

PREFRONTAL CORTICAL ORGANIZATION OF EXECUTIVE FUNCTION
IN DEPRESSION AND COMORBID ANXIETY

BY

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DISSERTATION

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ABSTRACT

Anxiety and depression are prevalent forms of psychopathology and are associated with significant impairment in multiple areas of life, including occupational, educational, and social functioning. In addition to their affective symptoms, anxiety and depression are associated with significant cognitive disruptions, yet our understanding of these impairments and their mechanisms is very limited. In particular, such cognitive deficits could be accounted for by fundamental deficits in specific aspects of executive function (EF), processes that are imperative for adaptive emotion regulation. Determining specific EF impairments in anxiety and depression has the potential to provide a mechanistic account of the development and maintenance of these highly comorbid disorders. Thus, understanding EF in an integrated manner across psychological and neurobiological levels is extremely relevant to mental health. The present dissertation aims to advance these literatures by identifying a behavioral model of EF impairment in anxiety and depression, and its associated neural correlates. Brain regions associated with implementing inhibition, a specific EF component of this model, are identified. The moderating effects of anxiety and depression on brain activity associated with inhibition-related functions are examined.

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CHAPTER 1

GENERAL INTRODUCTION

Anxiety disorders are the most common class of psychopathology (estimated lifetime prevalence of 29%), and major depression is the most common individual disorder (estimated lifetime prevalence 16.6%; Kessler et al., 2005a). Anxiety and depression are highly comorbid, and comorbidity is associated with greater symptom severity (Kessler et al., 2005b). These prevalent forms of psychopathology are associated with enormous personal and societal burdens, seriously impairing social, occupational, and educational functioning (Kessler et al., 2005a) and are associated with an increased risk for some medical conditions (Lecrubier, 2001). Although there is much evidence of serious compromise of cognitive function in depression and anxiety, the precise nature of cognitive dysfunction in depression and anxiety is markedly underspecified (Levin et al., 2007; Warren, Heller & Miller, 2008). For example, the DSM-IV-TR states only that depression is accompanied by difficulties in concentration, far under-representing the number and range of cognitive deficits. Furthermore, a mechanistic account (both cognitive and neural) of the etiology and maintenance of these cognitive impairments remains elusive. There are few models of the neural structures and functions associated with these problems, and the models available are limited, often highlighting one brain region only (e.g., anterior cingulate cortex) or describing multiple brain regions with little specificity regarding their functional significance. The importance of understanding how cognition, particularly executive function (EF), is disrupted in depression and anxiety is underscored by the fact that most non-pharmacological interventions for these disorders are based on altering cognitive processing (e.g., Mindfulness, Cognitive Behavioral Therapy) which require intact EFs.

Additionally, individual differences in emotion regulation strategies are implicated as key vulnerability factors in the development of psychopathology (Aldao & Nolen-Hoeksema, 2011; Davidson, Jackson, & Kalin, 2000). Adaptive emotion regulation depends on one's goals and values within a given context, as well as the ability to determine a response that is in line with obtaining those goals. This process involves EFs such as inhibition/control of inappropriate or impulsive responses and behaving in a way that is goal-consistent when experiencing negative emotions (Linehan, 1993). Therefore, determining specific EF impairments in depression and anxiety would not only inform current and potential methods of treatment, but may be useful for predicting which individuals would benefit from certain forms of therapy. Consequently, the present dissertation has three primary goals: 1) to identify meaningful dimensions of EF and to examine the impact of depression and anxiety on these constructs (using ecologically valid and experimentally based methods); 2) to identify brain regions associated with these EF dimensions; and 3) to determine how depression and anxiety moderate activity in these regions.

Chapter Organization

The present dissertation is organized into 5 chapters. Chapter 1 serves as a brief introduction of the overarching goals of the present research and the organization of this document. Chapter 2 is a manuscript that presents a behavioral model of EF impairment in depression and anxiety, testing specific hypotheses of domain-specific dysfunction, and discussing EF mechanisms of emotion regulation. Chapter 3 discusses the neural correlates of inhibition, an EF dimension identified in chapter 2. Chapter 4 examines the moderating effects of depression and anxiety on brain regions associated with inhibition identified in chapter 3. Finally, chapter 5 provides a general discussion that reviews the implications of these findings

and future directions for research. Notably, chapter 2 is written in the form of a manuscript ready to submit for publication.

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CHAPTER 2

THE STRUCTURE OF EXECUTIVE FUNCTION IN DEPRESSION AND ANXIETY

Abstract

Cognitive deficits are a prominent source of distress and functional impairment in both depression and anxiety, yet our understanding of these deficits and their mechanisms are limited. These cognitive deficits could be accounted for by fundamental deficit(s) in specific aspects of executive function (EF). Research on the structure of executive dysfunction in depression and anxiety has the potential to provide a mechanistic account of maladaptive patterns of behavior. Item-level exploratory and confirmatory factor analyses were conducted on an ecologically-sensitive measure of EF. Consistent with Miyake et al. (2001), a three-factor model of EF including updating, shifting, and inhibition best fit the data. Structural equation modeling examined the relationship of EF factors to dimensions of psychopathology (anxious apprehension, anxious arousal, anhedonic depression). All three dimensions of psychopathology predicted shifting impairment, with anxious apprehension exhibiting the strongest relationship. Additionally, anxious arousal and anhedonic depression were associated with deficits in updating and inhibition, with anxious arousal exhibiting the stronger relationship in both domains. Implications for the development and maintenance of psychopathology are discussed, including proposed mechanisms of emotion regulation.

Executive Function, Depression, and Anxiety

Interest in and awareness of cognitive impairments in depression and anxiety has been increasing. Executive function (EF) has been a particular target of research. According to Lezak et al. (2004), EFs are abilities that involve goal formation, problem-solving, planning, sequencing of events to carry out goal-directed plans, and effective performance. They are processes that serve to guide behavior towards a goal, particularly in novel or non-routine situations (Banich, 2009). Given the necessity of these processes in directing purposeful and adaptive behavior, it is not surprising that impaired EF is associated with severe disability in everyday life functions, including problems with relationships, maintaining employment, and sustaining a household (Angst, 1999; Elliott, 1998; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Heller, Nitschke, Etienne, & Miller, 1997; Jaeger, Berns, Uzelac, & Davis-Conway, 2006; Rogers et al., 2004).

Depression and anxiety have long been associated with cognitive biases, as opposed to cognitive deficits per se (Hertel, 1997; Hertel & Brozovich, 2010; Joormann, Teachman, & Gotlib, 2009; Levin et al., 2007; Mathews & MacLeod, 2005; McNally, 1998; Sarason, 1988; Warren, Heller, & Miller, 2008). In particular, depression and anxiety are associated with attentional biases to negative material. For example, depression is associated with a tendency to recall negative (e.g., negative autobiographical memories) better than positive material, and anxious individuals have demonstrated an increased likelihood of interpreting ambiguous information in a negative manner (see Warren et al., 2008, for review). Biases in the processing of information can lead to deficits in cognitive function and may be detrimental to an individual's ability to utilize effective emotion-regulation strategies. For example, biases in attention and memory may lead to inflexible and automatic appraisals, impeding the deliberate

use of coping strategies (e.g., cognitive restructuring, cognitive reappraisal processes) to regulate emotions (Gotlib & Joormann, 2010; Joormann & Gotlib, 2010). Such biases may also foster maladaptive emotion-regulation strategies (e.g., emotional suppression, rumination, catastrophizing, avoidance) and have therefore been implicated in the development and maintenance of emotional disorders (Gotlib & Joormann, 2010).

Although cognitive biases are associated with depression and anxiety, research suggests that the processes by which these biases emerge differ. Whereas anxiety is associated with attentional biases to threatening information (Bar-Haim, et al., 2007), depression is characterized by a memory bias for negative information (Mathews & MacLeod, 2005), which has been associated with difficulties disengaging from negative stimuli (Gotlib & Joormann, 2010). Furthermore, these biases may be the result of impairments in specific EFs that distinguish depression and anxiety. Joormann, Yoon, and Zetschke (2007) proposed that deficits in *inhibitory control* are related to problems disengaging from negative information in depression. In their attentional control theory, Eysenck, Derakshan, Santos, and Calvo (2007) argued that worry reduces attentional control and hypothesized that anxiety impairs *inhibition* and *shifting* functions, but not working memory *updating*. However, these predictions remain to be tested.

Research has repeatedly demonstrated that problems with attention, memory, and problem-solving have been associated with depression (Burt, Zembler, & Niederehe, 1995; Marx, Williams, & Claridge, 1992; Weiland-Fiedler et al., 2004). In general, these findings have primarily been considered in the broader context of the cognitive deficit literature in depression and as such are represented in diagnostic criteria (e.g., difficulty concentrating). Many studies in this line of research have narrowly focused on demonstrating cognitive deficits and biased processing in depression. Relatively few studies have examined individual differences in

specific cognitive processes that could lead to the development and/or maintenance of depression. Consequently, a comprehensive, mechanistic account explaining the cognitive deficits associated with depression is lacking. It is likely that EF impairments are fundamental to these broad cognitive problems (Austin, Mitchell, & Goodwin, 2001; Levin et al., 2007; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). Research has demonstrated that depression is associated with impaired performance on a wide range of EF tasks (for reviews, see Levin et al., 2007; and Rogers et al., 2004) and that diminished performance might be accounted for by deficits in specific EF domains (e.g. inhibition, see Joormann & Gotlib, 2010; shifting, see Austin et al., 2001).

Research on anxiety-related EF impairment is less well developed (for review, see Snyder, Kaiser, Warren, & Heller, in preparation), although some evidence of impairment exists. It has been suggested that anxiety may be associated with deficits in visuospatial working memory (Bredemeier, Berenbaum, Most, & Simons, 2009; Castaneda et al., 2010; Shackman et al., 2006), working memory capacity (e.g., Bredemeier & Berenbaum, under review; Eysenck, Payne, & Derakshan, 2005; Hayes, Hirsch, & Mathews, 2008) and shifting between mental sets (Airaksinen, Larsson, & Forsell, 2005), although these findings are inconsistent (e.g., Castaneda et al., 2010; Santos & Eysenck, 2005). Despite limited anxiety-related EF research, a prominent theory in cognitive research proposes that anxiety impairs performance because it reduces attentional control in the presence of salient distracters. Although attentional control theory represents significant progress in that it targets specific EF components (unlike cognitive theories of depression), this theory has not yet been fully tested. Moreover, this theory does not distinguish among dimensions of anxiety (i.e., anxious apprehension, anxious arousal).

In summary, there is some evidence that EF impairments are associated with depression and anxiety, although the research is inconsistent. Furthermore, although attentional biases have been assigned a prominent role in the depression and anxiety literatures, it is unclear whether these results reflect attentional problems and/or EF impairments distinct from attention. In particular, anxiety-related EF deficits have largely been unexplored. The present study seeks to advance the literature by investigating these impairments associated with specific dimensions of depression and anxiety by drawing upon an empirically-supported theory of EF, and utilizing a statistical framework that fosters systematic examination of executive impairment.

An Executive Function Framework: Executive Function Is Not Unitary

A significant problem in the study of EF has been conceptual in nature (Stuss & Alexander, 2000). EF is often difficult to define and is frequently framed or operationalized imprecisely (Jurado & Rosselli, 2007; Martin & Failows, 2010). Despite these limitations, neuropsychological research supports distinguishing EFs (see Miyake et al., 2000, for review), although the exact decomposition remains a matter of debate. Given the variable definitions of EF, it is not surprising that inconsistent findings of EF integrity/impairment in psychopathology have emerged.

In an influential contribution, Miyake et al. (2000) used latent variable analysis to demonstrate that EF is multi-dimensional, parsing it into three separable but related fundamental domains: 1) shifting between tasks/mental sets, 2) updating of working memory representations, and 3) inhibition of dominant or prepotent responses (recently re-conceptualized as subsumed by a more general ability to maintain task set; Miyake & Friedman, 2012). Although the component processes of shifting, updating, and inhibition are not intended to be an exhaustive list of executive processes (Miyake et al., 2000), they are frequently postulated in the literature as

important EFs and are relatively circumscribed in comparison to other executive processes (e.g., “planning”). Shifting is a fairly robust construct, defined as the ability to shift attention between different aspects of stimuli to be processed and also between several cognitive operations. Consequently, shifting ability is considered to be an important aspect of executive control (Norman & Shallice, 1986). The updating process involves monitoring and modifying the contents of working memory in real time based on new information. Updating is essential for a variety of everyday activities, including implementing multistep activities and organizing recently acquired information. Lastly, the term “inhibition” is defined in the context of this study as the ability to resist impulsive responses by pre-empting or stopping one’s behavior at the appropriate time (Guy, Isquith, & Gioia, 2004) and controlled suppression of a prepotent response (Miyake et al., 2000). In turn, the concept of inhibition refers to several different processes (Friedman & Miyake, 2004; Nigg, 2000). As defined here, inhibition closely maps onto Friedman and Miyake’s (2004) conceptualizations of resistance to distractor interference and prepotent response inhibition, two subprocesses of inhibition that were determined to be closely related via confirmatory factor analysis. In the Miyake et al. (2000) framework, inhibition incorporates resistance to distraction.

The processes of shifting, updating, and inhibition are considered to act as control functions for working memory. Working memory is conceptualized as the focus of attention and active representation and manipulation of context-specific information (Baddeley, 2003). Given the limited capacity of working memory (Engle, Kane, & Tuholski, 1999), it is imperative that the contents of working memory be updated efficiently, a task controlled by executive processes (Friedman & Miyake, 2004). EFs allow relevant information in, block intrusive irrelevant

material, and discard information that is no longer relevant (Engle et al., 1999). Individual differences in these processes could be associated with specific dimensions of psychopathology.

The Present Study

Given the methodological (e.g., task impurity problem; Burgess, 1997; see Miyake et al., 2000 for a review) and conceptual limitations in the definition and assessment of EF, and uncertainties about its relationship to depression and anxiety, it is not surprising that inconsistencies in the literature have emerged. Specific EFs are important to study as they are key processes in self-regulation abilities. Given that the experience of negative mood states and negative life events activates mood-congruent representations in working memory (Siemer, 2005), the ability to control the contents of working memory could be crucial in understanding *why* some individuals easily recover from negative affect and others initiate and persist in using maladaptive emotion-regulation strategies that maintain negative affect. Determining specific EF impairments in depression and anxiety has the potential to provide a mechanistic account of maladaptive patterns of behavior, as well as understanding emotion-regulation proclivities. The present study sought to advance the current state of the EF literature by examining the validity of EF constructs of updating, shifting, and inhibition as they manifest in daily life, and to determine how impairments in these processes distinguish psychopathology types.

The Behavior Rating Inventory of Executive Function – Self-Report (BRIEF-SR; Guy, Isquith, & Gioia, 2004) is a standardized, self-report questionnaire that measures several aspects of EF in an individual's environment, including aspects of shifting, updating/working memory, and inhibition. A challenge in assessing EF within formal and laboratory settings is that this structured format generally facilitates a restricted range of behaviors. Although formal and experimental measures may assess the EF potential or capacity of an individual, the situation

they present is not typically like those encountered in everyday life. That is, EF tests typically lack environmental supports/distractions that may facilitate/hinder an individual's function in everyday life. Consequently, questionnaires that attempt to measure performance in an individual's everyday environment appear to tap aspects of EF that may not be measured by standardized tests. Additionally, such questionnaires, including the BRIEF-SR, sample behavior over a longer period of time than is generally afforded by standardized testing. Thus, a benefit of the BRIEF-SR is its intended ecological validity. In order to determine the factor structure of the items comprising the BRIEF-SR's shifting, updating/working memory, and inhibition scales, an Exploratory Factor Analysis (EFA) was conducted in the present study. Notably, the items on the BRIEF-SR reflect self-reported activities of daily life and are not measurements obtained in the laboratory. The items comprising the scales labeled shifting, working memory/updating, and inhibition may not index the same constructs as articulated by Miyake et al (2000). Therefore, in the present study, subsequent latent factors were used to define EF constructs. The measurement model resulting from EFA was subsequently tested via confirmatory factor analysis (CFA) in a non-overlapping sample of participants. Structural equation modeling (SEM) was used to estimate relationships between the EF latent variables and dimensional measures of psychopathology, specifically anxious apprehension, anxious arousal, and anhedonic depression. It was hypothesized that anxious apprehension (i.e., worry) would be associated with problems in shifting mental sets and that anhedonic depression would be associated with EF impairment in inhibition and shifting domains. No known study to date has specifically examined shifting, updating, and inhibition processes associated with anxious arousal (i.e., intense fear and/or panic). Neuroimaging evidence supports distinct patterns of brain activity associated with anxious apprehension and anxious arousal during an EF task (Engels et al., 2007; 2010). Thus

the nature of anxiety EF impairment may depend on anxiety type. Carefully differentiating between anxious apprehension and anxious arousal may help to provide more conclusive findings in studies of anxiety and EF.

