginal positive correlation was detected between depression and this contrast in the right caudate ROI, and the strength of this relationship was not significantly different from the correlation detected for negative distractors, a pattern that suggests some degree of general responsiveness to emotional information in this region. In the remaining four ROIs, the correlations between depression and brain response to negative distractors were significantly (or marginally, in left PCC) stronger than those detected for positive distractors.

Table 6. Specificity of correlations between anhedonic depression and activation in unique regions outside those recruited across the group

Region of Interest	emotion word Stroop				color word Stroop		Interactions			
	Negative - Neutral		Positive-Neutral		Incongruent - Neutral		(Negative-Neutral) vs. (Positive-Neutral) difference in correlations		(Negative-Neutral) vs. (Incongruent-Neutral) difference in correlations	
	r	p	r	p	r	p	t	p	t	p
Brain activity specific to negative distractors										
brain stem	0.35	<0.01	<0.01	0.98	-0.11	0.31	2.71	<0.01	2.94	<0.01
left medial frontal gyrus	0.32	<0.01	-0.07	0.52	-0.07	0.49	3.14	<0.01	2.55	<0.01
left caudate	0.31	<0.01	0.01	0.94	-0.23	0.03	2.20	0.01	4.04	<0.01
left postcentral gyrus/ posterior cingulate cortex	0.27	0.01	0.07	0.48	-0.09	0.38	1.55	0.06	2.48	<0.01
Brain activity specific to emotional distractors										
right caudate	0.30	<0.01	0.19	0.07	-0.14	0.19	0.82	0.20	3.19	<0.01

In contrast, for incongruent (versus neutral) distractors, a significant negative correlation was detected between depression and brain response in left caudate (a pattern that opposes the

positive correlation detected between depression and activation to negative-neutral distractors). There were no other significant relationships between depression and this contrast within the other four ROIs. Across all five ROIs, the correlations detected between anhedonic depression and brain response to negative (versus neutral) distractors, were significantly more positive than such relationships for incongruent (versus neutral) distractors.

Taken together, this evidence suggests that the predictive effects of anhedonic depression on brain response to negative distractors are unique to cognitive control with negative information, and unlikely to represent altered response to emotion or cognitive control demands in general.

Discussion

These analyses provide evidence that anhedonic depression predicts increased activity in regions of the default mode network, subcortical structures, and in a region implicated in cognitive control, when ignoring negative distracting information. In addition, these data suggest that such increased activation is specific to cognitive control in the face of negative distractors, and is not driven by altered response to emotional or distracting information in general.

Anhedonic Depression Predicts Activation in Default Mode Network

Across the group and collapsing across level of depression, the set of DMN regions deactivated in response to negative (compared with neutral) distractors included areas of bilateral posterior cingulate, right anterior cingulate extending into medial prefrontal cortex, and bilateral parahippocampal gyrus. This pattern of deactivation is comparable with other research demonstrating default-mode deactivation in response to challenging tasks requiring external attention (e.g. Shulman et al., 1997). Notably, particular regions of DMN deactivation were

specific to negative (compared with neutral) distractors while other regions were deactivated more generally, also in response to emotional or incongruent (compared with neutral) distractors. The specificity and generality of such DMN deactivation suggest that across participants, some aspects of brain response to negative distractors are driven by negative valence while others are driven by processing demands shared across multiple types of distractors.

Subclinical anhedonic depression predicted increased activation in group-defined areas that were responsive to ignoring negative information, either specifically (as in right PCC) or especially (as in left PHG). Anhedonic depression also uniquely predicted increased activation in a more anterior region of left PCC in response to negative distractors. Notably, severity of anhedonic depression only correlated with brain response to negative distractors in these regions, and failed to predict similarly altered responses to positive or incongruent distractors. Taken together, this pattern of results supports the theory that people higher in depression show blunted deactivation in default mode regions in response to negatively valenced distractors because of the negative emotional content of those distractors. What might this altered pattern of deactivation signify for the cognitive functioning of people with elevated levels of depression?

Functional connectivity analyses have identified the PCC as one of two core hubs for the DMN (Andrews-Hanna, Reidler, et al. 2010) and the PCC is implicated in functions including self-reference (Johnson et al., 2002), emotional modulation (Sheline et al., 2009), and retrieval of autobiographical episodic memory, especially when co-active with MTL (Whitfield-Gabrieli & Ford, 2012). Previous research has demonstrated that people with depression show blunted deactivation in regions of PCC when viewing emotional pictures (Grimm et al., 2009) or ignoring negative words (Mitterschiffthaler et al., 2008), and depression predicts increased functional connectivity between midline cortical structures and affective regions (Greicius et al.,

2006). Depression also predicts altered recruitment of PCC regions when attempting to disengage from self-referential thinking (Johnson et al., 2009), or when making self-referential judgments (Grimm, Ernst, et al., 2009; 2011). In these same regions, increased activation in response to emotional or self-referential tasks has been shown to correlate with severity of depression and rumination, respectively (Grimm, Boesiger, et al., 2009; Johnson et al., 2009). Taken together, this research suggests that depressed individuals recruit posterior midline structures when confronted with negative or self-relevant information. Present findings are consistent with this evidence, and highlight the potential role of posterior midline structures as a substrate of cognitive reactivity to negative emotional information in subclinical depression.

In the present study, anhedonic depression also predicted increased activation in response to negative distractors in left PHG. The PHG is considered to be a key component within the medial temporal lobe subsystem of the DMN, is highly connected with posterior midline structures, and is implicated in episodic memory, future self-related imagery (Andrews-Hanna et al., 2010; Buckner, Andrews-Hanna, & Schacter, 2008), and associative “binding” of cues to context (Bar, 2007). Previous work has shown that depression predicts increased recruitment of hippocampal regions including PHG in response to negative stimuli (Anand et al., 2005; Sheline et al., 2009) and increased functional connectivity between PCC and PHG (Marchetti et al., 2012). This pattern of increased activation in PHG for negative distractors suggests the possibility that the cognitive reactivity that characterizes depression also may involve automatic retrieval of autobiographical memories in response to such cues. Because our task asked people to ignore the negative content of words, our results may provide insight on the mechanisms by which rumination (or worry) is involuntarily triggered. This interpretation, however, remains speculative without explicitly measuring autobiographical thinking.

In sum, the current research suggests that subclinical anhedonic depression predicts increased activation of specific regions of default mode network that are implicated in self-referential thinking and autobiographical memory retrieval in response to negative distractors. Because negative information should be ignored in our task, the pattern of blunted deactivation that we detected is likely to represent involuntary allocation of cognitive resources to the word meaning, which may reflect increased cognitive reactivity to negatively valenced material and possibly stronger associations between negative material and autobiographical memories.

