MODERATION BY DEPRESSION AND ANXIETY OF CONNECTIVITY AMONG BRAIN AREAS ASSOCIATED WITH MOTIVATION

BY

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DISSERTATION

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ABSTRACT

Pathological anxiety and depression are prevalent forms of psychopathology and are associated with significant impairment in multiple areas of life, including occupational and social functioning. Although both forms of psychopathology have been heavily researched, the factors involved in their etiology and maintenance are still a matter of debate and require further investigation. Levels of trait approach and avoidance motivation may be relevant for understanding the differential correlates of anxiety and depression, given research indicating that they have distinct relationships with dimensions of trait motivation. An integrative model of the brain regions instantiating the approach and avoidance motivational systems is needed to understand how dysfunction in these systems manifests in anxiety and depression. The present dissertation aims to advance these literatures by proposing a hierarchical model of the neural components implementing the approach and avoidance motivational systems and examining the functional relationships among the proposed brain regions for motivational control. This model is then used to delineate areas of motivational dysfunction associated with pathological anxiety and depression.

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CHAPTER 1

GENERAL INTRODUCTION

Pathological anxiety and depression are prevalent forms of psychopathology (Kessler et al., 2005) and are associated with significant impairment in multiple areas of life, including occupational and social functioning (Kessler, DuPont, Berglund, & Wittchen, 1999). Although both forms of psychopathology have been heavily researched, the factors involved in their etiology and maintenance are still a matter of debate and require further investigation (Watson, 2009). Additionally, anxiety and depression are highly comorbid (Clark & Watson, 1991). Thus, research is needed that accounts for this comorbidity in attempting to determine the factors involved in the initiation and maintenance of anxiety and depression and to inform potential interventions.

Levels of trait approach and avoidance motivation may be relevant for understanding the differential correlates of anxiety and depression, given research indicating that they have distinct relationships with dimensions of trait motivation. Specifically, depression has been associated with decreased levels of approach motivation and increased levels of avoidance motivation, whereas anxiety has been associated with only increased levels of avoidance motivation (Spielberg, Heller, et al., 2011). This study provides data on the relevance of motivational systems for anxiety and depression, although it does not clarify what components of the approach and avoidance motivational systems are dysfunctional, nor whether this dysfunction is a vulnerability factor for or a result of anxiety/depression. An integrative model of the brain regions instantiating the approach and avoidance motivational systems is needed to understand how dysfunction in these systems manifests in anxiety and depression.

The present dissertation aims to advance these literatures by proposing a hierarchical model of the neural components implementing the approach and avoidance motivational systems and examining the functional relationships among the proposed brain regions for motivational control. This model is then used to delineate potential areas of motivational dysfunction associated with pathological anxiety and depression. A central feature of this model is the proposal that regions of dorsolateral prefrontal cortex (DLPFC) bias processing in other brain regions in the model to be in line with goals (Spielberg, Miller, et al., 2011). It is possible that the deficits in goal-directed behavior occurring in anxiety and depression may be partially due to dysfunction in the biasing of brain regions in the model by DLPFC, although this hypothesis has yet to be examined. Thus, the present dissertation has three primary goals: (1) identify and model the brain regions associated with motivational biasing of goal-directed behavior; (2) test the hypothesis that DLPFC regions associated with motivation bias processing in other areas of the brain during goal-directed behavior; (3) test the hypothesis that anxiety and depression moderate the motivational biasing of goal-directed behavior.

Chapter Organization

The present dissertation is organized into six chapters. Chapter 1 serves as a brief introduction to the purpose and organization of the document. Chapter 2 presents an integrative hierarchical model of the neural instantiation of approach and avoidance motivation. This model builds, in part, on the findings of Spielberg, Miller, et al. (2011) indicating that regions of DLPFC are involved in integrating motivational and executive function processes. The task used in Spielberg, Miller, et al. contained stimuli that were not explicitly valenced. Given that differential sensitivity to valence is thought to be an important component of approach and avoidance motivation (Elliot & Thrash, 2002), it is possible that the integration of motivational

and executive function processes occurring in DLPFC may occur differently when task stimuli are valenced. Chapter 3 provides a test of this hypothesis, and a replication test of the hypothesis that regions of DLPFC are involved in integrating motivational and executive function processes. Chapter 4 provides a test of the hypothesis that regions of DLPFC associated with trait motivation are involved in biasing processing in other nodes in the model to be congruent with goals. Support for this hypothesis would provide evidence that these brain regions are functioning as a network. Building on the findings of Chapter 4, Chapter 5 tests the hypothesis that dysfunction associated with depression and pathological anxiety in processing in model nodes is due to dysfunctional biasing by regions of DLPFC associated with trait motivation. Finally, Chapter 6 provides a general discussion that reviews the implications of these findings for the model proposed in Chapter 2 and for depression and pathological anxiety. Chapters 2, 3, and 4 are written in the form of manuscripts ready to submit for publication.

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CHAPTER 2

A HIERARCHICAL MODEL OF THE NEURAL INSTANTIATION OF APPROACH AND AVOIDANCE MOTIVATION

Abstract

Approach/avoidance motivation has proven to be a useful conceptual framework to facilitate the understanding of the neural correlates of psychopathology and emotion, with lateralization in prefrontal cortex being a particular target of investigation. However, this literature has been limited by a lack of spatial specificity and has not identified the specific aspects of approach/avoidance motivation involved. There is a large body of available research that uses more spatially specific methodologies (e.g., functional magnetic resonance imaging) that can be used to inform the literature on approach/avoidance. However, this research has not taken advantage of the rich psychological literature on approach/avoidance motivation. Therefore, it would be beneficial to integrate the neuroscience literature with psychological conceptualizations of approach/avoidance motivation that deconstruct the fairly broad constructs of approach/avoidance into component processes. The present paper proposes an integrative model of the neural instantiation of approach/avoidance motivation that takes advantage of the strengths of each of these literatures.

A Hierarchical Model of the Neural Instantiation of Approach and Avoidance Motivation

Approach/avoidance motivation has proven to be a useful framework to facilitate the understanding of the neural correlates of psychopathology (Davidson, 2002) and emotion (Carver & Harmon-Jones, 2009). This framework has been applied to findings suggesting that the prefrontal cortex (PFC) is lateralized with respect to motivational direction, with left PFC associated with approach and right PFC with avoidance (for review see Spielberg et al., 2008). For example, rightward lateralization of PFC activity has been offered as a biological marker of susceptibility to depression, thought to be due to decreased levels of approach motivation (Shankman et al., 2007; Tomarken et al., 2004; Heller et al., 2003). However, until recently, research investigating approach/avoidance lateralization in PFC has relied primarily on the low-density measurement of electroencephalographic (EEG) activity, which does not allow for very specific spatial localization of activity related to approach/avoidance (Tomarken & Zald, 2009). Additionally, this research has not elucidated the specific aspects of approach/avoidance motivation that are associated with prefrontal asymmetry (Tomarken & Zald, 2009).

There is a large body of available neuroscience research that can be used to refine the understanding of the instantiation of motivation in the brain. Of particular interest is a relatively recent set of studies investigating the instantiation of goal pursuit and control processes in PFC (for review, see Badre & D'Esposito, 2009). However, this research has not taken advantage of the rich literature on approach/avoidance motivation (and motivation more generally), often preferring to rely on relatively simplistic conceptualizations of motivation (e.g., motivation as only energization of behavior, Kouneiher et al., 2009, supplementary figure 1), when motivation is explicitly discussed at all. This limits the utility of this research, because it cannot be used to further the understanding of more complex motivational processes. Therefore, it would be

beneficial to integrate the literature on goal pursuit processes in PFC with nuanced conceptualizations of approach/avoidance motivation that deconstruct the fairly broad constructs of approach/avoidance into component processes. Fortunately, highly researched conceptualizations that fulfill this criterion are available (e.g., Scholer & Higgins, 2008).

The present paper attempts to fill these gaps in the literature by presenting an integrative model of the neural instantiation of approach/avoidance motivation. In order to accomplish this, the present paper selectively reviews and integrates psychological research on the structure of approach/avoidance motivation with neuroscience research on approach/avoidance motivation, goal pursuit, and motivation more generally.

Motivation and Goal Pursuit

Although many definitions of motivation have been proposed, several functional aspects are fairly consistent. Specifically, many theories conceptualize motivation as internal processes that select goals based on their predicted value (e.g., reward or punishment), initiate behavior to achieve goals, and maintain goal-directed action (e.g., Campbell & Pritchard, 1976; Jones, 1955; Lindsley, 1957). Thus, motivation is necessary for an organism to pursue goals.

However, the construct of motivation does not encompass all processes needed to pursue goals. Many theorists have proposed that cognition interacts with motivational processes during goal pursuit (e.g., Locke & Latham, 2002; Sorrentino & Higgins, 1986). Although usually not explicitly defined, cognition has often been conceptualized as "those processes that mediate the acquisition and representation of knowledge about the world" (Kuhl, 1986, p. 407), including skills and abilities (Locke, 2000). This work rests on the assumption that motivation and cognition are separable processes (Kruglanski, 1999). However, there does not appear to be sufficient evidence to assume the veracity of this dichotomy, with many theorists asserting that

motivation and cognition are, at the very least, highly overlapping and interdependent (Lazarus, 1991; Miller, 1996, 2010; Sherman & Sherman, 1999), if not simply different facets of the same construct (Kruglanski, 1999; Sorrentino & Higgins, 1986).

Distinguishing between motivational and cognitive processes becomes even more difficult when considering executive function. Similar to cognition, the construct of executive function is often defined imprecisely and with a large amount of variability (Martin & Failows, 2010). At a broad level, executive function is often conceptualized as the processes by which goal-directed action is carried out (Banich, 2009). Therefore, executive function shares with motivation a fundamental focus on goal pursuit. However, these constructs appear to have separable aspects. For example, processes involved in the energization of behavior are often considered to be solely the province of motivation. Additionally, executive function is associated with abilities, such as shifting, updating, and inhibition (Miyake et al., 2000), that are not usually considered to be part of the construct of motivation. The present paper provides a model of how the psychological processes involved in the pursuit of goals are instantiated in the brain, rather than delineating those processes which belong to motivation vs. executive function (or cognition more generally). Given that the present paper builds on psychological models of motivation, a motivational framework will be privileged. Some of the processes discussed in the present paper under the rubric of motivation could just as validly be conceptualized as cognitive or executive function.

Hierarchical Approach and Avoidance Motivational Systems

A number of theorists have proposed the existence of two fundamental motivational systems, one oriented toward potential desirable outcomes, termed the approach motivational system, and one oriented toward potential aversive outcomes, termed the avoidance motivational

system (for reviews see Elliot & Covington, 2001; Lang et al., 1998). These motivational systems are hypothesized to form the "basic building blocks that underlie the complexity of human behavior" (Carver et al., 2000, p. 741).

Several researchers have suggested that the approach and avoidance motivational systems are comprised of a number of hierarchical levels, with lower levels of these models subservient to higher levels (Elliot, 2006; Lang et al., 1998; Scholer & Higgins, 2008). For instance, Higgins and colleagues (for a review see Scholer & Higgins, 2008) proposed a structure with three levels: the system, strategic, and tactical levels. They proposed that these levels are hierarchical but that the selection of approach and avoidance is independent at each level.

System Level. At the system level, approach and avoidance are defined in relation to the goal that is held. Specifically, the goal can be to approach a potential desirable outcome or avoid a potential undesirable outcome. The critical determinant at this level is how the individual views the goal-object, rather than the properties of the goal-object itself. Therefore, the same goal-object can be part of either an approach or avoidance goal, depending upon the individual's motivational orientation. For example, if two individuals strive to get an A grade on a test, one person could view an A grade as an accomplishment that will bring them pleasure (a desirable outcome), whereas the other person could view getting anything lower than an A grade as a failure that will bring them displeasure (an undesirable outcome). Based on their motivational orientation, the first individual wants to approach an A grade, whereas the second individual wants to avoid getting anything lower than an A grade.

Given that numerous conceptualizations of the goal construct are available in the literature, it is important to outline the specific operationalization used in order to avoid confusion (Elliot & Fryer, 2008). Elliot and Niesta (2009) provided a definition in the context of

their hierarchical model of approach and avoidance motivation. According to these authors, a goal is defined as a "cognitive representation of a future object that the organism is committed to approach or avoid" (p. 58). In this conceptualization, the goal construct includes a commitment to pursue the goal-object. This commitment, along with the representation of the object (e.g., stimulus properties, associated value), must be sustained over time. Thus, one function of the system level is to maintain the goal construct over time.

Strategic Level. At the strategic level, approach and avoidance are defined in relation to the means or process of attaining a potential desirable outcome or preventing a potential undesirable outcome. As shown in Figure 2.1, at the strategic level one can approach matches to a desirable outcome (i.e., outcomes consistent with the desired state) or mismatches to an undesirable outcome (i.e., outcomes inconsistent with the undesired state). Similarly, one can avoid mismatches to a desirable outcome (i.e., outcomes inconsistent with the desired state) or matches to an undesirable outcome (i.e., outcomes consistent with the undesired state). Therefore, when approaching a desirable outcome at the system level, one can either approach matches to that outcome or avoid mismatches to that outcome. For example, if the potential outcome was getting an A grade, approaching a match could be studying hard, and avoiding a mismatch could be staying away from situations that distract from studying. Similarly, when avoiding an undesirable outcome at the system level (e.g., not getting an A grade), one can either approach mismatches to that outcome or avoid matches to that outcome. In relation to the example above, studying hard would be approaching a mismatch, whereas staying away from situations that distract from studying would be avoiding a match. Approach and avoidance at the strategic level reflect general/broad plans or means, rather than the specific instantiations of means, which are instead captured in the tactical level.

As discussed above, at the system level individuals commit to approaching or avoiding a certain end-state. In contrast, at the strategic level, a commitment can be made to the goal-pursuit plan, which Gollwitzer (1999) labeled an implementation intention (for reviews see Gollwitzer, 1999, Parks-Stamm & Gollwitzer, 2009). Gollwitzer conceptualized implementation intentions as if-then plans that link goal-directed actions to anticipated opportunities to engage in these actions. More specifically, the individual commits to act in a certain way when specific situations are encountered. For example, if a student commits to the goal of approaching an A grade in a class, that student may form an approach plan to complete extra credit assignments (the action) whenever they are offered by the instructor (the situation). This example highlights the two components of an implementation intention, the action and the situation.

Research by Gollwitzer and colleagues indicates that forming implementation intentions increases the likelihood of goal attainment, especially for difficult-to-obtain goals (see Gollwitzer & Sheeran, 2006, for a meta-analysis of 94 studies indicating an effect size of $d = 0.65$). Gollwitzer (1999) attempted to explain this effect by suggesting that implementation intentions make the anticipated situation and planned response more cognitively accessible (i.e., primed). For instance, the increased accessibility of the anticipated situation makes that situation easier to detect in the presence of distraction. Further, the increased accessibility of the planned response makes that response easier to select in the presence of competing responses. Research has supported this hypothesis (for a review see Gollwitzer et al., 2004). For example, research indicates that forming implementation intentions enhances performance in tasks engaging executive function, such as switching and inhibition (Cohen et al., 2008). Additionally, forming implementation intentions was found to improve performance on an inhibition task in children with Attention Deficit Hyperactivity Disorder (ADHD, Gawrilow & Gollwitzer, 2008).

When implementation intentions are not formed, individuals must actively attend to the environment in order to detect opportunities to pursue the goal. This active monitoring is more effortful and does not take advantage of the benefits discussed above (Gollwitzer, 1999). However, in some circumstances the formation of implementation intentions can be detrimental, and active monitoring may be the more successful choice. For example, the formation of implementation intentions can interfere with the pursuit of concurrent goals (Achtziger et al., 2010) unless the situation and action committed to in the implementation intention subserve both goals. Additionally, the formation of implementation intentions can be detrimental when novel goal-pursuit situations are encountered, because the heightened accessibility of the situation committed to in the implementation intention can direct attention away from novel situations (Parks-Stamm et al., 2007). In summary, at the strategic level, approach and avoidance goal-pursuit plans are selected and can either be committed to (i.e., the formation of implementation intentions) or actively managed.

Tactical Level. At the tactical level, approach and avoidance are defined in relation to the specific ways a strategy could be implemented in a particular context. For example, if the strategy were to study hard, an approach tactic could be setting aside a specific time to study. An avoidance tactic could be making sure that no important study materials are missing. The tactical level is still at a higher level than the actual behavior that is implemented in a given situation, because an avoidance tactic can be implemented through physically approaching a stimulus and vice versa. For example, an avoidance tactic, such as ensuring that no important study materials are missing, could be implemented with approach behavior, such as approaching a classmate to ask them to show you their study materials or approaching the professor to ask them whether your study materials are adequate.

Although the levels are considered to be independent, Scholer and Higgins (2008) hypothesized that individuals tend to be consistent across levels (e.g., approach at the system level tends to be associated with approach at the strategy level). Higgins (2000, 2005) accounted for this consistency by proposing that inconsistency across levels leads to disruption in motivational orientation (i.e., approach or avoidance), which, in turn, leads to decreases in goal engagement (i.e., the amount of attention and effort invested in the goal). When there is consistency across levels, motivational orientation is maintained, and goal engagement is sustained.

Temperament Level. Elliot (2006) proposed a two-level hierarchical model of approach/avoidance motivation that appears complementary to that proposed by Scholer and Higgins (2008). This model consists of a temperament level situated above a goal-associated level that is similar to Scholer and Higgins' (2008) system level. The temperament level is comprised of general tendencies to be sensitive to desired (approach temperament) or undesired (avoidance temperament) potential outcomes and to adopt approach or avoidance goals accordingly (at the system level). For example, a student high on avoidance temperament who is faced with an upcoming test will be sensitive to the potential for failure (e.g., getting a low grade and looking stupid) and is likely to adopt the goal of getting an A on the test in order to avoid failure. In contrast, a student high on approach temperament in the same situation will be sensitive to the potential for success (e.g., getting a good grade and showing how smart they are) and is likely to adopt the goal of getting an A on the test in order to approach success. These two students share the same goal-object (i.e., getting an A), but the underlying reasons for that goal are different, which is reflected at the system level in Higgins' model (Scholer & Higgins, 2008).

Integrated Model. In summary, combining Scholer and Higgins' (2008) and Elliot's (2006) models, the present proposal offers a hierarchical model of approach/avoidance motivation that consists of four levels: temperamental, system, strategic, and tactical. The temperamental level consists of broad tendencies to be sensitive to desired or undesired potential outcomes and to implement approach or avoidance goals accordingly. The system level is comprised of the goal that is held, either approaching a desired outcome or avoiding an undesired outcome. The strategic level represents the general means or process by which the goal will be pursued, and, at the tactical level, the strategy is instantiated in a specific context.

It is proposed here that these levels can be conceptualized along a gradient of both abstraction and timescale, with higher levels being more abstract and having a longer timescale. For example, the strategic level is more abstract than the tactical level, because the tactical level represents the implementation of the strategy in a given context. The system level is more abstract than the strategic level, because the same goal can be subserved by several strategies (i.e., equifinality, Martin & Tesser, 2009). Similarly, the system level has a longer time scale than the strategic level, because the goal must be maintained over time, during which a number of strategies can be employed. The temperament level is the most abstract and has the longest time scale, as it reflects dispositions over the lifetime to activate a motivational orientation that is independent of specific goals.

The hierarchical model proposed here implies that higher levels in the structure exert control over lower levels. For example, to attain a goal held in the system level, the goal must be maintained over time and appropriate strategies employed at appropriate times. Therefore, the system level must engage the strategic level when needed. Consequently, the role of the system level can be conceptualized as biasing processing in lower levels of the structure in support of an

overarching goal. Given that multiple goals can be held at one time, the system level must also prioritize goals at any moment and bias processing accordingly. Therefore, one important function of this motivational system is the biasing of processing in lower levels to keep them in line with goals.

In conclusion, the integrated hierarchical model of approach/avoidance motivation proposed here is a nuanced conceptualization that deconstructs the fairly broad constructs of approach/avoidance into important component processes. It is proposed here that this psychological model can serve as a framework for understanding the processes examined in neuroscience research on motivational systems.

Neural Instantiation of Motivational Systems

A long line of research suggests that PFC is lateralized with respect to emotional/motivational valence, with right PFC associated with unpleasant emotion and avoidance motivation, and left PFC associated with pleasant emotion and approach motivation (for reviews see Heller, 1993; Davidson & Irwin, 1999). PFC lateralization with respect to emotional or motivational valence is supported by research using a number of different methodologies, including neuropsychological testing (e.g., Flor-Henry, 1976), brain lesion patients (e.g., Gainotti, 1972), and electroencephalography (EEG; e.g., Davidson et al., 1990). Although PFC asymmetries have regularly been observed in EEG and other methodologies, they have been elusive in studies employing functional magnetic resonance imaging (fMRI). This method complements EEG in that it provides better spatial resolution than traditional low-density EEG for locating specific areas of PFC involved in emotion and motivation. Herrington et al. (2005) were the first to demonstrate leftward lateralization for pleasant emotion using fMRI, which was localized to DLPFC. As discussed in Herrington et al. (2010), one reason why

lateralization findings are uncommon in fMRI may be that lateralization is usually not tested directly. Indeed, region (including hemisphere) is almost never a factor in analyses of fMRI data. Statements are often made about what are in effect multiple simple-effects tests without a systematic evaluation of the underlying interaction.

State Motivation and Executive Function. Preliminary research on the interactive contributions of motivation and executive function to goal-directed behavior is beginning to emerge, including studies that investigate the effects of state motivation on the neural processes associated with tasks of executive function (e.g., Pochon et al., 2002; Taylor et al., 2004). This research has consistently implicated areas of prefrontal cortex (PFC) in the integration of motivation and executive function processes (Gilbert & Fiez, 2004; Gray et al., 2005; Krawczyk et al., 2007; Locke & Braver, 2008; Rowe et al., 2008; Szatkowska et al., 2008). Such integration is consistent with conceptualizations of PFC as being necessary "to orchestrate thought and action in accordance with internal goals" (Miller & Cohen, 2001). For example, Pochon et al. (2002) examined the relation between reward processing, a facet of motivation, and performance on a working memory task. Results revealed that left DLPFC was activated by both working memory demands and increasing levels of reward. Taylor et al. (2004) conducted a similar study that examined the interaction between state motivation and working memory by manipulating motivation in terms of both reward and punishment. Consistent with the findings of Pochon et al. (2002), motivational processes interacted with working memory load in bilateral DLPFC.