Methods

Participants

Participants were recruited from a larger pool of undergraduates ($n = 1,140$), who completed a series of questionnaires for credit in a psychology course. The questionnaires assessed symptoms associated with anxiety and depression: the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; Molina & Borkovec, 1994) and the Anxious Arousal and Anhedonic Depression scales of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). Participants also filled out the BRIEF-SR during the same questionnaire session. Participant data were excluded from analyses if questionnaire data had missing values and/or illegible responses ($n = 17$). The final sample consisted of 635 females and 451 males¹ (mean age² = 18.7 years, $SD = 1.1$). Observations from the final sample ($N = 1,123$) were randomly selected for exploratory ($n = 561$) and confirmatory ($n = 562$) factor analyses. All participants were right-handed, native speakers of English with self-reported normal hearing and color vision.

Questionnaires and Procedures

Participants completed the BRIEF-SR questionnaire, involving 80 items assessing EF problems in daily life during the last 6-months on a 3-point scale (1 = *never*; 2 = *sometimes*; 3 = *often*). Research indicates that the BRIEF-SR has good clinical utility (e.g., Niendam,

¹ Thirty-seven individuals did not specify their gender

² Forty individuals did not specify their age

Horwitz, Bearden & Cannon, 2007) and internal consistency (Cronbach's alpha \geq .82 for inhibition, updating/working memory, and shift scales). Given that one goal of this study was to examine the ecological validity of shifting, updating, and inhibition EF constructs, only items from these scales ($n=35$) were subject to EFA.

The 16-item PSWQ was used to assess anxious apprehension (i.e., the tendency to engage in worry). Participants responded to questions such as "My worries overwhelm me," by rating how characteristic (1 = *not at all*, 5 = *very typical*) each statement was of them. The Anxious Arousal scale of the MASQ (MASQAA) consists of 17 items in which participants responded to statements such as "Startled easily." An eight-item subscale of the MASQ Anhedonic Depression (MASQAD8) was used as it has been shown to reflect depressed mood (Nitschke et al., 2001), and to predict current and lifetime depressive disorders (Bredemeier, Spielberg, Siltan, Berenbaum, Heller, & Miller, 2010). The MASQAD8 scale consists of items such as "Felt like nothing was very enjoyable." For both MASQ scales, participants rated how much they experienced each item during the previous week (1 = *not at all*, 5 = *extremely*). Research has shown that the PSWQ and MASQ have excellent test-retest reliability and good convergent and discriminant validity in undergraduate and clinical samples (Meyer, et al., 1990; Nitschke et al. 2001; Watson et al., 1995). Internal consistencies for the present sample were .93 and .86, respectively. Dimensional measures of anxiety and depression were selected because they have been shown to effectively distinguish these highly comorbid constructs, which share many overlapping symptoms (Nitschke et al., 2001). Moreover, related research suggests that different dimensions of depression and anxiety may be associated with distinct EF impairments. For example, low levels of positive affect, a characteristic of depression but not anxiety, has been linked to problems shifting attention (e.g., "cognitive inflexibility;" Compton, Wirtz, Pajoumand,

Claus, & Heller, 2004). Given that low levels of positive affect are specific to depression (Clark & Watson, 1991), it is possible that anhedonic depression may be associated with specific EF impairments that cannot be accounted for by high negative affect and/or comorbid anxiety.

Data Analysis

The distributional properties of the observed responses to the BRIEF-SR items do not have a multivariate-normal distribution. Research has indicated that using normal-theory estimation (e.g., Pearson product-moment correlations) factor analytic techniques for ordered, categorical responses to Likert-type scales could result in biased model fit statistics, negatively biased parameter estimates, inflated error variances, and extraction of illegitimate factors (Flora, Finkel & Foshee, 2003). Thus, as an alternative to the Pearson product-moment correlation, polychoric correlations were used for EFA and CFA (see Olsson, 1979, for explanation of appropriate use). Additionally, robust maximum likelihood estimation mean- and variance-adjusted weighted least squares (WLSMV; Muthén, du Toit & Spisic, 1997) was implemented, as this method has been shown to perform well when modeling categorical data (Brown, 2006; Flora & Curran, 2004).

The computer program Mplus 6.1 (Muthén & Muthén, 2010) was used to conduct factor analyses and SEM. Resulting items from EFA were used as indicators in CFA. CFA served as an objective test of the statistical fit against the EF factor model established using EFA in an independent sample. Model fit (CFA and SEM) was evaluated using the mean- and variance-adjusted chi-square goodness-of-fit statistic (χ^2 ; Muthén et al., 1997), the comparative fit index (CFI; Bentler, 1990), the Tucker-Lewis index (TLI; Tucker & Lewis, 1973), and root-mean-square error of approximation (RMSEA; Steiger, 1990). Simulation studies in Yu and Muthén (2001) suggest the following cut off values for categorical outcomes: CFI>.95, TLI>.95, and

RMSEA<.06, which are consistent with Hu and Bentler's (1999) recommendations. The error variances of two inhibition items were allowed to co-vary to account for similarity in question structure.

Scores on the dimensional measures of anxiety and depression were added as manifest variables. SEM was used to examine the relationships between the latent EF variables and the three psychopathology scores, as this method allows for these relationships to be estimated simultaneously and (unlike regression) explicitly accounts for measurement error in predictor variables. Additional structural tests of this model were conducted in order to evaluate potentially distinct relationships between EF latent variables and psychopathology scores. A series of nested models was created in which pairs of standardized psychopathology regression weights leading to one of the latent variables were constrained to be equal and were subsequently compared to a model in which all regression weights were allowed to be freely estimated. All difference tests of the nested models were performed using a chi-square difference procedure described by Asparouhov and Muthén (2006). Model χ^2 values and degrees of freedom are not reported for these nested model tests, as they are not interpretable when using WLSMV; only p-values are interpretable (Muthén, 2008).

Results

Exploratory Factor Analysis

Thirty-five items from the BRIEF-SR inhibit ($n=13$), shift ($n=10$), and update/working memory ($n=12$) scales were subjected to EFA. Given theoretical and empirical support for moderate correlations among inhibition, shifting, and updating EF processes (e.g., Miyake et al. 2000), an oblique rotation, the Promax method, was applied. In order to obtain simple factor structure, items were retained if their primary loading was $\geq .45$ and cross-loading was $\leq .2$.

Following procedures outlined by Brown (2006), factor retention was determined using multiple methods: examination of a scree plot of the eigen values, goodness of model fit statistics (χ^2 , RMSEA), and evaluation of the meaningfulness and interpretability of the factors that emerged. Poorly defined factors (e.g., a one-item loading) were eliminated.

Nineteen items (inhibit $n=10$; shift $n=4$; update $n=5$) were retained that met the above outlined criteria. Examination of the scree plot, model fit statistics, and interpretability of factors indicated that a three-factor solution best explained the relationships among the items. The complete three-factor solution is presented in Table 2.

Confirmatory Factor Analysis

Although the chi-square goodness-of-fit statistic (χ^2) is typically used to test the fit of CFA models, several fit statistics are reported here, given this statistic's sensitivity to large sample sizes and consequently excessive Type I error rates (see Kline, 2010, for review). The three-factor model was successfully estimated and associated with a χ^2_{61} value of 315, $p<.001$. Fit indices indicated that this three-factor model provided an excellent fit to the data (CFI=.968; TLI=.963; RMSEA=.045, 90% confidence interval = .038 to .052). All measurement weights were significant at $p<.001$ (see Table 3 for standardized estimates).

Structural Equation Modeling

Descriptive statistics of the psychopathology measures for the total sample are presented in Table 1. Criteria for evaluating model fit were identical to those for the CFA procedure. The model was successfully estimated and associated with a χ^2_{196} value of 578, $p<.001$. Fit indices indicated that this model provided an excellent fit to the data (CFI=.954; TLI=.950; RMSEA=.042, 90% confidence interval = .038 to .046). All measurement weights were

significant at $p < .001$ and were virtually identical to the measurement weights determined by the CFA procedure.

The psychopathology manifest variables (PSWQ, MASQAA, and MASQAD8) were modeled as exogenous (i.e., independent) variables predicting endogenous (i.e., dependent) EF latent variables. Increased levels of anxiety and depression were differentially associated with worse EF (see Figure 2.1). As shown in Table 4, PSWQ positively predicted problems with shifting, whereas MASQAA and MASQAD8 positively predicted problems with all three domains of EF. Additional structural tests determined that the magnitude of the γ for PSWQ predicting shifting was larger than the γ 's for MASQAA ($p < .001$) and MASQAD8 ($p < .001$). The magnitude of the γ for MASQAD8 predicting shifting was larger than the γ for MASQAA ($p < .04$). For updating, the γ for MASQAA was larger than MASQAD8 ($p = .02$) and PSWQ ($p < .001$); MASQAD8 γ was larger than PSWQ ($p < .01$). Finally, the magnitude of the γ for MASQAA predicting inhibition was larger than the γ 's for MASQAD8 ($p < .001$) and PSWQ ($p < .001$). The γ for MASQAD8 predicting inhibition was not significantly larger than the γ for PSWQ ($p = .08$).

Discussion

The purpose of the present study was to identify meaningful dimensions of EF and their relationship with depression and anxiety, with the specific goal of testing hypotheses that domain-specific EF deficits distinguish relevant dimensions of psychopathology. Present findings indicate distinct EF impairments as contributing factors to the maintenance and development of anxious apprehension, anxious arousal, and anhedonic depression, suggesting EF mechanisms of emotion regulation. EFA identified items from an ecologically valid measure of EF that were consistent with Miyake et al.'s (2000) EF framework. A three-factor structure

representing shifting, updating, and inhibition EF domains was found to provide an excellent fit to the data, and was replicated via CFA in an independent sample. SEM examined how individual differences in dimensions of depression and anxiety were associated with these specific domains of EF. Importantly, anhedonic depression and the two anxiety dimensions evidenced distinct patterns of relationships with EF. Specifically, all three dimensions of psychopathology predicted shifting impairment, with anxious apprehension exhibiting the strongest relationship. Problems with updating and inhibition were associated with anxious arousal and anhedonic depression, with anxious arousal exhibiting the stronger relationship in both domains.

As predicted, anxious apprehension positively predicted shifting impairment, suggesting that individuals who experience elevated levels of worry have limited cognitive control. This finding is consistent with Eysenck et al.'s (2007) prediction that "anxiety" impairs shifting, though it extends attentional control theory to a specific dimension of anxiety, anxious apprehension, and identifies shifting as a mechanism involved in worry. Impaired cognitive performance in a variety of cognitive domains (e.g., dual-task paradigms) are hypothesized to result from anxiety-related intrusive thoughts and worry preempting some of the processing and storage resources of working memory (e.g., Eysenck et al., 2007), a limited capacity system (Engle et al., 1999). According to attentional control theory, worry disrupts the "central executive" (or top-down attentional system) of working memory and subsequently impairs shifting and inhibition processes in anxious individuals, as these aspects of EF require attentional control. Although deficits in attentional control (e.g., Eysenck et al., 2007) could be consequences of a reduction in working memory capacity (Bredemeier & Berenbaum, under review), the present study demonstrated that impaired shifting in particular is a result of

increased anxious apprehension. Shifting could be a mechanism involved in the relationship between worry and elevated anxiety (anxious apprehension, GAD). For example, Borkovec (2004) proposed that worry is a cognitive avoidance strategy, in that it functions to prevent information processing associated with threat-related imagery. The engagement of worry is viewed as a maladaptive coping mechanism that is negatively reinforced (i.e., worry prevents engaging in a full fear response). Shifting is considered to act as a control function for working memory and is an EF process that is important in understanding failures of cognitive control in patient populations on laboratory tasks (Miyake et. al, 2000). Impaired shifting function could prevent appropriate selection of working memory contents that are pertinent to the task at hand, manifesting as worry, as well as difficulty making transitions, problem-solving inflexibility (e.g., approaching a problem with the same strategy), and difficulty changing focus from one mindset or topic to another.

As predicted, anhedonic depression was associated with deficits in inhibition and shifting EFs. In addition, anhedonic depression predicted deficits in updating. The present findings implicate deficits in all three EF domains as important factors in depression, which could lead to maladaptive emotion regulation strategies. The difficulty experienced by depressed individuals in ameliorating negative mood may be due to relative weaknesses in utilizing working memory resources effectively, resources that have been compromised by poor EF. For instance, the finding that anhedonic depression predicted impaired inhibition is consistent with research suggesting that characteristics of depression (e.g., rumination, negative memory bias) result from difficulties controlling access to mood-congruent material in working memory (Gotlib & Joormann, 2010; Hertel, 1997; 2004; Joormann, 2010; Joormann, Levens, & Gotlib, 2011). Specifically, it is hypothesized that inhibitory processes in particular are critical for efficient

working memory function, limiting the access of information and removing information that is no longer necessary (Friedman & Miyake, 2004). Individual differences related to dysfunctional inhibition would then lead to problems controlling mood-congruent activations in working memory and consequently may play a role in maladaptive emotion regulation strategies (Joormann & Gotlib, 2010). For example, in depression, emerging evidence suggests that difficulties inhibiting mood-congruent information in working memory result in prolonged processing of goal-irrelevant negative material, deterring recovery of negative mood and leading to sustained negative affect (Gotlib & Joormann, 2010). Furthermore, reduced control of mood-congruent material in working memory may precipitate ruminative tendencies and negative memory biases, maladaptive emotion regulation strategies that are characteristic of depression. If reduced control (via inhibition dysfunction) of mood-congruent material in working memory sets the stage for ruminative tendencies, impaired shifting may be the mechanism linking rumination and depression. Depressive and trait-like ruminative tendencies involve focusing on recurrent thoughts that are organized around a specific theme that is often emotionally charged (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). This perseverative style reinforces the recurrent thoughts in working memory, impeding switching to more positive and/or goal-related thoughts. The finding that depression was associated with worse shifting is consistent with recent work linking rumination with impaired mental flexibility (Altamirano, Miyake, & Whitmer, 2010; Joormann, Levens, & Gotlib, 2011). On a task that emphasized rapid goal shifting of emotion-neutral material (letter naming), Altamirano and colleagues (2010) demonstrated that higher ruminative tendencies predicted lower switching accuracy. In a sample of clinically depressed participants, Joormann and colleagues (2011) demonstrated that compared to control participants, depressed participants evidenced greater switch costs for

negative than for positive or neutral words during a working memory manipulation task. Moreover, in the depressed group, rumination predicted switch costs for negative words only. Taken together, these findings along with the present study suggest that impaired shifting is the mechanism fostering ruminative tendencies. In addition, negatively valenced stimuli may be particularly salient for depressed individuals, interfering with manipulating information in working memory.

Results revealed that depression was also associated with deficits in updating, implicating a platform for perseverative processing of the contents in working memory. This finding supports work suggesting that rumination and depression are also associated with dysfunctions in updating. To the degree that the experience of negative mood is associated with activation of mood-congruent representations in working memory (Siemer, 2005), impaired updating could result in increased interference by previously relevant negative material (Joormann & Gotlib, 2008). Moreover, a deficit in inhibiting goal-irrelevant representations and removing irrelevant negative material from working memory leads to prolonged negative affect and recurring negative thoughts. Using a modified Sternberg task, Joormann and Gotlib (2008) demonstrated that depressed individuals exhibited increased interference from irrelevant negative material when updating the contents of working memory, and that this pattern of results was specific for negative stimuli. In addition, these results could not be accounted for by negative mood state alone as depressed participants exhibited greater interference from negative material than did never-depressed participants who completed a sad mood induction prior to starting the task. Lastly, in the depressed group, higher rumination scores were associated with more difficulty removing task-irrelevant material from working memory (i.e., interference).