Anhedonic Depression Predicts Activation in Subcortical Regions

In the present study, higher levels of anhedonic depression also predicted neural response to negative distractors in subcortical regions that were not implicated across the group. Specifically, higher depression predicted increased activation in left and right caudate, and in a region of brain stem extending through dorsal areas of the pons and midbrain.

Previous research suggests that the caudate nucleus supports responses to both rewarding (Knutson & Cooper, 2005) and aversive stimuli (Drabant et al., 2012; Scott, Heitzeg, Koeppel, Stohler, & Zubieta, 2006). A recent meta-analysis showed that depression predicts increased activation of the caudate in response to aversive stimuli (Hayes & Northoff, 2011), a finding that converges with the current results. It may be that people with higher levels of depression are more sensitive to the aversive qualities of negative emotional content, i.e. increased punishment sensitivity (Santesso et al., 2008). However, given the range of stimuli that predict activation in this structure, researchers have also posited that the caudate may be recruited for the detection of salient information. In line with this theory, Zink and colleagues (2005; 2004; 2003) have shown that caudate activation is predicted by level of stimulus saliency, even when stimuli are neither positive nor negative. Thus the altered pattern of caudate responses to negative distractors that

we detected in the current study may also be driven by the greater personal salience of such information for people higher in depression, perhaps due to congruence between valence and negative self-schemata.

The correlation between anhedonic depression and brain response to distracting stimuli was specific to negative distractors in the left caudate, but not in the right caudate. In the right caudate, a marginal correlation emerged in which depression predicted greater activation for positive distractors, and the comparison between correlations did not yield a significant difference in brain response for negative versus positive distractors. In other research, depression predicted increased ratings of self-relevance for both positive and negative emotional stimuli (Grimm, Ernst, et al., 2011; 2009); therefore, it is also possible that any emotional information is perceived as more personally salient in depression. Future research may address these questions by assessing subjective ratings of various dimensions of saliency such as self-relevance, self-descriptiveness, and perceived importance of positive and negative stimuli.

Regions of brain stem such as those detected in our correlation analyses may include clusters of monoamine neurons (nuclei) that project widely to cortical and subcortical regions (Nieuwenhuys, Voogd, & Van Huijzen, 2008; Sasaki et al., 2008; Haines, 2006). At the level of image resolution in our current study, we cannot determine which nuclei may be driving the pattern of increased activation for people with higher depression (Sasaki et al., 2008). However, given the location of such activation in the median portion of the brain stem and at the levels of the pons and midbrain, we speculate that we may be capturing activation of raphe nuclei. These nuclei include primarily serotonergic neurons, which project to a range of areas including PFC, caudate-putamen, and the hippocampus (Michelson, Schmitz, & Steinbusch, 2007). Serotonergic dysfunction is theorized to be a key factor in the development and pathophysiology

of depression (Carver, Johnson, & Joormann, 2008; Lowry et al., 2008), and subregions of the dorsal raphe nucleus are selectively activated by stress and anxiety related stimuli (Lowry et al., 2008; Maier & Watkins, 2005). It may be that at higher levels of depression, people find negative information more arousing or stressful. Serotonergic output from the dorsal raphe nucleus influences a range of targets across the brain, including those detected in our analyses such as hippocampal and caudate regions. Together, these results suggest that a network of highly connected cortical and subcortical structures subserves the increased reactivity to negative information that characterizes depression.

Anhedonic Depression Predicts Activation in Cognitive Control Systems

We predicted that anhedonic depression would predict altered recruitment of cognitive control systems in response to negative, as well as positive or incongruent, distractors. This hypothesis was partially supported: anhedonic depression predicted increased recruitment of dACC in response to negative distractors. However, this relationship failed to emerge for the other distractor types. Furthermore, depression was not associated with activation in other cognitive control structures for negative distractors.

The anterior cingulate is an important node in the cascade of cognitive control (Banich, 2009) and as an emotion-attention interface (Davidson & Irwin, 1999). Dorsal regions of this structure are recruited in the service of cognitive control with both emotional (Bush, Luu, & Posner, 2000; Elliott, et al., 2000) and non-emotional information (Compton et al., 2003). One study showed that cognitive conflict and emotional content had additive effects on activation in this region (Chiew & Braver, 2011), suggesting that the dACC is responsive to increased needs for cognitive control that are driven by multiple factors. People who are depressed show increased recruitment of dACC in response to negative information, both when exerting

cognitive control with such information (Mitterschiffthaler et al., 2008; Elliott et al., 2002) or when making decisions about such information (Grimm, Ernst, et al., 2009). Our pattern of results converges with this research, and provides further evidence that depression predicts increased recruitment of a subset of the brain regions recruited for cognitive control.

Notably, we did not detect a relationship between anhedonic depression and over-recruitment of this region of dACC in response to other types of distractors, as has been shown in previous studies (e.g. Wagner, 2006). Furthermore, there were no relationships between depression and brain response to negative distractors in other cognitive control regions recruited across the group. For example, although regions of bilateral IFG were recruited across the group for ignoring emotional distractors, a result that is consistent with previous research (Berkman, Burklund, & Lieberman, 2009; Chiu, Holmes, & Pizzagalli, 2008), such recruitment was unaffected by depression, in contrast to previous research (Elliott et al., 2002; Wang et al., 2008). We also failed to detect relationships between anhedonic depression and recruitment of dorsolateral prefrontal cortex, in contrast to other research demonstrating hypoactivity in this region in response to negative or emotional information (Elliott et al., 2002; Herrington et al., 2010; Engels et al., 2010).

There may be several reasons for the divergence between our results and these previous studies. First, it may be that anhedonic depression has additional predictive effects in cognitive control systems that can only be identified by conducting whole-brain correlations that also take into account specific forms of anxiety. The co-occurrence of depression with anxiety can obscure opposing effects of each phenomenon (Heller, 1990; Heller, Etienne, & Miller, 1995; Snyder, Kaiser, Whisman & Munakata, submitted). In the present study, because we were interested primarily in the effects of anhedonic depression, we chose to focus on simple whole-

brain correlations. This strategy permits us to explore the broad effects of anhedonic depression, i.e. both pure and shared variance. However, this strategy does not identify regions that are implicated specifically by the interaction between depression and anxiety. Other analyses have investigated how the effects of anhedonic depression are moderated by co-occurring anxiety, and have suggested that altered recruitment of other cognitive control regions can only be revealed through such whole-brain interaction analyses (see Engels et al., 2010).

Second, it may be that magnitude of activation in prefrontal cortical regions is only one aspect of how depression predicts brain response. In one study investigating cognitive control with negatively valenced information, researchers found that depression did not predict altered magnitude of activation in left IFG, but did predict greater spatial variance in the recruitment of this region (Berman et al., 2011). This study suggests the utility of future analyses to examine other aspects of neural response, besides magnitude of activation.