Savine and Braver (2010) examined the interaction of state reward processing with a different aspect of executive function, task switching. Consistent with the findings of both Pochon et al. (2002) and Taylor et al. (2004), Savine and Braver (2010) found that reward level interacted with task-switching in left DLPFC, such that the possibility of a reward was associated

with increased task-switching activation. Importantly, right DLPFC did not exhibit this interactive effect, and a test of laterality indicated that the difference in this effect between hemispheres was significant. Additionally, activation in left DLPFC was positively associated with behavioral facilitation of task-switching, and this facilitation was increased when a reward was possible.

Thus, at least three studies suggest that DLPFC is essential for the neural integration of motivation and executive function processes. These studies can be interpreted as manipulating the system level of the hierarchical model of motivation, because they manipulate the reasons for the goal (i.e., to do well in order to obtain a reward or avoid a punishment). Thus, this research suggests that the system level is instantiated in (at least) DLPFC, which is consistent with research suggesting that DLPFC is involved in representing and maintaining goals (e.g., MacDonald et al., 2000). Although involvement of DLPFC was observed in all three studies, activation was left-lateralized in Pochon et al. (2002) and Savine and Braver (2010) but bilateral in Taylor et al. (2004). Inconsistencies in the lateralization of DLPFC activation may be due to differences in the motivational manipulation used across the studies. More specifically, the differences in lateralization patterns might be due to the fact that Pochon et al. (2002) and Savine and Braver (2010) employed only a reward manipulation, consistent with leftward lateralization, whereas Taylor et al.'s (2004) motivational manipulation included both reward and punishment, which should engage both hemispheres. The picture is further clouded by the fact that neither Pochon et al. (2002) nor Taylor et al. (2004) actually tested laterality effects. Thus, the extent of the inconsistency is not clear. However, although preliminary and in need of further investigation, the significant lateralization test in Savine and Braver (2010) suggests that DLPFC activation in relation to state motivation and executive function is, in fact, lateralized.

Trait Motivation and Executive Function. Extending the work on state motivation and executive function, recent research has examined the interaction of trait motivation with executive function. Spielberg et al. (2011) investigated moderation of neural activation associated with the color-word Stroop (1935) task by approach and avoidance temperament. Neural activation associated with incongruent words was contrasted with activation associated with congruent words, and approach and avoidance temperament scores, computed using a confirmatory factor analysis, were entered as between-subject predictors. Hemispheric lateralization was tested directly using methods similar to those of Herrington et al. (2010).

Consistent with previous research on state motivation and regional brain activity, approach temperament moderated activation in two regions of left DLPFC (a relatively anterior region in BA 8 and 9 and a relatively posterior area in BA 9 only), and avoidance temperament moderated activation in one region of right DLPFC (BA 9 and 6), all of which were lateralized effects. These areas of DLPFC have been associated with a number of other functions. Specifically, these regions have been implicated in behavioral inhibition, planning upcoming action, attending to cues predicting the occurrence of a motivationally salient event, and responding when motivationally salient events occur (Abler et al., 2006; Bickel et al., 2009; Kaladjian et al., 2009; Volle et al., 2005). Incorporating this research with their findings, and consistent with Herrington et al. (2010), Spielberg et al. (2011) hypothesized that these regions of DLPFC are involved in implementing a motivational set that biases lower-order processing (i.e., attention to ink color vs. word meaning) to be congruent with goals. Given that the temperament level of the hierarchical model of motivation discussed above is hypothesized to reflect tendencies to adopt approach/avoidance goals (at the system level), it is likely that the areas identified in this study are involved in the instantiation of the system level. These findings

have recently been replicated using an emotion-word Stroop task (Spielberg et al., 2010), supporting the generalizability of these conclusions. Importantly, these studies provide a starting point from which to begin mapping the levels of the hierarchical model of motivation to brain areas in which they are instantiated.

Intertemporal Choice. Neuroscience research in the field of intertemporal choice, which investigates choices between outcomes that differ in temporal delay and reward/punishment magnitude, provides another avenue to examine the instantiation of motivational systems in the brain. Humans are often faced with choices between options that differ in the timescale of the potential outcomes. Often, one option is associated with a shorter delay and a smaller reward, whereas the delay in the other option is longer and the reward value greater. For example, an individual may have the goal of losing weight and be faced with the choice of whether to eat a fattening desert. In order to maximize gain/minimize loss over time, goals (e.g., losing weight) must be maintained in the face of competing options (e.g., eating cake now), which is a process that can be associated with the system level of the hierarchical model of approach/avoidance, because this level is involved with the maintenance of goals. Although the choice with the longer delay has an objectively better outcome, this option is often not chosen, because humans discount the value of delayed rewards (Ainslie, 2001). The rate of future discounting can be thought of as a measure of impulsiveness, because it reflects the tendency to forgo larger, long-term rewards in order to gain more immediate satisfaction (Ainslie, 1975). This contention is supported by research indicating that more impulsive individuals (e.g., children with ADHD) discount future rewards more than less impulsive individuals (Barkley et al., 2001).

Recent research employing neuroscience methods has attempted to identify brain regions involved in integrating temporal delay into the decision-making process. Several studies suggest

that DLPFC and posterior cingulate cortex (PCC) are involved in decisions to forgo proximal reward or incur proximal punishment in order to maximize benefit over time, providing further support for the hypothesis that the system level is instantiated (in part) in DLPFC. Specifically, several studies have found that greater activation in DLPFC and PCC predicted the choice of the larger, later outcome (Ballard & Knutson, 2009; McClure et al., 2007; Weber & Huettel, 2008; Wittmann et al., 2007). As well, activation in DLPFC and PCC has been found to be positively correlated with the length of the delay associated with outcomes (Ballard & Knutson, 2009; Luhmann et al., 2008). Finally, gray matter volume in DLPFC has been found to be positively associated with the tendency to choose the larger, later outcome over the smaller, more immediate outcome (Bjork et al., 2009).

In these studies, the delay and magnitude associated with each option were explicitly presented to participants. Therefore, maximizing reward over time required only the ability to resist the earlier option. In many real-world choices, however, the magnitude and delay of the outcome will not be explicit. For example, when choosing whether to forgo eating (immediately available) cake in order to lose weight, the impact of cake eating on weight and how long it will be until the desired amount of weight will be lost (if cake is not eaten), will usually be unclear. In these situations, learning history can play an important role in determining which choice will be selected (e.g., how quickly a specific individual has lost weight in the past). Several studies have examined intertemporal choice when participants must learn the contingencies associated with different options. For example, Tanaka et al. (2004) employed a decision making task in which participants had to learn to incur small, immediate losses in order to gain large, delayed rewards. Results revealed that learning to obtain larger, later rewards was associated with increased activation in left DLPFC and PCC, which is consistent with research linking these brain regions

to forgoing proximal reward or incurring proximal punishment in order to maximize reward over time.

Yarkoni et al. (2005) employed a task similar to that of Tanaka et al. (2004). However, in their task, the strategy of forgoing more immediate rewards to obtain the delayed reward did not always maximize the total reward over time. Instead, it was optimal to choose the immediate reward in one of the conditions. Results revealed that DLPFC activation was associated with optimum performance (i.e., maximizing total reward) on the task. Specifically, when reward was maximized by sacrificing smaller, earlier rewards to obtain larger, later rewards, sustained activation in DLPFC across the entirety of the trials was greater than activation during the time at which participants actually made choices. When reward was maximized by choosing smaller, earlier rewards, DLPFC exhibited greater activation during the actual choice period, relative to the sustained activation across trials. This indicates that the involvement of DLPFC is not restricted to obtaining delayed rewards. Rather, DLPFC appears to be involved in maximizing overall benefit.

Taken together, this research supports the hypothesis that DLPFC is involved in maximizing benefit/minimizing harm over time. This would involve both the maintenance of appropriate goals in the face of competition (e.g., forgoing a small proximal reward for a larger, delayed reward) and the selection of appropriate strategies (e.g., determining whether obtaining proximal rewards or forgoing proximal rewards for larger, delayed rewards will maximize total benefit over time). Therefore, this research provides evidence that DLPFC is involved in instantiating both the system and strategic levels of the hierarchical model of motivation.

Posterior cingulate cortex also appears to play a significant role in maximizing total reward over time. Research by Maddock (1999) indicates that PCC is involved in integrating

emotional and motivational information into memory during recall. This suggests a role for PCC in the anticipation of delayed rewards. When choosing between potential rewards, a representation of each outcome, incorporating motivationally relevant information based on past experience, is needed in order to evaluate the predicted subjective value of the outcome. In addition, the anticipation period itself can have value (Berns et al., 2007), because anticipation can be pleasant or unpleasant (or neutral). Better ability to incorporate motivationally relevant information into anticipation when considering a potential outcome will make that option seem more attractive (or unattractive if the outcome is unpleasant).

The involvement of PCC in the anticipation of potential goals is supported by several studies, including a study that found increased PCC activation when participants self-reflected on both approach- and avoidance-related goals (Johnson et al., 2006). Additionally, dissociation in PCC activation to motivationally-relevant stimuli has been found in relation to approach and avoidance (Touryan et al., 2007). Specifically, when an approach orientation was induced, greater activation in PCC was observed during the evaluation of pleasant stimuli (relative to unpleasant stimuli). In contrast, when an avoidance orientation was induced, greater activation in PCC was observed during the evaluation of unpleasant stimuli. Finally, a recent study (Peters & Buchel, 2010) directly investigated the impact of imagery associated with potential future outcomes on temporal discounting. Participants performed a classic delay discounting task in which they chose between immediate and delayed rewards. Before performing the task, participants identified a number of planned future events (e.g., going to a workshop, going to a friend's wedding). In one condition, the delayed reward choice was linked to one of the identified future events (i.e., the reward would be given on the day that the event occurs). Results revealed that rewards were discounted less heavily in this condition, relative to a control

condition in which no links to future events were presented. Additionally, vividness ratings of future events correlated negatively with the rate of discounting, such that greater vividness was associated with less discounting. Importantly, PCC exhibited greater activation when links were presented, relative to the control condition, suggesting that PCC is involved in the imagery process. As well, the subjective value of the delayed reward option (i.e., the objective value multiplied by the delay discount rate) was correlated with brain activation for each condition. In PCC, this correlation was significantly greater during the condition in which links to future events were presented, suggesting that PCC is involved in representing the value of future outcomes through associated imagery. These findings are consistent with a model of the neural instantiation of prospection proposed recently (Buckner & Carroll, 2008). Prospection is the process by which past memories are used to envision potential future scenarios, and this process can be used to assist in planning for future goals. Buckner and Carroll (2008) suggest that PCC, along with other areas including genual anterior cingulate, is vital to the process of prospection.

In summary, the present review of the literature on intertemporal choice supports the hypothesis that DLPFC plays an essential role in goal pursuit and additionally implicates PCC as being an important component due to its involvement in the representation of motivationally salient aspects of potential future outcomes. In combination with the research reviewed above on the interaction of motivation and executive function, this research provides a starting point for a model of motivation in the brain.

A Model of Motivation in the Brain

Converging lines of research suggest that DLPFC implements a motivational set that biases lower-order neural processes to facilitate the achievement of goals. It is proposed here that this research can be interpreted by applying the framework of the hierarchical model of

motivation (Elliot, 2006; Scholer & Higgins, 2008) to a set of related proposals (for reviews see Badre & D'Esposito, 2009; Botvinick, 2008) that superior, lateral prefrontal cortex (SLPFC), including DLPFC, is organized along a dimension of abstraction. Generally, more anterior regions (e.g., BA 10, DLPFC) are involved in the most abstract aspects of goal-directed processing (e.g., maintaining the ultimate goal), and more posterior regions (e.g., supplementary motor area [SMA]) are involved in processing the least abstract aspects (e.g., programming motor sequences).

There is some disagreement regarding the nature of the abstraction that organizes SLPFC. One proposal is that the abstraction is temporal in nature. Specifically, goals become more abstract as the timescale of the task they direct increases (Badre & D'Esposito, 2009). Another proposal is policy abstraction, in which more abstract goal representations are more general than lower-level goal representations (Badre & D'Esposito, 2009). According to Botvinick (2008), timescale is likely the key parameter that governs the organization of SLPFC. Specifically, more anterior regions guide behavior over a longer time-span than do more posterior regions.

It is proposed here that the gradient of abstraction and timescale evident in the hierarchical model of motivation can be mapped onto this SLPFC gradient, with the system level associated with more anterior SLPFC and lower levels (i.e., strategic, tactical) moving sequentially more posterior. The temperament level would be associated with the activity/reactivity of these regions (especially those instantiating the system level) rather than being associated with a specific region of the SLPFC. Additionally, it is proposed here that SLPFC is lateralized with respect to motivational orientation, with left SLPFC associated with approach and right SLPFC associated with avoidance. This organization is pictured in Figure 2.2. As shown, approach at the system level can recruit both approach and avoidance at the strategic

level. However, approach at the system level is more likely to recruit approach at the strategic level, as indicated by the thicker arrows.

Support for this proposal can be found in a recent study by Kouneiher et al. (2009), which examined the integration of motivation and cognition in the context of a model of PFC abstraction proposed by Koechlin and colleagues (Koechlin et al., 2003; Koechlin & Summerfield, 2007). In this model, posterior DLPFC is hypothesized to be involved in contextual control (i.e., control based on rules related to the immediate context), whereas anterior DLPFC is hypothesized to be involved in episodic control (i.e., control based on a past event which indicates that a certain set of rules should be applied in the current context). The most anterior region, frontopolar PFC (e.g., BA 10), is hypothesized to be involved in branching control (i.e., maintaining a task set in memory while another task is carried out).

Kouneiher et al. (2009) found that rewards/punishments associated with the context (the current trial) and the episode (the current set of trials, which were preceded by a cue signaling the possible incentives) moderated posterior and anterior DLPFC activation, respectively. They also found an anterior-to-posterior gradient in medial PFC, with dorsal anterior cingulate cortex (dACC) activation moderated by episodic motivation and pre-supplementary motor area activation moderated by contextual motivation. They proposed that reward/punishment-related signals from medial PFC influence DLPFC, which is carrying out what they term cognitive control, thus accounting for the observed association with motivation in DLPFC. Indeed, they tested this hypothesis with structural equation modeling and found that the data were consistent with the hypothesis that medial areas influence lateral areas. However, they did not test whether the effect of reward/punishment on lateral areas was (completely or partially) mediated through

medial areas, leaving open the question of whether the influence of medial areas on lateral areas is sufficient to account for the observed effect of reward/punishment on DLPFC.

If full mediation is found to be present, these finding appear to be inconsistent with the model of motivation proposed in the present paper. However, a closer examination of what Kouneiher et al. (2009) consider motivation vs. cognitive control indicates that no such inconsistency is present. Specifically, they conceptualize motivation as only the energization of behavior, whereas cognitive control refers to the selection of appropriate behaviors (i.e., the direction of behavior; see Kouneiher et al., 2009, supplementary Figure 1). In the present proposal, motivation is hypothesized to encompass both of these factors.

Support for the proposal that the hierarchical model of approach/avoidance motivation can be mapped onto an anterior/posterior gradient of SLPFC can also be found in a recent study investigating the effect of forming implementation intentions on neural activation associated with goal pursuit (Gilbert et al., 2009). The task contained two conditions, which differed only in whether implementation intentions were externally provided to participants by experimenters. Given that the formation of implementation intentions reduces the need for active engagement of the strategic level (discussed above), and given that the conditions were of equal difficulty and potential monetary reward level, the conditions differed only on the extent to which the strategic level was actively engaged during the task. Consistent with the present proposal, engagement of the strategic level (i.e., when participants were not provided with implementations intentions) was positively associated with activation in two areas of left anterior SLPFC (BA's 8 & 10). When participants were provided with implementation intentions, the only area of SLFPC exhibiting differential activation was left premotor cortex (BA 6).

Orbitofrontal Cortex. In addition to SLPFC, several other areas are likely to be important components of a model of motivation in the brain. As discussed above, PCC appears to play an important role in anticipatory processes. Another potential region is orbitofrontal cortex (OFC), which has been linked to the maintenance of the current and expected motivational value of stimuli (O'Doherty & Dolan, 2006). This area likely provides information about stimulus value to superior areas such as DLPFC (Szatkowska et al., 2008). However, there is some question regarding the timescale of the value representations maintained in OFC (e.g., Roesch et al., 2007). Several studies suggest that the values maintained in OFC are relative to the individual's current state, rather than to potential future states involved in longer-term goals (e.g., Schoenbaum et al., 1998). Additionally, several studies indicate that OFC is associated with choosing smaller, earlier rewards in intertemporal choice paradigms (e.g., Bjork et al., 2009; Tanaka et al., 2004). Therefore, it may be that OFC is involved in value maintenance only for short-term goals. For longer-term goals, PCC may play a similar function by integrating motivationally salient information into memory that is recalled during anticipation.

Research indicates that, like SLPFC, OFC may be organized along a gradient of abstraction. Specifically, a recent meta-analysis indicates that posterior OFC is more closely associated with primary reinforcers (e.g., sweet taste), whereas anterior OFC is more closely associated with abstract reinforcers (e.g., money; Kringelbach & Rolls, 2004). Additionally, O'Doherty and Dolan (2006) have suggested that anterior, medial OFC is associated with maintaining a common neural currency, allowing the values of different types of reinforcers to be compared.

A medial vs. lateral distinction in OFC has been proposed by O'Doherty (for review see O'Doherty, 2007). Specifically, medial OFC is thought to represent the value of rewards,

whereas lateral OFC is thought to represent the value of punishments. However, there appears to be some disagreement regarding the role of lateral OFC. Specifically, Elliott et al. (2000) suggested that lateral OFC is activated when previously rewarded behavior must be inhibited, rather than representing the value of punishments per se. Kringelbach and Rolls (2004) incorporated both views and suggested that lateral OFC represents the value of punishments and signals that behavior should change.

This organization of OFC conflicts with the proposal that left PFC is associated with pleasant valence and approach motivation and right PFC with unpleasant valence and avoidance motivation (Heller, 1993; Davidson & Irwin, 1999). However, a recent meta-analysis suggests that OFC is lateralized with respect to emotional valence, although not in the predicted direction (Wager et al., 2008). Specifically, bilateral medial and right lateral OFC was associated with pleasant emotional experience, whereas left middle and lateral OFC was associated with unpleasant emotional experience. The association between bilateral, medial OFC and pleasant valence is consistent with O'Doherty's (2007) proposal. However, the findings of this meta-analysis raise questions regarding the role of lateral OFC that should be pursued in future research.

Anterior Cingulate Cortex. Anterior cingulate cortex (ACC) is likely to be another important component of a model of motivation. One relatively new theory of ACC function is that ACC is involved in encoding the predicted value associated with actions (for a review see Rushworth & Behrens, 2008). This includes the immediate reward or punishment value, as well as the value of potential information about future events prompted by the action. Additionally, ACC is hypothesized to influence the degree to which information gained from current actions influences future decisions (Rushworth & Behrens, 2008). Information represented in ACC is

needed to efficiently create action plans to pursue goals, suggesting that ACC provides this information to SLPFC, including DLPFC. In relation to the hierarchical model of motivation, information held in ACC will be particularly relevant at the strategic and tactical levels. An important consideration is to determine the regions of ACC that provide this information, given that several parcellations of ACC have been proposed. One influential parcellation (Bush et al., 2000; Mohanty et al., 2007) divided ACC into two sections; dorsal ACC was hypothesized to be more involved in putatively cognitive tasks such as error processing, whereas rostral ACC was hypothesized to be more involved in putatively emotional tasks. A more recent parcellation employed both diffusion tractography, which estimates the degree of white matter connectivity with other brain regions, and a meta-analysis of fMRI studies (Beckmann et al., 2009). This analysis identified a region (roughly corresponding to the dorsal ACC region identified by Bush et al. [2000] but extending around the genu of the corpus callosum into rostral ACC) that was heavily connected to DLPFC and surrounding cortex and was reliably activated by reward manipulations. Given that this ACC region displays both motivation-related activation and connectivity to DLPFC, it is likely that this region provides motivational information regarding actions to DLPFC.

The Proposed Model

The model proposed here (illustrated in Figure 2.3) posits that the system, strategic, and tactical levels of the hierarchical model of approach/avoidance motivation are instantiated along an anterior to posterior gradient of SLPFC (including DLFPC). Further, the present review suggests that OFC and ACC provide information about stimulus and action value, respectively, to these areas. Lastly, PCC is involved in integrating motivationally salient information into the anticipation of potential future outcomes.

As an example of how the model may work with a specific goal, an individual may have the approach goal of losing weight in order to feel attractive, which would be maintained in anterior, left SLPFC (e.g., BA 10, anterior DLPFC). In order to pursue this goal, an area of left SLPFC posterior to this (e.g., posterior DLPFC) would be involved in the selection of an approach strategy and would engage ACC in order to obtain information regarding the potential value of different strategies. In this example, two approach strategies could be exercising regularly and eating healthy foods. The healthy eating strategy could be low value/high cost if the individual frequently encounters high calorie food and has not been successful in the past in losing weight by eating healthily. In contrast, the exercise strategy could be high value/low cost if the individual has easy access to exercise equipment and has been successful in losing weight with exercise in the past, and this would likely be the strategy chosen. Anterior cingulate would also be engaged by a more posterior region of left SLPFC (e.g., pre-SMA) in order to determine the value of different approach tactics when judging which tactic to employ. For example, if the strategy were to exercise, an approach tactic could be going to the gym to participate in an exercise class or calling a friend to jog with. If the individual is embarrassed about showing their fitness level in front of strangers, the gym class tactic could be low value/high cost, whereas the tactic of jogging with a friend could be high value/low cost if the friend is sympathetic because they are also out of shape and attempting to lose weight, and this would likely be the tactic chosen. Finally, when faced with a conflicting goal, for example to enjoy a sugary dessert, anterior SLPFC would engage PCC in anticipatory imagery of the future state of being thin, whereas OFC would be involved in representing the value of the dessert relative to the current state.

Although the brain areas currently integrated into the model are proposed to be fundamental to the pursuit of goals, they are almost certainly not the only brain areas involved. Other brain regions are likely involved in instantiating fundamental components of motivation and are not yet incorporated in the present model. In addition, specific situations will necessitate the engagement of brain areas that instantiate processes more specific to the demands of that situation. For example, although engagement of Broca's area is not necessarily fundamental to goal pursuit generally, it may be vital in situations where verbal rehearsal is needed to complete the task.