Given the separability of EF domains in the present study, the finding that anhedonic depression contributed to deficits in all three domains raises the question of whether depression is equally related to different types of executive dysfunction. Although it is generally agreed that depression is associated with EF deficits (e.g., Levin et al., 2007), there is little direct evidence that compares depression and its relationships with specific EF domains. In the present research, subsequent analyses were performed comparing the magnitude of the regression coefficients (i.e., γ s) relating anhedonic depression to the three domains of EF. The γ for MASQAD8 predicting shifting was larger than γ 's for inhibition and updating, and γ s for inhibition and updating did not differ. To the degree that shifting, updating, and inhibition share variance, it is likely that they share common resources, or "capacity sharing," (Pessoa, 2009). In a process called "executive competition," Pessoa (2009) proposed that resources devoted to one EF component will detract from resources available for another and that this process is modulated by the affective significance of information. On the surface, the finding that anhedonic depression shows a greater relationship with impaired shifting than with updating and inhibition is consistent with this proposal. However, the lack of explicit tests of such EF impairments during specific task performances precludes firm conclusions.

Results indicated that anxious arousal was also associated with deficits in all three domains of EF, although the pattern of impairment was distinct from depression. Post-hoc analyses were performed comparing the magnitude of the regression coefficients (i.e., γ s) relating anxious arousal to the three domains of EF. Whereas anhedonic depression exhibited the greatest impairment in shifting, anxious arousal demonstrated equal impairments in inhibition and updating (γ s for inhibition and updating were significantly greater than shifting) functions. The present findings implicate a unique pattern of deficits in all three EF domains (with greater

deficits in inhibition and updating) as contributing factors in anxious arousal. Although no known study to date has specifically examined inhibition, shifting, and updating in anxious arousal, its distinctive characteristics and EF research on anxiety-related clinical diagnoses (albeit limited; see Snyder et al., in preparation, for review) provide some basis for speculation of the present findings. Anxious arousal, characterized by somatic tension and sympathetic hyperarousal (Watson, Clark et al., 1995; Watson, Weber et al., 1995), is a prominent feature of panic disorder and specific phobias. Perhaps the difficulty experienced by anxiously-aroused individuals in ameliorating panic-like symptoms may be due to crucial deficits in inhibitory processes, processes that are conceptualized as critical for efficient working memory function (Miyake & Friedman, 2004). Moreover, it is also possible that this particular pattern of compromised EF is susceptible to “short-circuiting” in the presence of unpleasant emotional stimuli (e.g., triggers for panic symptoms). More research is needed to link specific EF deficits associated with specific symptoms of anxious arousal.

Although the present study provides new insights into specific domains of EF affected by specific dimensions of psychopathology, there are some limitations. First, the study was restricted to an undergraduate sample of college students, and results may not generalize to more cognitively diverse samples. For example, the degree of separability of EF may be less pronounced in general community samples (e.g., Legree, Pifer, & Grafton, 1996) and across the lifespan. To the degree that distinct brain regions implement these executive processes, neuroimaging evidence suggests that older adults recruit additional bilateral prefrontal regions (for a review, see Reuter-Lorenz & Lustig, 2005). Thus, generalizability to additional samples remains to be established. Nonetheless, present findings could serve as a baseline measure of executive dysfunction in early development of depression and anxiety. Second, the present

research assumed that dimensions of depression and anxiety influenced the development of executive dysfunction. Although executive dysfunctions are often viewed as sequelae of psychopathology, this is not the only pattern of cognitive influence. It is possible that specific EF deficits confer vulnerability to the development and maintenance of psychopathology, or that there is a bidirectional relationship. Notably, the present SEM was re-analyzed with EF latent variables as exogenous (independent) variables predicting endogenous (dependent) psychopathology manifest variables (PSWQ, MASQAA, and MASQAD8). All paths remained intact, supporting a bidirectional pattern of influence.

Despite these limitations, the present research demonstrates that domain-specific EF impairments are important factors in the maintenance and development of distinct dimensions of depression and anxiety, implicating specific maladaptive emotion-regulation processes. EF deficits may impair an individual's ability to evaluate, initiate, or engage in pleasurable activities/stimuli that promote pleasant emotional states. Importantly, the present study highlights naturally occurring executive dysfunction in everyday living that is associated with depression and anxiety, extending previous EF research obtained in formal (and typically artificial) evaluation settings. Indeed, the cognitive processes that formal tests of EF purport to measure are still not well known, and the range of behaviors/activities in an individual's everyday environment that require these same processes remains to be established (Burgess, Alderman, Volle, Benoit, & Gilbert, 2009). Moreover, this is the only within-subjects study to date that explicitly assesses the relationships of specific EF impairments, at the level of latent variables, among anxious apprehension, anxious arousal, and anhedonic depression. As evidenced here, discovering the nature of executive dysfunction depended on carefully differentiating these dimensions of psychopathology.

That these separate dimensions of psychopathology were associated with distinct cognitive deficits has implications for the development and implementation of effective treatment interventions. Present results indicate that deficits in domain-specific EFs affect different aspects of daily life. Accordingly, assessment of specific EF profiles could aid in developing therapeutic goals tailored to the needs and particular symptoms experienced by a given patient. As part of the psychoeducational component of psychotherapy, EF profiles could clarify how anxiety and/or depression affect the individual's thought processes, decision making, and maintenance of symptoms. For example, an individual who has problems shifting may need help with planning strategies to facilitate easier transitions among daily tasks. Individuals who struggle with selecting among options may benefit from learning how to structure their environment (Snyder et al., in preparation). Understanding EF profiles could inform the clinician of potential barriers to treatment in widely used interventions for mood and anxiety disorders (e.g., Cognitive Behavioral Therapy, Mindfulness, Behavioral Activation therapy). These non-pharmacological interventions for mood and anxiety disorders are based on altering cognitive processing (e.g., thought restructuring exercises, monitoring cognition and behavior) that depend on intact EFs. Understanding the role of EF in treatment compliance could direct the clinician to alternative strategies for implementing effective interventions (e.g., writing a homework summary for individuals with working memory deficits). In addition, preliminary evidence suggests that EF training may actually improve response to non-pharmacological interventions (e.g., CBT; Mohlman, 2008), although research is needed to examine which aspects of EF are most critical for the efficacy of these interventions. Future research should continue to examine executive function impairment in depression and anxiety to increase our

understanding of the role of these cognitive processes in the development and maintenance of psychopathology, and assess changes in these processes in response to EF-specific interventions.

Table 1

Self-Report Psychopathology Scores (N=1123)

Questionnaire	Mean	SD	Min	Max
PSWQ (Anxious Apprehension)	48.69	13.45	16	80
MASQAA (Anxious Arousal)	28.31	8.55	17	80
MASQAD8(Anhedonic Depression)	17.15	5.19	8	39

Note. PSWQ = Penn State Worry Questionnaire (Meyer et al., 1990). MASQAA = Mood and Anxiety Symptom Questionnaire Anxious Arousal scale (Watson, et al., 1995). MASQAD8 = Mood and Anxiety Symptom Questionnaire Anhedonic Depression 8-item subscale (Bredemeier et al., 2010; Nitschke, Heller, Imig, McDonald, & Miller, 2001; Watson et al., 1995).

Table 2

Exploratory Factor Analysis: Three-Factor Solution

		Factor		
		1	2	3
Promax-Rotated Pattern Coefficient				
Item				
	I71	0.93	-0.02	-0.17
	I54	0.80	0.09	-0.10
	I79	0.65	-0.04	0.19
	I66	0.62	0.00	0.02
	I61	0.61	-0.06	0.15
	I19	0.57	0.17	-0.04
	I10	0.56	0.01	-0.10
	I80	0.56	-0.02	0.11
	I37	0.53	-0.15	0.08
	I28	0.52	0.04	0.13
	S27	-0.03	0.87	0.02
	S9	0.03	0.86	-0.04
	S18	0.01	0.80	0.02
	S36	0.03	0.58	0.12
	WM73	0.01	0.01	0.83
	WM63	-0.07	0.09	0.80
	WM48	0.00	-0.05	0.76
	WM3	-0.14	-0.01	0.69
	WM39	0.19	-0.03	0.57

Interfactor Correlations

Factor		
		0.23
2		
		0.46
		0.23
3		

Note. $N=561$. $\chi^2_{117}=258$, $p<.001$. RMSEA = 0.046. Entries in bold are the highest loading per item. I=Inhibition;

S=Shifting; WM=Working Memory. The number indicates the item number on the BRIEF-SR.

Table 3

Confirmatory Factor Analysis: Standardized Regression Coefficients

Item	Factor		
	Inhibit	Shift	Update
I79	0.82	-	-
I61	0.72	-	-
I80	0.68	-	-
I28	0.64	-	-
I54	0.62	-	-
I66	0.61	-	-
I71	0.59	-	-
I19	0.59	-	-
I37	0.58	-	-
I10	0.47	-	-
S18	-	0.88	-
S27	-	0.87	-
S9	-	0.77	-
S36	-	0.59	-
WM73	-	-	0.90
WM48	-	-	0.79
WM63	-	-	0.74
WM39	-	-	0.73
WM3	-	-	0.67

Interfactor Correlations

Factor		
	0.32	
Shift	0.44	0.33
Update		

Note. $N=562$. $\chi^2_{61}=315$, $p<.001$. CFI=.968; TLI=.963; RMSEA=.045. All measurement weights were significant at $p<.001$. I=Inhibition; S=Shifting; WM=Working Memory. The number indicates the item number on the BRIEF-SR.

Table 4

Structural Equation Modeling: Standardized Regression Coefficients

Variable	λ	p
Exogenous variable: PSWQ		
Updating	<.01	0.98
Shifting	0.45	<.01
Inhibition	<.01	0.91
Exogenous variable: MASQAA		
Updating	0.32	<.01
Shifting	0.08	0.04
Inhibition	0.34	<.01
Exogenous variable: MASQAD8		
Updating	0.17	<.01
Shifting	0.22	<.01
Inhibition	0.11	<.01

Note. $N=1123$. $\chi^2_{196}=578$, $p<.001$. CFI=.954; TLI=.950; RMSEA=.042.

Updating, shifting, and inhibition represent latent variables derived from EFA and CFA.

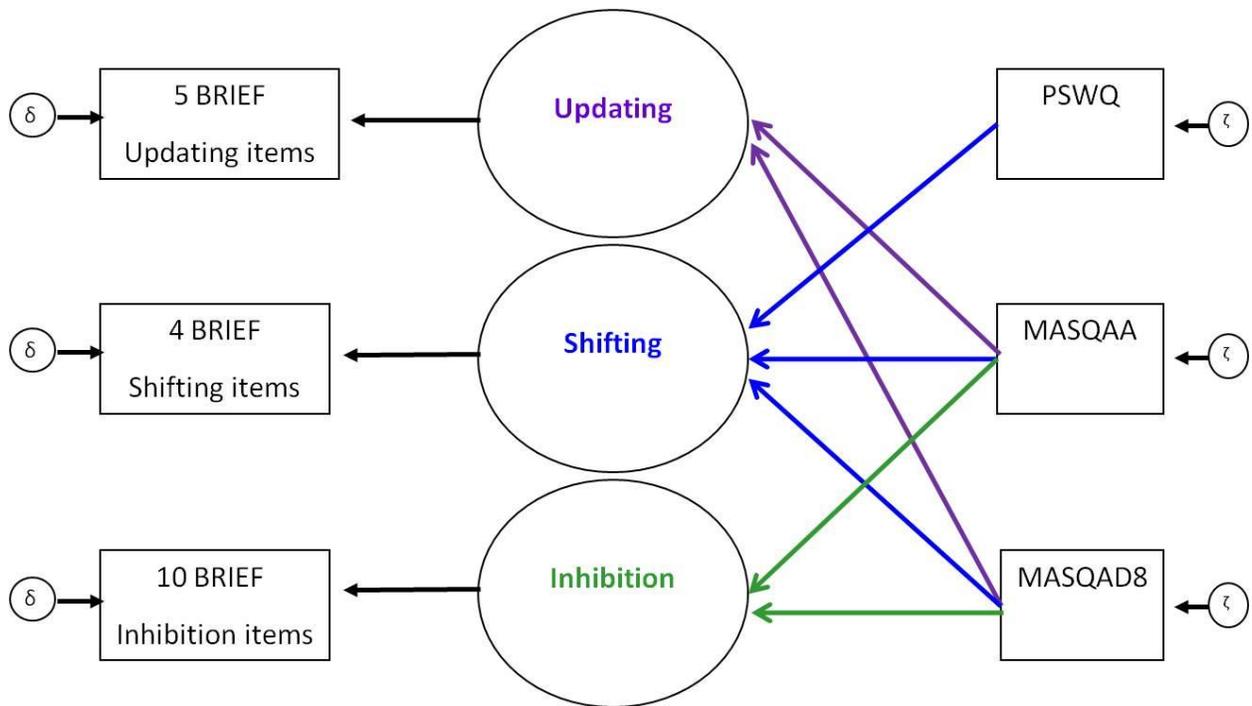


Figure 2.1: Structural equation model for $N=1123$. Psychopathology measures predicting latent executive function variables updating, shifting, and inhibition. PSWQ = Penn State Worry Questionnaire. MASQAA = Mood and Anxiety Symptom Questionnaire Anxious Arousal scale. MASQAD8 = Mood and Anxiety Symptom Questionnaire Anhedonic Depression 8-item subscale. BRIEF = Behavior Rating Inventory of Executive Function. The covariances between the latent variables, error terms, and the individual BRIEF items are not pictured for conciseness.

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CHAPTER 3

NEURAL MECHANISMS OF INHIBITION-RELATED FUNCTIONS:

DLPFC AND COGNITIVE CONTROL

Inhibition and Executive Function

Executive function (EF) is a broad term that encompasses many critical skills and cognitive functions, including those that guide, control, inhibit, and monitor behavior. Often included are aspects of decision-making and risk evaluation, planning, goal-setting, switching between task sets, self-evaluation, and monitoring of actions (Lezak, 2004). Given the necessity of EF in directing purposeful and adaptive behavior in novel or non-routine situations (Banich, 2009), cognitive disruptions in these processes are a prominent source of distress and impairment.

Inhibitory processes are considered to be critical when it comes to understanding executive control and its translation to real-world, everyday behavior. Despite a lack of consensus on how best to define EF, neuropsychological and neuroimaging (Collette et al., 2005) research indicates that executive control may be usefully characterized as a collection of correlated yet dissociable processes: inhibition, set shifting, and working memory updating (e.g., Miyake et al., 2000). Friedman, Miyake, and colleagues found that inhibition was more closely related to attention problems, depressive symptoms, and externalizing behaviors than were shifting and updating (for review, see Friedman et al., 2008). Inhibition-related functions in particular are critical for efficient working memory function, limiting the access of information and removing information that is no longer necessary (Friedman & Miyake, 2004).

Not only do inhibitory processes play a critical role in aspects of daily life, but they have come to be viewed as central players within numerous domains of psychology. Deficient

inhibition-related processes have been implicated in a range of clinical disorders such as schizophrenia (Williams, 1996), substance abuse (Kaufman, Ross, Stein, & Garavan, 2003), anxiety disorders (Eysenck, Derakshan, Santos, & Calvo, 2007; Snyder, Kaiser, Warren, & Heller, in preparation), depression (Joormann & Gotlib, 2010; Levin et al., 2007; Snyder, in press), and ADHD (Barkley, 1997). Changes in inhibition-related functions have been used to explain cognitive development (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Casey, Tottenham, Liston, & Durston, 2005), some age-related cognitive declines (Hasher & Zachs, 1988; Kramer, Humphrey, Larish, Logan, & Strayer, 1994), learning difficulties, and behavioral problems (Young, et al., 2009). Occasional failures in normal cognition are also thought to represent inhibitory disruption as suggested by lapses in speech, thought, action, and intention (e.g., Broadbent, Cooper, FitzGerald, & Parkes, 1982).

Given the importance of understanding inhibition-related functions in the context of cognitive control, as successes and failures in this domain have real consequences in everyday life, and given that individual differences in inhibition-related functions have been implicated as risk factors for a broad range of psychopathology, including depression and anxiety, one goal of the present study is to better understand the neural and behavioral organization of inhibitory functions. More specifically, how is self-reported inhibition as manifested in everyday life related to individual differences in inhibitory control abilities?