Anhedonic Depression Fails to Predict Behavioral Performance

Anhedonic depression failed to predict differences in behavioral measures of executive functioning ability for any distractor type. Research investigating performance on this task as it relates to depression sometimes has (Gotlib & Cane, 1987; Gotlib & McCann, 1984; Mitterschiffthaler et al., 2008), and sometimes has not (Herrington et al., 2010), detected increased RT interference for negative words. Because depression predicted greater task-irrelevant processing of negative words, as signified by the reduced deactivation in default mode regions, we might expect impaired behavioral performance (Whitfield-Gabrieli & Ford, 2012). However, because depression also predicted increased recruitment of dACC, a region implicated in cognitive control, it may be that at higher levels of depression people are able to compensate for hyperactivity in default mode regions (Clark, Chamberlain, & Sahakian, 2009). These results

are aligned with previous research showing the people higher in depression exhibit greater recruitment of specific cognitive control systems to accomplish similar levels of behavioral performance.

Future Directions

The present study investigated anhedonic depression from a dimensional perspective, and in a subclinical population. Previous research has tended to focus on behavioral and neurobiological functioning in currently depressed populations, from a categorical perspective. This approach is valuable in identifying changes in functioning that emerge, on average, for people in a current depressive episode. However, a growing literature suggests that altered recruitment of default mode or cognitive control systems not only characterizes clinical depression, but also may be risk markers prior to the onset of a clinical episode, and may persist after episode remission (Marchetti et al., 2012). Examining depression from a dimensional view, and thus characterizing individual differences in depressive traits in a typical population, is increasingly important as we strive to define mechanisms of risk and resilience. However, we cannot conclude that the patterns of brain responses to negative distractors detected in the present study would be the same in a diagnostic group. Future research may expand on the current findings by including a currently depressed, clinical comparison group.

Future longitudinal investigations would also provide insight about vulnerability to clinical depression and the chronic nature of the disease. The current study cannot determine whether these patterns of altered brain functioning change, or persist, as an individual moves in or out of a depressive episode. Such questions could be pursued by assessing brain responses to negative distractors at multiple time points including depression onset, remission, and recurrence.

In conclusion, the current research provides evidence that subclinical anhedonic depression predicts brain activation in several systems when exerting cognitive control to ignore negative distractors. First, depression predicted blunted deactivation in default mode regions implicated in emotion modulation and autobiographical thinking. Second, depression predicted recruitment of subcortical systems involved in arousal, serotonergic functioning, and detection of salient information. Third, depression predicted activation in an anterior cingulate region implicated in cognitive control, and specifically, in selecting and evaluating responses. These relationships between depression and neural responses were specific to cognitive control with negative distractors, and were not driven by altered response to emotional or distracting information in general. Together, this evidence provides support for the theory that depression is related to altered functioning in both default mode and cognitive control systems. In the current study, this altered functioning was specifically related to negative emotional content, a finding that converges with theories of increased cognitive reactivity to negative information in depression. Future clinical research may clarify whether these neural signatures change over the course of chronic depression, or in response to specific interventions (e.g. mindfulness-based or cognitive therapies) that are designed to target cognitive reactivity and rumination.

CHAPTER III

STUDY 2

Introduction

Increased sensitivity to the negative effects of stress is theorized to be core to the causes, consequences, and phenomenology of clinical and subclinical depression (Hammen, 2005; Hasler, Drevets, Manji, & Charney, 2004; McEwen, 2005; Monroe & Simons, 1991; Pizzagalli, Bogdan, Ratner, & Jahn, 2007). However, the nature of the relationship between stress and depression is complex and remains poorly understood. For example, despite evidence for the adverse effects of stress, stress exposure can also have positive effects on mood and behavioral functioning (Dienstbier, 1989). It is important to identify the conditions under which stress promotes or disrupts functioning in order to specify more precisely the relationship between stress and depression.

One factor that appears to be especially important in shaping the effects of stress exposure is whether or not the individual can learn to behaviorally control stressors. Stress controllability has primarily been investigated in “learned helplessness” research (reviews in Seligman, 1972, and Maier, 1984). In this research, exposure to uncontrollable stress (defined as stress that cannot be escaped or modulated by behavioral responses, despite efforts to do so), leads to passivity, negative affect, and disrupted performance on learning or problem-solving tasks (Hiroto, 1974; Hiroto & Seligman, 1975; Jones, Nation, & Massad, 1977; DeVellis, McEvoy-DeVellis, & McCauley, 1978; Hirt & Genshaft, 1981; Kofta & Sedek, 1989). In contrast, exposure to controllable stress (usually defined as stress that can be escaped or modulated by learning

specific behavioral responses) leads to unimpaired or even improved performance on the same types of cognitively demanding tasks (Thornton & Jacobs, 1971; Thornton & Powell, 1974; Benson & Kennelly, 1976; Eisenberger, Park, & Frank, 1976; Eisenberger et al., 1979).

Early efforts to extend this research to depressed populations yielded mixed results. Some studies showed that depressed individuals fail to benefit from behavioral control, exhibiting comparable (poor) performance after stress exposure regardless of whether or not stressors were controllable (e.g. Kilpatrick-Tabak & Roth, 1978; Miller & Seligman, 1976). In contrast, other studies showed that exposure to controllable stress “treatment” led to improved performance on subsequent learning tasks in depressed people (e.g. Klein & Seligman, 1976). Such conflicting findings may be a consequence, in part, of the failure to take into account individual differences in stress responses, which may obscure the adaptive effects of behavioral control for depressed individuals.

The effects of stress on behavioral functioning are moderated by the intensity of an individual’s (physiological or subjective) responses to stress. Such stress responses are determined both by individual differences in stress sensitivity and by the objective intensity of stressors. Previous research has shown that exposure to moderately intense stress or stress chemicals (e.g. glucocorticoids) predicts improved behavioral performance, while high-intensity exposure predicts impaired performance (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). These effects are especially evident in tasks that recruit executive function (EF), such as those placing demands on working memory (Schoofs, Wolf, & Smeets, 2009), selective attention (Oei, Tollenaar, Spinhoven, & Elzinga, 2009), or “cognitive flexibility” (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007). Because depressed individuals are characterized by heightened

sensitivity to stress (Burke et al., 2005), they may benefit from behavioral control only when stress exposure is less intense.

In support of this idea, our previous research in a non-depressed population indicated that stress controllability and subjective response to stress interact to affect performance on a test of general EF, the color-word Stroop task (Kaiser Henderson, Snyder, Gupta, & Banich, 2012). Exposure to controllable and subjectively moderate stress led to improved performance, but exposure to stress that was subjectively more severe or that was uncontrollable predicted impaired performance. A next step in this research is to investigate whether controllability and subjective response are factors that moderate the effects of stress exposure for people at higher levels of depression. Such investigation may help to clarify the conditions under which stress exposure is harmful versus helpful for people with clinical or subclinical depression, and thus inform development of behavioral therapies that capitalize on the helpful effects of stress.