The proposed model has a number of implications for future research. For example, the type of task manipulation used in a study (i.e., approach vs. avoidance) should be carefully considered, because this information should guide hypotheses about what hemisphere is primarily involved. If a task manipulation could be both approach- and avoidance-related (e.g., across participants), the power of the experiment may be diluted, because some participants primarily engage left SLPFC, whereas others engage right. Another implication is that when conducting research aimed at understanding goal-pursuit or control processes in the brain, researchers should be aware of the motivational level(s) (e.g., system vs. tactical) manipulated by their task and examine specific areas of SLPFC (e.g., anterior DLPFC vs. pre-SMA) accordingly. If a task manipulation engages different levels at different times, and this is not accounted for in the analysis strategy, power may also be reduced, because SLPFC regions will not be consistently activated during the manipulation. Alternatively, if a task manipulation simultaneously engages multiple levels, specificity regarding regions of SLPFC involved may be lost. Another consideration implicated by the present model is the time frame at which goal

manipulations operate (e.g., relative to a current or future state) which should be examined to determine whether value information is likely to be represented in OFC and/or PCC.

Most importantly, the present paper provides a framework which can inform research in a number of fields. For example, the present model can be used to generate novel hypotheses for psychological research on goal-pursuit processes based on what is known about the brain regions involved in implementing those processes. Additionally, the present paper presents a more spatially specific model of the areas of PFC involved in instantiating motivational processes than is currently extant in the laterality literature, and the present model can be used to make hypotheses more spatially specific. For example, the model can guide the placement of sources in EEG source localization research, which can assist in disentangling activity related to multiple, simultaneously occurring goal-pursuit processes associated with different brain areas in the model. Finally, the present model can improve the utility of neuroscience research on goal-pursuit and control process by providing a framework, incorporating a rich psychological conceptualization of approach/avoidance motivation, in which to place this research.

Reflected in the present model is an attempt to draw on nuanced conceptualizations of approach/avoidance motivation (i.e., Elliot, 2006; Scholer & Higgins, 2008) to provide a more specific (both spatially and in regard to the specific processes involved) model of how motivation is instantiated in the brain. This model benefits from being informed by several, often disconnected, literatures, including psychological research on the structure of approach/avoidance motivation and neuroscience research on approach/avoidance motivation, goal pursuit, and motivation more generally.

		System level	
		Approach goal (desired outcome)	Avoidance goal (undesired outcome)
Strategic level	Approach strategy	Approach matches to desired outcome	Approach mismatches to undesired outcome
	Avoidance strategy	Avoid mismatches to desired outcome	Avoid matches to undesired outcome

Figure 2.1. Relationship between the system and strategic levels of the hierarchical model of motivation. Figure adapted from Higgins, Roney, Crowe, & Hymes (1994).

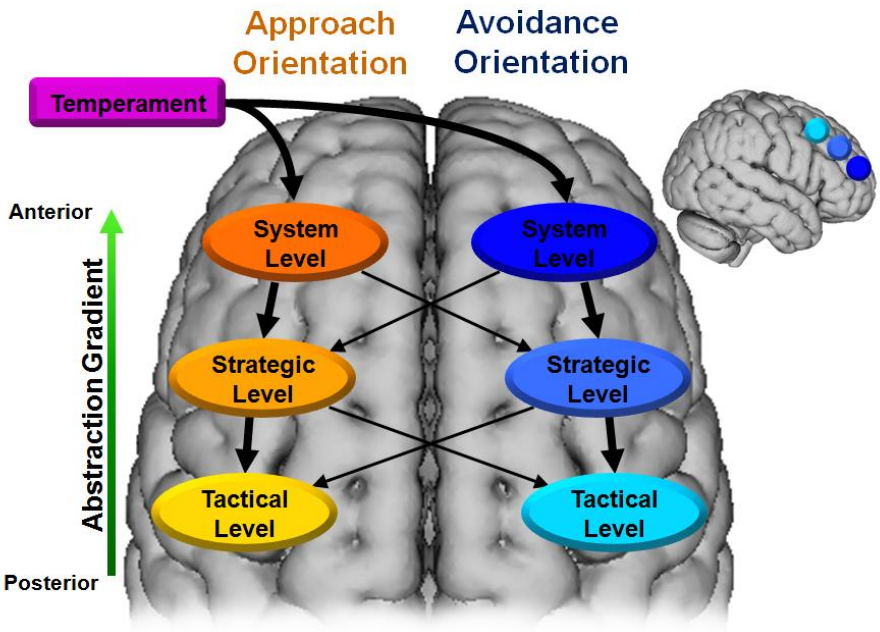

Figure 2.2. Lateralized organization of superior, lateral prefrontal cortex with regard to the hierarchical model of motivation. The thickness of the arrows corresponds to the hypothesized strength of the relationship. The larger brain is an axial view of the superior surface of the brain viewed from above. The smaller brain is a sagittal view of the lateral surface of the right hemisphere. The location and coverage of the ovals/circles is meant to represent a relative placement of areas rather than a delineation of specific cortex.

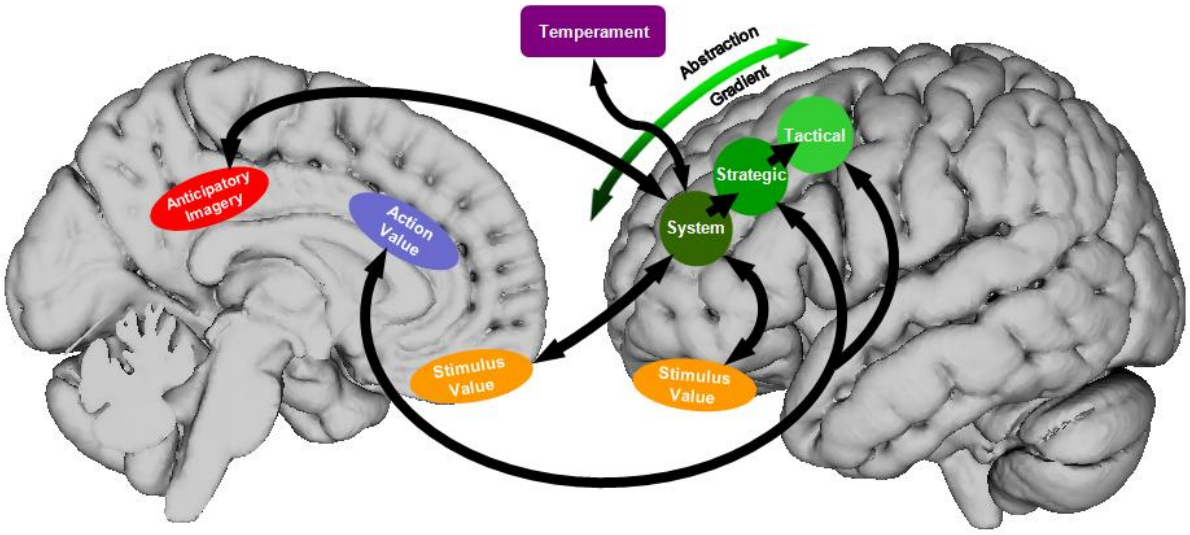

Figure 2.3. Motivational organization of superior, lateral prefrontal cortex and relationship with other brain areas in the model. Red oval = Posterior Cingulate Cortex. Blue oval = Anterior Cingulate Cortex. Orange ovals = Orbitofrontal Cortex. Green circles = Superior, Lateral Prefrontal Cortex. Only left hemisphere is shown, right hemisphere is similarly organized. The location and coverage of the circles/ovals is meant to represent a relative placement of areas rather than a delineation of specific cortex.

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CHAPTER 3

TRAIT MOTIVATION MODERATES NEURAL ACTIVATION ASSOCIATED WITH GOAL PURSUIT

Abstract

Research indicates that regions of left and right dorsolateral prefrontal cortex (DLPFC) are involved in integrating motivational and executive function processes related to approach and avoidance goals, respectively. Given that sensitivity to pleasant and unpleasant stimuli is an important feature of conceptualizations of approach and avoidance motivation, respectively, it is possible that these regions of DLPFC are preferentially activated by valenced stimuli. The present study tested this hypothesis using a task in which goal pursuit was threatened by distraction from valenced stimuli while functional magnetic resonance imaging data was collected. Analyses examined whether the impact of trait approach and avoidance motivation on neural processes associated with executive function differed depending on the valence or arousal level of the distractor stimuli. Present findings did not find differential sensitivity to valence in the areas of DLPFC under investigation, although a region directly posterior to DLPFC did differentiate valence. Present findings support the hypothesis that the regions of DLPFC under investigation are involved in integrating motivational and executive function processes and indicate the involvement of a number of other brain areas in maintaining goal pursuit.

Trait Motivation Moderates Neural Activation Associated with Goal Pursuit in the Face of Emotional Distraction

Motivation is fundamental to the pursuit of goals, as it is involved in selecting goals based on their predicted value (e.g., reward or punishment value), initiating behavior to achieve goals, and maintaining goal-directed action (e.g., Campbell & Pritchard, 1976; Jones, 1955; Lindsley, 1957). A number of theorists have proposed the existence of two fundamental motivational systems, one oriented toward potentially desirable outcomes, termed the approach motivational system, and one oriented toward potentially aversive outcomes, termed the avoidance motivational system (for reviews see Elliot & Covington, 2001; Lang, Bradley, & Cuthbert, 1998). These motivational systems are hypothesized to form the "basic building blocks that underlie the complexity of human behavior" (Carver, Sutton, & Scheier, 2000, p. 741), because they are central to attaining the goals necessary for survival.

Approach and avoidance motivation are thought to be instantiated in neurobiological systems that are sensitive to the positive/desirable or negative/undesirable properties of stimuli, respectively (Elliot & Thrash, 2002). These systems are theorized to influence attention to and emotional processing of the rewarding and punishing features of stimuli as well as behavioral responses to motivationally-relevant stimuli (Elliot & Thrash, 2002). Individual differences in the activity and/or reactivity of these approach and avoidance motivational systems are conceptualized as temperament types (Clark, Watson, & Mineka, 1994; Elliot & Thrash, 2002), based on research indicating they are heritable, present early in life, and stable over the lifespan (Buss & Plomin, 1984). Further, approach and avoidance temperament types are hypothesized to influence the development of other personality dimensions, such as extraversion and positive

emotionality in relation to approach temperament, and neuroticism and negative emotionality in relation to avoidance temperament (Elliot & Thrash, 2002).

Another set of processes hypothesized to be necessary for the pursuit of goals are those related to executive function, which are conceptualized as processes involved in the execution of goal-directed action (Banich, 2009). One prominent model proposed by Miyake and colleagues (Miyake et al., 2000) separates executive function into three processes: (a) shifting between mental sets, (b) updating working memory representations, and (c) inhibition of preponent responses. Although both sets of processes are thought to be essential to the pursuit of goals, the manner in which they interact is still a matter of debate (Pessoa, 2009).

Integration of Motivation and Executive Function in Dorsolateral Prefrontal Cortex

Consistent with conceptualizations of prefrontal cortex (PFC) as being necessary "to orchestrate thought and action in accordance with internal goals" (Miller & Cohen, 2001), recent research has implicated dorsolateral prefrontal cortex (DLPFC) and surrounding areas as being involved in the integration of motivation and executive function processes (e.g., Lee & Wang, 2009; Spielberg, Miller, et al., 2011). For example, research has found that DLPFC activation increases as both working memory demands and reward levels increase (Pochon et al., 2002), and research suggests that the interaction of state motivational processes and working memory load is instantiated in bilateral DLPFC (Taylor et al., 2004).

Inconsistencies have emerged in this research regarding the role of hemispheric lateralization in the relationship of DLPFC and motivational processes, with at least one study reporting activation selectively in left DLPFC (Pochon et al., 2002) and others reporting bilateral DLPFC activation (e.g., Taylor et al., 2004). A long line of research that suggests that PFC is lateralized with respect to motivational/emotional valence, with right PFC associated with

avoidance motivation and unpleasant emotion, and left PFC associated with approach motivation and pleasant emotion (for reviews see Heller, 1993; Davidson & Irwin, 1999). Thus, differences in the motivational manipulation(s) used across studies (reward versus punishment) could account for discrepancies regarding hemispheric lateralization in the literature. Another relevant factor not examined in these studies is the influence of individual differences in motivational temperament on the lateralization of DLPFC activation during executive function tasks. To address these questions, Spielberg, Miller, et al. (2011) investigated moderation of neural activation associated with incongruent versus congruent words on the color-word Stroop (1935) task by approach and avoidance temperament. Consistent with previous research on the integration of state motivation and executive function processes (Taylor et al., 2004), approach temperament moderated activation in two regions of left DLPFC, whereas avoidance temperament moderated activation in one region of right DLPFC, all of which were lateralized effects. Avoidance temperament also unexpectedly moderated activation in a region of left DLPFC, overlapping one of the areas associated with approach, suggesting that research on laterality, which often examines only hemispheric difference scores, has been overlooking important bilateral contributions to motivational processes.

The regions of DLPFC identified in Spielberg, Miller, et al. (2011) have been associated with a number of other functions. Specifically, these regions have been implicated in behavioral inhibition, planning upcoming action, attending to cues predicting the occurrence of a motivationally salient event, and responding when motivationally salient events occur (Abler, Walter, Erk, Kammerer, & Spitzer, 2006; Bickel, Pitcock, Yi, & Angtuaco, 2009; Kaladjian et al., 2009; Volle et al., 2005). Incorporating this research with their findings, Spielberg, Miller, et al. hypothesized that these regions of DLPFC are involved in implementing a motivational set

that biases lower-order processing (i.e., attention to ink color vs. word meaning) to be congruent with goals. Thus, DLPFC appears to play a central role in the pursuit of goals.

Brain Areas Involved in Other Aspects of Goal Pursuit

Orbitofrontal Cortex

In addition to DLPFC, a number of other brain areas have been implicated in the instantiation of processes important for the pursuit of goals. Orbitofrontal cortex (OFC) has been linked to the maintenance of the current and expected motivational value of stimuli (O'Doherty & Dolan, 2006) and likely provides information about stimulus value to superior areas such as DLPFC (Szatkowska, Bogorodzki, Wolak, Marchewka, & Szeszkowski, 2008). O'Doherty (2007) proposed a medial vs. lateral distinction in OFC, with the medial and lateral areas representing the value of rewards and punishments, respectively. However, there is disagreement in the literature regarding the role of lateral OFC in motivation. Elliott, Dolan, and Frith (2000) suggested that lateral OFC is activated when previously rewarded behavior must be inhibited, rather than representing the value of punishments, per se. Kringelbach and Rolls (2004) incorporated both views and suggested that lateral OFC represents the value of punishments and signals that behavior should change.

This organization of OFC conflicts with the proposal that left PFC is associated with approach motivation and pleasant valence and right PFC with avoidance motivation and unpleasant valence (Heller, 1993; Davidson & Irwin, 1999). A recent meta-analysis suggests that OFC is lateralized with respect to emotional valence, although not in the predicted direction (Wager et al., 2008). Bilateral/medial and right/lateral OFC was associated with pleasant emotional experience, whereas left middle and lateral OFC was associated with unpleasant emotional experience. The association between bilateral, medial OFC and pleasant valence is

consistent with O'Doherty's (2007) proposal. In summary, although there appears to be some consistency in proposals of OFC organization regarding medial OFC, there is still debate regarding the role of lateral OFC.

Anterior Cingulate Cortex

Another area hypothesized to be important for goal pursuit is anterior cingulate cortex (ACC), which has been implicated in encoding the predicted values associated with actions (for a review see Rushworth & Behrens, 2008). This includes the immediate reward or punishment value, as well as the value of potential information about future events prompted by the action. Information represented in ACC is needed to efficiently create action plans to pursue goals, suggesting that ACC provides this information to DLPFC.

Several parcellations of ACC have been proposed. One influential parcellation (Bush, Luu, & Posner, 2000; for a direct test see Mohanty et al., 2007) divides ACC into two sections: dorsal ACC, hypothesized to be involved in putatively cognitive tasks such as error processing, and rostral ACC, hypothesized to be involved in putatively emotional tasks. A more recent study that employed diffusion tractography and meta-analysis techniques (Beckmann, Johansen-Berg, & Rushworth, 2009) identified a region (roughly corresponding to the dorsal ACC region identified by Bush et al. [2000] but extending around the genu of the corpus callosum into rostral ACC) that was heavily connected to DLPFC and surrounding cortex and was reliably activated by reward manipulations. Given that this ACC region displays both motivation-related activation and connectivity to DLPFC, it is likely that this region provides motivational information regarding actions to DLPFC. This suggests that the role of this portion of ACC in goal pursuit is to provide information to DLPFC regarding the value of potential actions which is then used to select the appropriate course of action from among the available options.

Amygdala

Although often discussed solely in the context of unpleasantly valenced emotions, particularly fear (Baxter & Murray, 2002), research has supported a role for the amygdala in pleasantly valenced emotions and reward learning as well (Baxter & Murray, 2002; Holland & Gallagher, 2004; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). In particular, research has implicated the amygdala as important for the identification of the motivational relevance of stimuli and the enhancement of feature processing in salient stimuli (Pessoa & Adolphs, 2010). Thus, these studies suggest that amygdala is differentially engaged by the salience of stimuli, independent of valence. In summary, the role of the amygdala in goal pursuit appears to be in biasing the processing of perceptual information such that salient information is given more weight.

Basal Ganglia

Basal ganglia (BG), a set of subcortical nuclei that includes striatum, globus pallidus, substantia nigra, and subthalamic nucleus, has been heavily implicated in a number of reward processes (Haber, 2009) and, to a lesser extent, punishment processes (e.g., Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Redgrave, Coizet, & Reynolds, 2010). For example, research finds nucleus accumbens is activated during anticipation of appetitive stimuli (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005). Additionally, striatum receives projections from a diverse set of areas involved in goal pursuit, including DLPFC, ACC, OFC, amygdala, and midbrain dopaminergic nuclei, and is thought to integrate information from processes in these areas (Haber, 2010).

The striatal targets of these cortical projections appear to be organized topographically (Haber, 2009). Specifically, moving from ventral to dorsal striatum, focal projections appear to

be organized in this order: ventral-medial PFC, OFC, dorsal ACC, DLPFC, pre-motor/motor cortex (Haber, 2009, 2010; Tremblay, Worbe, & Hollerman, 2009). These areas receiving focal projections appear to partially overlap, providing one method by which information conveyed by such afferents may be integrated (Haber, 2010). In addition to areas of focal projection from cortex, diffuse projections from each of these cortical areas are found throughout striatum, providing another method by which information conveyed by these afferents can be integrated (Haber, 2010). This integrated information can feed back through the output nodes of BG (i.e., substantia nigra and internal segment of globus pallidus) to influence processing in these cortical areas (Gerfen & Bolam, 2010).

Present Study

One important aspect of motivational processes not tested in Spielberg, Miller, et al. (2011) is the hypothesized differential sensitivity to the valence of stimuli associated with temperamental motivation (i.e., approach temperament associated with greater sensitivity to pleasant valence, avoidance temperament associated with greater sensitivity to unpleasant valence). Sensitivity to pleasant valence, for example, could lead to increased distraction from goals if the pleasantly valenced stimuli are salient and task-irrelevant. Therefore, rather than being solely related to enhanced goal pursuit, it is possible that greater levels of temperamental motivation may also lead to disrupted goal pursuit in the presence of motivationally salient, but task-irrelevant, distracters. Consequently, greater recruitment of brain areas associated with maintaining goals would be needed to compensate for this disruption. Thus, one aim of the present study was to test the hypothesis that approach and avoidance temperament are associated with increased sensitivity to pleasant and unpleasant stimuli (valence manipulation), respectively, and greater compensatory recruitment of brain regions to maintain goal pursuit.

Emotionally arousing stimuli, independent of the valence, are often salient for goals and, therefore, should attract attention. In a context where the arousing aspect of the stimuli is irrelevant, this would lead to distraction from the goal and subsequent engagement of brain regions involved in maintaining task performance. A second aim of the present study was to test the hypothesis that brain areas observed to be differentially moderated by motivation in the context of tasks without an explicit emotional manipulation would be similarly engaged to ignore emotionally arousing information (arousal manipulation), which would suggest that these areas are engaged in the integration of motivational and executive function processes regardless of the nature of the distraction that threatens to interrupt the goal.

To examine these hypotheses, the present study used fMRI to examine moderation of neural activation by trait approach and avoidance motivation in an emotion-word Stroop task (Williams, Mathews, & MacLeod, 1996). Unlike the color-word Stroop, the word meaning is distracting in the emotion-word Stroop, because it is emotionally valenced and arousing. The emotion-word Stroop task used in the present study included a valence manipulation (pleasant and unpleasant words) and an arousal manipulation (low and high arousal words).

Hypotheses

Based on existing research, approach temperament was hypothesized to be associated with greater distraction by pleasant words, and avoidance temperament was hypothesized to be associated with greater distraction by unpleasant words. Both approach and avoidance temperament were hypothesized to be associated with distraction by arousing words. The hypothesized effects of this distraction on brain activation are specified below.

DLPFC. Approach and avoidance temperament were both hypothesized to be associated with increased engagement of the DLPFC areas identified in Spielberg, Miller, et al. (2011) as a

compensatory strategy to maintain goal pursuit and ignore emotionally arousing words. Additionally, approach temperament was hypothesized to differentially moderate left DLPFC with respect to the valence of the distracters, such that greater approach temperament was associated with greater activation to pleasant distracters (relative to unpleasant). Similarly, avoidance temperament was hypothesized to be associated with greater activation to unpleasant distracters (relative to pleasant) in bilateral DLPFC.

OFC. Approach temperament was hypothesized be associated with greater activation to pleasant distracters in bilateral medial and right OFC, whereas avoidance temperament was hypothesized to be associated with greater activation to unpleasant distracters in left middle and lateral OFC, given research implicating these areas in the maintenance of appetitive and aversive value, respectively.

ACC. Approach and avoidance temperament were hypothesized to be associated with greater activation to pleasant and unpleasant distracters, respectively, in the ACC region that research suggests provide action-related value information to DLFPC.

Amygdala. As discussed above, research suggests that amygdala is differentially engaged by the salience of stimuli, independent of valence (Baxter & Murray, 2002). However, because approach temperament is thought to increase the salience of pleasant stimuli, it was hypothesized that amygdala activation to pleasant stimuli would increase as a function of approach temperament. Further, it was hypothesized that amygdala activation to unpleasant stimuli would increase as a function of avoidance temperament.

BG. Given its proposed role in integrating information from DLPFC, OFC, and ACC, BG was hypothesized to show a pattern of activation similar to that of the brain areas that project to it. Specifically, BG was hypothesized to show greater activation to pleasant distracters as a

function of approach temperament, greater activation to unpleasant distracters as a function of avoidance temperament, and greater activation to emotionally arousing distracters as a function of both temperament types.