Behavioral inhibition has been theorized to relate to a broad range of psychopathology (e.g., Nigg, 2000) that are associated with poor executive control (e.g., Dalley, Everitt, & Robbins, 2011). Prepotent response inhibition, a more specific ability to deliberately suppress a dominant or automatic response, has also been linked to poor executive control, and is partially dependent on frontal-lobe function (e.g., Milham et al., 2001; Milham & Banich, 2005).

Although these two inhibition-related functions are distinguishable (Friedman & Miyake, 2004; Young et al., 2009), it is not clear the extent to which they reflect the same or different neural mechanisms. Specific inhibition-related functions are important to study, as they are key processes in self-regulation abilities, including emotion regulation (Zelazo & Cunningham, 2007). Intact inhibitory functions are crucial for working memory, a function supported by dorsolateral prefrontal cortex (Wager & Smith, 2003). To the degree that the experience of negative mood states and negative life events activates mood-congruent representations in working memory (Siemer, 2005), identifying specific inhibition-related functions could constitute relatively specific targets for interventions that are EF component or process focused. A small but growing number of studies demonstrate that training-related increases in working memory ability can yield improvements in a range of cognitive skills (Brehmer, Westerberg, & Backman, 2012; Chein & Morrison, 2010; Jaeggi, Buschkuhl, Jonides, & Shah, 2011; Popov et al., 2011), improvements in cognitive function in clinical populations with known inhibitory impairment (e.g., Klingberg, et al., 2005), and improvements in quality of life (e.g., Vogt et al., 2009). Furthermore, the generalizability of training-related increases in working memory ability to non-trained tasks is hypothesized to occur when the transfer task recruits overlapping cortical regions (e.g. Jonides, 2004; Olesen et al., 2004). Thus, identifying brain regions that support inhibition-related functions could provide a mechanistic account of the development and maintenance of psychopathology, as well as inform current and potential methods of treatment. In general, neuroimaging studies of inhibition frequently implement a single measure of inhibition (i.e., typically response inhibition). Thus, it is unclear whether the same neural mechanisms associated with response inhibition implement self-reported inhibition in everyday life. The present study capitalized on an ecologically sensitive measure of self-reported

inhibition derived in Warren et al. (in prep; Chapter 2) in order to compare patterns of brain activity with a commonly-used, laboratory-based response inhibition task.

Self-reported inhibition in everyday life was measured using the BRIEF inhibition factor score developed by Warren et al. (in prep; Chapter 2). The BRIEF inhibition factor score reflects the ability to resist impulsive responses (Guy, Isquith, & Gioia, 2004) and the tendency to act prematurely without foresight in social situations. The color-word Stroop task is well established in the fMRI literature (see Banich, 2009, for a review) and is known to recruit EF processes, including response inhibition and top-down attentional control (directing attention to a less automatic process, i.e. color identification over word reading; Liu, Banich, Jacobson, & Tanabe, 2006). Although the Stroop task has been characterized as being closely related to a facet of cognitive inhibition, resistance to interference (Nigg, 2000), Friedman and Miyake (2004) determined that Stroop performance loaded heavily on a prepotent response inhibition latent factor. Conceptually, the Stroop task differs from resistance to interference tasks in that the response that must be avoided is a dominant response (MacLeod, 1991) as opposed to a non-dominant irrelevant distractor, such as those used in flanker-type tasks. Thus, the Stroop task was used as a measure of prepotent response inhibition. However, to the degree that these inhibition-related processes overlap (e.g., Friedman and Miyake (2004) showed that prepotent response inhibition and resistance to distractor interference constructs were correlated ($r = .67$) and work in concert, and they may be implemented by similar brain regions (Wilson & Kipp, 1998).

Inhibition and Brain Organization

Neuroimaging studies exploring inhibition processes have demonstrated the involvement of various regions in the cingulate, prefrontal, and parietal areas. In general, measures of “cognitive” and “emotional” inhibition appear to rely partially on prefrontal cortex (Dillion &

Pizzagalli, 2007). However, the exact functional significance of regions associated with inhibitory processes is unknown (Collette et al., 2006). Given that the term “inhibition” is often inadequately defined (Aron, 2007; Nigg, 2000), it is likely that the tasks used in neuroimaging studies have differed in their exact inhibitory requirements, with engagement of heterogeneous cerebral areas. Despite this lack of specificity, neuroimaging studies frequently identify dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex (ACC) as serving inhibitory functions, although lesion studies implicate right IFG in particular (see Aron, Robbins, & Poldrack, 2004, for a review). More specifically, IFG is thought to be activated when an individual needs to resolve interference among potentially conflicting attributes of a stimulus (Nelson et al., 2003; for left IFG, see Jonides & Nee, 2006, for review), and ACC is engaged when conflicting stimulus-response associations are present (Banich et al., 2009; Nelson et al., 2003). Given Miyake et al.’s (2000) unity and diversity of EFs model (i.e., inhibition, updating, and shifting are correlated yet separable processes), it is likely that inhibition interacts with other cognitive functions in these tasks, making it difficult to determine which brain regions are involved in a specific implementation of this function. Moreover, DLPFC, ACC, and IFG are all typically activated in inhibition paradigms, because they likely interact to facilitate task performance. That is, DLPFC is associated with top-down control (e.g., Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008), maintaining goals, and updating information (e.g., Wager & Smith, 2003), ACC detects response conflict and monitors performance (see Banich et al., 2009, for a review), and IFG may function to inhibit incorrect responses (Aron et al., 2004) as well as playing a more general role in responding to salient, task-related cues as part of an EF network (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010).

Through latent-variable analysis, Friedman and Miyake (2004) demonstrated that prepotent response inhibition and resistance to distractor interference are separable at the cognitive level, although they share some common features. Specific types of inhibition could differentially contribute to the overall behavioral impact of inhibition dysfunction as seen in various disorders. Thus, understanding the relationship between specific inhibitory-related functions and the neural structures that implement them could provide insights into the development and maintenance of various disorders.

Examining the extent to which the distinctions found at the cognitive level can be demonstrated at the neural level could prove to be informative about individual differences in inhibition-function processes, as behavioral deficits may not be readily apparent. More specifically, performance effectiveness (e.g., achieving a goal) may not be affected, but *how* the individual performs the task may not be efficient (Eysenck & Calvo, 1992; Eysenck et al., 2007). Thus, compensatory strategies that are not behaviorally apparent may be measured using neuroimaging techniques.

The Experimental Problem

Colloquially, the term inhibition is used to describe the outcome of behaviors in everyday life (e.g., impulsivity), although the contribution of specific inhibitory functions is not well understood. Notably, most formal tests of EF were developed and administered in understandably artificial environments (e.g., laboratory; controlled testing environment). Although research is advancing in determining the cognitive processes that these formal tests of EF actually measure (e.g., Miyake, et al., 2000), the degree to which activities of daily life require these same processes is unclear (Burgess, Alderman, Volle, Benoit, & Gilbert, 2009). The present study sought to empirically demonstrate the nature of the relationship between the

type of inhibition that has been demonstrated clearly in a laboratory setting, i.e., prepotent response inhibition, and self-reported inhibition as measured in everyday life, by examining brain activity using neuroimaging. Given that individual differences in inhibition-related functions have been implicated as risk factors for a broad range of psychopathology, it is important that the nature of inhibition-related processes be specified. As the term inhibition is a broad construct and has been broadly applied across research paradigms, the implications for its explanatory utility and potential avenues for intervention are limited. Following empirical support for separable, inhibition-related functions at the behavioral level (Friedman & Miyake, 2004), it is possible that self-reported inhibition in everyday life and response inhibition recruit separable and/or overlapping neural mechanisms.

As a level of analysis, neuroimaging fosters a process-oriented approach to understanding how an individual or population approaches task performance, providing information that is inaccessible through self-report and behavioral assessment (Miller & Keller, 2000). For example, compensation strategies via recruitment of additional/alternative brain regions for task performance may result in normal performance, such that behavior cannot distinguish any impairment. The present study examined the similarities and/or differences in the neural mechanisms supporting ecologically-sensitive versus laboratory-based measures of inhibition functions in order to clarify the broader construct of inhibition. Individual differences in specific inhibition-related functions at the level of neural mechanisms might be more strongly tied to the maintenance and development of psychopathology rather than the broader construct of inhibition as a whole would be. Thus, identifying meaningful behavioral and functional components of “inhibition” may be a more fruitful approach in identifying mechanisms that foster variation in cognitive abilities and emotion regulation. Furthermore, cognitive neuroscience research has

demonstrated that the relationship between EF and working memory relies, in part, on inhibition-related functions (e.g., Burgess, Gray, Conway, & Braver, 2011). Given the importance of inhibition-related functions for efficient working memory function (Friedman & Miyake, 2004), individual differences in these cognitive processes could be key to understanding cognitive difficulties in psychopathology.

The inhibition constructs used in the present study were previously validated through factor analytic work by Warren et al. (in prep; self-reported inhibition in everyday life) and Friedman and Miyake (2004; prepotent response inhibition via the Stroop task). Importantly, treating EF as a multidimensional construct enables increased specificity about the nature of executive involvement in various cognitive, neuropsychological, and clinical constructs. In the clinical domain, considering the multiple components of EF has led to better specification of the nature of executive deficits associated with psychopathology (e.g., Warren et al., in prep).

Based on the review above, it is anticipated that regions involved in a frontal-parietal network supporting inhibition-related process will be associated with both self-reported inhibition in everyday life and prepotent response inhibition. In addition, however, it is anticipated that distinct neural mechanisms may be associated with the two aspects of inhibition under investigation. It is anticipated that Stroop interference, a measure of prepotent response inhibition, will reflect greater active suppression than the BRIEF factor score, as the nature of the task presents directly conflicting semantic and response-related representations. In other words, responding to the color of the ink during the Stroop incongruent condition (“RED” in blue ink) is a weak response relative to the dominant word-reading tendency and is associated with active suppression and EF. As such, it is expected that RT interference (as a measure of prepotent response inhibition) will be associated with DLPFC, ACC, and IFG activity, as these regions

have been implicated in implementing cognitive control, as well as response inhibition (Banich, 2009; Banich et al., 2000; Milham & Banich, 2005). In particular, it is anticipated that RT interference will be associated with posterior DLPFC activity, as this region is considered to be critically involved in performance of this task, in part by biasing other brain regions towards processing task-relevant information (e.g., color of the ink) and away from task-irrelevant information (reading the color word). In contrast, the latent factor of self-reported inhibition will be associated with mid-DLPFC activity, as this region is implicated in maintaining task-relevant information and top-down attentional control (Banich, 2009; Kane & Engle, 2002). Given that response-inhibition paradigms have dominated much of the inhibition neuroimaging literature, it is unknown whether self-reported inhibition as measured in everyday life will elicit IFG and ACC activity. To the degree that self-reported inhibition relies on stopping behavioral responses, it is likely to be associated with IFG activation. However, a correlation with ACC is less likely, as this region's contribution to cognitive control is thought to be recruited during tasks that generate conflicting, response-related representations (Banich, 2009).

Methods

Participants

Eighty-five paid undergraduate participants (52 females, age $M = 19.08$, $SD = 1.04$) with varying levels of anxiety and depression were recruited from a larger study (Warren, Heller, & Miller, in prep) examining emotion and executive function. All participants were right-handed, native speakers of English with self-reported normal color vision and hearing, with no neurological disorders or impairments. Participants were given a laboratory tour, informed of the procedures of the study, and screened for claustrophobia and other contraindications for MRI participation. The study was approved by the University of Illinois at Urbana-Champaign

Institutional Review Board. Participants were excluded if they had ever experienced loss of consciousness ≥ 10 minutes or exhibited current substance abuse or dependence, mania, or psychosis. Additional exclusion criteria included excessive motion or scanner artifact ($n=8$), signal loss due to substantial uncorrected magnetic susceptibility in areas of interest ($n=1$), or Stroop reaction time errors greater than 3 standard deviations from the sample mean ($n=1$).

Measures of Inhibition

Inhibition in everyday life. The Behavior Rating Inventory of Executive Function – Self-Report (BRIEF-SR; Guy, Isquith, & Gioia, 2004) is a standardized, self-report questionnaire that measures several aspects of executive function in an individual’s everyday life, including inhibition. Through a series of item-level factor analyses using the BRIEF-SR, Warren et al. (in prep) identified shifting, updating and inhibition latent factors consistent with Miyake et al.’s (2000) EF framework. For the present study, the inhibition-item weights (λ s; $N=1123$) identified in Warren et al. (in prep) were used to compute participants’ BRIEF inhibition scores. The BRIEF self-reported inhibition score indexes an individual’s ability to resist impulsive responses by pre-empting or stopping one’s behavior at the appropriate time (Guy, Isquith, & Gioia, 2004). As defined in Warren et al. (in prep), the BRIEF inhibition factor score is an ecologically-sensitive measure for the tendency to act prematurely in social situations. Notably, the BRIEF inhibition factor score reflects self-reported activities of daily life, sampling reported behavior outside of the laboratory (e.g., “I interrupt others,” “I am impulsive”). Elevated scores represent impaired cognitive control, manifesting behaviorally as disinhibition and impulsivity. In order to examine the relationship between brain activation and behavioral (dis)inhibition, BRIEF inhibition factor scores were converted to z scores and entered in regressions as predictors of brain activity.

Inhibition in the laboratory. Participants completed the color-word Stroop task (Stroop, 1935) during fMRI data acquisition (see below) in which they were asked to press a button indicating the color of the ink in which color words and neutral words were printed, ignoring the dominant tendency to read the words. During the incongruent condition of the Stroop task, cognitive interference is created by the actual meaning of the presented word relative to the ink color in which it is presented (e.g., “RED” in blue ink).

Average RT for correct-response trials was computed for incongruent (e.g., “RED” in blue ink) and neutral trials (e.g., “LOT” in red ink). RT interference scores were computed by subtracting each participant’s average neutral RT from their average incongruent RT, divided by their sum (i.e., [incongruent RT minus neutral RT]/[incongruent RT plus neutral RT]), and converted to z scores across all subjects. Higher interference scores indicated that participants took longer to respond to the ink color with incongruent stimuli than neutral words. No-response trials were excluded from behavioral analyses. In order to examine the relationship between brain activation and prepotent response inhibition, RT interference z scores were entered in regressions as predictors of brain activity.

Experimental Task and Stimuli

Color-Word Stroop task. Participants completed color-word and emotion-word Stroop tasks during an fMRI session, and also completed an EEG procedure and a diagnostic interview in other sessions. Only findings from the color-word Stroop task are presented here. The order of presentation of the two tasks within the fMRI session was counterbalanced. The color-word Stroop task consisted of blocks of color-congruent or color-incongruent words alternating with blocks of neutral words. Half of the trials in the congruent and incongruent blocks were neutral to prevent the development of word-reading strategies. This type of blocked-design color-word

Stroop task has been shown to effectively elicit Stroop interference (Banich et al., 2000; Milham & Banich, 2005; Milham, Banich, Claus, & Cohen, 2003; Siltan et al., 2010). There were eight orders of stimulus presentation blocks that were counterbalanced across subjects (i.e., each participant received 1 out of 8 possible orders). In addition to the word blocks, there were four fixation blocks (one at the beginning, one at the end, and two in the middle of the session) and five rest blocks (one at the beginning, one at the end, and one between each word block). In the fixation condition, a fixation cross intensified in place of word presentation, and in the rest condition the subject was instructed to rest and keep their eyes open while the screen was blank.

Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue) on a black background, with each color occurring equally often with each word type. The task consisted of congruent trials in which the word named the ink color in which it was printed (e.g., the word “RED” printed in red ink), incongruent trials in which the word named a color incongruent with the ink color in which it was printed (e.g., “GREEN” printed in red ink), and neutral trials in which the word was unrelated to color (e.g., “LOT” in red ink). Neutral words were matched with color words on word frequency and length. Participants responded to the color of the ink with their middle and index fingers using left- and right-hand response boxes.