We examined four hypotheses in the current study. First, we predicted that exposure to controllable stress would lead to significantly better performance on the color-word Stroop task (greater reduction in reaction-time interference from pre- to post-stress exposure) than exposure to uncontrollable stress. Second, we predicted that the effects of exposure to controllable (but not uncontrollable) stress would be moderated by subjective response. We predicted that people who experienced controllable stressors as moderately intense would show improved performance, but those who experienced stressors as highly intense would show impaired performance despite having behavioral control. Third, we predicted that the effects of exposure to controllable (but not uncontrollable) stress would also be moderated by depression. We predicted that people who were more severely depressed or who had a clinical diagnosis of depression would show less improvement in Stroop performance than healthy individuals

following controllable stress exposure. Fourth, we predicted that the influence of depression in moderating the effects of controllable stress exposure would in turn be mediated by subjective stress response. For complete mediation, we predicted that once subjects are equated on subjective stress response, the effects of controllable stress on Stroop performance would be similar for those at high or low levels of depression severity.

Methods

Recruitment and Sample Characteristics

Participants were women aged 18-50 recruited from the Boulder, Colorado community and local clinics. We chose to restrict our sample to women because of the increased prevalence of depression in women (Kessler et al., 2003) and evidence for sex differences in physiological and subjective responses to stress (Kajantie & Phillips, 2006; Ordaz & Luna, 2011).

Inclusion criteria were: a) native or fluent English speaker, b) no history of psychotic symptoms, psychotic disorders, bipolar disorders, or pervasive developmental delays; and c) diagnosis of either no lifetime depressive disorders, history of MDD as primary diagnosis, or current episode of MDD as primary diagnosis.

We assessed inclusion criteria through phone screening prior to enrollment and a diagnostic interview conducted at the time of the research session. For the latter, masters-level researchers administered the Structured Clinical Interview for the DSM-IV, patient version (SCID-IP; First, Spitzer, Gibbon, & Williams, 2007). The SCID-IP is a semi-structured psychiatric interview widely used for diagnostic purposes in clinical and research settings. All research interviewers received formal training in SCID administration and coding at the University of Colorado Boulder and had at least two years of SCID interviewing experience. An independent researcher

with comparable training performed reliability checks on 20% of interviews, yielding high inter-rater reliability across diagnoses ($\kappa=0.78$).

A total of 117 women completed phone screen assessments. During the screening and intake process, 18 women were excluded due to: diagnosis of Bipolar I Disorder ($n=6$); history of MDD secondary to another diagnosis (e.g. Alcohol Dependence; $n=9$); non-English speaker ($n=2$); or intoxication ($n=1$). An additional nine women failed to enroll either because they declined participation ($n=4$) or withdrew prior to enrollment ($n=5$).

The final sample included 90 women, randomly assigned to either controllable stress (CSt, $N=45$) or uncontrollable stress (USt, $N=45$) exposure. Two CSt participants failed to complete subjective ratings of stress due to computer error; electronic (task and self-report) data for a third CSt participant was lost due to researcher error; a fourth CSt participant failed to complete self-report measures because she left the session early for personal (non-study-related) reasons.

Participants provided informed consent and all study procedures were approved by the University of Colorado Boulder Institutional Review Board. Participants were tested individually in a private room at the Department of Psychology and Neuroscience at the University of Colorado Boulder.

Procedures

At the beginning of the research session, all participants completed baseline assessment of state affect and executive functioning ability. Next, participants were exposed to the stress manipulation, in which they either could (controllable) or could not (uncontrollable) learn how to behaviorally control a noise stress. Following this, participants were asked to complete post-stress administrations of the executive functioning task and the measure of state affect. Finally, participants completed measures assessing their subjective responses to the stress manipulation,

perceived control, current level of anhedonic depression, and the diagnostic interview. We chose to conduct cognitive testing and stress exposure early in the session in consideration of potential variance between participants in the duration and mood effects of the individual diagnostic interview. At the end of the session, all participants received debriefing, psychoeducation materials about depression and the purpose of the research study, and referral information.

Assessment of state affect. Participants completed the Positive and Negative Affect Questionnaire (PANAS-X; Watson & Clark, 1999) both before and after cognitive testing as a measure of state affect. Both subscales of positive and negative affect are found to have high internal consistency for clinical and community samples (Cronbach's alpha of .83 to .91). Participants rate each of 20 items on a 1 (low) to 5 (high) scale based on the extent to which they feel that way currently, in the moment.

Test of executive functioning: the color-word Stroop. Participants completed the color-word Stroop to provide a measure of general EF at baseline and again following stress exposure (Friedman et al., 2008; Stroop, 1935). On each trial, a word written in one of four ink colors (green, yellow, red or blue) appeared in the center of the screen for 2000ms and participants identified the ink color as quickly as possible by hitting the corresponding button on the keyboard. Prior to beginning the first Stroop task, participants were given 16 practice trials in which XXXX stimuli were presented to familiarize them with the location of the response keys for each color. During the task, trials were presented in two blocks (48 trials each; 38% incongruent and 62% neutral across blocks). Incongruent words feature conflict between ink color and word meaning (e.g. "red" written in blue ink), whereas neutral words do not (e.g. "sum" written in blue ink). Comparing reaction time (RT) to incongruent versus neutral words isolates the individual's ability to exert cognitive control in the face of highly distracting

information, over and above basic perceptual processing abilities and response speed. Therefore, the calculation of percent difference in incongruent versus neutral RT ($(\text{incongruent RT} - \text{neutral RT}) / \text{neutral RT}$) yields an interference score that indexes general executive functioning. A computer system captured accuracy and reaction time (RT) via millisecond-accurate keyboard press.

Stress manipulation. Our stress manipulation included exposure to either controllable or uncontrollable noise stress (a 3000 Hz variable tone; see Hiroto & Seligman, 1975) concurrent to performance of a choice-reaction time (RT) task (see Kaiser Henderson, et al., 2012). Prior studies have operationalized *uncontrollability* as non-contingency between instrumental actions and outcomes, often accompanied by high rates of failure feedback (Dickerson & Kemeny, 2006). In the current experiment, we structured the manipulation of uncontrollability to include both non-contingency and increased rates of failure. In contrast, the controllable stress condition included both true contingency and (accurate) high rates of success feedback. The CSt and USt groups did not differ on noise exposure, task stimuli, or response requirements.