Method

Participants

Participants were recruited from a larger pool of undergraduates, who completed a series of questionnaires as partial fulfillment of enrollment in an introductory psychology course. The questionnaires included the Penn State Worry Questionnaire (PSWQ, Meyer, Miller, Metzger, & Borkovec, 1990; Molina & Borkovec, 1994) as a measure of anxious apprehension and portions of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995), which contains measures of anxious arousal and anhedonic depression. Participants were contacted if they scored above the 80th percentile on one of the three psychopathology dimensions and below the 50th percentile on the other two dimensions (creating three "pure" groups), if they scored above the 80th percentile on all three psychopathology dimensions (creating a "comorbid" group), or below the 50th percentile on all three psychopathology dimensions (creating a "control" group). Group membership was ignored in data analyses for the present study except when testing whether group membership was a confounding effect[1]. Participants were then screened for claustrophobia, left-handedness, history of serious brain injury, abnormal hearing or vision, metal in their body, pregnancy, or non-native English.

[1] For all fMRI analyses performed, a second analysis was conducted with psychopathology group entered as a between-subject factor. These analyses tested whether the relationship between temperament score and brain activation (and hemisphere in the laterality analysis) differed by psychopathology group. No findings differed by psychopathology group, indicating that the results of the present study are not driven by sample selection. It can also be noted that this sampling strategy covers all but about 1 SD of the range of scales.

A total of 107 participants completed the laboratory protocol. Participants were not used if (a) they moved more than 3.3 mm relative to the volume used for registration (the middle volume of the time series) or more than 2 mm relative to the previous volume (one participant exceeded this criterion only during the last block of words; therefore, this block was not used), (b) if they committed errors on 15% or more of the trials, (c) if they exhibited reaction times greater than 3 standard deviations from the mean, (d) if their scans exhibited apparent signal loss due to magnetic susceptibility in areas of interest, or (e) if their scans exhibited activation patterns that appeared to be due to residual motion-related variance. This left 80 participants (47 female, mean age = 19). Seventy-six of the participants in the present sample overlapped with the sample used in Spielberg, Miller, et al. (2011). One participant's scans exhibited scanner artifact throughout the time series. Independent components analysis, as implemented in MELODIC (Beckmann & Smith, 2004), was used to isolate and remove this artifact. After removal, no artifact was apparent.

Questionnaires

To measure Approach and Avoidance Temperament, three questionnaires were administered that have been previously associated with these constructs (Elliot & Thrash, 2002): the Behavioral Inhibition and Behavioral Activation Scales (Carver & White, 1994), the Neuroticism and Extraversion sub-scales of the NEO-Five Factor Inventory (Costa & McRae, 1992), and the Negative and Positive Temperament sub-scales of the General Temperament Survey (Watson & Clark, 1993). These scales were used as indicators in confirmatory factor analysis using AMOS. Based on previous research (Elliot & Thrash, 2002; Spielberg, Heller, et al., 2011; Spielberg, Miller, et al., 2011), two latent factors were modeled, with Behavioral Activation, Extraversion, and Positive Temperament used as indicators for approach

temperament, and Behavioral Inhibition, Neuroticism, and Negative Temperament used as indicators for avoidance temperament. Maximum likelihood estimation was used, and the two latent factors were allowed to co-vary freely. Factor scores were extracted with the regression method to use as measures of approach and avoidance temperament.

Stimuli and experimental design

Participants completed two tasks, an emotion-word Stroop and a color-word Stroop (findings from the latter are presented in Spielberg, Miller, et al., 2011). The order of presentation of the two tasks was counterbalanced across participants. In the emotion-word Stroop task, 256 trials were presented in 16 blocks (four pleasant, four unpleasant, and eight neutral) of 16 trials each, with a variable ITI (2000 +/- 225 ms) between trial onsets. A trial began with presentation of a word for 1500 ms, followed by a fixation cross for an average of 500 ms. Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue), each color occurring equally often with each word type. Blocks of pleasant or unpleasant words alternated with blocks of neutral words. The order of presentation of blocks in the present investigation was counterbalanced for each participant. 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.

The 256 word stimuli were selected from the Affective Norms for English Words set (Bradley & Lang, 1998). Sixty-four were pleasant (e.g., birthday, ecstasy, laughter), 64 were unpleasant (e.g., suicide, war, victim), and two sets of 64 were neutral (e.g., hydrant, moment, carpet). The words were carefully selected on the basis of established norms for valence, arousal,

frequency of usage in the English language (Bradley & Lang, 1998), and number of letters. Words ranged from three to eight letters (visual angle 6 – 16 degrees). Each word was centered on a black background and projected. Participants responded with their index and middle fingers using a four-button response box (James Long Company) under each hand.

fMRI data collection

The fMRI data were 370 three-dimensional (3D) images acquired using a Siemens gradient-echo echo-planar imaging sequence (TR 2000 ms, TE 25 ms, flip angle 80°, FOV = 220 cm) on a Siemens Allegra 3T scanner. Each image consisted of 38 oblique axial slices (slice thickness 3 mm, 0.3mm gap, in-plane resolution 3.4375 mm X 3.4375 mm) acquired parallel to the anterior and posterior commissures. After the fMRI acquisition, a 160-slice MPRAGE structural sequence was acquired (spatial resolution 1 mm X 1 mm X 1 mm) and used to warp the participant's functional data into standard space.

fMRI data reduction and preprocessing

Image processing and statistical analysis were implemented primarily using FMRI Expert Analysis Tool v5.98 (FEAT, www.fmrib.ox.ac.uk/analysis/research/feat/), part of the FSL analysis package (www.fmrib.ox.ac.uk/fsl). The first three time points (fMRI volumes) of the data set corresponding for each subject will be discarded to allow the MR signal to reach a steady state. Functional data for each participant were motion-corrected using rigid-body registration, implemented in FSL's linear registration tool, MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Data were intensity-normalized, such that the mean intensity (across time and across voxels in the brain) was constrained to be equal across participants. Next, data were temporally filtered with a nonlinear high-pass filter that attenuates frequencies below 1/212 Hz. and spatially smoothed using a 3D Gaussian kernel (FWHM = 5 mm). Temporal low-pass

filtering was carried out using AFNI's 3dDespike tool (http://afni.nimh.nih.gov/) to remove intensity spikes.

fMRI data processing

Regression analyses were performed on the processed functional time series of each participant using FMRIB's Improved Linear Model (FILM) with autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Four predictors, one for each word type block (pleasant, neutral, unpleasant) and one modeling the rest condition, were included in the regression model (fixation was left unmodeled). For each predictor, the vector of assigned weights corresponding to word type was convolved with a gamma function to better approximate the temporal course of the blood-oxygen-dependent (BOLD) hemodynamic response function. Each predictor yielded a per-voxel effect-size parameter estimate (β) map representing the magnitude of activation associated with that predictor.

In order to create comparisons of interest, β values for the relevant parameters were contrasted. Two comparisons of interest were created. A valence comparison (VAL) was created by contrasting the pleasant condition with the unpleasant condition. An arousal comparison (ARO) was created by averaging the pleasant and unpleasant conditions and contrasting this average against the neutral condition. For each participant, these functional activation maps were non-linearly warped into a common stereotaxic space (the 2009 Montreal Neurological Institute [MNI] 152 symmetrical 1mm x 1mm x 1mm template; Fonov, Evans, McKinstry, Almli, & Collins, 2009) using FMRIB's Non-Linear Image Registration Tool (FNIRT; Andersson, Jenkinson, & Smith, 2007).

Group inferential statistical analyses were carried out using FMRIB's Local Analysis of Mixed Effects (FLAME). To examine the task main effects, a t-test of the mean across all

participants was conducted for VAL and ARO. To examine moderation by motivational temperaments, VAL and ARO were entered as dependent variables into second-level multiple regression analyses with approach and avoidance scores as predictor variables[2]. Each moderation-related regression analysis produced two β maps, one corresponding to the unique variance associated with approach temperament (with the shared variance associated with avoidance removed) and one corresponding to the unique variance associated with avoidance temperament (with the shared variance associated with avoidance removed). T-tests were conducted on the βs for approach and avoidance and then converted to z-scores to determine the significance of the βs. For the VAL contrast, 1-tailed t-tests based on a priori hypotheses (pleasant > unpleasant for approach, unpleasant > pleasant for avoidance) were used. For the ARO contrast, 2-tailed t-tests were used. Based on a priori hypotheses, several masks were used to constrain the number of voxels under consideration. These masks were of 1) bilateral frontal lobe gray-matter, in addition to the entire cingulate gyrus, 2) bilateral amygdala, 3) bilateral basal ganglia, and 4) ventral prefrontal gray-matter. Additionally, in order to examine the task main effects, a whole-brain gray-matter mask was used, because no a-priori hypotheses were made regarding these effects.

Monte Carlo simulations via AFNI's AlphaSim program were used to estimate the overall significance level (probability of a false detection) for thresholding the 3D functional z-

[2] fMRI analyses conducted using FEAT were rerun using FSL's outlier de-weighting (Woolrich, 2008) procedure to test whether findings were driven by outliers. Findings were virtually identical, indicating that findings were not due to outliers. Two additional analyses were conducted in order to rule out the potential confounding effects of structural differences that may correlate with approach or avoidance temperament. First, voxel-based morphometry analysis was performed with approach and avoidance temperament predicting gray-matter density. Approach and avoidance did not predict gray matter density in any of the areas in which approach and avoidance predicted fMRI activation. Second, approach and avoidance FEAT analyses were rerun with gray-matter density as a voxel-dependent covariate, thus removing any shared variance between temperament and gray-matter density. Approach and avoidance continued to significantly predict activation in all clusters.

map image (Ward, 2000). These simulations were conducted for several individual voxel z-threshold values, providing the appropriate cluster size giving an overall two-tailed family-wise error rate of 0.05. An individual voxel level threshold of $p = 0.04$ was used in combination with minimum cluster sizes of 1,560 mm^3 (frontal lobe), 351 mm^3 (amygdala), 585 mm^3 (basal ganglia), 897 mm^3 (ventral-prefrontal gray-matter), and 2,340 mm^3 (whole-brain gray-matter).

Lateralization was tested using a locally written Matlab program. This program conducted a repeated-measures homogeneity-of-slopes ANCOVA, with hemisphere as the repeated measure, approach and avoidance scores as continuous predictors, and fMRI activation as the dependent variable. This ANCOVA was conducted on a per-voxel basis, with the resultant β map thresholded in the manner described above. For lateralization analyses, the masks were described above were edited to contain only the right hemisphere, and an individual voxel level threshold a threshold of $p = 0.04$ was used in combination with minimum cluster sizes of 1,287 mm^3 (frontal lobe mask), 312 mm^3 (amygdala), 507 mm^3 (basal ganglia), and 741 mm^3 (ventral-prefrontal gray-matter). Additionally, because a priori hypotheses were made regarding lateralization in DLFPC, a mask of DLPFC gray matter (cluster size threshold = 741 mm^3) was used to test the laterality of DLPFC clusters.

Behavioral Analyses

Mean reaction time (RT) and error frequency were calculated for each condition, for each participant. To calculate the effect of task on RT, two orthogonal paired-sample t-tests were conducted, one in which pleasant was compared to unpleasant and one in which the average of pleasant and unpleasant was compared to neutral. Similar comparisons were used with related-samples Wilcoxon signed rank tests to calculate the effect of task on error rate. A VAL RT interference score was calculated by subtracting the unpleasant RT from the pleasant RT. A VAL

error rate difference score was similarly calculated. An ARO RT interference score was calculated by subtracting neutral RT from the average of pleasant and unpleasant RTs. An ARO error difference rate score was calculated by subtracting neutral error frequency from the sum of pleasant and unpleasant error frequencies (it was not necessary to calculate the mean of pleasant and unpleasant because the number of neutral trials was equal to the sum of the pleasant and unpleasant trials). RT interference and error rate difference score were entered as dependent variables in regression analyses (logistic regression was used with error difference scores) with approach and avoidance temperament entered simultaneously as predictors.

To assess the potential effect of neural activity related to motivational temperaments on behavioral performance, a score for each ROI identified in the earlier analysis in which approach temperament and avoidance temperament predicted fMRI activation (i.e., not the lateralization analysis in which hemisphere was a factor) was created by averaging β values across voxels in each ROI, for each participant. ROI scores were then correlated with RT interference and error rate difference scores. Spearman rank-order correlations were used for error analyses.

Results

Confirmatory Factor Analysis

The two-factor model of scales contributing to approach and avoidance scores was successfully estimated and was associated with a non-significant χ^2 value of 10.3 ($p = .25$, 8 degrees of freedom). The comparative fit index value (Bentler, 1990) was 0.993, and the root mean square error of approximation value (Brown & Cudeck, 1993) was 0.060, indicating that the model provided excellent fit to the data. All measurement weights were significant at $p < 0.001$, and the standardized estimates are provided in Table 1.

Behavioral Analysis

Paired-sample t-tests for RT did not reveal differences between emotion conditions (e.g., pleasant vs. unpleasant; $p < .05$). The related-samples Wilcoxon signed rank test revealed more errors in the high arousal blocks (mean = 6.8) than the neutral blocks (mean = 5.6, $p < .001$). Error rates in the pleasant and unpleasant blocks did not differ. Neither approach nor avoidance temperament predicted RT interference or differences in error rates.

Main Effects of Task

Table 2 lists brain regions where main effects of VAL and ARO were observed.

Valence-Related Activation Moderated by Temperament

Table 3 lists brain regions where activation related to VAL was moderated by trait approach or avoidance temperament. No areas emerged in which VAL activation was moderated by approach temperament. As illustrated in Figure 3.1, four clusters emerged in which VAL activation was moderated by avoidance temperament. In line with present hypotheses, greater levels of avoidance temperament were associated with a greater response to unpleasant distracters, relative to pleasant distracters, in right middle frontal gyrus/precentral gyrus, left putamen, and right amygdala. Additionally, greater levels of avoidance temperament were associated with a greater response to unpleasant distracters in medial precentral gyrus/paracentral lobule.

Arousal-Related Activation Moderated by Temperament

Table 4 lists brain regions where activation related to ARO was moderated by trait approach or avoidance temperament. In line with present hypotheses, activation to arousing distracters in left DLPFC and bilateral putamen increased as approach temperament increased, as illustrated in Figure 3.2. The area of left DLPFC identified in the present study overlapped both

areas found to be associated with approach temperament in Spielberg, Miller, et al. (2011). Unexpectedly, four additional clusters emerged in which activation to arousing distracters increased as a function of approach temperament. These included a cluster in genual ACC/paracingulate/left frontal pole, two clusters in posterior cingulate (one of which also included medial precentral gyrus), and one cluster in left anterior/middle OFC/frontal pole.

As illustrated in Figure 3.3, results for avoidance motivation were also consistent with hypotheses. Specifically, activation to arousing distracters in regions of right and left DLPFC, overlapping the areas identified in Spielberg, Miller, et al. (2011), increased as avoidance temperament increased. The left DLPFC cluster partially overlapped with the left DLPFC cluster associated with approach temperament by 732 mm^3 (34% of the approach cluster, 12% of the avoidance cluster). Also in line with present hypotheses, activation to arousing distracters in bilateral putamen and right nucleus accumbens/caudate increased as a function of avoidance temperament. Unexpectedly, activation to arousing distracters in two areas of right inferior frontal gyrus, one that extended superior into middle frontal gyrus and one that extended inferior into agranular OFC, increased as avoidance temperament increased. Additionally, activation to arousing distracters in a large cluster that included genual ACC, dACC, PCC, paracingulate, supplementary motor area, medial frontal pole, medial precentral gyrus, and right superior frontal gyrus increased as avoidance temperament increased.

Correlations between Brain Activation and Behavior

In order to explore the potential influence of the brain areas associated with motivation on successful behavioral performance, an average β for each cluster, for each participant, was calculated and correlated with RT interference and error rate difference. These correlations are presented in Table 4. Valence-related activation in the medial precentral gyrus/paracentral lobule

associated with avoidance exhibited a positive correlation with RT interference, indicating that increased activation to unpleasant distracters, relative to pleasant, was associated with greater RT to unpleasant, relative to pleasant.

Four clusters in which approach temperament moderated arousal-related activation exhibited positive correlations with RT interference, indicating that activation to emotionally arousing distracters in these areas was related to longer relative reaction times to arousing words. This included all three cingulate clusters and the left DLPFC cluster. No reliable associations emerged between approach-related clusters and error interference.

Six clusters in which avoidance temperament moderated arousal-related activation exhibited positive correlations with RT interference, indicating that activation to emotionally arousing distracters in these areas was related to longer relative reaction times to arousing words. These were both DLPFC clusters, both IFG clusters, the cluster that included ACC, and the nucleus accumbens/caudate cluster. Four of these clusters also exhibited positive correlations with error interference, indicating that arousal related activation in these areas was associated with more errors to arousing distracters.

Lateralization Analyses

Given work indicating that motivation influences laterality of activation in frontal regions, analyses were carried out to examine whether the activity in regions associated with each temperament type (approach, avoidance) were asymmetric across the hemispheres. As indicated in Table 3, the left putamen cluster was the only valence-related area to exhibit significant lateralization, with greater activation to unpleasant distracters in the left hemisphere. In line with present hypotheses, the left DLPFC area related to approach temperament exhibited significant lateralization, with greater activation to arousing distracters in the left hemisphere. As

indicated in Table 4, four areas in which arousal-related activation varied as a function of avoidance exhibited significant lateralization. In line with present hypotheses, this included the right DLPFC area, along with the right inferior and middle frontal gyrus cluster and the cluster located in the caudate head (the portion of this cluster located in nucleus accumbens was not lateralized).

Discussion

The findings of the present study partially supported the hypothesis that approach and avoidance are differentially sensitive to valence. Avoidance motivation was associated with greater activation to unpleasant distracters in several of the hypothesized brain areas, although sensitivity was not observed in behavioral performance. No areas exhibited greater activation to pleasant distracters as a function of approach temperament. The hypothesis that approach and avoidance temperament would both be associated with greater recruitment of brain areas involved in maintaining goal pursuit to compensate for distraction due to emotionally arousing distracters was supported. This increased recruitment was observed for both approach and avoidance in a number of areas, including DLPFC.

Dorsolateral Prefrontal Cortex

The present findings confirm the importance of DLPFC in integrating motivational and executive function processes. As hypothesized, approach temperament was associated with greater activation to arousing distracters in a region of left DLPFC that substantially overlapped the two clusters found to be associated with approach temperament in Spielberg, Miller, et al. (2011), and this effect was lateralized as predicted. Also in line with hypotheses, avoidance temperament was associated with greater activation to arousing distracters in regions of right and left DLPFC that substantially overlapped the two clusters found in Spielberg, Miller, et al. to be

associated with avoidance temperament. Again similar to the findings of Spielberg, Miller, et al., the right DLPFC effect was lateralized, whereas the left DLFPC effect was not. Consistent with Spielberg, Miller, et al., these findings indicate that motivational temperaments are associated with increased engagement of DLPFC to maintain goal pursuit.

One interpretation of these findings is that these DLPFC areas are recruited to compensate for the distraction induced by the arousing nature of the distracters. If this were the case, it would be plausible to expect activation in these areas to be associated with better performance (decreased RT interference). However, activation in all three DLPFC areas was associated with increased RT interference to arousing words. This finding calls into question the interpretation that DLFPC is involved in maintaining the goal (i.e., ignore word meaning) in the face of distraction. An alternative interpretation of the positive correlation between activation and RT interference is that greater distraction, reflected in increased RT interference, is associated with greater compensatory activation in DLPFC areas, but this compensation is not completely successful, and, as a result, the correlation remains positive. Future research should investigate whether the positive relationship between RT interference and DLFPC activation reflects compensatory recruitment.

Present hypotheses regarding moderation of valence-related activation in DLPFC by motivational temperaments were not supported. Specifically, approach temperament did not moderate activation to pleasant distracters in left DLPFC, and avoidance temperament did not moderate activation to unpleasant distracters in bilateral DLPFC. Additionally, approach and avoidance temperament did not moderate valence-related behavioral performance. Taken together with the DLPFC findings for arousal, these findings suggest that motivational temperaments are not differentially sensitive to stimuli valence, which conflicts with prominent

conceptualizations of these constructs (Elliot, 2006). However, this may be due to the fact that the valenced stimuli are task-irrelevant, and differential sensitivity to valence in DLPFC may be present when the valenced stimuli are the focus of goal-pursuit (e.g., approach temperament associated with increased sensitivity to appetitive goals).

Future research should examine whether activation in the regions of DLPFC observed in the present study differentially varies as a function of approach and avoidance temperament when the goal itself is valenced. For example, activation in left DLPFC may increase as a function of approach temperament when the goal is appetitive (e.g., monetary reward), but not when the goal is aversive. Additionally, distracter word meaning was not directly relevant to the goal being pursued (attending to ink color) in the present study. It is possible that differential sensitivity to valence associated with motivational temperaments would be observed in DLPFC if the distracters were directly relevant to the task at hand. For example, if the goal were to identify whether a face was expressing disgust, approach temperament may show increased reaction time to pleasant faces vs. unpleasant faces.

Although right DLPFC was not differentially sensitive to unpleasant valence as a function of avoidance temperament, a cluster located posterior to DLPFC in right MFG/precentral gyrus exhibited increased activation to unpleasant distracters as avoidance temperament increased. Therefore, it may be that integration of avoidance motivation and executive function processes also occurs in an area posterior to DLPFC, and the specific motivational processes involved are those more sensitive to distracter valence, such as biasing attention towards motivationally congruent stimuli. Support for this hypothesis comes from the finding that the superior portion of this cluster is located in what has been labeled the human frontal eye field (Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005), an area that has been

implicated in both top-down and bottom-up attentional processing (Corbetta, Patel, & Schulman, 2008; Dosenbach, et al., 2006).

Cingulate Cortex

Similar to the findings for DLPFC, several clusters emerged in which approach and avoidance temperament moderated activation related to arousal, rather than valence as hypothesized. First, approach and avoidance temperament were both associated with increased activation in cingulate. Approach moderated activation in genual anterior cingulate, in the anterior end of the cingulate area hypothesized to be related to maintaining the value of actions, as well as posterior cingulate (PCC). Avoidance moderated activation in a larger swath of cortex, including both areas moderated by approach and extending further both dorsally and rostrally from genual anterior cingulate.

Although not hypothesized, moderation of activation in PCC is consistent with research implicating this region as having an important role in goal pursuit. Specifically, research suggests that PCC is activated when individuals forgo proximal reward or incur proximal punishment in order to maximize reward over time (Ballard & Knutson, 2009; McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007; Weber & Huettel, 2008; Wittmann, Leland, & Paulus, 2007). Additionally, research by Maddock (1999) indicates that PCC is involved in integrating emotional and motivational aspects into memory during recall, which suggests a role for PCC in the anticipation of delayed rewards. This hypothesis is consistent with a recent theory that PCC, along with other areas such as genual ACC, are involved in using "past experiences adaptively to imagine perspectives and events beyond those that emerge from the immediate environment" (p. 49, Buckner & Carroll, 2007).