Participants received 256 trials presented in 16 blocks (4 congruent, 4 incongruent, and 8 neutral) of 16 trials each, with a variable ITI (± 225 ms) averaging 2000 ms between trial onsets. A trial began with the presentation of a word for 1500 ms, followed by a fixation cross for an average of 500 ms. There was a brief rest period after every fourth block. Additionally, there were four fixation blocks (one at the beginning, one at the end, and two in the middle) in which a brighter fixation cross was presented by for 1500 ms. No participants failed to understand the task instructions or the mapping between colors and buttons after completing practice trials.

Stimuli, word presentation, and reaction-time measurement were controlled by STIM software (James Long Company, Caroga Lake, NY).

Image acquisition. Participants were given task instructions and informed of all relevant information about the procedure before participating. Participants completed 32 practice trials during a low-resolution anatomical scan.

A series of 370 fMRI images (16 images per block of 16 stimuli plus rest and fixation periods) were acquired using a gradient-echo echo-planar pulse sequence (TR 2000 ms, TE 25 ms, flip angle 80°, FOV=22 cm) on a 3T Siemens Allegra head-only scanner. Thirty-eight contiguous oblique axial slices (slice thickness 3 mm, in-plane resolution 3.4375 x 3.4375 mm², .3 mm gap between slices) were acquired parallel to the anterior and posterior commissures. After the EPI sequence, a 160-slice MPRAGE structural sequence was acquired (slice thickness 1 mm, in-plane resolution 1x1 mm) for registering each participant's functional data to standard space. Prior to the EPI sequence, gradient field maps were collected for correction of geometric distortions in the EPI data caused by magnetic field inhomogeneity (Jezzard & Balaban, 1995).

fMRI data reduction and analysis. Functional image processing and analysis relied on tools from the FSL analysis package (e.g., MCFLIRT, PRELUDE, FILM, FUGUE, FEAT, FLAME; <http://www.fmrib.ox.ac.uk/fsl>) and AFNI (<http://afni.nimh.nih.gov/afni/>). Additional region-of-interest (ROI) analyses were carried out using locally written Matlab programs (e.g., Herrington et al., 2005) and IBM SPSS Statistics version 19.0.

Functional data for each participant was motion-corrected using rigid-body registration, implemented in FSL's linear registration tool, MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). The first 3 volumes of each participant's functional data were discarded to allow the MR signal to reach a steady state. Each time series was temporally filtered with a nonlinear high-pass

filter to attenuate frequencies below 1/212 Hz (to remove drift in signal intensity), mean-based intensity-normalized by the same single scaling factor, and spatially smoothed using a 3D Gaussian kernel (FWHM 5 mm) prior to analysis. Temporal low-pass filtering was carried out using AFNI's 3dDespike tool (<http://afni.nimh.nih.gov/>) to remove intensity spikes. The ends of two participants' time series were truncated due to excessive motion. All other participants demonstrated less than 3.3 mm absolute motion or 2 mm relative motion. After motion correction and temporal low-pass filtering, each time series was corrected for geometric distortions caused by magnetic field inhomogeneity. Remaining preprocessing steps, single-subject statistics, and group statistics were completed with FEAT.

Blood-oxygen-level-dependent (BOLD) activity during the color-word Stroop task was assessed using FILM (FMRIB's Improved Linear Model). Statistical maps were generated via multiple regression on each intracerebral voxel (Woolrich et al., 2001). An explanatory variable (EV) was created for each trial type (congruent, neutral, incongruent, and rest; fixation condition left unmodeled) and convolved with a gamma function to better approximate the temporal course of the BOLD hemodynamic response function (e.g., Aguirre et al., 1998). The contrast of particular interest for this study is the incongruent versus neutral condition, because incongruent trial performance requires executive function to exert top-down control and resolve conflict. Thus, it is expected that this contrast would yield posterior DLPFC activation and ACC activation (i.e., ACC is involved in response evaluation and selection). To the degree that portions of DLPFC are involved in maintaining an attentional set, DLPFC activation should remain consistent. Each EV (i.e., regressor) yielded a per-voxel effect-size parameter estimate (β) map representing the magnitude of activity associated with that EV for a given participant. Functional activation maps for each contrast were transformed into MNI stereotactic space

(Montreal Neurological Institute 152 symmetrical 1 mm x 1 mm x 1 mm template; Fonov, Evans, McKinstry, Almlie, & Collins, 2009) using FMRIB's Non-Linear Image Registration Tool, FNIRT (Andersson, Jenkinson, & Smith, 2007).

Group inferential statistical analyses were carried out using FLAME and SPSS. To identify ROIs for subsequent analysis, activated voxels were identified for the incongruent vs. neutral contrast via two-tailed, per-voxel t-tests on contrast β maps converted to z-scores. Monte Carlo simulations via AFNI's AlphaSim program estimated the overall significance level (probability of a false detection) for thresholding these 3D functional z-map images (Ward, 2000). These simulations used a gray-matter mask to limit the number of voxels under consideration ($2,340 \text{ mm}^3$) and provided a cluster size (390) and z-value ($z = 2.97$) combination to use for thresholding, resulting in an overall family-wise error rate of .05. Clusters that survived thresholding were defined as ROIs for further analysis. In order to explore brain regions uniquely associated with inhibition-related constructs, BRIEF inhibition factor score, RT interference, updating, and shifting factor scores from Warren et al. in prep, (each converted to a z score) were entered as predictors in whole-brain, per voxel, cross-subject regression analyses in FSL. Although there is empirical support for moderate correlations among some aspects of EF (Miyake et al., 2000; Warren et al., in prep), these components are also behaviorally, genetically, and neutrally dissociable (e.g., Collette et al., 2005, Friedman et al., 2008; Miyake et al., 2000; Warren et al., in prep). Thus, two different higher-level analyses were conducted. First, separate regressions were performed for each EF measure (without the shared variance from the other EF measures removed), essentially providing zero-order correlations between EF components and each brain voxel. Second, brain areas showing distinct relationships with EF measures were examined by including all EF measures (BRIEF inhibition, RT interference, updating and

shifting) as covariates in one regression model. No significant correlations emerged between brain activity and updating or shifting for either higher-level analysis. Thus, results were virtually identical in both higher-level analyses, indicating that shifting and updating covariates were appropriate to include in the main regressions, as each measure appears to be capturing what it intends. Each regression analysis produced a β map corresponding to the unique variance associated with each inhibition construct.

Results

Behavioral Data

All participants demonstrated color-choice accuracy of at least 85%. As a manipulation check, we examined RT interference for color-word trials. As expected, participants demonstrated more RT interference for incongruent-word trials ($M = 814$ ms, $SD = 160$ ms) than for congruent-word trials ($M = 633$ ms, $SD = 103$ ms), $t(84) = 15.3$, $p < .001$, and neutral-word trials ($M = 652$ ms, $SD = 103$ ms), $t(84) = 15.2$, $p < .001$.

Descriptive statistics and the zero-order correlation for the inhibition measures are presented in Table 5 and Table 6, respectively.

fMRI Data

Brain-activation results were consistent with anticipated regions of interest generally associated with inhibition-related processes. Importantly, a functional differentiation of DLPFC emerged for the two measures of inhibition. Worse self-reported inhibition (increased BRIEF factor score) was associated with more mid-DLPFC activation whereas increased RT interference was associated with less posterior-DLPFC activity during blocks of incongruent words relative to neutral words (see Figure 3.1). Specific activation findings are discussed separately for each predictor.

Brain regions uniquely associated with BRIEF inhibition factor score. Table 7 lists the seven regions that were positively correlated with the BRIEF inhibition factor score. In line with hypotheses, higher levels of BRIEF inhibition factor score were associated with more activation in left mid-DLPFC (middle frontal gyrus) and left IFG, regions that are generally associated with implementing inhibition-related processes (see Figure 3.1). Additional clusters emerged in frontal pole, OFC, and supramarginal and angular gyrus regions. There were no significant clusters negatively correlated with BRIEF inhibition factor score.

Brain regions uniquely associated with RT interference. Table 8 lists a network of regions that were negatively correlated with RT interference. In line with hypotheses, higher levels of RT interference were associated with less activation in left posterior-DLPFC (middle frontal gyrus), bilateral IFG, and ACC, as well as regions that are generally associated with attentional control and motor response coordination (e.g., premotor cortex, frontal eye fields, posterior parietal cortex, precuneus; see Figure 3.1). Additional clusters emerged in occipital cortex, thalamus and caudate, parahippocampal gyrus, frontal pole, OFC, and supramarginal and angular gyrus regions (see Figure 3.1). There were no significant clusters positively correlated with BRIEF inhibition factor score.

Discussion

As hypothesized, DLPFC activity was associated with both measures of inhibitory functions, BRIEF inhibition factor score and RT interference, but each measure exhibited distinct relationships with DLPFC. Results thus provide empirical support for distinctions between types of inhibition, as these processes were associated with separable neural mechanisms. In general, more behavioral disinhibition (elevated BRIEF factor score) was associated with increased activity in brain regions typically associated with inhibitory functions (left DLPFC, left IFG,

bilateral inferior parietal cortex). In contrast, increased RT interference was associated with decreased brain activity in these regions as well as ACC (see Figure 3.1). Furthermore, behavioral disinhibition was associated with increased activity in mid-DLPFC, and greater RT interference was associated with less activity in posterior-DLPFC. These differential patterns of inhibition-related processes suggest a distinct role for each DLPFC area.

The cascade of control model (Banich, 2009; Banich et al., 2000; Milham & Banich, 2005) identifies four aspects of EF that are critical for inhibiting responses, which rely on distinct areas within PFC: (1) biasing responses towards task-relevant processes (the relevant task or mental set), (2) biasing attention towards task-relevant representations (the relevant stimulus or response required), (3) selecting the information that should guide responding, and (4) evaluating the response. Furthermore, this model proposes that distinct areas of DLPFC implement these functions which are necessary for executive control. In this model, posterior DLPFC imposes a top-down attentional set toward task-relevant processes, maintains the overall task goals, and subsequently biases other brain regions (e.g., mid-DLPFC, dorsal ACC, parietal cortex) toward processing task-relevant information. In contrast, mid-DLPFC is involved in selecting and maintaining the most relevant aspects of task stimuli (Banich, 2009) and is considered to be a critically involved in tracking and multitasking functions.

In the context of present findings, the behavioral manifestation of a high BRIEF inhibition factor score is impulsivity. Thus, mid-DLPFC hyperactivity associated with increased BRIEF inhibition factor score could reflect paying attention to too many task representations, and/or hyper-focusing on stimulus properties, which could disrupt the selection of the most relevant of the representations to which to respond. In other words, perhaps mid-DLPFC is functioning like a leaky filter when it comes to impulsivity. In line with this interpretation,

hyperactivity in mid-DLPFC has been linked to over-engagement with irrelevant features of stimuli (the meaning of threat-related words in an emotion-word Stroop task), interfering with processing task-relevant features (word color; Engels et al., 2010).

In contrast, a negative correlation between RT interference and posterior DLPFC was observed, such that the greater the RT interference, the less brain activity (or vice versa). Given DLPFC's prominent role in top-down attentional control (Milham, et al., 2003), if posterior DLPFC fails to impose a top-down attentional set toward task-relevant processes (inferred by decreased activity), we would anticipate greater RT interference. Results are consistent with other findings (Banich et al., 2000; Milham & Banich, 2005; Milham, et al., 2003).

Consistent with the cascade-of-control model, RT interference was also associated with areas of ACC that are involved in response selection and response evaluation. Specifically, the model asserts that there is a temporal cascade of cognitive operations, such that, following DLPFC activation, dorsal ACC selects the appropriate response among available response options. When incorrect responses are made during a task, more anterior regions of the ACC signal the posterior DLPFC to assert greater top-down control for task performance, requiring re-initiation of certain steps in the temporal cascade of events. In addition to posterior DLPFC and ACC, regions of activation for RT interference were consistent with those implicated in a distributed network associated with response inhibition, including bilateral IFG, as well as regions that are generally associated with attentional control and coordinating motor responses (e.g., premotor cortex, frontal eye fields, posterior parietal cortex, precuneus; Banich, 2009; Corbetta, Patel, & Shulman, 2008).

Interestingly, RT inference correlated with activity in a network of brain regions implicated in task-related expectations and preparation (i.e., goal-directed, executive control),

whereas self-reported inhibition was associated with activity in regions hypothesized to reorient attention from top down goal-directed control toward more stimulus-driven processing (Crocker et al., submitted). According to Corbetta et al. (2008), adaptive behavior relies on the interaction between functionally separate cortical systems specialized for selection of sensory information. The dorsal frontoparietal network, involved in goal-directed attention, includes posterior MFG (posterior-DLPFC), premotor areas, frontal eye fields (FEF), and dorsal parietal cortex (intraparietal sulcus and superior parietal lobule), whereas the ventral frontoparietal network (bottom-up, stimulus-driven system) includes anterior parts of MFG (mid-DLPFC), IFG, supramarginal gyrus, anterior insula, and temporal parietal junction (TPJ). In the context of a given task, dorsal attention regions such as posterior-DLPFC, dorsal parietal cortex, and FEF, along with anterior insula and ACC (implicated in a task-control network; Dosenbach, Visscher, Palmer, Miezin, & Wenger, 2006) are hypothesized to suppress the ventral network by sustained top-down signals. Suppression of ventral network activity has been interpreted as preventing an inappropriate response to irrelevant stimuli (Shulman et al., 2003).

Although the source of top-down signals is still under investigation, cortical regions such as MFG may link dorsal and ventral networks (see Corbetta et al., 2008, for review). Although speculative, perhaps the distinct functional patterns of inhibition-related processes implemented by DLPFC (mid-DLPFC hyperactivity reflecting behavioral disinhibition; posterior-DLPFC hypoactivity reflecting greater RT interference) may play a role in integrating the dorsal and ventral systems. It is plausible that decreased top-down control, as evidenced by decreased activation associated with greater RT interference, over the ventral network results in inappropriate reorienting to distracting stimuli (greater behavioral disinhibition/impulsivity) as manifested in everyday life. However, these interpretations are speculative as neuroimaging the

functional differences between brain regions associated with inhibitory processes provides limited insight. Methods examining how these regions communicate with one another during a task (e.g., functional connectivity) could be employed to test their contributions to the overall functions of networks.

Maintaining top-down attentional control is typically assumed to be the main function of DLPFC. However, current results suggest a more nuanced role of DLPFC as sub-regions were differentiated by two aspects of inhibition-related functions. DLPFC dysfunction has been implicated as a contributory source of cognitive impairment in a range of psychopathology, including depression and anxiety (Engels et al., 2007; 2010; Herrington et al., 2010, Levin et al., 2007; Siltan et al., 2010; Warren et al., 2008). Although inhibition-functions alone are not likely the *only* factors that are associated with cognitive dysfunction in psychopathology, their differing neural mechanisms certainly have probative value. For example, theories of depression (Joormann et al., 2007) and anxiety (Eysenck et al., 2007) postulate inhibitory dysfunction as a source of symptom development and maintenance, although specific inhibitory-functions are not addressed. Thus, assessing individual differences in specific inhibition-related functions and their neural mechanisms might be a more profitable approach in understanding how “inhibition” contributes to cognitive and emotional disruptions in psychopathology.

In conclusion, results provide evidence for overlapping and unique brain regions supporting the inhibitory functions of self-reported inhibition and prepotent response inhibition. In particular, inhibition-related functions differentiated specific regions within left DLPFC, an important structure that has been associated with implementing cognitive control and working memory. These results suggest the potential importance of utilizing an EF framework for understanding how some individuals persist in utilizing maladaptive emotion regulation

strategies that may confer vulnerability to psychopathology. In particular, DLPFC dysfunction often accompanies dimensions of depression and anxiety (Engels et al., 2007; 2010; Herrington et al., 2010, Levin et al., 2007; Siltan et al., 2010; Warren et al., 2008). Moreover, as cognitive training programs develop, training goals might include alleviation of particular symptoms (e.g., rumination, worry) that may rely on specific inhibition-related functions. Results suggest the need for greater specificity of inhibition-related functions in order to explain psychological phenomena and associated brain activity.