The choice-RT task required participants to choose behavioral responses based on perceptual features in the display (Figure 3). For each trial, an arrow pointing either left or right appeared inside a fixation box on the computer monitor. Participants responded to the direction of the arrow as quickly as possible by pressing the corresponding button on the keyboard. All participants completed a practice block (40 trials) without any stress exposure, to familiarize themselves with the choice-RT task.

Figure 3. Stress manipulation







	GROUP	
BLOCK	Controllable Stress (CSt)	Uncontrollable Stress (USt)
Practice		
feedback	none	none
Block 1		
feedback	failure (slow response) success (fast response)	failure (type of feedback unrelated to response speed) success
Block 2		
feedback	failure (slow response) success (fast response)	failure (feedback unrelated to response speed) success
noise stress	LONG (slow response) SHORT (fast response)	(noise AND feedback unrelated to response speed)

Figure 3. The stress manipulation consisted of a choice-RT task accompanied by controllable (CSt) or uncontrollable (USt) aversive noise. The CSt group received accurate feedback regarding response speed, and noise exposures were contingent on responses. The USt group received inaccurate feedback, and noises were unrelated to response speed or feedback. Amount and duration of noise exposures were consistent between groups.

In the two testing blocks (60 trials each), participants were instructed to pursue two performance goals: 1) to respond accurately and fast enough to beat a challenging time limit, for which they received performance feedback indicating success (yellow fixation box) or failure (blue fixation box) (blocks 1 and 2); and 2) to learn how their responses controlled the duration of a noise stressor that was evoked by each response (block 2 only).

For the CSt group, feedback and noise exposures were controllable: fast, accurate responses elicited short noises accompanied by success feedback, while slow or inaccurate responses elicited long noises coupled with failure feedback. A moving-window for response speed ensured that every participant was able to beat the time limits on 80% of trials.

For the USt group, feedback and noise exposures were uncontrollable, both 1) because feedback and noises were not contingent on response speed, and 2) because feedback was biased to indicate a higher rate of failure (blue fixation box for 50% of trials, regardless of response speed or accuracy). Groups were matched on their true response success and noise exposure: as

in the CSt group, a moving-window for response speed ensured that every participant was actually able to beat the time limits on 80% of trials, and every participant received a short noise on 80% of trials. However, unlike the CSt group, the USt participants received non-contingent performance feedback that was biased for failure, and short and long noises were random and unrelated to their response speed or performance feedback.

Participants listened to the auditory stressor (either 2000ms or 4000ms in duration) through headphones, with volume calibrated at 72-80dB. Accuracy and RT were captured via keyboard press.

Assessment of subjective stress and perceived control. At the end of testing, participants rated the following on a 1 (low) to 9 (high) scale: 1) how stressful was the noise? 2) how stressful was the arrow task? (choice-RT task demands), 3) to what extent do you believe someone else would have performed better than you? (social comparison), 4) how well do you believe you performed? (reverse scored). The scores for these scales were summed to yield a composite score of subjective stress for each participant, with higher scores indicating more extreme responses to the stress manipulation and lower scores indicated more moderate responses. Also at the end of testing, participants reported perceived control over the noise stress on a 1 (low) to 9 (high) scale.

Assessment of depression. We approached our investigation of depression from both dimensional and clinical (categorical) perspectives. The cognitive impairments and dysregulation in stress systems that are core to depressive phenotypes exist on a continuum, and are present in people reporting subclinical symptomatology (Brooks & Robles, 2009; Nakano et al., 2008; Burke et al., 2005; Paelecke-Habermann, Pohl, & Leplow, 2005). However, it is also possible that some aspects of such cognitive dysfunction and altered stress responses emerge only when a

depressed individual has crossed a critical threshold of severity into a clinical episode (Solomon, Ruscio, et al., 2006). Therefore, we included both dimensional and clinical measures in the current study.

For a dimensional measure of depression, participants completed the Mood and Anxiety Symptom Questionnaire (Nitschke, Heller, Imig, McDonald, & Miller, 2001; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). The 22-item Anhedonic Depression (AD22) subscale of the MASQ provides a well-validated, continuous measure of depressive symptoms (Cronbach's alpha of 0.68 to 0.99, Watson, Clark, et al., 1995). Participants rate the degree to which they have experienced each depressive symptom within the past week, on a 1 to 5 scale, yielding a sum for each participant ranging from 22 to 110 with higher scores indicating more severe depression.

To assess depression from a clinical, categorical perspective, we administered the Structured Clinical Interview for the DSM-IV - patient version (see recruitment, above). This assessment enabled us to group participants in one of three groups: current depression (MDD: current diagnosis of MDD), previous history of depression (pMDD: past diagnosis of MDD, but no current diagnosis), or healthy (healthy: no lifetime diagnosis of any mood disorders).

Statistical Methods

Reaction time analyses were conducted by calculating an average for each trial type. Incorrect trials and trials on which RTs were less than 200ms or exceeded 3 standard deviations above the within-subject mean were excluded from analyses. RTs were natural log transformed to reduce the skew common to RT data and which violates the statistical assumption of normal distribution necessary for regression analysis.

Outlier detection was accomplished in two ways: 1) observations on self-report measures that exceeded 3 standard deviations above or below the group mean were excluded from analyses; 2) for any significant regression effects, standardized df beta was calculated to detect observations that had undue influence on the analysis according to the standard threshold (df beta $> 2/(\sqrt{n})$). This procedure resulted in no more than two participants excluded from any analysis.

Baseline t-test analyses were conducted to test for differences between groups in severity of anhedonic depression, psychiatric diagnoses, pre-stress state affect, and pre-stress Stroop ability. As a manipulation check, a set of t-test analyses were conducted to investigate group differences in perceived controllability of, and subjective responses to, the stress exposure. In addition, analyses were conducted to test for differences between groups in motor speed during the stress manipulation (t-test), and to examine potential relationships between motor speed and depression, subjective stress, or Stroop performance (via correlation or by including motor speed as a covariate in regression).

Experimental analyses were performed with multiple regression. In this analysis technique, the effects of each variable are statistically controlled when examining the effects of other variables.

In our first experimental regression, we predicted changes in Stroop interference (post-pre stress exposure) by subjective stress response (linear and quadratic effects; see Kaiser Henderson, et al., 2012 for discussion); controllability group (expressed as a contrast-coded predictor, CSt=1, USt=-1); and the interactions of these variables. In this analysis, the significance of the controllability group contrast is a test of our first hypothesis: exposure to controllable stress predicts significantly greater improvement in Stroop interference than exposure to uncontrollable stress. The significance of the interaction between controllability

group and subjective stress is a test of our second hypothesis: the effect of controllability on Stroop performance is moderated by subjective response to stress. We conducted follow-up regression analyses within experimental groups to further investigate the relationship between subjective stress response and changes in Stroop interference for people exposed to controllable (or uncontrollable) stress.