PCC involvement has also been found in studies directly examining approach and avoidance motivation. Specifically, PCC activation has been found to increase when participants self-reflected on both approach- and avoidance-related goals (Johnson et al., 2006). Additionally, dissociation in PCC activation with respect to motivationally relevant stimuli has been found in relation to approach and avoidance (Touryan et al., 2007). Specifically, when an approach orientation was induced, greater activation in PCC was observed during the evaluation of pleasant stimuli (relative to unpleasant stimuli). In contrast, when an avoidance orientation was induced, greater activation in PCC was observed during the evaluation of unpleasant stimuli. This finding appears, at first, to conflict with the finding in the present study that motivational temperaments moderated arousal-, rather than valence-, related PCC activation. However, the valenced stimuli were goal-irrelevant in the present study, whereas, in Touryan et al. (2007), the valenced stimuli were directly relevant to the goal. As discussed above in relation to DLPFC, differential responses may be present only when the valenced stimuli are goal-relevant, a question for future research.

Orbitofrontal Cortex

Similar to the findings for DLPFC and ACC, approach and avoidance temperament moderated arousal-related activation in OFC, rather than valence-related activation as hypothesized. One interpretation of this discrepancy is that the stimulus value, with respect to the goal of the task used in the present study, was not dependent on the particular valence of the word. Rather, it was the arousing nature of the stimuli that was distracting, as evidenced by an increased error rate for high arousal distracters, and the value of these stimuli as impediments to the goal varied as a function of the arousal level. If this is true, activation in OFC in the present study should reflect the arousal level of the stimulus, because stimulus value is thought to be

maintained in OFC (O'Doherty, 2007). In contrast, stimulus value (and OFC activation) would be more likely to reflect the valence of the stimulus in a task with valenced target stimuli.

The location of the OFC activation moderated by motivational temperaments in the present study was opposite to that hypothesized and was, in fact, consistent with DLFPC lateralization. Specifically, approach moderated activation in left anterior, middle OFC, and avoidance moderated activation in right, agranular OFC. However, neither of these effects was significantly lateralized, and, when the overall cluster threshold was lowered to $p < 0.10$, avoidance significantly moderated activation in left agranular OFC as well. The findings for avoidance temperament are consistent with the OFC parcellation proposed by O'Doherty (O'Doherty 2007), in which punishment-related stimuli are hypothesized to be associated with lateral OFC.

Amygdala

As hypothesized, amygdala activation to unpleasant distracters increased as a function of avoidance temperament. Given research indicating that amygdala is involved in identifying the motivational relevance of stimuli (Pessoa & Adolphs, 2010), this finding suggests that avoidance temperament is associated with the assessment of unpleasant stimuli as being more salient than pleasant stimuli. The present hypothesis that amygdala activation to pleasant distracters would increase as a function of approach temperament was not supported. Taken together, these two findings are consistent with research indicating that, when valenced stimuli are task-irrelevant, amygdala responses are greater to unpleasantly valenced than pleasantly valenced, stimuli (Straube, Pohlack, Mentzel, & Miltner, 2008).

Basal Ganglia

The hypothesis that arousal-related basal ganglia activation would increase as a function of approach and avoidance temperament was supported in bilateral putamen for both approach and avoidance and the head of the caudate for avoidance temperament. The putamen clusters observed for both approach and avoidance are located in an area of putamen that receives projections from pre-motor cortex (Haber, 2010) and is thought to be involved in action preparation (Tremblay, et al., 2009). Therefore, moderation of activation in this area of putamen may reflect the influence of motivation on action preparation. Research suggests that the area of caudate found in the present study receives projections from DLPFC, ACC, and OFC and is involved in integrating information from these areas (Haber, 2010). This caudate region projects back to cortex through connections with globus pallidus and substantia nigra (Gerfen & Bolam, 2010), providing a route by which integrated information from DLPFC, ACC, and OFC can influence ongoing processing in these cortical areas.

Present hypotheses regarding basal ganglia and valence-related activation were partially supported. Specifically, activation to unpleasant distracters in left putamen increased as a function of avoidance temperament. This cluster partially overlapped the left putamen cluster in which arousal-related activation was moderated by avoidance and is within the region of putamen that receives projections from pre-motor cortex (Haber, 2010) and is implicated in action preparation (Tremblay, et al., 2009). This suggests that avoidance motivational information differentially influences the preparation of actions related to unpleasant stimuli. The hypothesis that activation in basal ganglia to pleasant distracters would increase as a function of approach temperament was not supported. However, this hypothesis was based on the proposal that approach temperament would moderate activation to pleasant distracters in cortical areas,

particularly DLPFC, which was not found. Therefore, the broad hypothesis that BG would show a similar pattern of activation as the brain areas that project to it was supported.

Right Inferior and Middle Frontal Gyri

Unexpectedly, arousal-related activation in right inferior frontal gyrus/middle frontal gyrus increased as a function of avoidance temperament, and this effect was lateralized. Although unexpected, this finding is consistent with research implicating this area in the detection of cues that indicate a response should be inhibited (Aron, 2010), and the detection of salient, unexpected stimuli (Corbetta, et al., 2008). This is consistent with both the task used in the present study, which involves inhibiting distraction related to the arousing nature of the words, and conceptualizations of avoidance motivation, which include increased vigilance for potential threat and for information indicating that the goal-pursuit strategy is incorrect (Elliot & Thrash, 2002).

Strengths and Limitations

The present study benefited from direct tests of laterality, the use of a relatively large sample size for the fMRI literature, and careful measurement of approach and avoidance temperament by estimation of latent factors from multiple indices. It extends the literature on the neural integration of approach and avoidance motivation and executive function processes by examining this integration in the context of emotionally valenced and arousing distraction. As with any study, however, there are several limitations that must be considered when interpreting the results. First, the present study used only self-report measures of approach and avoidance temperament. Future research would benefit from additional behavioral performance measures, such as differential detection of cues indicating monetary reward and punishment (e.g., Henriques, Glowacki, & Davidson, 1994). Second, motivational stimuli (e.g., monetary

reward/punishment) were not central to the goal of the present task. Future research should examine the interaction of state and trait motivation and how these processes are integrated with executive function processes to accomplish goals. Third, all potentially relevant aspects of executive function were not recruited by the task used in the present study. Future research could extend the present findings by examining how processes related to other aspects of executive function, such as shifting and updating (Miyake et al., 2000), are integrated with motivational processes.

In spite of these limitations, the present study adds to the literature by supporting the proposed role for DLPFC in the integration of motivational and executive function processes and implicating a network of other brain areas as being involved in maintaining goal pursuit, including OFC, ACC, PCC, and basal ganglia. Additionally, present findings suggest that approach temperament is not associated with differential sensitivity to pleasant stimuli when those stimuli are goal-irrelevant. Future research should determine whether differential sensitivity for pleasant stimuli is present when the valenced stimuli are either central to or highly related to the goal being pursued. Results from the present study do indicate that avoidance temperament is associated with a differential sensitivity to unpleasant stimuli, given the finding that valence-related activation in amygdala, right IFG, and right MFG varied as a function of avoidance temperament.

Table 1

Self-Report Indicators for Approach and Avoidance Temperament.

Indicator Variable	Standardized Coefficient Value
Approach Temperament	
BAS	0.75
NEO-FFI Extraversion	0.96
GTS Positive Temperament	0.79
Avoidance Temperament	
BIS	0.80
NEO-FFI Neuroticism	0.98
GTS Negative Temperament	0.89

Note. BAS = Behavioral Activation Scale (Carver & White, 1994). NEO-FFI = NEO-Five Factor Inventory (Costa & McRae, 1992). GTS = General Temperament Survey (Watson & Clark, 1993). BIS = Behavioral Inhibition Scale (Carver & White, 1994).

Table 2

Main Effects of Task

Region	Cluster Size (mm^3)	Direction of Relationship	Mean z-value	Location		
				X	Y	Z
Valence						
L STG/IFG/OFC (BA 11/38/47)	3,571	Positive	2.46	-48	16	-25
M OFC/frontal pole/rACC/paracingulate (BA 6/8/9/10/11/24/25/32)	24,959	Positive	2.59	-3	55	11
L thalamus	2,671	Positive	2.35	-7	-4	1
M PCC/cuneus (BA 18/23/30/31)	3,732	Positive	2.40	-9	-42	6
R precentral gyrus/postcentral gyrus/IPL (BA 3/4/40)	3,079	Negative	-2.50	42	-24	56
Arousal						
L STG/MTG/IFG/ITG/OFC/MFG/insula/fusiform gyrus/precentral gyrus/supramarginal gyrus/angular gyrus/precuneus (BA 6/7/8/9/11/13/19/20/21/22/37/38/39/44/45/46/47)	60,027	Positive	3.29	-47	28	-7
R STG/MTG (BA 21/38)	3,458	Positive	2.42	42	18	-35
M OFC/M & L frontal pole/M & L SFG (BA 6/8/9/10/11)	33,463	Positive	3.05	-3	53	32
R declive/lingual gyrus/cuneus (BA 17/18/19)	8,215	Positive	2.52	16	-103	1
R MFG/IFG/precentral gyrus (BA 6/9/10/45/46/47)	8,998	Positive	2.65	51	24	-4
L lingual gyrus/cuneus (BA 17/18)	4,659	Positive	2.60	-11	-103	1

Table 2 con't

L PCC (BA 23/30/31)	2,515	Positive	2.66	-5	-44	30
R uncus/parahippocampus/culmen/PCC/precuneus (BA 20/23/28/30/31/35/36)	16,715	Negative	-2.78	10	-58	13
L uncus/parahippocampus/culmen/PCC/precuneus (BA 20/23/28/30/31/35/36)	14,870	Negative	-2.86	-34	-38	-14
B SPL/MFG/precentral gyrus/postcentral gyrus/precuneus/R MTG/ITG/insula/STG/putamen/ IPL/supramarginal gyrus/paracentral gyrus/SFG/M dACC/PCC (BA 2/3/5/6/7/8/13/21/22/24/31/40/41/42/43/44)	96,519	Negative	-2.68	55	-16	2
L STG/insula/putamen/precentral gyrus/postcentral gyrus/IPL (BA 2/3/4/6/13/22/40/41/42)	26,926	Negative	-2.69	-64	-15	5

Note. L = left. R = right. M = medial. B = bilateral. SFG = superior frontal gyrus. MFG = middle frontal gyrus. IFG = inferior frontal gyrus. STG = superior temporal gyrus. MTG = middle temporal gyrus. ITG = inferior temporal gyrus. rACC = rostral anterior cingulate cortex. dACC = dorsal anterior cingulate cortex. PCC = posterior cingulate cortex. SPL = superior parietal lobule. IPL = inferior parietal lobule. OFC = Orbitofrontal Cortex. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 space, with the x axis moving from left to right.

Table 3

Valence-Related Activation Moderated by Approach and Avoidance Temperament.

Region	Cluster Size (mm^3)	Mean z-value[†]	Location		
			X	Y	Z
Approach Temperament					
No clusters observed					
Avoidance Temperament					
R MFG/precentral gyrus[a] (BA 6)	1,649	-2.10	54	5	36
M precentral gyrus/paracentral lobule[a] (BA 4/5/6)	2,227	-2.17	3	-22	69
L putamen[b‡]	1,242	-2.15	-24	2	-7
R amygdala[c]	566	-2.10	22	-9	-14

Note. L = left. R = right. M = medial. MFG = middle frontal gyrus. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 2009 space, with the x axis moving from left to right. [†] = negative z-values indicate that avoidance correlates negatively with pleasant – unpleasant (i.e., positive correlation with unpleasant – pleasant). [a] = frontal lobe mask correction. [b] = basal ganglia mask correction. [c] = amygdala mask correction. [‡] = cluster is lateralized.

Table 4

Arousal-Related Activation Moderated by Approach and Avoidance Temperament.

Region	Cluster Size (mm^3)	Mean z-value	Location X	Location Y	Location Z
Approach Temperament					
L DLPFC[a‡] (BA 8/9)	2,150	2.38	-34	31	49
Genual ACC/paracingulate/L frontal pole[a] (BA 10/32)	3,166	2.33	-6	47	11
PCC[a] (BA 23/30/31)	1,758	2.50	7	-49	11
PCC/M precentral gyrus[a] (BA 4/6/31)	5,354	2.39	-5	-34	37
R putamen[b]	1,091	2.40	29	-2	7
L putamen[b]	903	2.43	-32	-14	-4
L anterior/middle OFC/frontal pole[c] (BA 10/11)	982	2.42	-37	58	-3
Avoidance Temperament					
R DLPFC[a‡] (BA 6/9)	1,714	2.39	43	14	37
L DLPFC/frontal pole[a] (BA 8/9/10)	6,158	2.35	-32	29	46
M Genual ACC/dACC/PCC/frontal pole/ paracingulate/SMA/precentral gyrus/R SFG[a] (BA 6/8/9/10/24/30/31/32/33)	36,061	2.52	0	-46	25
R IFG/MFG[a‡] (BA 9/44/45/46)	5,712	2.54	55	21	7
R caudate head[b‡]	1,834	2.55	14	21	8
R putamen[b]	1,106	2.42	34	-10	2

Table 4 con't

L putamen[b]	648	2.35	-30	-16	2
R agranular OFC/IFG[c]	1,220	2.48	35	24	-10

Note. L = left. R = right. M = medial. DLPFC = dorsolateral prefrontal cortex. ACC = anterior cingulate cortex. dACC = dorsal ACC. PCC = posterior cingulate cortex. SMA = supplementary motor area. SFG = superior frontal gyrus. MFG = middle frontal gyrus. IFG = inferior frontal gyrus. OFC = orbitofrontal cortex. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 2009 space, with the x axis moving from left to right. [a] = frontal lobe mask correction. [b] = basal ganglia mask correction. [c] = ventral prefrontal mask correction. ‡ = cluster is lateralized.

Table 5

Correlations between Regions of Interest and Behavior

Region	RT	*p-value*	Errors	*p-value*
Valence				
Avoidance Temperament				
R MFG/precentral gyrus	.08	.490	-.02	.862
M precentral gyrus/paracentral lobule	**.24**	**.029**	.10	.392
L putamen	.15	.172	-.02	.884
R amygdala	.15	.190	.14	.232
Arousal				
Approach Temperament				
L DLPFC	**.37**	**.001**	.03	.798
M genual ACC/paracingulate/L frontal pole	**.44**	**<.001**	.15	.18
M PCC	**.26**	**.021**	.05	.680
M PCC/precentral gyrus	**.33**	**.003**	.13	.26
L anterior/middle OFC/frontal pole	.20	.081	.07	.549
R putamen	.01	.938	-.03	.816
L putamen	.13	.250	.02	.885
Avoidance Temperament				
R DLPFC	**.26**	**.019**	**.24**	**.030**
L DLPFC/frontal pole	**.35**	**.002**	.17	.144
M genual ACC/dACC/PCC/frontal pole/ paracingulate/SMA/precentral gyrus/R SFG	**.38**	**.001**	**.26**	**.023**
R IFG/MFG	**.29**	**.010**	**.31**	**.005**
R agranular OFC/IFG	**.38**	**<.001**	**.32**	**.004**
R nucleus accumbens/caudate head	**.31**	**.006**	.20	.074
R putamen	.04	.760	.05	.655
L putamen	.06	.574	.07	.536

Table 5 con't

Note. L = left. R = right. M = medial. DLPFC = dorsolateral prefrontal cortex. ACC = anterior cingulate cortex. dACC = dorsal ACC. PCC = posterior cingulate cortex. SMA = supplementary motor area. SFG = superior frontal gyrus. MFG = middle frontal gyrus. IFG = inferior frontal gyrus. OFC = orbitofrontal cortex. BA = Brodmann's area. RT = reaction time interference. Errors = error rate interference. Correlations for RT are Pearson product-moment correlations. Correlations for Errors are Spearman rank-order correlations.

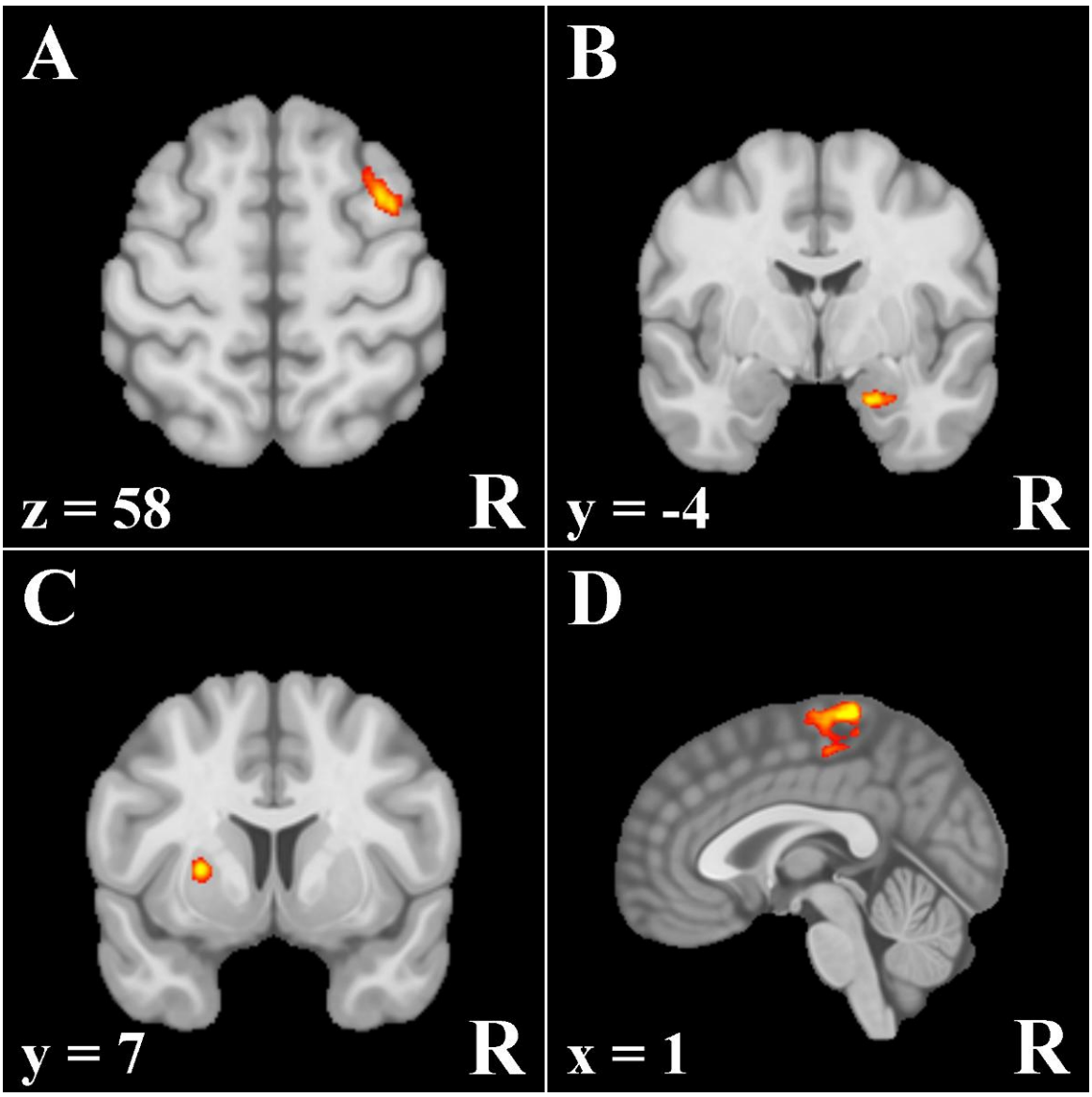

Figure 3.1: Moderation of activation to unpleasant distractors by avoidance temperament. R = right. x, y, and z = coordinates in MNI 2009a space. A = cluster in right middle frontal and precentral gyri (including human frontal eye field). B = cluster in right amygdala. C = cluster in left putamen. D = cluster in medial precentral gyrus/paracentral lobule.

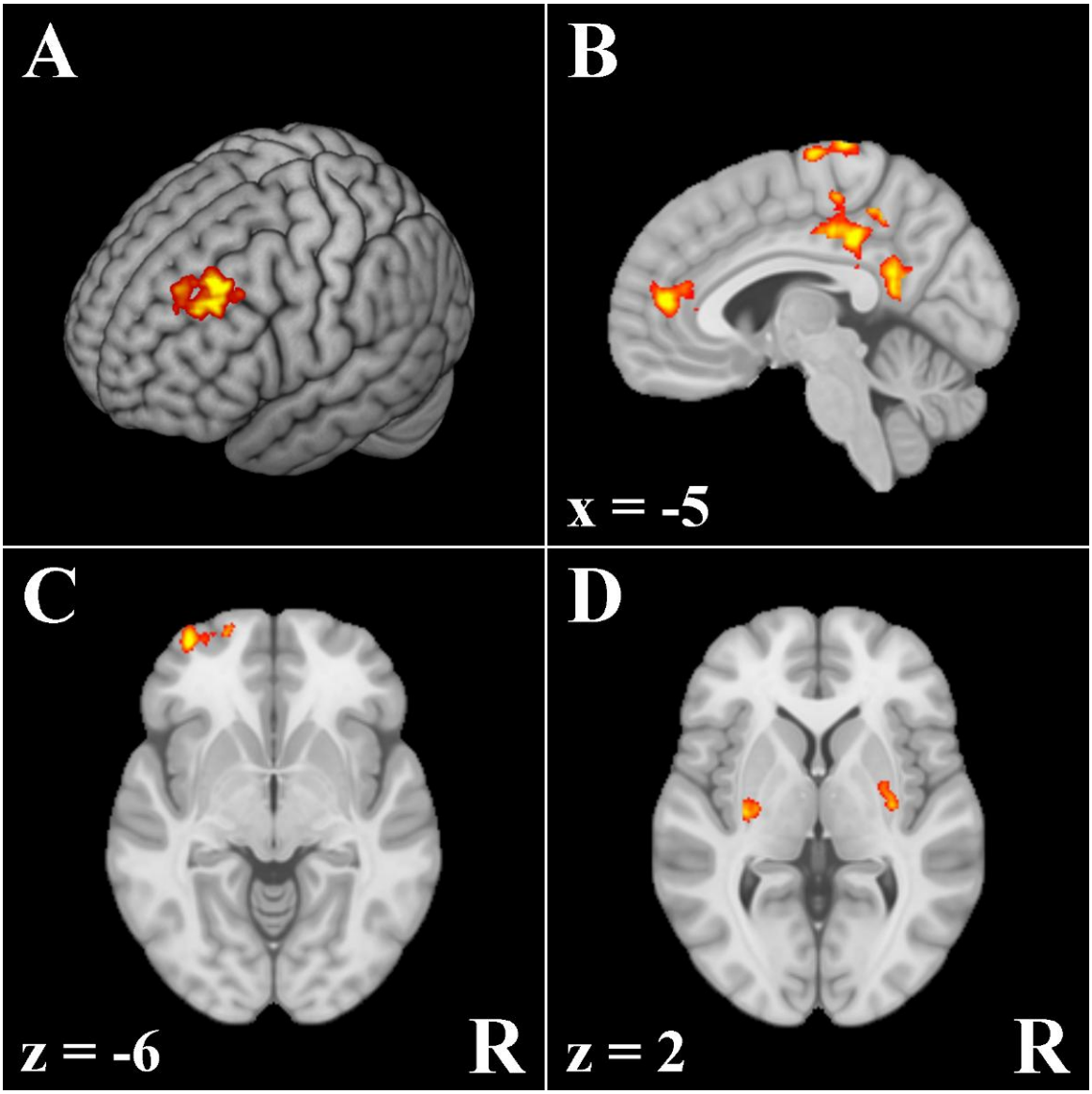

Figure 3.2: Moderation of activation to emotionally arousing distractors by approach temperament. R = right. x, y, and z = coordinates in MNI 2009a space. A = cluster in left dorsolateral prefrontal cortex. B = clusters in genual anterior cingulate cortex, posterior cingulate cortex, and posterior cingulate cortex/medial precentral gyrus. C = cluster in left orbitofrontal cortex/frontal pole. D = clusters in right and left putamen.