Table 5

Descriptive Statistics

Questionnaire	M	SD	Min	Max
PSWQ (Anxious Apprehension)	49.08	18.03	17	80
MASQAA (Anxious Arousal)	27.56	7.58	17	48
MASQAD8 (Anhedonic Depression)	16.89	5.77	8	33
Inhibition Measure	M	SD	Min	Max
BRIEF Factor Score	9.18	2.09	6.32	15.82
RT Interference	0.11	0.60	-0.30	0.23

Note. $N = 85$. PSWQ = Penn State Worry Questionnaire (Meyer et al., 1990). MASQAA = Mood and Anxiety Symptom Questionnaire Anxious Arousal scale (Watson et al., 1995). MASQAD8 = Mood and Anxiety Symptom Questionnaire Anhedonic Depression 8-item subscale (Bredemeier et al., 2010; Nitschke, Heller, Imig, McDonald, & Miller, 2001; Watson et al., 1995). RT Interference computed by $([\text{incongruent RT} - \text{neutral RT}] / [\text{incongruent RT} + \text{neutral RT}])$.

Table 6

Zero-Order Correlations among Psychopathology and Inhibition-related Measures

Measure	1	2	3	4
1. PSWQ (Anxious Apprehension)	--			
2. MASQAA (Anxious Arousal)	.48**	--		
3. MASQAD8 (Anhedonic Depression)	.49**	.51**	--	
4. BRIEF Factor Score	.10	.35**	.29**	--
5. RT Interference	.12	.13	.11	.13

Note. ** Correlation is significant at .01 (two-tailed).

Table 7

Distinct Effects of BRIEF Inhibition Factor Score

Region	Cluster Size (mm ³)	Mean Z	COM Location			Max Z Location		
			X	Y	Z	X	Y	Z
Incongruent versus Neutral Words ^a								
LH frontal pole, OFC	397	3.30	-46	39	-16	-48	40	-17
LH inferior frontal gyrus (IFG), anterior insula	1346	3.25	-46	16	0	-51	17	-2
LH frontal pole, IFG-pars triangularis	423	3.35	-47	39	6	-46	40	6
RH lateral occipital cortex, angular gyrus, TPJ	498	3.18	53	-59	21	53	-60	20
LH middle frontal gyrus (mid-DLPFC)	402	3.19	-40	26	28	-43	25	27
LH supramarginal gyrus	4851	3.26	-54	-53	41	-54	-44	52
RH angular gyrus, lateral occipital cortex	558	3.31	48	-55	54	50	-56	54

Note. $N = 85$. COM = center of mass. RH = right hemisphere. LH = left hemisphere. DLPFC = dorsolateral prefrontal cortex. OFC = orbitofrontal cortex. TPJ = temporoparietal junction. Location coordinates are in MNI152 2009 space.

^az-scores > 2.9677 , cluster-size ≥ 390 (corrected $p < .05$).

Table 8

Distinct Effects of RT Interference

Region	Cluster Size (mm ³)	Mean Z	COM Location			Max Z Location		
			X	Y	Z	X	Y	Z
Incongruent versus Neutral Words ^a								
Bilateral thalamus, caudate; LH OFC, insula, IFG	30997	-3.67	-12	-5	5	-6	-21	11
RH OFC, insula, IFG	7029	-3.45	36	17	-11	28	17	-16
RH temporal occipital fusiform cortex	442	-3.23	37	-47	-21	36	-42	-21
RH lingual gyrus	566	-3.31	5	-81	-15	4	-80	-12
LH lateral occipital cortex, posterior ITG	4764	-3.32	-38	-77	-11	-46	-62	-8
RH temporal occipital fusiform cortex, ITG	1119	-3.25	45	-61	-16	46	-56	-18
LH lateral occipital cortex, occipital pole	581	-3.20	33	-89	-10	35	-86	-9
RH middle temporal gyrus	1316	-3.44	54	-30	-7	54	-31	-7
RH parahippocampal gyrus	549	-3.42	20	-30	-9	22	-28	-8
dACC and rACC	19171	-3.49	0	25	32	10	25	24
Bilateral precuneus cortex	14804	-3.54	-7	-67	39	-7	-66	45
RH frontal pole	942	-3.40	26	54	13	28	55	9
LH middle frontal gyrus (posterior-DLPFC)	1980	-3.49	-54	15	32	-53	13	41
RH angular gyrus	399	-3.28	58	-52	24	58	-51	23

Table 8 con't

Note. $N = 85$. COM = center of mass. RH = right hemisphere. LH = left hemisphere. DLPFC = dorsolateral prefrontal cortex. OFC = orbitofrontal cortex. IFG = inferior frontal gyrus. ITG = inferior temporal gyrus. dACC = dorsal anterior cingulate cortex. rACC = rostral anterior cingulate cortex. FEF = frontal eye field. Location coordinates are in MNI152 2009 space.

^az-scores > 2.9677 , cluster-size ≥ 390 (corrected $p < .05$).

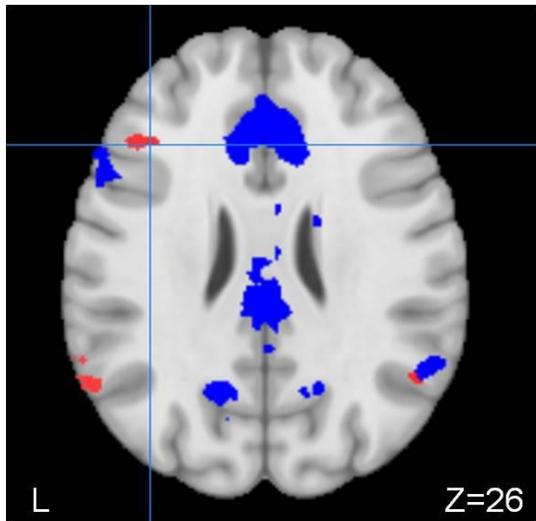


Figure 3.1: Areas that are uniquely associated with either self-reported inhibition in everyday life or prepotent response inhibition. Red = increased brain activation associated with behavioral inhibition as measured by BRIEF inhibition factor score. Blue = decreased brain activation associated with prepotent response inhibition as measured by RT interference. L = Left. Location of crosshairs emphasizes a functional differentiation of mid-DLPFC (red) and posterior DLPFC (blue) regions.

CHAPTER 4

INTERACTIONS OF ANXIETY AND DEPRESSION MODERATE BRAIN ACTIVITY ASSOCIATED WITH RESPONSE INHIBITION

Inhibition and Psychopathology

Despite the diverse and interesting findings from information-processing paradigms, cognitive biases in anxiety and depression have generally not been explicitly and systematically studied in relation to the basic cognitive mechanisms of executive control. A better understanding of the relationship between specific cognitive control functions, particularly inhibition, and their role in affective symptoms may improve our theoretical understanding of information processing impairments in anxiety and depression. Elevated symptoms on dimensions of psychopathology (anxious apprehension, anxious arousal, anhedonic depression) have been associated with risk for the development of anxiety and mood disorders (e.g., Behar, Alcaine, Zullig, & Borkovec, 2003; Bredemeyer et al., 2010). Thus, discerning whether specific executive function (EF) impairments are associated with dimensions of psychopathology could have implications for understanding the development and/or maintenance of anxiety and depression.

Intact inhibition-related processes are considered to be crucial for working memory and efficient EF (Friedman & Miyake, 2004). Some researchers have hypothesized that anxiety and depression are associated with deficits in inhibitory control. According to attentional control theory (Eysenck et al., 2007), anxiety enhances the influence of a bottom-up, stimulus-driven attentional system (influenced by salient stimuli) over a top-down, goal driven system (influenced by current task goals). Anxiety impairs performance because it is associated with impaired inhibition, a function that is considered to be key in restraining attention from task-

irrelevant stimuli and responses. Similarly, depression is hypothesized to have deficient inhibitory control. Joormann and colleagues (2007, 2010) have proposed that deficits in inhibitory control are related to difficulties preventing irrelevant information from entering working memory, with problems disengaging from negative information, and with difficulties removing previously relevant information from working memory. Thus, difficulties disengaging attention from negative material and inhibiting the processing of that material may lead to prolonged activation of negative content in working memory.

Although there is support for inhibitory dysfunction in anxiety and depression, the literature to date is inconclusive (Derakshan & Eysenck, 2009; Snyder, in press; Snyder, Henderson, Warren, & Heller, in preparation). Several explanations could account for such mixed results. Cognitive tasks that are generally employed include multiple aspects of cognitive function that might be impaired in psychopathology, making it difficult to draw firm conclusions about the presence of inhibitory deficits specifically (Henry & Crawford, 2005). In addition, the concept of “inhibition” is broad, and tasks that are assumed to measure inhibition vary in their definition of it, making it difficult to ascertain the nature of the function measured (see chapter 3 for review). Finally, evidence suggests that co-occurring disorders may have additive and interactive effects on brain activity and EF (e.g. Basso et al., 2007; Engels et al., 2010; Heller, Etienne, & Miller, 1995; Herrington et al., 2010; Keller et al., 2000; Moritz et al., 2001), as well as clinical outcomes (e.g. Emmanuel, Simmonds, & Tyrer, 1998). Yet many studies fail to assess or control comorbidity, making it difficult to parse the effects of specific dimensions of psychopathology on EF and related brain activity. In particular, few studies have examined the relationship of specific EF impairments to dimensions of anxiety and depression (anxious

apprehension, anxious arousal, anhedonic depression) that are known to be associated with different patterns of activity in relevant brain regions.

Neural Correlates of Psychopathology and Executive Function

Relatively few studies have addressed the relationship between anxiety, depression, and EF at the neural level. Neuroimaging studies have identified regions including prefrontal cortex (particularly DLPFC and IFG), ACC, and areas within parietal cortex with abnormal function in depression (Davidson & Henriques, 2000; Engels et al., 2010; Heller & Nitschke, 1997; Herrington, Heller, Mohanty, Engels, Banich, Webb, et al., 2010; Levin et al., 2007; Mayberg, 1997; Mayberg, et al., 1999; Pizzagalli et al., 2006; Rogers et al., 1998, 2004; Warren et al., 2008). Research on attentional bias rather than EF impairment has dominated much of the anxiety literature, and neuroimaging studies are no exception. However, results of these paradigms (usually testing inhibition of irrelevant distracting stimuli such as during an emotion-word Stroop task) highlight regions that are also involved in EF. For example, Bishop, Duncan, and Lawrence (2004) demonstrated that individuals high in state anxiety showed decreased activation of the lateral prefrontal cortex (associated with attentional control) when threat-related distracting stimuli were present. Bishop (2008) showed that high trait anxiety was associated with deficiencies in recruiting brain regions supporting prefrontal attentional control (e.g., DLPFC) needed to inhibit distracting stimuli under conditions of low attentional demand.

Research has implicated various brain regions associated with EF impairment in anxiety and depression, and a clear picture has yet to emerge. Both methodological and conceptual issues are likely culprits. Anxiety disorders are highly comorbid with each other and with depression (Kessler et al., 2005a, 2005b) and have overlapping symptoms (e.g., negative affect; Clark & Watson, 1991). Additionally, research suggests that comorbidity has additive and

interactive effects on prefrontal regions and EFs (e.g., Engels et al., 2010; Heller, Etienne, & Miller, 1995; Herrington et al., 2010; Keller et al., 2000; Moritz et al., 2001). Many studies have failed to assess or control for comorbidity either experimentally or statistically, which Heller and Nitschke (1998) have argued is critical for disentangling discrepancies and inconsistencies in the literature. In addition, anxiety and depression are often assessed via self-report questionnaires, many of which include symptom questions that are not specific to either anxiety or depression (Nitschke, et al., 2001).

Importantly, many studies have failed to distinguish between types of anxiety (for review, see Engels et al., 2010; Snyder et al., in preparation). Despite overlapping symptoms and high rates of comorbidity, research indicates that depression is distinguishable from two types of anxiety, anxious apprehension and anxious arousal (Nitschke, Heller, Imig, McDonald, & Miller, 2001; Heller et al., 1997; Nitschke et al., 1999). Anxious apprehension is characterized by worry and verbal rumination (Andrews & Borkovec, 1988; Barlow, 1991; 2002), whereas anxious arousal is characterized by somatic tension and sympathetic hyperarousal (Watson, Clark et al., 1995; Watson, Weber et al., 1995). Depression is characterized by decreased responsiveness to pleasurable stimuli (i.e., anhedonia; APA, 2000) and the absence of positive affect (Watson, Clark et al., 1995). When these distinctions are taken into account, distinct patterns of neural activity emerge. For example, Engels et al. (2007; 2010) demonstrated that anxious apprehension is associated with increased left IFG (Broca's area) activity, whereas anxious arousal is associated with increased right temporal gyrus activity. Furthermore, depression is associated with rightward lateralization of DLPFC activity (Herrington et al., 2010).

The Experimental Problem

Deficits in inhibition are hypothesized to play a prominent role in the affective and cognitive symptoms of anxiety and depression. In particular, intrusive thoughts such as worry and rumination are hallmark characteristics of anxiety and depression, respectively, and several researchers have suggested that these symptoms are a result of impaired inhibition (Eysenck, et al., 2007; Hertel, 1997, 2004; Joormann, 2005). Anxiety has been associated with broad impairments in attentional control, including increased distractibility and impaired processing efficiency (i.e., resource utilization) as opposed to performance effectiveness (i.e., percentage of correct responses; Eysenck, et al., 2007; Eysenck & Derakshan, 2011). Research in depression has repeatedly demonstrated problems with attention, memory, and problem-solving abilities (Burt, Zembar, & Niederehe, 1995; Levin et al., 2007; Marx, Williams, & Claridge, 1992; Weiland-Fiedler et al., 2004), and impaired inhibition is hypothesized to facilitate these cognitive disruptions via effects of working memory (e.g., Joorman & Gotlib, 2010). Thus, making an explicit link among individual differences in specific inhibition-related functions and dimensions of anxiety and depression is important for understanding the intricate relationship between affective experiences and cognitive control.

In line with this goal, the present study examined the relationship of brain activity associated with specific inhibition functions and its relationship with distinct dimensions of anxiety and depression (anxious apprehension, anxious arousal, and anhedonic depression). The study used empirically validated, inhibition-specific measures (inhibition in everyday life, Warren et al., in prep; prepotent response inhibition, Friedman & Miyake, 2004), and a dimensional approach to psychopathology. Regional brain activity associated with self-reported inhibition in everyday life (measured via BRIEF inhibition factor score; Warren et al., in prep)

and prepotent response inhibition (indexed by Stroop RT interference score; see chapter 3) were used as dependent variables in multiple regressions. Anxious apprehension, anxious arousal, anhedonic depression, and their interactions served as independent variables.

These analyses served several hypotheses designed to understand the relationship among critical dimensions of psychopathology and their modulation of neural mechanisms supporting inhibition-related functions. Understanding the nature and role of inhibition-related deficits and their relationships with anxiety and depression may provide some insight regarding factors that confer vulnerability to psychopathology. For example, although it is generally assumed that EF deficits are a by-product of anxiety and depression, it is possible that EF deficits may predispose individuals to develop psychopathology (e.g., Warren et al., in prep; see chapter 2). Although theories postulate anxiety- and depression-related disruptions in inhibition as a potential source of cognitive and emotional dysfunction, the modulation of neural mechanisms supporting such functions remains to be established. Given empirical support from hemodynamic neuroimaging studies that have properly accounted for comorbidity between depression and anxiety or comorbidity among anxiety types (Engels et al., 2007, 2010; Herrington et al., 2010), it is anticipated in general that depression will be associated with decreasing left DLPFC and ACC activity and that co-occurring anxiety of either type (anxious apprehension and anxious arousal) will increase activity in these regions (e.g., Engels et al., 2007, 2010). Given that anxiety is thought to manifest as greater activation in brain areas associated with attentional control in distracting conditions, (see Eysenck & Derakshan, 2011, for review), it is anticipated that anxiety will increase activity in mid- and posterior-DLPFC regions, as they have been implicated in playing prominent roles in attentional control (e.g., Banich, 2009) . In contrast, it is hypothesized that depression will be associated with opposing affects on posterior-DLPFC activity as previous

work has shown hypoactivation in this area (e.g., Herrington et al., 2010). It is also anticipated that anxious apprehension, characterized by worry and anticipatory anxiety, will increase left IFG activity (Engels et al., 2007).

Methods

Participants

The same participants discussed in chapter 3 were used for the present study. See chapter 3 for details.