In our second experimental regression, we predicted changes in Stroop interference (post-pre stress exposure) by anhedonic depression; controllability group (expressed as a contrast-coded predictor, CSt=1, USt=-1); and the interactions of these variables. The significance of the interaction between controllability group and anhedonic depression is a test of our third hypothesis: the effect of controllability on Stroop performance is moderated by severity of depressive symptoms. Follow-up regressions were conducted within each experimental group to predict changes in Stroop interference by anhedonic depression. These analyses served to clarify the predictive effects of depression on changes in Stroop performance for people exposed to controllable (or uncontrollable) stress.

We conducted a third set of experimental regressions (Baron & Kenny, 1986) designed to explore our fourth hypothesis, that the moderating influence of depression is in turn mediated by subjective response to stress. To demonstrate mediation, the following must be true: changes in Stroop interference are predicted by anhedonic depression; subjective responses to stress are predicted by anhedonic depression; subjective stress predicts Stroop performance when controlling for depression. For complete mediation, the effect of depression in predicting Stroop performance is zero when controlling for subjective stress response (Kenny, Kashy, & Bolger, 1998).

Finally, we conducted (a fourth and fifth set of) regressions in which we replaced the continuous measure of anhedonic depression with orthogonal contrast-codes for current depression (MDD = 2, healthy = -1, and pMDD = -1); and previous depression (healthy = 1, pMDD = -1, and MDD = 0). These analyses examined the moderating effects of depression, but from a clinical vantage point.

We deviated continuous measures around the mean/2 to make the centered score of zero interpretable as representing a low level of either depression or subjective stress. Such deviation is necessary when interpreting the main effects of continuous variables in the context of a model that includes those variables in interactions. All effects are controlling for other variables in the regression model.

Results

Baseline Analyses

Controllability groups did not differ on demographic or clinical variables (Table 7). Both controllability groups reported comparable, moderately high levels of anhedonic depression ($M=58.10$), $t(85)=1.66$, $p=0.13$, and similar baseline levels of positive, $t(86)=1.30$, $p=0.20$, and negative affect, $t(86)=0.69$, $p=0.49$.

In addition, both groups exhibited comparable Stroop interference at baseline, $t(87)=-0.30$, $p=0.77$, and similar accuracy on incongruent, $t(87)=-1.24$, $p=0.22$, and neutral trials, $t(86)=-1.65$, $p=0.10$.

Table 7. Demographic information

	Uncontrollable Stress Group (N=45)	Controllable Stress Group (N=45)
Age M (SD)	29.18 (8.94)	28.62 (7.98)
Race (% European American)	93.33%	88.89%
Ethnicity (% Hispanic)	4.44%	4.44%
Current Major Depressive Disorder (% Diagnosis)	22.22%	24.44%
Lifetime Major Depressive Disorder (% Diagnosis)	64.44%	55.56%
Lifetime Anxiety Disorder (% Diagnoses)	26.67%	28.89%
Lifetime Substance or Alcohol Use Disorder (% Diagnoses)	17.78%	13.33%
Lifetime Eating Disorder (% Diagnoses)	4.44%	8.89%

No group difference (p 's > 0.05) in demographics or current or lifetime psychiatric disorders

Manipulation Checks

As predicted, participants in the CSt group reported significantly higher perceived control ($M=6.36$) during the stress manipulation than the USt group ($M=3.27$), $t(85)=7.87$, $p<0.01$, $R^2=0.42$. In addition, CSt participants reported significantly less intense subjective responses to the stress manipulation ($M=14.50$) than USt participants ($M=17.04$), $t(85)=-2.47$, $p=0.02$, $R^2=0.07$.

We examined whether controllability group predicted differences in reaction time during the stress manipulation. If such differences exist, then subsequent effects of the controllability manipulation on Stroop performance could be interpreted as being driven by differences in motor speed. There were no differences between groups in choice-RT response speed across blocks, $t(89)=1.33$, $p=0.19$. Furthermore, there were no significant correlations between choice-RT response speed and subjective stress, $r(87)=0.14$, $p=0.19$, or changes in Stroop interference,

$r(89)=-0.05$, $p=0.61$, and including choice-RT response speed as a covariate failed to affect any Stroop analyses. Therefore, we report simple analyses only.

Experimental Analyses

Effects of controllability and subjective responses to stress on executive functioning. To investigate our first hypothesis, that exposure to controllable stress predicts significantly greater improvement in Stroop interference than exposure to uncontrollable stress, we examined the significance of controllability group as a predictor variable in our first experimental regression. Controlling for subjective responses to stress, people in the CSt group showed significantly greater reduction (i.e. improvement) in Stroop interference than those in the USt group, $F(1,81)=4.35$, $p=0.04$, $R^2=0.05$.

To investigate our second hypothesis, that subjective response to stress moderates the effect of controllability on Stroop interference, we examined the significance of the interaction between subjective response and controllability group. As predicted, this interaction was significant, $F(1,81)=12.06$, $p<0.01$, $R^2=0.13$, indicating that the linear effect of subjective stress on Stroop interference varied between the controllable and uncontrollable stress conditions. Follow-up analyses revealed an effect of subjective response to stress within the CSt group, $F(1,39)=8.04$, $p<0.01$, $R^2=0.17$. Moderately low subjective responses to controllable stress predicted improved Stroop interference, but as subjective response increased, Stroop performance was impaired. In contrast, there was no effect of subjective stress response on Stroop interference within the USt group, $F(1,43)=1.88$, $p=0.18$. There were no quadratic effects of subjective stress detected across the group or within either experimental group (p 's > 0.20), therefore this variable was dropped from further analyses.

Effects of controllability and severity of depressive symptoms on executive functioning.

Our third hypothesis proposed that severity of depressive symptoms moderates the effect of controllability on Stroop interference. To investigate this prediction, we examined the significance of the interaction between anhedonic depression and controllability group in our second experimental regression. This interaction was marginally significant, indicating that the difference in Stroop performance between CSt and USt subjects became smaller at higher levels of depression, $F(1,82)=3.01, p=0.08, R^2=0.04$. In addition, there was a significant main effect of anhedonic depression, in which more severe depressive symptoms predicted greater impairment in Stroop performance across either type of stress exposure, $F(1,82)=7.29, p<0.01, R^2=0.08$. Follow-up analyses revealed that within the CSt group, higher depression predicted worse Stroop performance, $F(1,41)=8.47, p<0.01, R^2=0.17$. However, within the USt group, there was no significant effect of anhedonic depression on changes in Stroop interference, $F(1,43)=1.15, p=0.29$.