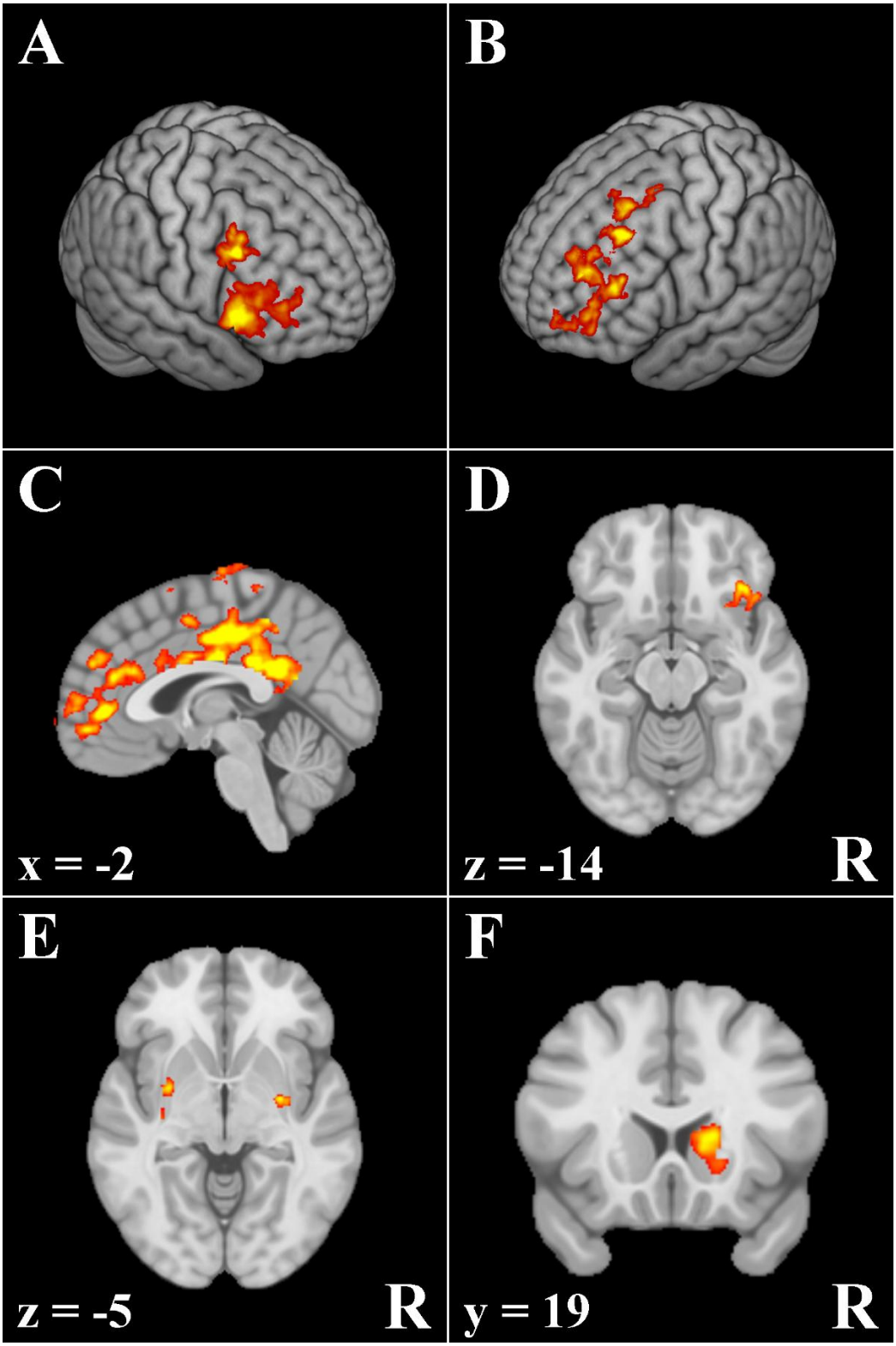

Figure 3.3

Figure 3.3 con't

Figure 3.3: Moderation of activation to emotionally arousing distractors by avoidance temperament. R = right. x, y, and z = coordinates in MNI 2009a space. A = clusters in right dorsolateral prefrontal cortex and inferior/middle frontal gyri. B = cluster in left DLPFC/frontal pole. C = cluster in genual and dorsal anterior cingulate cortex/posterior cingulate cortex/frontal pole/paracingulate/supplementary motor area/precentral gyrus/right superior frontal gyrus (not visible). D = cluster in right agranular orbitofrontal cortex/inferior frontal gyrus. E = clusters in left and right putamen. F = cluster in right putamen/nucleus accumbens (not visible).

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CHAPTER 4

TOP-DOWN BIASING BY REGIONS OF DORSOLATERAL PREFRONTAL CORTEX ASSOCIATED WITH APPROACH AND AVOIDANCE MOTIVATION WHEN GOAL-PURSUIT IS THREATENED

Abstract

Research indicates that regions of dorsolateral prefrontal cortex (DLPFC) are important for goal pursuit and are involved in integrating processes related to approach and avoidance motivation with those related to executive function. DLPFC is hypothesized to function within a network of brain regions involved in goal pursuit and to bias processing in other regions to be congruent with goals. The present study tested this hypothesis by examining the relationship between regions of DLPFC found to be associated with trait approach and avoidance motivation and other brain regions thought to be important for goal pursuit while participants performed a task in which goal pursuit was threatened. Present analyses located regions in which the correlation between BOLD activity in that region and activity in DLPFC was greater when goal pursuit was threatened. Present findings support a role for DLPFC in the biasing of processing in a number of brain regions to be congruent with goals, including orbitofrontal cortex, anterior and posterior cingulate cortex, amygdala, and basal ganglia. Findings were largely replicated in a second independent sample, indicating that the findings are reliable.

Top-Down Biasing by Regions of Dorsolateral Prefrontal Cortex Associated with Approach and Avoidance Motivation When Goal-Pursuit is Threatened

A long line of research indicates that dorsolateral prefrontal cortex (DLPFC) is centrally involved in the pursuit of goals (e.g., MacDonald et al., 2000). One potential role for DLPFC during goal pursuit is the integration of motivational and executive function processes that are necessary for goal pursuit. This hypothesis has been supported by research examining the integration of executive function processes and processes related to state motivation (i.e., motivation induced by the presence of immediate reward/punishment; Taylor et al., 2004) and trait motivation (i.e., temperamental tendencies to be sensitive to, and motivated by, potential appetitive or aversive outcomes; Spielberg et al., 2011; Spielberg, Heller, & Miller, in prep). However, the role of DLPFC in relation to other brain regions thought to instantiate motivational processes important in goal pursuit has not been explicitly examined. The goal of the present study was to extend this literature by testing the hypothesis that the role of motivation related regions of DLPFC is to influence processing in other nodes of a network of brain areas involved in goal pursuit to be congruent with motivational biases during goal-directed behavior.

A Network for Goal Pursuit

Research supports the existence of two fundamental motivational systems, one oriented toward potential desirable outcomes, termed the approach motivational system, and one oriented toward potential aversive outcomes, termed the avoidance motivational system (for reviews see Elliot & Covington, 2001; Lang et al., 1998). Support has been found for the presence of stable individual differences in the activity/reactivity of these motivational systems, and these differences have been hypothesized to reflect temperament types (Elliot & Thrash, 2002). Recent research indicates that approach temperament, reflecting stable differences in the approach

motivational system, is associated with left-lateralized regions of DLPFC, and avoidance temperament, reflecting stable differences in the avoidance motivational system, is associated with a right lateralized region of DLPFC (Spielberg et al., 2011; Spielberg et al., in prep). These findings suggest that left DLPFC is differentially associated with the pursuit of approach-related goals and right DLPFC with the pursuit of avoidance-related goals, which is consistent with a large body of research suggesting that prefrontal cortex (PFC) is lateralized with respect to motivational direction/emotional valence (for a review see Spielberg et al., 2008).

However, there is also evidence that certain regions of DLPFC are associated with both approach and avoidance temperament (Spielberg et al., 2011; Spielberg et al., in prep), suggesting that some areas of DLPFC implement general motivational processes that are not specific to approach or avoidance motivation. These findings are consistent with the theory proposed by Spielberg et al. (2011) that the role of DLPFC in goal pursuit is to integrate motivational and executive function processes and bias processing in other brain regions to be congruent with goals. Although DLPFC is thought to be fundamentally involved in goal pursuit, it is unlikely that DLPFC functions in isolation. Rather, DLPFC is likely part of a network, with each node having distinct roles in the pursuit of goals (Miller & Cohen, 2001). The present study tested this hypothesis by examining the influence of DLPFC on processing in brain regions that research suggests are active during goal pursuit, specifically orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala, and basal ganglia (BG).

Orbitofrontal Cortex

OFC is thought to be involved in maintaining the current and expected motivational value of stimuli (O'Doherty & Dolan, 2006) and to provide information about stimulus value to DLPFC (Szatkowska et al., 2008). DLPFC is thought to use this information in the selection of

appropriate goals. A medial/lateral parcellation of OFC may be particularly important to consider with respect to a goal pursuit network, given that research suggests that medial and lateral OFC are involved in maintaining reward values and punishment values, respectively (Elliott et al., 2000; Kringelbach & Rolls, 2004; O'Doherty, 2007). However, the medial/lateral parcellation does not incorporate hemispheric laterality, which research suggests is an important organizing factor for PFC with respect to motivation and emotion (Heller, 1993; Davidson & Irwin, 1999).

A recent meta-analysis (Wager et al., 2008) suggests that OFC is lateralized with respect to emotional valence, although not in the same direction as more superior areas, such as DLPFC. Specifically, Wager et al. (2008) found that bilateral medial and right lateral OFC were associated with pleasant emotional experience, whereas left middle and left lateral OFC were associated with unpleasant emotional experience. The association between right lateral OFC and pleasant valence is inconsistent with the proposed medial/lateral organization of OFC (O'Doherty, 2007), which suggests that OFC organization depends on the type of processes examined, with those processes related to motivation having a somewhat different organization that those related to emotional experience. Thus, the organization of OFC appears still to be a matter of debate, with evidence depending heavily on the specific processes being studied.

Anterior Cingulate Cortex

ACC is also thought to have a central role in the pursuit of goals (Rushworth, Behrens, Rudebeck, & Walton, 2007). One popular theory of ACC is that it is involved in the detection of error/conflict (e.g., Carter, Braver, Barch, Botvinick, Noll, & Cohen, 1998). However, ACC activation has also been observed in contexts without error/conflict, such as in the detection of cues signaling reward (Bush, Vogt, Holmes, Dale, Greve, Jenike, & Rosen, 2002). One relatively new theory that sought to reconcile the extant theories of ACC function proposes that ACC is

involved in encoding the predicted value associated with actions, including both the immediate reward/punishment value and the value of information learned by carrying out the action (for a review see Rushworth & Behrens, 2008).

Thus, ACC appears to play an important role in the creation of efficient action plans during goal pursuit. Given that DLPFC has also been implicated in the selection of optimal action plans (Frith, 2000), the creation of action plans may occur through interactions between ACC and DLPFC. The findings of a recent study that employed both diffusion tractography and a meta-analysis of fMRI studies (Beckmann et al., 2009) are consistent with this hypothesis. This study identified a region (roughly corresponding to what has been labeled dorsal ACC [Bush, Luu, & Posner, 2000] and extending around the genu of the corpus callosum) that was reliably activated by reward manipulations and had abundant white-matter connections with DLPFC and surrounding cortex, suggesting that this ACC region provides motivational information regarding actions to DLPFC.

Amygdala

In addition to DLPFC, OFC, and ACC, amygdala has been implicated as being important for the pursuit of goals. Specifically, amygdala is involved in the identification of motivationally relevant stimuli and the enhancement of perceptual processing of such stimuli (Pessoa & Adolphs, 2010). Although traditionally discussed with regard to the identification of unpleasantly valenced stimuli (e.g., Adolphs, Tranel, Damasio, & Damasio, 1995), amygdala is also involved in the identification of pleasantly valenced stimuli (e.g. Holland & Gallagher, 2004; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005), suggesting that its engagement is not dependent on valence. However, context moderates differential amygdala activation as a function of valence. For example, when stimuli are task-irrelevant, amygdala responses to

unpleasantly-valenced stimuli are greater than to pleasantly-valenced stimuli (Straube, Pohlack, Mentzel, & Miltner, 2008). In contrast, amygdala activation is greater to pleasantly-valenced than unpleasantly-valenced stimuli when the stimuli are task-relevant (Williams, McGlone, Abbott, & Mattingley, 2005).

Basal Ganglia

Another set of regions thought to be important for the pursuit of goals is BG, which is made up of striatum, globus pallidus, substantia nigra, and subthalamic nucleus. This set of sub-cortical nuclei has been implicated in a number of motivational processes (Haber, 2009), such as the anticipation of rewarding stimuli (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005) and the reinforcement of actions (Tricomi, Delgado, & Fiez, 2004). As the input node of BG, the striatum receives projections from DLPFC, ACC, OFC, amygdala, and other areas important in goal pursuit, and the internal segment of globus pallidus and substantia nigra project back to these regions (via the thalamus; Gerfen & Bolam, 2010). Based on these patterns of connectivity, it has been researchers have proposed that BG is involved in integrating motivational information from diverse areas and using this integrated information to moderate ongoing processing in target brain areas (Haber, 2009).

Summary

In summary, a number of brain areas play vital roles in goal-directed behavior and may form a neural network implementing goal pursuit. The role of OFC appears to be the maintenance of the motivational value of stimuli, whereas the role of at least one region of ACC appears to be the maintenance of the motivational value of actions. Amygdala appears to play a role in the identification of salient stimuli and enhancement of the processing of the features of such stimuli. The role of BG appears to be the integration of information from diverse cortical

and subcortical areas, which then feeds back to influence ongoing processing. Finally, certain regions of DLPFC are theorized in the present paper to bias processing in OFC, ACC, amygdala, and BG to be congruent with task goals.

Present Studies

Although research suggests that all of the brain areas discussed above are important for goal pursuit, the manner in which they function as a network remains unclear. One important aspect of this network is the proposed role of DLPFC in top-down biasing of other brain regions to be congruent with goals, which was tested here using a task that threatens goal pursuit, the color-word Stroop task (Stroop, 1935). More specifically, analyses tested the hypothesis that connectivity between DLPFC and other areas of the proposed network increases when goal pursuit is threatened by distracting information (i.e., when word meaning and ink color are incongruent) relative to when no such distraction is present (i.e., when word meaning and ink color are congruent). Thus, the present investigation examined psychophysiological interactions between DLPFC activation and task condition (incongruent and congruent) predicting activation in the brain areas discussed above.

The specific areas of DLPFC examined here were the clusters found in Spielberg et al. (2011) to be moderated by trait approach and avoidance motivation, which included one cluster in left DLPFC that was associated with approach temperament and one cluster in right DLPFC that was associated with avoidance temperament. Additionally, one cluster in left DLPFC was examined that merged two overlapping clusters associated with approach and avoidance identified in Spielberg et al., given that this area may implement general processes not specific to approach or avoidance motivation. Thus, three DLPFC clusters were used: 1) one in left DLPFC

related to approach temperament, 2) one in right DLPFC related to avoidance temperament, and 3) one in left DLPFC related to both approach and avoidance.

The first study presented here used the same data set examined in Spielberg et al. (2011). However, because this data set was used to identify the DLPFC seed clusters, it is possible that the findings could be biased by overfitting of the seed clusters. Specifically, cluster shape in Spielberg et al. may have been partially determined by error variance shared with other areas of the brain. Therefore, a second study was conducted that used an independent participant sample to rule out potential confounding effects due to overfitting of the seed clusters.

Study 1

Methods

Participants. Participants were the same sample of undergraduate students used in Spielberg et al. (2011). Participant data were not used if they (a) moved more than 3.3 mm relative to the volume used for registration (the middle volume of the time series) or more than 2 mm relative to the previous volume, (b) committed errors on 15% or more of the trials, (c) exhibited reaction times greater than 3 standard deviations from the mean, (d) exhibited apparent signal loss due to magnetic susceptibility in areas of interest, or (e) exhibited activation patters that appeared to be due to residual motion artifact. The final sample consisted of 82 participants (57% female, mean age = 19.1). One participant's scans exhibited scanner artifact throughout the time series. Independent components analysis, as implemented in MELODIC (Beckmann & Smith, 2004), was used to isolate and remove this artifact. After removal, no artifact was apparent.

Stimuli and Experimental Design. Participants completed two tasks, a color-word Stroop and an emotion-word Stroop (duration of each task = 12 min 20 sec) in fMRI and EEG

sessions (findings from the emotion-word Stroop and EEG sessions are not presented here). The order of presentation of the two tasks and the two sessions was counterbalanced across participants. In the color-word Stroop task, blocks of color-congruent or color-incongruent words alternated with blocks of neutral words. Additional neutral trials were intermixed 50:50 in congruent and incongruent blocks 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., 2000b; Milham & Banich, 2005; Milham, Banich, Claus, & Cohen, 2003). The order of presentation of blocks in the present investigation was counterbalanced for each participant. 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.

The task consisted of 256 trials presented in 16 blocks (four congruent, four incongruent, and eight neutral) of 16 trials each, with a variable ITI (2000 +/- 225 ms) between trial onsets. A trial began with presentation of a word for 1500 ms, followed by a fixation cross for an average of 500 ms. Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue), 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’’ 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 for word frequency and length. Each word (visual angle 6 – 16 degrees) was centered on a

black background and projected. Participants responded to the color of the ink with their index and middle fingers using a four-button response box (James Long Company) under each hand.

fMRI Data Collection. The fMRI data were 370 three-dimensional (3D) images acquired using a Siemens gradient-echo echo-planar imaging sequence (TR 2000 ms, TE 25 ms, flip angle 80°, FOV = 220 cm) on a Siemens Allegra 3T scanner. Each image consisted of 38 oblique axial slices (slice thickness 3 mm, 0.3mm gap, in-plane resolution 3.4375 X 3.4375 mm) acquired parallel to the anterior and posterior commissures. After the fMRI acquisition, a 160-slice MPRAGE structural sequence was acquired (spatial resolution 1 mm X 1 mm X 1 mm) and used to warp the participant's functional data into standard space.

fMRI Data Reduction and Preprocessing. Image processing and statistical analysis were implemented primarily using FEAT v5.98 (FMRI Expert Analysis Tool, FMRIB's Software Library, http://www.fmrib.ox.ac.uk/analysis/research/feat/), part of the FSL analysis package (http://www.fmrib.ox.ac.uk/fsl). The first three time points (fMRI volumes) of the data set corresponding to each task for each subject were discarded to allow the MR signal to reach a steady state. Functional data for each participant were motion-corrected using FMRIB's linear registration tool, MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2003), intensity-normalized, temporally filtered with a nonlinear high-pass filter, and spatially smoothed using a 3D Gaussian kernel (FWHM = 5 mm). Temporal low-pass filtering was carried out using AFNI's 3dDespike tool (http://afni.nimh.nih.gov/).

fMRI Data Processing. Psychophysiological interaction analyses were performed on the preprocessed functional time series of each participant using FILM, FMRIB's Improved Linear Model with autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). For each participant, a separate analysis was conducted for each of the three DLPFC ROIs. For each

DLPFC ROI, a predictor was created by extracting the mean value across all voxels in the ROI for each of the 370 time points. In each analysis, six predictors were entered: 1) one of the DLPFC predictors, 2) a congruence predictor (IvC) that modeled the difference between incongruent and congruent conditions (coded as 1 during the incongruent condition, -1 during the congruent condition, 0 at all other times), 3) the interaction (i.e., product) of these two predictors, and 4-6) three predictors of no interest that modeled the variance associated with the sum of the incongruent and congruent conditions, the neutral condition, and the rest condition. The IvC predictor and the three predictors of no interest were convolved with a gamma function to better approximate the temporal course of the BOLD hemodynamic response function (this convolution was performed on the IvC predictor prior to creating the interaction term). Each predictor yielded a per-voxel effect-size parameter estimate (β) map representing the magnitude of activation associated with that predictor. For each participant, these functional activation maps, as well as the corresponding structural MRI map, were warped into a common stereotaxic space (the 2009 Montreal Neurological Institute [MNI] 152 symmetrical 1mm x 1mm x 1mm template; Fonov, Evans, McKinstry, Almli, & Collins, 2009) using FMRIB's Non-Linear Image Registration Tool, FNIRT (Andersson, Jenkinson, & Smith, 2007).

Group inferential statistical analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). The β maps corresponding to the interaction terms were entered as dependent variables into separate one-sample, 2-tailed t-tests. Each t-test produced one β map that corresponded to the mean of the interaction across the sample. The t-tests were then converted to z-scores to determine the significance of the βs.