Psychopathology Questionnaires

Questionnaires. Dimensional measures of anxiety and depression, the Penn State Worry Questionnaire (PSWQ; Molina & Borkovec, 1994) and the Anxious Arousal and Anhedonic Depression scales of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995), were administered during the participant's first visit to the lab (see Table 5). Anxious apprehension (i.e., worry) was measured using the 16-item PSWQ (e.g., “My worries overwhelm me”). Anxious arousal, characterized by somatic tension and sympathetic hyperarousal, was measured using the relevant 17-item subscale of the MASQ (MASQAA; e.g., “startled easily”). Anhedonic depression, characterized by depressed mood and a lack of positive affect, was measured using an 8-item subscale from the MASQ (MASQAD8; e.g., “Felt like nothing was very enjoyable”), as it has been shown to predict current and lifetime depressive disorders (Bredemeier, Spielberg, Siltan, Berenbaum, Heller, & Miller, 2010). Past research has shown that these measures have good test-retest reliability and good convergent and discriminant validity in undergraduate and clinical samples (Nitschke et al., 2001; Watson et al., 1995).

Dimensional measures of anxiety and depression were selected because they have been shown to effectively distinguish these highly comorbid constructs, which share many

overlapping symptoms (Nitschke et al., 2001). Indeed, dimensional approaches to understanding the complex relationships between emotion and brain function have proven more fruitful than a categorical approach (Warren et al., 2008), and are consistent with recent calls to integrate neuroscience and clinical research to identify fundamental mechanisms of psychopathology (Cuthbert & Insel, 2010; Sanislow et al., 2010).

Experimental Task and Stimuli

Color-Word Stroop task. Participants completed the color-word Stroop task, a classic EF task, during fMRI acquisition. For full details, see chapter 3.

fMRI Data Analysis

For full details, see chapter 3. Briefly, Warren and colleagues (chapter 3) investigated the moderation of brain activity associated with the color-word Stroop (1935) task by two inhibition-related functions, self-reported inhibition as manifested in everyday life (BRIEF inhibition factor score), and RT interference, a measure of prepotent response inhibition. Brain activity associated with incongruent words (“RED” in blue ink) was contrasted with activity associated with neutral words, and the two inhibition scores were entered as between-subject predictors. Clusters associated with inhibition in everyday life and RT interference that surpassed statistical thresholding were identified as regions of interest (ROIs). To assess the potential effect of psychopathology on neural activity related to these specific inhibition processes, a score for each ROI identified in which BRIEF inhibition factor score and RT interference predicted fMRI was created by averaging β values across voxels in each ROI, for each participant. ROI scores were then entered as the dependent variable in hierarchical linear regressions in which PSWQ, MASQAA, MASQAD, and their interactions were entered as regressors.

Results

Behavioral Data

Descriptive statistics for all of the measures are presented in Table 5, and zero-order correlations among psychopathology and inhibition measures are presented in Table 6.

Moderation of brain activity by psychopathology associated with behavioral disinhibition

No significant moderation of depression, anxiety, or their interactions emerged with any of the self-reported inhibition ROIs.

Moderation of brain activity by psychopathology associated with RT interference

Four, two-way interactive effects for anxiety and depression for response-inhibition-related brain activity emerged in three regions. A PSWQ x MASQAA interaction emerged for left posterior DLPFC (Figure 4.1). Tests of simple slopes showed that low levels of anxious arousal are associated with increased brain activity in left posterior DLPFC at high levels of anxious apprehension [$t(78) = -2.46, p < .05$] but with decreased activation at low levels of anxious apprehension [$t(78) = 2.27, p < .05$; Figure 4.1]. A PSWQ x MASQAA interaction was found for right middle temporal gyrus (MTG; Figure 4.2). Tests of simple slopes showed that high anxious apprehension was associated with low right MTG activation at high levels of anxious arousal [$t(78) = -2.86, p < .01$] but with increased activation at low levels of anxious arousal [$t(78) = 2.02, p = .05$]. Finally, two interactions emerged for right frontal pole (Figures 4.3 and 4.4). Similar to right MTG, increased anxious apprehension was associated with decreased right frontal pole activation at high levels of anxious arousal [$t(78) = -3.47, p < .001$] but with increased activation at low levels of anxious arousal [$t(78) = 2.91, p < .01$; Figure 4.3]. Additionally, a PSWQ x MASQAD interaction emerged in which high levels of anhedonic

depression were associated with decreased right frontal pole activity at low levels of anxious apprehension [$t(78) = -3.55, p < .001$; Figure 4.4].

Discussion

Select patterns of brain activation that emerged in the present study for response inhibition were modulated by psychopathology, contributing to understanding EF deficits in anxiety and depression. A two-way interaction emerged for left posterior-DLPFC in which greater activity was associated with high anxious apprehension when anxious arousal was low. Anxious apprehension typically involves elaborate verbal processing and worry. Given that posterior DLPFC is involved in imposing top-down attentional control and maintaining task set, hyperactivity in this area may reflect an attempt to compensate for anxious apprehension (which can be inferred to impair the efficiency of this inhibition-related function). Considerable evidence suggests that anxiety is often associated with increased susceptibility to distraction (see Derakshan & Eysenck, 2009, for review), hypothesized to reflect impaired inhibition (e.g., Eysenck & Derakshan, 2011). According to attentional control theory, anxiety impairs processing *efficiency* to a greater extent than it impairs performance effectiveness (i.e., quality of performance) and manifests in greater activation in brain regions associated with attentional control. Present findings suggest that anxious apprehension (i.e., worry), a specific dimension of anxiety, at least when anxious arousal is low, is more susceptible to distraction and thus to impaired efficiency of inhibition during cognitively demanding tasks (i.e., difficulty inhibiting the dominant tendency to read the color word). The fact that anxious apprehension and anxious arousal are not associated with deficits in performance (i.e., errors) likely reflects compensation by posterior-DLPFC (inferred by hyperactivity).

When worry (anxious apprehension) was low, brain activity in right MTG increased as anxious arousal increased. Right MTG is a region that is thought to interact with a network of regions involved in detecting and responding to threat (e.g., Compton et al., 2003; Corbetta et al., 2008). This region may be a part of a system that functions adaptively to switch between top-down attentional control and more stimulus-driven processing (Corbetta et al., 2008). Using an emotion-word Stroop task, Engels et al. (2007) demonstrated that negative emotion words elicited greater right middle-temporal/inferior-temporal activity in an anxious arousal group. Additionally, in a non-overlapping sample, Engels et al. (2010) found that anxious arousal increased depression-related suppression of activity in this region, in response to threatening words. Importantly, present results generalize Engels' et al. (2007, 2010) findings to non-emotional contexts, suggesting that anxious arousal, in the presence of other types of psychopathology, interferes with an inhibition-related function for cognitive control.

Similar to the pattern observed for right MTG, anxious arousal activity in right frontal pole (BA10) increased when anxious apprehension was low, but decreased when anxious apprehension was high. Additionally, anxious apprehension increased depression-related suppression of activity in this region. Rostral PFC (BA10) has been implicated in supporting a wide range of functions including prospective memory, multitasking, and “mentalizing” or reflecting on mental states (see Burgess et al., 2007, for review). According to the gateway hypothesis (Burgess et al., 2007), rostral PFC is part of a cognitive control system that biases the relative influence of stimulus-independent and stimulus-oriented thought (Burgess, Simons, Dumontheil, & Gilbert, 2005). Lateral regions of rostral PFC are associated with stimulus-independent cognition, the mental processes that accompany self-generated or self-maintained thought that is not provoked or directed toward an external stimulus (i.e., task-irrelevant

thought). Medial regions of rostral PFC are associated with stimulus-oriented cognition, or attending behavior that is required to concentrate on the task at hand. The right frontal pole region in the present study overlaps with the lateral area of rostral PFC identified by Burgess et al. (2007) as supporting stimulus-independent function. Anxious apprehension modulation of brain activity in this region (when other psychopathology is low) could reflect task-irrelevant thoughts such as worry, an example of stimulus-independent cognition. These findings suggest that weakened inhibition-related functions observed in anxious arousal increase worry-related activity in right lateral PFC, interfering with task efficiency.

Contrary to hypotheses, no significant moderation of anxiety, depression, or their interactions emerged with any of the self-reported inhibition ROIs. A possible explanation for the lack of significant findings is the general nature of conditions that self-reported inhibition measures. The self-reported inhibition score indexes everyday scenarios which could occur under a range of conditions. Although the self-reported inhibition score may be sensitive to neural mechanisms supporting this function, the measure may not be specific enough to capture anxiety and depression deficits. In other words, the self-reported inhibition score is not reflective of a specific task condition. In support of this explanation, attentional control theory posits that, under conditions in which there is no specific task goal, high-anxious individuals have a low level of motivation and make minimal use of attentional control mechanisms (Eysenck & Derakshan, 2011). In contrast, when the task goals are clear, such as in the color-word Stroop task, high-anxiety individuals are highly motivated and engage in compensatory strategies (i.e., effortful processing). That is not to imply that task goals are not clear in everyday life. Rather, it is possible that the effects of anxiety and depression on self-reported inhibition are less robust because of the range of contexts it may be indexing. In other words, the signal is being lost in

the noise. In support of this explanation, it is noteworthy to mention that left IFG (a BRIEF inhibition ROI) showed a trend for PSWQ x MASQAA moderation, such that the main effect of worry was moderated by anxious arousal ($\Delta R^2 = 0.06, p = .14$). This finding is consistent with Engels et al. (2007), who used an emotion-word Stroop task.

Overall, neural activity in select brain regions associated with RT interference was modulated by co-occurring anxiety types and depression. In particular, when anxious arousal was low, anxious apprehension was associated with increased brain activity in left posterior-DLPFC, right MTG, and right frontal pole. Consistent with attentional control theory, present findings of anxiety-modulated increases in brain activity could reflect inefficient neural recruitment during an EF task. More specifically, anxious apprehension appears to manifest as hyperactivity in brain regions associated with attentional control in distracting conditions. Moreover, the interaction of anxious apprehension and depression implies that worry “boosted” depression-related hypoactivity in right frontal pole, suggesting a buffering effect. Present findings reveal possible brain mechanisms of anxiety- and depression-related deficits in cognitive control, particularly susceptibility to distraction, which rely on distinct areas within PFC and MTG.

Present findings have implications for theories of anxiety and depression. Intrusive thoughts and memories are a common symptom in anxiety and mood disorders and are a key source of distress and dysfunction. Individuals with anxiety disorders demonstrate impaired cognitive performance in a variety of cognitive domains, hypothesized to result from anxiety-related intrusive thoughts and worry (e.g., Eysenck et al., 2007). Individuals with depression demonstrate difficulty inhibiting attention to negative emotional stimuli (see Peckham et al., 2010 for a meta-analysis), and may have difficulty disengaging from negative information,

leading to rumination (Joormann, 2010). Present findings elucidate possible brain mechanisms of interference (susceptibility to distraction) that could help to explain established deficits in aspects of EF, attention, and memory in anxiety and depression (see Warren et al., 2008, for review). The patterns of activation demonstrated in the present study reveal possible brain mechanisms supporting inhibitory-related functions and their modulation by different combinations of anxiety and depression in the context of a cognitive control task. As anxiety and depression frequently co-occur, it can be difficult to disentangle whether an individual's attentional problems are related to anxiety, depression, or both. As interest in the potential role of EF as a target of intervention is increasing (Brehmer, Westerberg, & Backman, 2012; Chein & Morrison, 2010; Jaeggi, Buschkuhl, Jonides, & Shah, 2011), identification of specific EF deficits and associated patterns of brain activity in psychopathology will likely serve the development and/or modification of effective interventions. Present results support the identification of differential patterns of brain activity implementing cognitive control abilities as a way of informing evidenced-based treatments. In particular, mindfulness-based treatments involve training individuals to use attentional control methods. Additionally, preliminary evidence suggests that EF training may actually improve response to non-pharmacological interventions (e.g., CBT; Mohlman, 2008), although research is needed to examine which aspects of EF are most critical for the efficacy of these interventions.

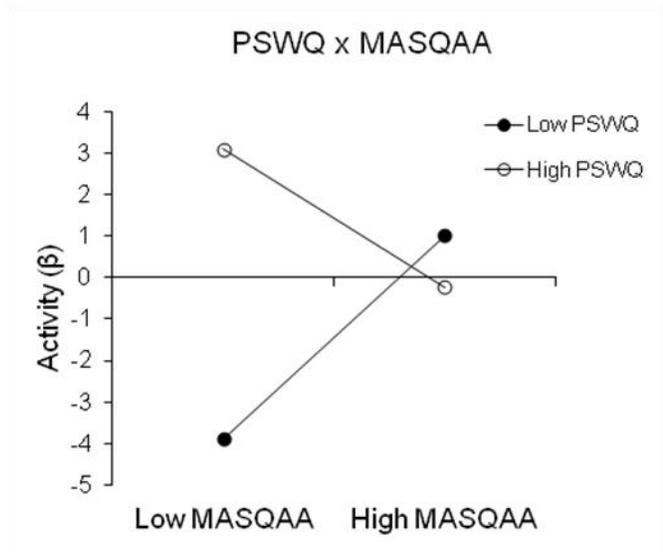
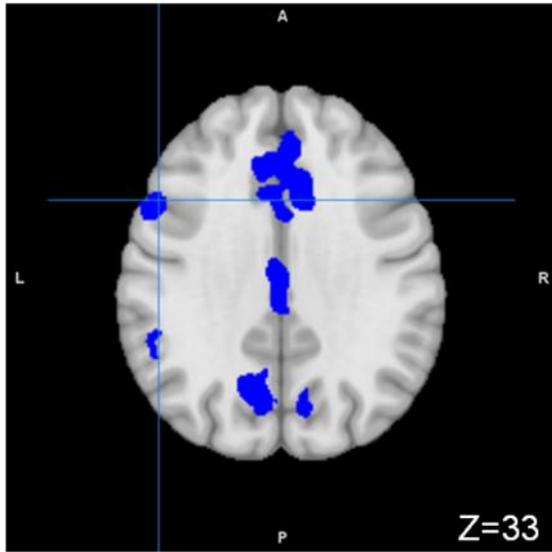


Figure 4.1: Left posterior DLPFC activation for RT interference. Graphing the PSWQ x MASQAA interaction illustrates that anxious apprehension's relationship with left posterior DLPFC depends on the level of co-occurring anxious arousal.

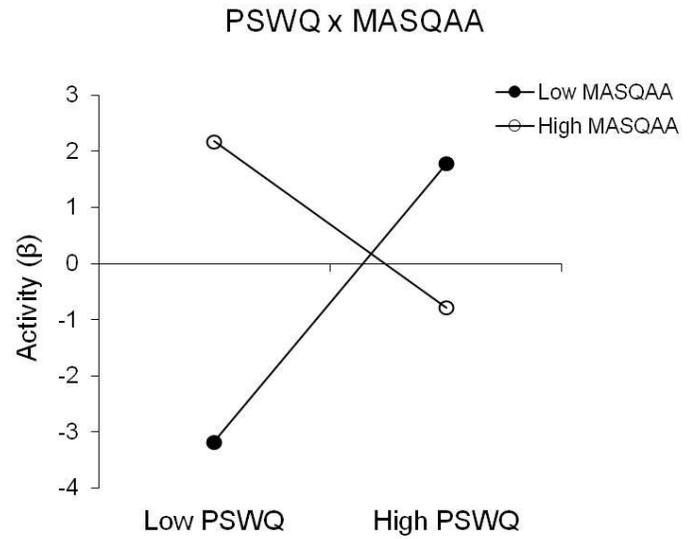
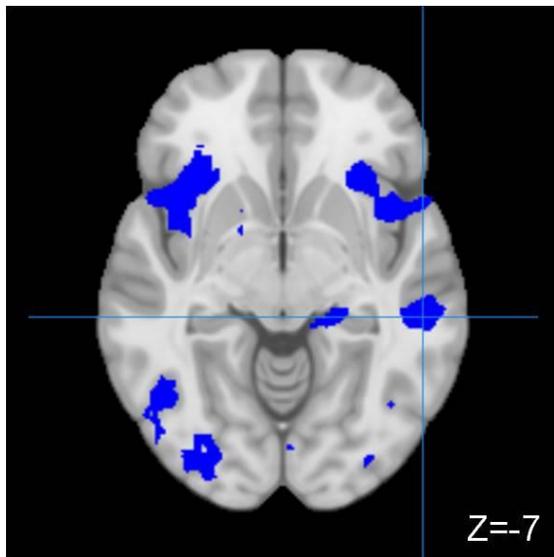


Figure 4.2: Right MTG activation for RT interference. Graphing the PSWQ x MASQAA interaction illustrates that anxious apprehension's relationship with right MTG depends on the level of co-occurring anxious arousal.