Figure 4. Lower subjective response to controllable (but not uncontrollable) stress predicts improvement in color-word Stroop performance across varying levels of depression severity

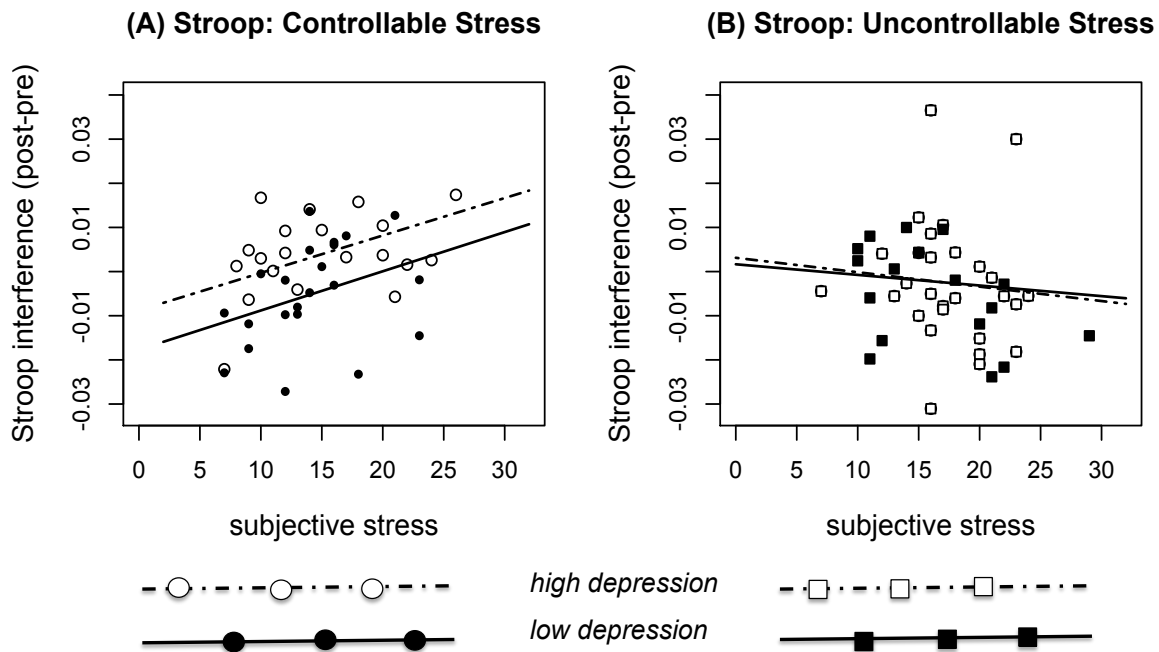


Figure 4. Change in Stroop interference predicted by anhedonic depression, subjective stress and controllability. (A) Within the CSt group, significant linear effects of subjective stress at low or high levels of anhedonic depression (depression scores are median split for graphical display only). (B) Within the USt group, no relationship between subjective stress and Stroop performance, regardless of level of anhedonic depression.

Our fourth hypothesis proposed that the moderating influence of depression on the effect of controllable stress exposure is in turn mediated by subjective stress response. In a regression predicting subjective responses to stress by anhedonic depression, people who were more severely depressed reported more extreme responses to stress exposure $F(1,82)=6.79, p=0.01, R^2=0.08$. Together with the results reported above, this pattern indicates that elevated depression predicts both more extreme subjective responses and worse Stroop performance. Next, we conducted regressions within each experimental group predicting changes in Stroop interference

by subjective responses to stress, anhedonic depression, and the interaction of these variables. Within the CSt group, the effect of subjective response to stress was significant when controlling for anhedonic depression, $F(1,36)=5.08$, $p=0.03$, $R^2=0.12$, a pattern that is consistent with mediation. However, the effect of anhedonic depression also remained significant, even though participants were equated on subjective stress, $F(1,36)=6.72$, $p=0.01$, $R^2=0.16$, and there was no interaction between anhedonic depression and subjective response, $F(1,36)=1.19$, $p=0.28$. These results suggest that the effect of anhedonic depression on Stroop performance following exposure to controllable stress is partially mediated by subjective response to stress, but that each of these factors has significant (additive) effects (Figure 4). In contrast, there were no effects of depression, subjective response to stress, or interactions between these variables within the USt group (p 's > 0.12).

Diagnosis of depression and the effects of controllability on executive functioning.

Finally, we investigated the moderating effects of current or previous diagnosis of depression on the relationship between controllable (or uncontrollable) stress and Stroop performance. In our fourth experimental regression, across the full group, the interactions between controllability group and neither current, $F(1,82)=1.47$, $p=0.23$, nor previous, $F(1,82)=1.06$, $p=0.31$, diagnosis of depression were significant. However, there was a main effect of current diagnosis on Stroop performance: people who met criteria for a current depressive episode performed significantly more poorly on the Stroop following either type of stress exposure, $F(1,82)=6.51$, $p=0.01$, $R^2=0.07$. In follow-up analyses within the CSt group, current diagnosis of depression predicted significantly worse Stroop performance, $F(1,41)=9.08$, $p<0.01$, $R^2=0.18$, but history of depression diagnosis failed to predict performance, $F(1,41)=0.73$, $p=0.40$. Within the USt group, there were no significant effects of current or history of depression (p 's > 0.14).

To test whether the influence of depression diagnosis in moderating the effects of controllable stress exposure was mediated by subjective response to stress, we conducted a fifth set of regression analyses to investigate mediation. We found that people with a current diagnosis of depression reported marginally more extreme subjective responses to stress than people with no current diagnosis, $F(1,82)=3.59$, $p=0.06$, $R^2=0.04$, but there was no difference in subjective responses to stress detected between people with or without a previous diagnosis, $F(1,82)=1.06$, $p=0.31$. Next, a regression was conducted within each experimental group predicting changes in Stroop interference by subjective responses to stress, contrast codes for current or previous depression, and the interaction of these variables. Within the CSt group, higher levels of subjective response to stress predicted poorer Stroop performance when controlling for diagnosis of current or previous depression, $F(1,36)=4.97$, $p=0.03$, $R^2=0.12$. The effect of current clinical depression also remained significant, controlling for subjective responses to stress, $F(1,36)=8.43$, $p<0.01$, $R^2=0.19$. There were no interactions between subjective response and contrast codes for current or previous depression (p 's > 0.13). In contrast, no significant effects of subjective stress or clinical status were detected within the USt group (p 's > 0.19).

Discussion

Depression and stress are intimately related (Hammen, 2005; Monroe & Simons, 1991; Monroe & Reid, 2009), yet the complex effects of stress on mood and cognitive functioning remain ambiguous (Arnsten, 2009; Lupien et al., 2007). Controllability is a key factor that shapes the effects of stress exposure, but the protective effects of behavioral control have been inconsistent for people with depression. The current study investigated the question of how

controllable versus uncontrollable stress affects high-level cognitive functioning in women at varying levels of depression. Critically, this research integrated an examination of stress sensitivity (here, as assessed via subjective response to stressors) with the goal of clarifying how individual differences in such sensitivity may relate to depression and the effects of behavioral control.