Monte Carlo simulations via AFNI's AlphaSim program were used to estimate the overall significance level for thresholding the 3D functional z-map image (Ward, 2000). These

simulations provided the appropriate cluster size, which, in combination with an individual voxel z-threshold of $p = 0.04$, gave an overall two-tailed family-wise error rate of 0.05. Four masks of a priori regions of interest were used to limit the number of voxels under consideration. Specifically, these masks were of 1) ventral prefrontal cortex (including OFC; cluster threshold = 897 mm^3), 2) cingulate and paracingulate gyri (cluster threshold = 819 mm^3), 3) amygdala (cluster threshold = 351 mm^3), and 4) striatum and globus pallidus (cluster threshold = 585 mm^3).

Confound Detection Analyses. An additional set of analyses was conducted in order to rule out the potential confound that the findings for a given DLPFC cluster were being driven by shared variance with the other DLPFC two clusters, rather than variance specific to that cluster. Specifically, analyses were rerun with new DLPFC predictors (and associated interaction predictors) that captured only the unique variance associated with that DLPFC cluster. These predictors were created for each participant, for each DLPFC cluster, by partialling out the variance associated with the two other DLPFC predictors. In addition to the new DLPFC and interaction predictors and the other predictors included in the original analyses (i.e., IvC and the predictors of no interest), two predictors were included in each analysis. These were the predictors corresponding to the timeseries from the other two DLPFC clusters and were included so that the shared variance, which was removed from the new DLPFC predictor, would also be removed from the error term to ensure that the tests were not biased toward Type II errors. In order to ensure that the inclusion of these two predictors did not interfere with the test of the interaction, the variance associated with the interaction was partialled out of the two predictors before entering them into the model. These analyses were thresholded in the same manner as the

original analyses described above, except that 1-tailed t-tests were used, given that the direction of the effect of interest was specified by the original analysis.

Interaction Decomposition. For each DLPFC cluster, the interaction analysis identifies voxels in other brain regions with timeseries that show significantly different correlations with DLPFC depending on the task condition (incongruent vs. congruent). Thus, the interaction analysis tests whether there is a significant difference in correlations between conditions and can also indicate the sign of that difference (e.g., the correlation is more positive during incongruent than congruent). However, these analyses cannot provide the size or sign of the individual correlations for each condition, which limits the interpretations that can be made about the relationships.

Therefore, analyses were conducted to determine the size and sign of the individual correlations for each condition. For each cluster that emerged from an interaction analysis, the timeseries data for that cluster were extracted separately for the incongruent and congruent blocks and regressed (separately for incongruent and congruent) on the relevant DLPFC seed cluster timeseries. Only timepoints corresponding to when the convolved congruence predictor had reached its maximum absolute value were used, leaving 12 timepoints per block. These regressions were conducted using the Mixed procedure in SPSS version 18. Participant was the nesting variable, and block and timepoint were repeated factors. The level 1 covariance matrix was modeled with a lag 1 autoregressive function. Regression β's were converted into correlations using the t-value and degrees of freedom corresponding to that β. Specifically, the t-value was divided by the square root of the sum of the degrees of freedom and the squared t-value.

Results

Overlapping Approach and Avoidance Cluster in Left DLPFC. The first set of analyses was conducted with the left DLPFC cluster found to be associated with both approach and avoidance temperament in Spielberg et al. (2011). Table 6 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held (i.e., a stronger association during the congruent than incongruent condition). Also listed in Table 6 are the correlations between the identified brain regions and activation in this DLPFC cluster for each condition (i.e., incongruent and congruent).

As illustrated in Figure 4.1A, two clusters emerged in OFC. One cluster was located in right agranular OFC extending into inferior frontal gyrus (IFG) and insula, and the second cluster was located in right anterior-middle OFC. Three clusters emerged in cingulate, as illustrated in Figure 4.1B. One large cluster was located in dorsal ACC (dACC), genual ACC (gACC), and paracingulate gyrus. Additionally, two clusters emerged in posterior cingulate gyrus (PCC), one of which extended into precuneus. As illustrated in Figure 4.1C, one cluster emerged in left amygdala. Additionally, two clusters emerged in BG, as illustrated in Figure 4.1D. One cluster was located in right putamen and globus pallidus, and the other cluster was located in right caudate.

With the exception of the putamen/globus pallidus cluster, all clusters remained significant when only the unique variance associated with the seed cluster was used, indicating that these findings are not due to the shared variance with other DLPFC seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Approach Temperament Cluster in Left DLPFC. The second set of analyses was conducted with the left DLPFC cluster found to be selectively associated with approach temperament in Spielberg et al. (2011). Table 6 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held. Also listed in Table 6 are the correlations between the identified brain regions and activation in this DLPFC cluster for each condition (i.e., incongruent and congruent).

Three clusters emerged in OFC, as illustrated in Figure 4.1E. One cluster was located in right agranular OFC, one in left agranular and posterior-middle OFC, and the third in medial-anterior OFC. As illustrated in Figure 4.1F, one cluster emerged in cingulate located in dACC, gACC, subgenual ACC, and paracingulate gyrus. Two clusters emerged in bilateral amygdala, shown in Figure 4.1G. Additionally, three clusters emerged in BG, illustrated in Figure 4.1H. Two clusters were located in bilateral putamen/globus pallidus, and one cluster was located in right caudate.

All clusters remained significant when only the unique variance associated with the seed cluster was used, indicating that these findings are not due to the shared variance with other seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Avoidance Temperament Cluster in Right DLPFC. The third set of analyses was conducted with the right DLPFC cluster found to be selectively associated with avoidance temperament in Spielberg et al. (2011). Table 6 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held. Also listed in Table

6 are the correlations between the identified brain regions and activation in the DLPFC cluster for each condition (i.e., incongruent and congruent).

As illustrated in Figure 4.1I, two clusters emerged in OFC. One cluster was located in left agranular and posterior-middle OFC, and the second cluster was located in medial-anterior OFC and frontal pole. Two clusters emerged in cingulate, as illustrated in Figure 4.1J. One large cluster was located in dACC, gACC, subgenual ACC, and paracingulate gyrus, and the second cluster was located in PCC, extending into precuneus. One cluster emerged in left amygdala, shown in Figure 4.1K. Additionally, as illustrated in Figure 4.1L, three clusters emerged in BG. One cluster was located in right nucleus accumbens, putamen, and globus pallidus, one in left putamen, and one in right caudate.

With the exception of the amygdala cluster, all clusters remained significant when only the unique variance associated with the seed cluster was used, indicating that these findings are not due to the shared variance with the other DLPFC seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Discussion

The hypothesis that activity in regions of dorsolateral prefrontal cortex associated with trait approach and avoidance motivation would exhibit greater positive correlations with activity in orbitofrontal cortex, anterior cingulate, amygdala, and basal ganglia when goal pursuit was threatened was supported in all three of the DLPFC clusters investigated in Study 1. Although the present analysis strategy is correlational in nature and cannot speak to causal direction, the present findings support the hypothesis that regions of DLPFC thought to be involved in the

integration of motivational and executive function processes (Spielberg et al., 2011; Spielberg et al, in prep) bias processing in these cortical and subcortical regions to be congruent with goals.

Orbitofrontal Cortex. Several areas of OFC were found to exhibit greater connectivity with DLPFC clusters when goal pursuit was threatened, and there did not appear to be a discernable pattern of differential connectivity between the three DLPFC areas that were investigated. Specifically, both left DLPFC clusters exhibited increased connectivity with right agranular OFC, and the right DLPFC cluster and the left DLPFC cluster associated with approach temperament both exhibited increased connectivity with left agranular OFC, left posterior-middle OFC, and anterior-medial OFC. The finding that the left and right DLPFC areas associated with approach and avoidance temperament, respectively, exhibited increased connectivity with similar OFC areas suggests that the processing occurring in these OFC areas is not specific to a particular type of goal pursuit (approach vs. avoidance). Similarly, the fact that these DLPFC areas did not exhibit differential connectivity either by hemisphere or medial/lateral parcellation suggests that, although there may be some functional organization of OFC according to emotional valence or reward/punishment value (e.g., O'Doherty, 2007; Wager, et al., 2008), the processes occurring in these OFC areas are not specific to approach or avoidance goal pursuit.

Cingulate Cortex. Several areas of cingulate were found to exhibit greater connectivity with DLPFC clusters when goal pursuit was threatened, including the region of ACC hypothesized to be involved in maintaining action values. In fact, this area of ACC exhibited increased connectivity with all three DLPFC clusters when goal pursuit was threatened, suggesting that it plays a central role in maintaining goal pursuit. Additionally, all three DLPFC clusters exhibited greater connectivity with genual ACC when goal pursuit was threatened.

Relevant to the maintenance of goal-pursuit, this area has been implicated in using past memories to envision potential future outcomes, a process known as prospection (Buckner & Carroll, 2007).

Prospection is essential to goal pursuit, because a representation of each potential outcome, based on past experience, is needed in order to evaluate the predicted subjective value of that outcome. The ability to incorporate motivationally relevant information into anticipation when considering a potential outcome will make that option seem more attractive (or unattractive if the outcome is unpleasant). PCC, which has also been implicated in prospection (Buckner & Carroll, 2007), exhibited greater connectivity with two of the DLPFC clusters when goal pursuit was threatened in the present study. Research suggests that the aspect of prospection that PCC is involved in is the incorporation of the emotional and motivational aspects of memories into imagined scenarios (Maddock, 1999). This hypothesized role for PCC has been supported by several studies, including one that found greater PCC activation when participants considered approach- and avoidance-related goals (Johnson et al., 2006). Additionally, a recent study found that PCC activation was associated with imagining potential future outcomes, and activation in PCC predicted both the subjective value of a delayed reward option and the choice of this delayed reward over a smaller, but less delayed reward (Peters & Buchel, 2010). In summary, the present findings suggest that regions of DLPFC associated with trait motivation bias processing in two nodes of a network involved in prospection of future goals.

Amygdala. All three DLPFC clusters were found to exhibit greater connectivity with amygdala when goal pursuit was threatened, although the relationship between right DLPFC and amygdala did not survive when only the unique variance in the right DLPFC cluster was used, indicating that this finding may be an artifact of variance shared with the other DLPFC clusters.

The finding of increased connectivity between DLPFC and amygdala when goal pursuit was threatened suggests that DLPFC recruited amygdala in a compensatory fashion to identify and enhance processing of the salient stimulus features (i.e., ink color).

Basal Ganglia. All three DLPFC clusters were found to exhibit greater connectivity with basal ganglia when goal pursuit was threatened. Perhaps unsurprisingly, all three DLPFC clusters exhibited connectivity with an area of right caudate that has been found to be connected with DLPFC (Haber, 2009), although the relationship with one of the left DLPFC clusters did not survive when only the unique variance in the left DLPFC cluster was used. All three DLPFC clusters also exhibited greater connectivity with right putamen (two of the clusters were also associated with the contralateral area of left putamen) when goal pursuit was threatened. This area of putamen, along with the caudate area mentioned above, have been found to be associated with action selection and preparation (Tremblay, Worbe, & Hollerman, 2009), providing one possible means by which DLPFC can influence behavior.

Conclusions

In summary, Study 1 provided support for the involvement of DLPFC areas associated with motivation in biasing processing in other brain areas involved in goal pursuit to be congruent with goals. Additionally, the findings of Study 1 indicated that each DLPFC cluster independently influenced the brain areas examined. However, Study 1 suffers from a potential confound due to the fact that the data set used to examine connectivity was the same data set used to initially identify the DLPFC clusters. This may be problematic, because the cluster shape may have been partially determined by error variance shared with other areas of the brain. To address this potential confound, an independent sample of unselected individuals from the

community was used as a replication sample in Study 2. The use of this sample also served to test the generalizability of the present findings beyond an undergraduate population.

Study 2

Methods

Participants. The sample consisted of unselected participants recruited from the community using advertisements placed in local newspapers. Participant screening and data quality procedures were identical to that used in Study 1. A total of 120 participants completed the protocol, and data from 102 participants (63% female, mean age = 34.2) passed data quality screening.

Stimuli, Experimental Design, and Data Analyses. The stimuli, experimental design, and data analysis procedures were identical to that used in Study 1.

Results

Overlapping Approach and Avoidance Temperament Cluster in Left DLPFC. The first set of analyses was conducted with the left DLPFC cluster found to be associated with both approach and avoidance temperament in Spielberg et al. (2011). Table 7 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held. Also listed in Table 7 are the correlations between the identified brain regions and activation in this DLPFC cluster for each condition (i.e., incongruent and congruent).

As illustrated in Figure 4.2A, four clusters emerged in OFC. Two clusters were located in bilateral agranular OFC, extending into IFG and insula. Additionally, two clusters were located in bilateral anterior-middle OFC. One cluster emerged in cingulate, illustrated in Figure 4.2B, located in dACC, gACC, subgenual ACC, paracingulate gyrus, PCC, and precuneus. As

illustrated in Figure 4.2C, two clusters emerged in bilateral amygdala. Four clusters emerged in BG, as illustrated in Figure 4.2D. Two clusters emerged in bilateral putamen and globus pallidus, and two clusters emerged in bilateral caudate.

All clusters remained significant when only the unique variance associated with the DLPFC cluster was used, indicating that these findings are not due to the shared variance with other DLPFC seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Approach Temperament Cluster in Left DLPFC. The second set of analyses was conducted with the left DLPFC cluster found to be selectively associated with approach temperament in Spielberg et al. (2011). Table 7 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held. Also listed in Table 7 are the correlations between the identified brain regions and activation in this DLPFC cluster for each condition (i.e., incongruent and congruent).

Two clusters emerged in OFC, as illustrated in Figure 4.2E. One cluster was located in right agranular OFC, and one in medial-anterior OFC. As illustrated in Figure 4.2F, three clusters emerged in cingulate. One cluster emerged in dACC and paracingulate gyrus, one in gACC, and one in PCC. One cluster emerged in right amygdala, shown in Figure 4.2G. Additionally, three clusters emerged in BG, illustrated in Figure 4.2H. The first cluster was located in right nucleus accumbens, caudate, putamen, and globus pallidus, the second in right caudate, and the third in left putamen and globus pallidus.

Several clusters did not remain significant when only the unique variance associated with the DLPFC seed cluster was used. These included the clusters in subgenual ACC and right

caudate. Additionally, the clusters in medial-anterior OFC and PCC did not remain significant, although these clusters were evident when an individual z-threshold of $p = 0.05$ (corrected for multiple comparisons) was used, suggesting that these effects are present, albeit weak. All other clusters remained significant when only the unique variance associated with the DLPFC seed cluster was used, indicating that these findings are not due to the shared variance with other DLPFC seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Avoidance Temperament Cluster in Right DLPFC. The third set of analyses was conducted with the right DLPFC cluster found to be selectively associated with avoidance temperament in Spielberg et al. (2011). Table 7 lists brain regions that evidenced stronger positive correlations with activation in this DLPFC cluster during the incongruent condition than congruent condition. No clusters emerged in which the opposite pattern held. Also listed in Table 7 are the correlations between the identified brain regions and activation in this DLPFC cluster for each condition (i.e., incongruent and congruent).

As illustrated in Figure 4.2I, three clusters emerged in OFC. Two clusters emerged in bilateral agranular OFC, and one cluster emerged in left and medial anterior OFC and frontal pole. Two clusters emerged in cingulate, as illustrated in Figure 4.2J. One large cluster was located in dACC, gACC, and paracingulate gyrus, and the second cluster was located in PCC, extending into precuneus. No clusters emerged in amygdala. Additionally, as illustrated in Figure 4.2K, four clusters emerged in BG. One cluster was located in left nucleus accumbens, one in left putamen, one in right putamen and globus pallidus, and one in left caudate.

With the exception of the clusters in right putamen/globus pallidus and left caudate, all clusters remained significant when only the unique variance associated the DLPFC seed cluster

was used, indicating that these findings are not due to the shared variance with other DLPFC seed clusters. All clusters exhibited larger positive correlations with DLPFC activation during incongruent blocks than during congruent blocks.

Discussion

The findings of Study 2 largely replicated Study 1 findings, indicating that the results of Study 1 cannot be attributed to using the same sample to identify the DLPFC clusters and test the network connectivity model. Additionally, this replication supports the generalizability of the present findings beyond the undergraduate sample used in Study 1, who were relatively homogenous in age and education. Most importantly, this replication provides further support for the hypothesis that regions of DLFPC thought to be involved in the integration of motivational and executive function processes (Spielberg et al., 2011; Spielberg et al., in prep) bias processing in OFC, cingulate, amygdala, and basal ganglia to be congruent with goals.

DLPFC Cluster Associated With Approach and Avoidance Temperament. As shown in Table 8, all areas found in Study 1 to exhibit greater connectivity with this DLPFC cluster when goal pursuit was threatened were also observed in Study 2. In addition to this replication, results of Study 2 also indicated increased connectivity bilaterally in all areas in which increased connectivity was found in only one hemisphere in Study 1. Specifically, increased connectivity was found bilaterally in agranular OFC/IFG/insula, anterior-middle OFC, amygdala, putamen/globus pallidus, and caudate, whereas increased connectivity was found for these regions in only one hemisphere in Study 1. As well, increased connectivity was observed in subgenual ACC in Study 2, in addition to the genual and dorsal ACC areas found in Study 1, suggesting a larger pattern of connectivity may be present between DLPFC and cingulate than evidenced in Study 1.

DLPFC Cluster Associated With Approach Temperament. Study 2 largely replicated the Study 1 findings for the left DLPFC cluster associated with approach temperament, as shown in Table 8. However, a number of areas were not replicated, including left agranular and posterior-middle OFC, left amygdala, subgenual ACC, and the part of dACC near the genu. This suggests that these areas exhibit weaker or inconsistent connectivity with this DLPFC cluster. Importantly, replications were found in medial-anterior and right agranular OFC, right amygdala, dorsal and genual ACC, and all of the regions of BG found in Study 1. Thus, the overall hypothesis that this area of DLPFC would exhibit increased connectivity with these cortical and subcortical areas was supported by the findings of Study 2. Additionally, in Study 2, both left nucleus accumbens and PCC exhibited increased connectivity when goal pursuit was threatened, whereas these areas were not observed in Study 1.

DLPFC Cluster Associated With Avoidance Temperament. As shown in Table 8, Study 2 largely replicated the Study 1 findings for the right DLPFC cluster associated with avoidance temperament. However, some areas were not replicated, including posterior-middle OFC, left amygdala, subgenual ACC, and right caudate and nucleus accumbens. This suggests that these areas exhibit weaker or inconsistent connectivity with the right DLPFC cluster. Given that the left amygdala finding in Study 1 did not survive when only the unique variance associated with the right DLPFC cluster was used and that left amygdala was not found in Study 2, it seems likely that the Study 1 finding was driven by shared variance with other DLPFC clusters.

Importantly, replications were found in left agranular and medial-anterior OFC (although the cluster in Study 2 was largely inferior to the cluster found in Study 1), dorsal and genual ACC, PCC, and bilateral putamen. Although the cluster in right caudate was not replicated in

Study 2, a cluster was observed in contralateral left caudate (not found in Study 1).Thus, the overall hypothesis that the right DLPFC cluster would exhibit increased connectivity with these cortical and subcortical areas was supported by the findings of Study 2. Additionally, in Study 2, both right agranular OFC and left nucleus accumbens exhibited increased connectivity when goal pursuit was threatened, whereas these areas were not observed in Study 1.

General Discussion

Across two independent samples, the findings of the present study support the hypothesis that the role of these DLPFC regions is to influence processing in other nodes of the network to be congruent with goals when goal pursuit is threatened. This network included regions of OFC, ACC, amygdala, and BG.

Present findings also indicate that each of the DLPFC clusters examined has an independent relationship with OFC, ACC, amygdala, and BG, with the exception of the right DLPFC cluster and amygdala. The finding that each DLPFC cluster independently influenced brain regions in the network indicates that the regions of DLPFC examined are each providing a distinct influence on goal pursuit. Specifically, the left and right DLPFC clusters related to approach and avoidance motivation, respectively, may each be providing top-down biasing specific to the particular type of goal related to that cluster (i.e., approach or avoidance goals). The cluster related to both approach and avoidance motivation may be providing top-down biasing independent of motivational direction. Additionally, present findings indicate that these relationships are consistent, given that they were generally replicated in Study 2. This provides support for the hypothesis that these areas are consistently functioning as nodes in a network involved in goal pursuit.

Supporting present hypotheses, DLPFC clusters exhibited increased connectivity with OFC when goal pursuit was threatened. Given the proposed association of medial and lateral OFC with the maintenance of reward and punishment values, respectively (O'Doherty, 2007), it would have made sense for the left and right DLFPC clusters associated with approach and avoidance motivation to exhibit specific relationships with medial and lateral OFC, respectively. However, this was not found to be the case, as both DLPFC clusters were consistently associated with both medial and lateral OFC. When only the consistent findings across Studies 1 and 2 are considered, there does appear to be a pattern of cross-hemispheric connectivity. Specifically, both left DLPFC clusters consistently exhibited increased connectivity with right agranular OFC, and the right DLPFC cluster consistently exhibited increased connectivity with left agranular OFC. Agranular OFC, along with adjacent anterior insula, has been implicated in parsing the most salient stimuli for current goals from all internal and external stimuli (e.g., Seeley, et al., 2007), indicating that DLPFC areas associated with motivation may be biasing what is identified as salient. The consistent pattern of cross-hemispheric connectivity found in the present study is consistent with a meta-analysis that found that OFC exhibited the reverse pattern of lateralization as DLPFC with regard to emotional valence (Wager, et al., 2008). However, it should be noted that this reflects only the findings that were consistent across Studies 1 and 2, and it is possible that there is a more complicated pattern of connectivity given that bilateral clusters that did not replicate across studies were also observed.

As hypothesized, the present study found that, when goal pursuit was threatened, all three DLFPC clusters exhibited increased connectivity with the area of ACC thought to be involved in maintaining the average value of actions (Rushworth & Behrens, 2008). This is consistent with that hypothesis that regions of DLPFC are recruiting this region of ACC during the selection of

the appropriate action to take. In addition to this cingulate area, PCC and gACC were observed in the present study to consistently show increased connectivity with DLPFC (all three DLPFC clusters for gACC; the right cluster and one of the left clusters for PCC). Researchers have proposed that these areas of cingulate are involved in using past memories to generate potential future scenarios, information that can be used to aid prediction of future events (Buckner & Carroll, 2007). Thus, present findings suggest that DLPFC is engaging several areas of cingulate associated with different predictive functions in order to determine the best course of action.

Also in line with present hypotheses, two of the DLPFC clusters consistently exhibited increased connectivity with amygdala when goal pursuit was threatened. This suggests that DLPFC is recruiting amygdala, likely along with agranular OFC/insula, to bias the stimulus features that are considered salient during the incongruent condition (i.e., ink color). This biasing by DLPFC is not needed during the congruent condition, because both ink color and word meaning contain the same information.