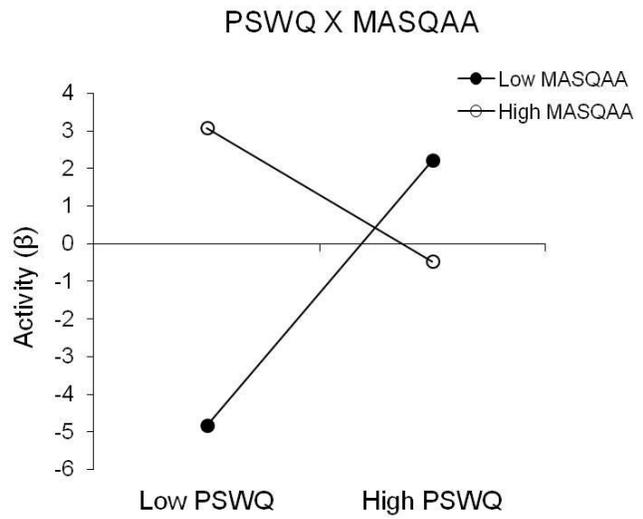
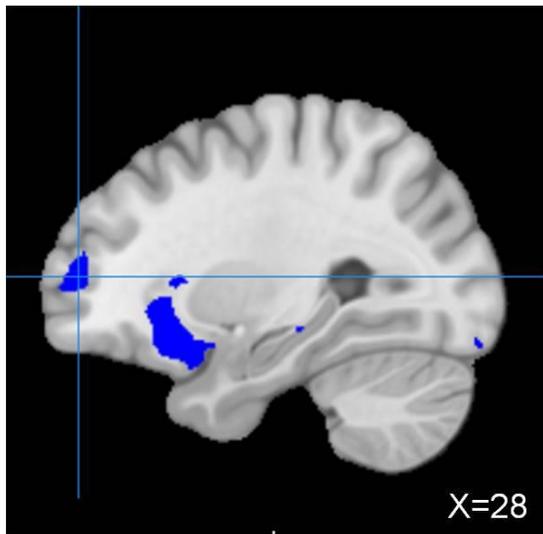


Figure 4.3: Right frontal pole activation for RT interference. Graphing the PSWQ x MASQAA interaction illustrates that anxious apprehension's relationship with right frontal pole depends on the level of co-occurring anxious arousal.

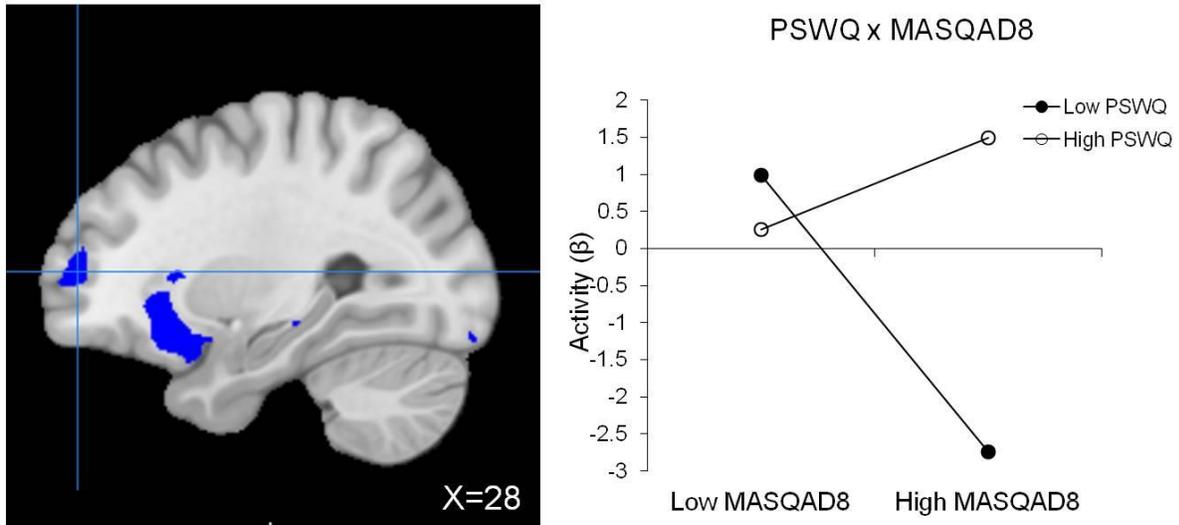


Figure 4.4: Right frontal pole activation for RT interference (same region pictured in Figure 4). Graphing the PSWQ x MASQAD8 interaction illustrates that anxious apprehension's relationship with right frontal pole depends on the level of co-occurring anhedonic depression.

CHAPTER 5

INTEGRATION AND FUTURE DIRECTIONS

The primary goal of the present dissertation was to address the hypothesis that disrupted executive functions (EFs), defined as abilities that guide goal-directed behavior and allow for flexible responses to environmental demands, are a primary source of cognitive problems in pathological anxiety and depression. Joormann and colleague's (2007) hypothesis that depression is related to deficits in inhibition was supported; however, depression was also associated with deficits in updating and shifting, demonstrating broader EF impairments than previously considered. In addition, depression exhibited a stronger relationship with shifting impairment than inhibition or updating. This suggests that, although the etiology and maintenance of depression may be related to broad executive dysfunction, this influence is stronger for shifting. In a similar vein, Eysenck and colleagues' (2007) hypothesis that "anxiety" is related to shifting and inhibition impairments was supported. However, consistent with previous neuroimaging evidence demonstrating distinct patterns of brain activity associated with anxious apprehension vs. anxious arousal during an EF task (Engels et al., 2007, 2010), the nature of anxiety dysfunction depended on carefully differentiating these dimensions. Anxious apprehension was associated with shifting impairments only, whereas anxious arousal demonstrated impairments in all three domains. Furthermore, anxious arousal demonstrated equal impairments in inhibition and updating domains. This suggests that the influence of shifting is important for anxious apprehension, but less so for the development and maintenance of anxious arousal.

These differences in executive dysfunction patterns underscore the importance of distinguishing anxiety dimensions. More importantly, the fact that each psychopathology

dimension exhibited distinct combinations of EF deficits suggests that impairments in cognitive control (and emotion-regulation), whether these impairments are overtly apparent or not, are complex. Executive dysfunction in anxious arousal and depression could not be accurately accounted for by examining one aspect of EF. Furthermore, if the focus is on just one dimension of EF, as has often been the case in the literature, it is possible that what might appear to be a primary EF deficit in depression or anxiety may actually be the result of another correlated, yet separable EF component (e.g., inhibition vs. shifting for depression).

Results from a series of studies yielded a number of intriguing findings that elucidate the nature of executive function in healthy individuals and provide insights into executive dysfunction associated with specific dimensions of anxiety and depression. In chapter 2, EFA established and CFA replicated meaningful dimensions of self-reported EF that are consistent with Miyake et al.'s (2000) updating, shifting, and inhibition framework. SEM determined that all three dimensions of psychopathology evidenced shifting impairment and that anxious apprehension and anhedonic depression were also associated with updating and inhibition impairments. Furthermore, anxious apprehension demonstrated the strongest relationship with shifting, whereas anxious arousal exhibited stronger relationships with updating and inhibition. These findings designate distinct EF impairments as contributing factors to the maintenance and development of anxiety and depression, suggesting EF mechanisms of emotion regulation and targets for intervention. Although clinicians and applied clinical researchers may feel that such distinctions within EF and psychopathology may not be relevant to their work, such a precise understanding may be extremely valuable in modifying and/or developing effective treatments. Moreover, as research in this area continues to develop, it is likely that deficits in different EF processes will affect different aspects of daily life, contributing to the maintenance of particular

symptoms. Thus, by implementing comprehensive EF assessments, specific EF profiles could assist with the development of therapeutic goals, as well as the delivery of such treatment.

Chapter 3 provided empirical support for distinctions between types of inhibition-related functions, as these processes were associated with separable neural mechanisms. Moreover, results suggested that sub-regions of DLPFC are differentially sensitive to self-reported inhibition and RT interference. Using the regions of interest that emerged in chapter 3, chapter 4 demonstrated that interactions among dimensions of psychopathology moderated brain activity associated with RT interference. In general, the presence of anxious apprehension or anxious arousal (when other psychopathology was low) was associated with increasing brain activity in regions associated with cognitive control. In particular, anxious apprehension was observed to boost activity in right frontal pole, counteracting the hypoactivity seen in depression, suggesting a buffering effect. Present results are consistent with other neuroimaging evidence demonstrating that excessive anxiety may require more effort (as indexed by greater PFC activity) to achieve the same level of performance on EF tasks that healthy control participants demonstrate. The present finding that anxiety-modulated hyperactivity in brain regions associated with cognitive control suggests a vulnerability to distraction, even in conditions when there is no manipulated threat (i.e., color-word Stroop task). In the same vein, Siltan et al. (2011) found that, as anxious apprehension increased, increased dACC activity (another key region associated with implementing cognitive control) was associated with greater Stroop interference (less efficient performance). However, there are limits to compensation, and it is important to determine when compensation may break down, such as when individuals with excessive anxiety are under stress. Under such conditions, the functional impairments that may emerge (and that may be overtly apparent) are likely to be in the contexts in which they are most detrimental (e.g. during a

final exam or important work task). Interestingly, mindfulness-based interventions are used to ameliorate attentional control deficits associated with anxiety and depression, helping individuals to increase the ability to regulate their attention (Baer, 2003). Present findings call attention to the non-unitary natures of both EF and anxiety (anxious apprehension and anxious arousal), and these distinctions could have implications for mindfulness-based interventions. These findings, when considered in the context of existing research, highlight a number of directions for future research examining executive dysfunction associated with anxiety and depression.

Future research examining cognitive deficits associated with anxiety and depression should employ a number of strategies utilized in the present study. First, rather than using complex neuropsychological tasks that rely on a number of cognitive functions for performance, research may be best served by choosing relatively simple tasks that are designed to primarily elicit single aspects of EF (e.g., shifting, updating, and inhibition). Notably, measures with low reliabilities necessarily lead to low zero-order correlations. Thus, it is important to explore the psychometric properties (e.g., test-retest reliability) of the tasks in order to evaluate appropriateness of use. Second, in order to reduce the task impurity problem (Burgess, 1997), and improve construct validity and power, it is valuable to administer multiple tasks tapping each EF component of interest. When feasible, statistical techniques such as factor analysis and structural equation modeling should be employed to isolate critical aspects of EF that are disrupted in specific dimensions psychopathology. Such latent variable approaches are particularly desirable as they explicitly account for measurement error in predictor variables (unlike regression) and remove method variance. Third, behavioral measures can be profitably supplemented with self-report and psychophysiological measures such as neuroimaging. Utilizing multiple approaches can off-set inherent limitations within each approach. For

example, biological measures such as neuroimaging can provide information that may be inaccessible through self-report and behavioral assessment (Miller & Keller, 2000). Of particular importance, neuroimaging can reveal when individuals are adopting alternative strategies for task performance that may be maladaptive and eventually break down. In the context of the present dissertation, anxious apprehension and anxious arousal were associated with increasing brain activity in regions associated with cognitive control (interpreted as compensation), yet these dimensions of anxiety were not related to task accuracy (i.e., errors). Thus, such differential patterns of attentional control difficulties could inform evidenced-based treatments for anxiety and depression that involve remediating attentional control methods, such as mindfulness-based techniques (Baer, 2003; Segal, Williams, & Teasdale, 2002).

Finally, future research should consider the use of dimensional measures assessing anxiety and depression. Given the difficulty in distinguishing the boundaries between clinical diagnoses, the high levels of symptom overlap between diagnoses, and the high heterogeneity within diagnoses (Krueger, Watson & Barlow, 2005; Widiger & Samuel, 2005), it has been suggested that it may be more meaningful to investigate the existence of fundamental components of psychopathology. Dimensional approaches to understanding the complex relationships between emotion and brain function have proven more fruitful than a categorical approach (Warren et al., 2008). Furthermore, discerning dimensions such as anxious apprehension, anxious arousal, anhedonic depression, and their interactions with a wide range of environmental and developmental factors may be a more productive approach to understanding a particular clinical phenotype.

Although findings from the present research provide new insights into specific domains of EF affected by specific dimensions of psychopathology, there are some limitations. The

present series of studies were restricted to an undergraduate sample and may not generalize to more cognitively diverse samples. Thus, generalizability to additional samples (e.g., community-based, samples across the life-span) remains to be established. Present findings could nevertheless serve as a baseline measure. Additionally, it should be noted that the methods used are not sufficient to establish causal relationships. In the context of the present research (chapter 2 specifically), path analysis (i.e., SEM) results are consistent with the authors' *hypothesized* models of EF and psychopathology, though causality cannot be determined, as the true causal model is unknown (Kline, 2011). For chapters 3 and 4, the interpretation of findings should be qualified by the fact that the analysis strategy was correlational in nature and cannot determine causality or direction of influence.

Moreover, in addition to neuroimaging of functional differences between brain regions associated with inhibitory processes, insights could be gained by analyzing functional connectivity among regions. Such methods could be employed to examine how these regions communicate with one another during a task, as well as to determine their contributions to the overall functions of networks. Present findings, especially mid- and posterior-DLPFC regions, could be used as seed clusters. Lastly, there is evidence that individual differences in dopamine function could affect activation patterns (e.g., Gibbs & D'Esposito, 2005). Dopamine is well known to play an important role in complex cognitive functions such as working memory and cognitive control and has high concentrations in PFC, a region that is associated with implementing these cognitive processes (Cools & D'Esposito, 2011). Although the present research cannot speak to the potential effects of individual differences in dopamine levels, future research using genetic, neuroimaging, and behavioral methods could be profitably combined to

develop more complete models of how aspects of prefrontal function are neurally implemented, how they support EF, and their complex relationships with psychopathology.

In addition to anxiety and depression being associated with EF impairment, present findings suggest that executive dysfunction plays a role in the etiology of anxiety and depression (chapter 2). These findings have implications for developmental models of psychopathology, as well as intervention and treatment. It is commonly assumed that cognitive deficits are a by-product of anxiety and depression and that they will improve upon successful treatment. However, it is possible that executive dysfunction is a factor predisposing to developing anxiety and/or depression. For example, in addition to playing a role in the development, implementation, and execution of daily plans and goals (Banich, 2009), EFs may affect our ability to evaluate potentially pleasurable stimuli or activities. EF deficits could make it challenging for individuals to initiate and/or maintain activities promoting pleasant emotional states or engage in adaptive coping behaviors that would buffer against the effects of life stress (Monroe & Reid, 2009). Moreover, persistent EF deficits could contribute to episodes of relapse or confer vulnerability to developing comorbid disorders.

Perhaps more importantly, findings that support specific EF deficits associated with anxiety and depression suggest that these deficits are appropriate targets for intervention. Difficulties with different aspects of EF may present barriers to current treatment methods. For example, an individual who has trouble shifting might need help planning strategies to transition more easily between daily tasks. In addition to structuring treatment to work with and around EF deficits, there is some evidence that EF training actually improves response to cognitive behavioral therapy (CBT; Mohlman, 2008). Interestingly, a growing number of studies demonstrate that cognitive training, targeting working memory function, can yield improvements

in a range of cognitive skills (Brehmer, Westerberg, & Backman, 2012; Chein & Morrison, 2010; Jaeggi, Buschkuhl, Jonides, & Shah, 2011). Cognitive remediation strategies have demonstrated improvements in cognitive function in clinical populations with known inhibitory impairment (e.g., ADHD; Klingberg, et al., 2005). Furthermore, the generalizability of cognitive training-related increases in working memory to non-trained tasks is hypothesized to occur when the transfer task recruits overlapping cortical regions (e.g. Jonides, 2004; Olesen et al., 2004). However, it is unknown what aspects of EF are most critical for CBT efficacy (or for other treatment methods such as mindfulness), and therefore might benefit most from training. It is also unknown which brain regions are the most critical for transfer of cognitive remediation strategies to be effective in everyday life, although given present findings DLPFC is a likely candidate. More research is clearly needed to explore how EF training might improve treatment outcomes.

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