The results of the current study replicate previous findings that controllability and subjective response to stress are factors that interact to shape the effects of stress on performance of a test of general executive functioning (Kaiser Henderson et al., 2012). People who were able to learn how to behaviorally control stressors exhibited greater improvement in Stroop performance than those exposed to uncontrollable stress. However, amongst those capable of learning such control, only people who experienced stress exposure as moderately intense showed improved performance, but those who reported more extreme responses tended to exhibit impaired performance despite having behavioral control.

In addition, our results are consistent with previous research indicating that the protective effects of behavioral control are diminished at higher levels of depression. In the current study, either severity of current depressive symptoms or current diagnosis of depression each moderated the effects of controllability. Women who reported higher levels of anhedonic depression, or who met criteria for current diagnosis of depression, tended to perform more poorly on the Stroop task following exposure to controllable stress when compared to their non-depressed or less severely depressed peers.

The current results suggest that the diminishing benefits of behavioral control at higher levels of depression are in part mediated by heightened subjective sensitivity to stress. Women who reported more severe depressive symptoms (or were currently in a depressive episode) reported

more extreme subjective responses to stress, which in turn predicted poorer Stroop performance. Therefore, one reason that having behavioral control over stressors may be less protective for severely depressed individuals is because the same exposure provokes a more intense experience of stress. This pattern of increased subjective sensitivity highlights the importance of teasing apart the effects of stress responses and depression in controllability research. In previous research, impairments in performance that were driven by heightened stress sensitivity may have masked the benefits of behavioral control.

However, the current results also indicate that the benefits of behavioral control are blunted at elevated levels of depression for reasons other than increased subjective sensitivity. Even when participants were equated on subjective responses to controllable stress, increased depression still predicted relatively poorer Stroop performance. This pattern of partial mediation suggests that the cognitive functions of people with depression may be more sensitive to the effects of stress exposure, and underscores the point that individual differences in stress reactivity are not solely captured by subjective report.

To capture additional dimensions of stress sensitivity and responses to stress, future research should include physiological measures in conjunction with subjective measures. Subjective responses to stress are related to physiological responses but not isomorphic to them (e.g. Schoofs et al., 2009). Previous research has shown that depression predicts altered stress reactivity on a biological (and implicit) level, e.g. altered cortisol response (Burke et al., 2005; Hasler et al., 2004). Such altered reactivity may contribute to the relatively poorer Stroop performance exhibited by people with more severe depression, even after differences in subjective sensitivity were controlled. Assessing physiological response would provide insight

on subjective and objective reactivity to stress at varying levels of depression, and how such reactivity relates to cognitive functioning.

This research has implications for clinical treatment. Behavioral interventions are based on the theory that depressive symptoms can be alleviated, and daily functioning improved, by guiding clients to engage in active behaviors in the pursuit of goals (Kaiser, Hubley, & Dimidjian, in press). Although such behaviors are adaptive, they are also often inherently stressful due to the challenging nature of the activation strategies (e.g. attend a social event after a period of withdrawal, or go for a walk despite increased fatigue). The present research suggests that the exposure to controllable, (subjectively) moderately stressful challenges may be an important source of therapeutic benefit. From this perspective, the active ingredients of behavioral therapy may consist of not only the rewarding outcomes of behavioral goals, but also the (stressful, but appropriately moderate) journey to obtain such goals through personal actions.

However, our results also highlight the importance of adjusting behavioral activation goals to suit the client's unique profile of stress sensitivity. Previous research indicates that behavioral interventions are highly effective in treating depression, but the nature of specific activation goals (e.g. degree of challenge or effort) must be carefully tuned to the individual client (Dimidjian, Barrera, Munoz, Martell, & Lewinsohn, 2010). Assessment of stress sensitivity and executive function ability at intake may provide useful information to clinicians for building an idiographic case conceptualization and plan for therapy. Future studies investigating controllability and reactivity in clinical settings may clarify the role of stress in behavioral interventions, and suggest new directions for treatment development.

CHAPTER IV

GENERAL DISCUSSION

Cognitive control functioning is altered at higher levels of depression. Previous research has suggested that changes in cognitive control functioning are especially likely to emerge when depressed individuals are confronted by specific types of salient stimuli, such as stressors or negative emotional information. In the current research studies, higher levels of depression predicted altered brain activation in response to negative distractors. In addition, depression predicted greater sensitivity to stress in the form of more extreme subjective responses and poorer performance on a test of general executive functioning following stress exposure.

Future studies may investigate the specificity, and neurobiological mechanisms, of other types of salient information that are related to altered cognitive functioning in depression. In Study 1, we focused on cognitive control in the face of negative emotional information. However, as in Study 2, people with elevated depression also exhibit altered cognitive control when exposed to stress, and either shared or unique neural substrates may characterize brain response to these stimuli. Examination of the specificity and mechanisms of cognitive control dysfunction in the face of other salient information would complement the results of the present studies.

While Study 1 had the goals of exploring why and how cognitive control is affected at higher levels of depression, Study 2 investigated a question of resilience: what factors protect the ability to effectively exert cognitive control, and how do these factors operate in depression? From a clinical perspective, we know that depressed clients are especially vulnerable to the disruptive

effects of stressful or negative life events on cognitive functioning. Furthermore, we know that cognitive control is necessary for goal-directed behavior within the therapy session and for accomplishing between-session work. Therefore strategies for protecting or improving executive functioning in the face of stress are vital to promote the client's ability to engage in treatment. Study 2 would suggest that learning to exert behavioral control with moderately intense stressors (e.g. challenging activities) may promote cognitive resilience. In line with this model, behavioral interventions are based on the theory that depressive symptoms can be alleviated by encouraging clients to engage in active, adaptive behaviors in the pursuit of goals and thus break habits of avoidance and withdrawal. The current research results suggest that these interventions aid in goal-directed behavior, at least in part, because they include exposure to controllable, individualized challenges. Future research exploring the active ingredients in behavioral and other therapies, and potential changes in cognitive control functioning over the course of therapy, would provide insight on these clinical tools.

In conclusion, these research studies were designed to investigate different facets of cognitive control functioning in depression. Both studies focused on cognitive control exerted in the face of salient stimuli, e.g. negative emotional information or stress. However, each study addressed a unique set of questions about depression and cognitive control functioning. We look forward to expanding on this program of research in the future, to further characterize the nature and consequences of cognitive dysfunction in depression and explore potential avenues for treatment development.

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