All three DLPFC clusters consistently exhibited increased connectivity with regions of BG when goal pursuit was threatened, supporting present hypotheses. Unsurprisingly, this included an area of caudate that research indicates is connected to DLPFC (Haber, 2009). Also found were areas of putamen that research suggests influence action selection and preparation (Tremblay, Worbe, & Hollerman, 2009), providing a means by which DLPFC may influence behavior.

Strengths and Limitations

The present study benefited from the use of two samples that are quite large for the fMRI literature and the use of an independent sample to validate the present findings. Additionally, an empirically based method of identifying the seed clusters was used to locate clusters involved in

the integration of motivational and executive function processes, which is likely to be a vital function for efficient goal pursuit. As with any study, however, there are several limitations that must be considered when interpreting the results. First, the connectivity analysis method used is correlational in nature and cannot determine the presence or direction of causality. Future research should employ methods that can inform causality, such as Granger (1969) causality analysis. Second, the present study used a task in which the goal was consistent across the entire task, leaving unclear the role of DLPFC when a new task set must be initiated. Future research should examine DLPFC connectivity during a task in which participants have to switch back and forth between task sets, because research suggests that more anterior areas of PFC (e.g., BA 10) may be involved in switching between task sets (Koechlin & Summerfield, 2007).

In spite of these limitations, the present study provides important insight into the role of DLPFC in biasing other brain areas involved in goal-directed behavior to be consistent with task goals. Consistent with hypotheses, areas of DLPFC associated with the integration of motivational and executive function processes exhibited increased positive correlations with OFC, ACC, amygdala, and BG when goal pursuit was threatened, supporting a role for DLPFC in biasing processing in these areas as part of a network of goal pursuit.

Table 6

Areas Exhibiting Condition-Dependent Correlations with DLPFC Clusters in Study 1

Region	Cluster Size (mm^3)	Mean z-value	Location X	Location Y	Location Z	Inc r	Con r
L DLPFC Associated with Approach and Avoidance Temperament							
R anterior-middle OFC (BA 10/11)	1,303	2.50	31	65	-6	.19	.10
R agranular OFC/IFG/insula (BA 11/13/47)	3,215	2.47	47	23	-10	.27	.19
M dACC/gACC/paracingulate gyrus (BA 6/24/32/33)	11,666	2.56	8	25	28	.41	.33
M PCC (BA 23/31)	1,032	2.31	2	-37	24	.31	.22
M PCC/precuneus (BA 7/31)	1,807	2.53	6	-50	45	.37	.26
L amygdala	622	2.68	-18	1	-22	.23	.12
R putamen/globus pallidus‡	840	2.29	11	-6	-5	.23	.10
R caudate	1,146	2.86	13	6	12	.32	.24
L DLPFC Associated with Approach Temperament							
M anterior OFC (BA 11)	1,625	2.50	3	52	-23	.08	-.01
L agranular OFC/posterior-middle OFC (BA 11/47)	4,163	2.49	-30	9	-20	.20	.10
R agranular OFC (BA 11/47)	2,429	2.35	21	5	-18	.17	.07
M dACC/gACC/subgenual ACC/paracingulate gyrus (BA 6/9/24/32/33)	7,692	2.39	0	21	28	.22	.12
L amygdala	1,217	2.69	-19	-2	-15	.13	.01
R amygdala	535	2.36	22	3	-18	.08	.03
L putamen/globus pallidus	3,158	2.45	-28	-19	5	.14	.06
R putamen/globus pallidus	1,440	2.39	28	-2	-2	.13	.05
R caudate	767	2.46	9	0	12	.13	.08

Table 6 con't

R DLPFC Associated with Avoidance Temperament							
M anterior OFC/frontal pole (BA 10)	2,322	2.39	2	67	4	.14	.07
L agranular OFC/posterior-middle OFC (BA 11/47)	2,911	2.49	-47	19	-8	.21	.12
M dACC/gACC/subgenual ACC/paracingulate/PCC (BA 6/9/23/24/31/32/33)	20,674	2.56	1	42	0	.30	.22
M PCC/precuneus (BA 7/31)	2,782	2.44	-6	-54	23	.30	.16
L amygdala‡	381	2.50	-17	-1	-24	.11	.01
L putamen	1,011	2.45	-33	-15	-3	.21	.14
R NAc/putamen/globus pallidus	5,103	2.53	22	-5	-8	.29	.17
R caudate	1,271	2.39	15	10	13	.24	.18

Note. L = left. R = right. M = medial. OFC = orbitofrontal cortex. IFG = inferior frontal gyrus. ACC = anterior cingulate cortex. dACC = dorsal ACC. gACC = genual ACC. PCC = posterior cingulate cortex. NAc = nucleus accumbens. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 2009 space, with the x axis moving from left to right. Inc r = correlation with DLPFC seed cluster timeseries during the incongruent condition. Con r = correlation with DLPFC seed cluster timeseries during the congruent condition. ‡ = cluster did not survive when only using the unique variance associated with the seed cluster.

Table 7

Areas Exhibiting Condition-Dependent Correlations with DLPFC Clusters in Study 2

Region	Cluster Size (mm^3)	Mean z-value	Location X	Location Y	Location Z	Inc r	Con r
L DLPFC Associated with Approach and Avoidance Temperament							
L anterior-middle OFC (BA 10)	1,112	2.45	-40	51	3	.33	.23
R anterior-middle OFC (BA 10/11)	4,696	2.56	28	53	-12	.29	.18
L agranular OFC/IFG/insula (BA 11/13/47)	1,740	2.51	-29	28	-6	.33	.23
R agranular OFC/IFG/insula (BA 11/13/47)	4,396	2.69	49	21	-2	.30	.18
M dACC/gACC/subgenual ACC/ paracingulate gyrus/PCC/precuneus (BA 6/7/9/23/24/29/31/32/33)	33,943	2.70	-1	38	11	.53	.42
L amygdala	384	2.30	-25	-4	-15	.25	.13
R amygdala	1,134	2.88	26	-1	-17	.24	.11
L putamen/globus pallidus	2,556	2.59	-19	4	6	.28	.15
R putamen/globus pallidus	3,661	2.50	20	5	1	.31	.18
L caudate	2,278	2.68	-10	0	11	.40	.33
R caudate	3,062	2.80	13	-2	16	.37	.26
L DLPFC Associated with Approach Temperament							
M anterior OFC‡ (BA 10/11)	1,186	2.37	1	56	-14	.09	.00
R agranular OFC (BA 11/47)	1,156	2.52	38	25	-16	.08	.01
M dACC/paracingulate (BA 6/23/24/32)	5,785	2.58	-2	5	39	.15	.04
M gACC‡ (BA 32)	1,120	2.30	6	50	-1	.13	.07
M PCC‡ (BA 29/31)	1,918	2.34	2	-47	36	.18	.06

Table 7 con't

R amygdala	730	2.69	27	-1	-15	.10	.01
L putamen/globus pallidus	2,078	2.44	-15	0	6	.14	.05
R NAc/caudate/putamen/globus pallidus	3,889	2.42	12	-2	-1	.15	.02
R caudate‡	741	2.65	16	4	21	.12	.04
R DLPFC Associated with Avoidance Temperament							
L/M anterior OFC/frontal pole (BA 10/11)	1,433	2.54	-9	68	-13	.11	.02
L agranular OFC (BA 11/47)	2,274	2.41	-36	25	-20	.22	.13
R agranular OFC (BA 11/47)	1,221	2.85	43	17	-11	.27	.17
M dACC/gACC/paracingulate (BA 6/9/24/32)	7,193	2.44	-7	20	40	.37	.25
M PCC/precuneus (BA 7/23/29/20/29/31)	9,749	2.63	-8	-49	30	.36	.27
L putamen	696	2.33	-31	6	6	.20	.09
R putamen/globus pallidus‡	1,385	2.27	32	3	5	.27	.16
L caudate‡	608	2.44	-15	-13	22	.29	.19
L NAc	615	2.36	-13	13	-5	.21	.13

Note. L = left. R = right. M = medial. OFC = orbitofrontal cortex. IFG = inferior frontal gyrus. ACC = anterior cingulate cortex. dACC = dorsal ACC. gACC = genual ACC. PCC = posterior cingulate cortex. NAc = nucleus accumbens. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 2009 space, with the x axis moving from left to right. Inc r = correlation with DLPFC seed cluster timeseries during the incongruent condition. Con r = correlation with DLPFC seed cluster timeseries during the congruent condition. ‡ = cluster did not survive when only using the unique variance associated with the seed cluster.

Table 8

Areas Exhibiting Condition Dependent Correlations with DLPFC Clusters Across Both Studies

L DLPFC Associated with Approach and Avoidance Temperament	
Orbitofrontal Cortex:	R anterior-middle OFC, R agranular OFC/IFG/insula
Cingulate Cortex:	M dACC/gACC/paracingulate gyrus/PCC/precuneus
Amygdala:	L amygdala
Basal Ganglia:	R putamen/globus pallidus, R caudate
L DLPFC Associated with Approach Temperament	
Orbitofrontal Cortex:	R agranular OFC, M anterior OFC
Cingulate Cortex:	M dACC/subgenual ACC/paracingulate gyrus
Amygdala:	R amygdala
Basal Ganglia:	L putamen/globus pallidus, R putamen/globus pallidus, R caudate
R DLPFC Associated with Avoidance Temperament	
Orbitofrontal Cortex:	M anterior OFC/frontal pole, L agranular OFC
Cingulate Cortex:	M dACC/gACC/paracingulate/PCC/precuneus
Amygdala:	-
Basal Ganglia:	L putamen, R putamen/globus pallidus

Note. L = left. R = right. M = medial. OFC = orbitofrontal cortex. IFG = inferior frontal gyrus. ACC = anterior cingulate cortex. dACC = dorsal ACC. gACC = genual ACC. PCC = posterior cingulate cortex.

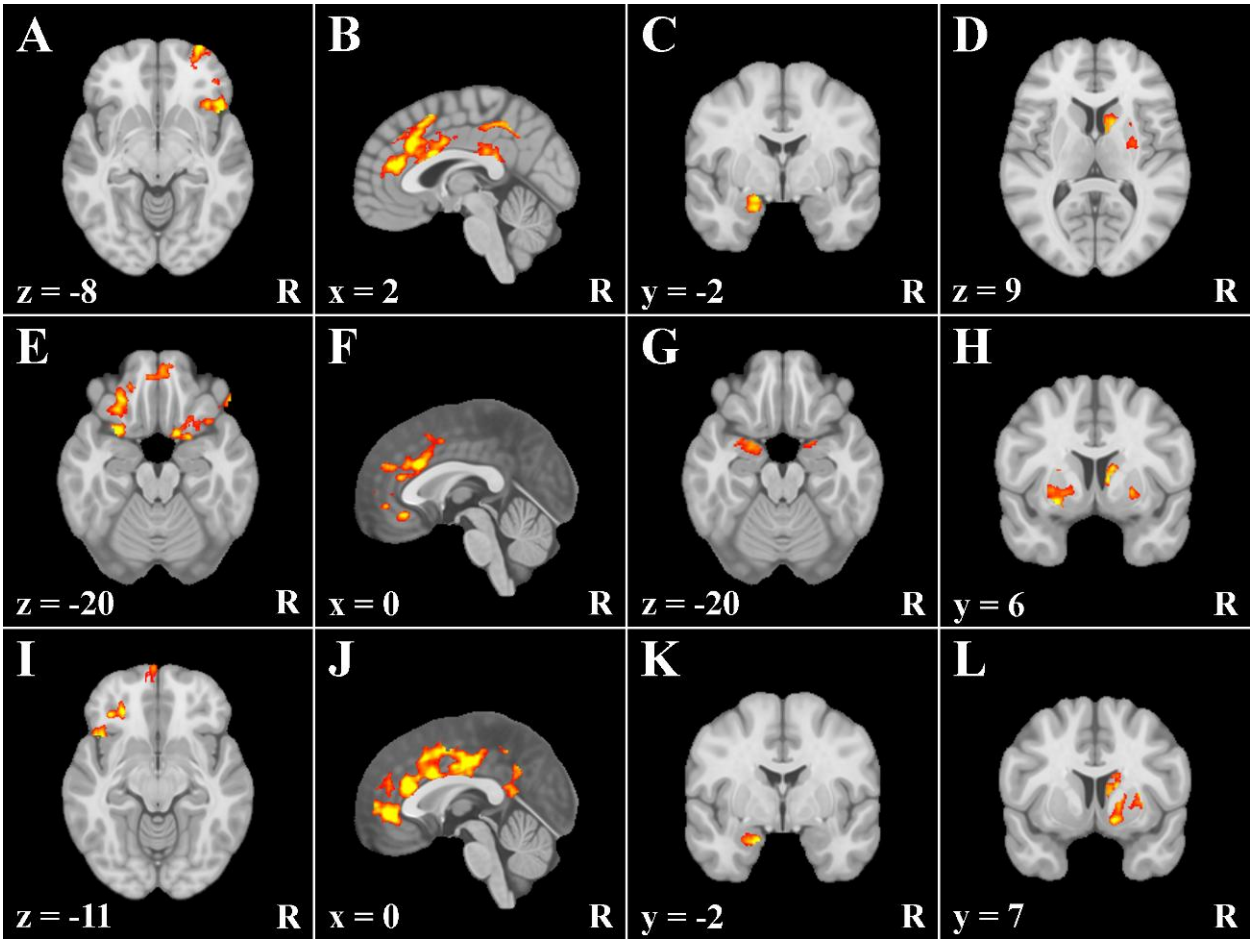

Figure 4.1: Areas Exhibiting Condition Dependent Correlations with DLPFC Clusters in Study 1. R = right. x, y, and z = coordinates in MNI 2009a space. A – D = clusters exhibiting greater connectivity with the left DLPFC cluster associated with approach and avoidance temperament. E – H = clusters exhibiting greater connectivity with the left DLPFC cluster associated with approach temperament. I – L = clusters exhibiting greater connectivity with the right DLPFC cluster associated with avoidance temperament.

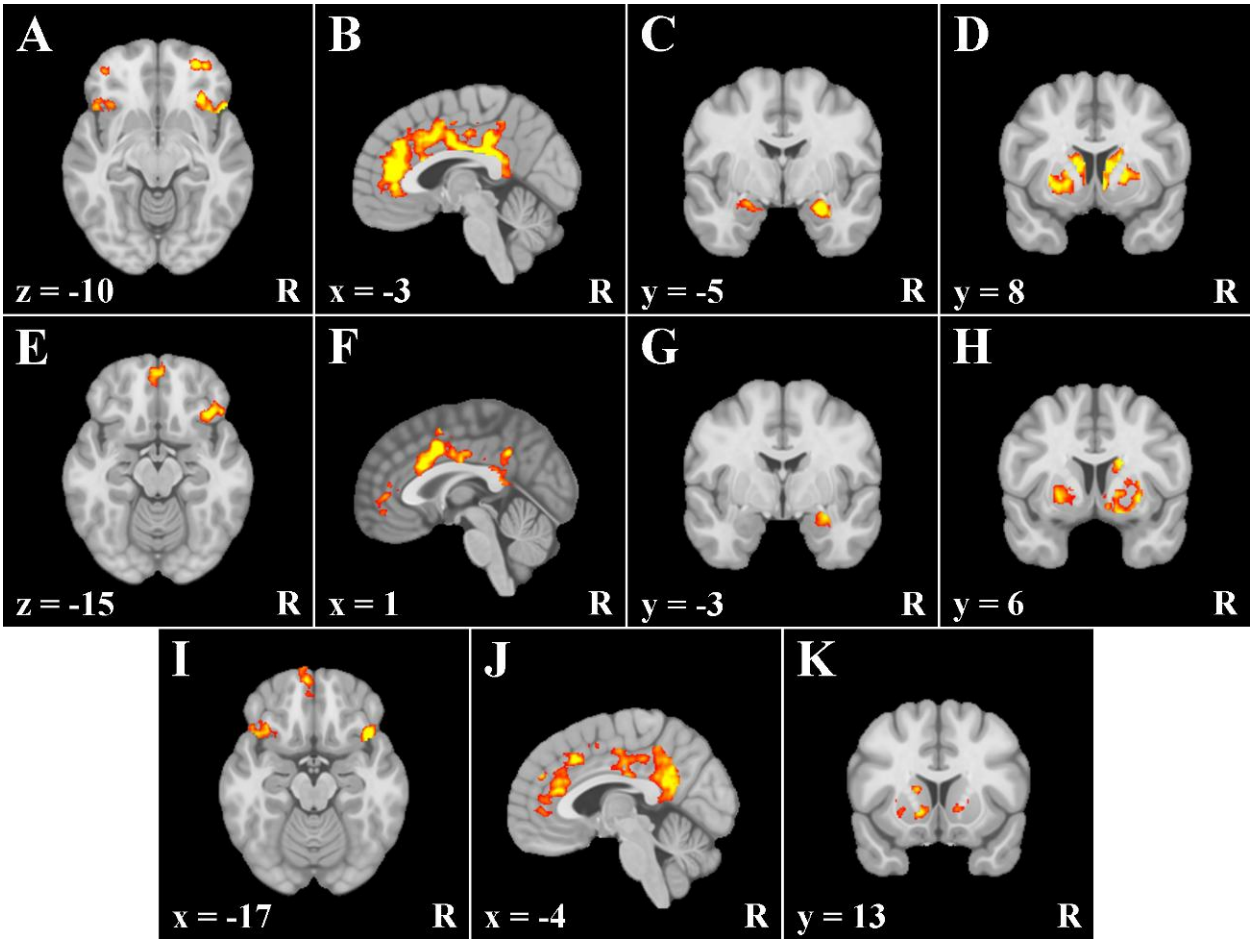

Figure 4.2: Areas Exhibiting Condition Dependent Correlations with DLPFC Clusters in Study 2. R = right. x, y, and z = coordinates in MNI 2009a space. A – D = clusters exhibiting greater connectivity with the left DLPFC cluster associated with approach and avoidance temperament. E – H = clusters exhibiting greater connectivity with the left DLPFC cluster associated with approach temperament. I – K = clusters exhibiting greater connectivity with the right DLPFC cluster associated with avoidance temperament.

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CHAPTER 5

ANXIETY AND DEPRESSION MODERATE FUNCTIONAL CONNECTIVITY ASSOCIATED WITH TOP-DOWN ATTENTIONAL CONTROL

Pathological anxiety and depression are prevalent forms of psychopathology (Kessler et al., 2005) and are associated with significant impairment in multiple areas of life, including occupational and social function (Kessler, DuPont, Berglund, & Wittchen, 1999). These impairments are associated with substantial costs to society in the form of decreased occupational productivity and increased utilization of health care resources (Simon, Ormel, VonKorff, & Barlow, 1995; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000). Research on the development and maintenance of anxiety and depression would benefit both affected individuals and society, given that this type of research has the potential to inform prevention and treatment interventions. Although both anxiety and depression have been heavily researched, the factors involved in their etiology and maintenance remain a matter of debate and require further investigation (Watson, 2009).

Pathological anxiety and depression are both characterized by high levels of general distress and are highly comorbid (i.e., negative affect, Clark & Watson, 1991). Despite the high comorbidity, anhedonic depression is distinguishable from two types of anxiety, anxious apprehension and anxious arousal (Nitschke, Heller, Imig, McDonald, & Miller, 2001; Nitschke, Heller, Palmieri, & Miller, 1999). At the symptom level, anxious apprehension is characterized by worry and verbal rumination (Andrews & Borkovec, 1988; Barlow, 1986, 1991), 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 depressed mood and decreased response to pleasurable stimuli (APA, 2000). Neuroscience research supports the

distinction between these constructs. For example, anxious apprehension is associated with increased activation in Broca's area (Engels et al., 2007, 2010), anxious arousal with increased activation in right temporal gyrus (Engels et al., 2007, 2010), and depression with greater rightward lateralization in dorsolateral prefrontal cortex (DLPFC, Herrington et al., 2010). Thus, the extant literature supports the hypothesis that anxious apprehension, anxious arousal, and depression represent separate forms of psychopathology and underscores the importance of investigating their distinct etiological components.

Dysfunction in Goal Pursuit

One fundamental difficulty found in individuals with anxiety and depression is dysfunction in goal pursuit. Beck (1967) hypothesized that decreased approach of previously valued goals and increased avoidance of "the usual pattern or routine of life" (p. 29) are fundamental manifestations of depression. As well, anxiety has been associated with increased desire to avoid potentially threatening outcomes (e.g., Maner & Schmidt, 2006). Dysfunction in goal pursuit could be due to abnormal function in a number of processes that are important for goal-directed behavior. One fundamental set of processes important in goal pursuit are those related to approach and avoidance motivation (Elliot, 2006). The approach motivational system is oriented toward guiding behavior in pursuit of potential desirable goals, whereas the avoidance motivational system is oriented toward guiding behavior away from potential aversive goals (Elliot & Thrash, 2002). Understanding potential dysfunction in these systems would advance research on anxiety and depression, because this dysfunction may be a dispositional risk factor involved in the etiology and maintenance of these forms of psychopathology. For example, dysfunction in approach motivation in depression might lead an individual to have fewer

pleasant experiences, which could reinforce the expectation that they would not have pleasant experiences in the future.

Emerging research indicates that anxious apprehension, anxious arousal, and anhedonic depression are differentially associated with approach and avoidance temperament. Spielberg, Heller, et al. (2011) examined the relationship between motivational temperaments and anxious apprehension, anxious arousal, and anhedonic depression using structural equation modeling and found that avoidance temperament exhibited a positive relationship with all three measures of psychopathology, with anxious apprehension exhibiting the strongest relationship. In contrast, approach temperament exhibited a negative relationship with anhedonic depression and weak and inconsistent positive relationships with both types of anxiety. Taken together, the findings support the relevance of approach and avoidance motivation for anxiety and depression. They also indicate some specificity in these relationships, such that increased avoidance may predispose toward both pathological anxiety and depression, whereas decreased approach may be specific to depression. Thus, anxiety and depression are associated with hyper- and hypoactivation in motivational systems.

Although there is evidence of dysfunction in motivational systems in anxiety and depression, it remains unclear what components of the approach and avoidance motivational systems are dysfunctional. Chapter 2 proposed a model of the neural instantiation of approach and avoidance motivation that can be used as a framework for identifying potential areas of dysfunction in pathological anxiety and depression. This model consists of a network of brain areas thought to instantiate different processes that are important for goal-pursuit. Briefly, orbitofrontal cortex (OFC) has been associated with the maintenance of the average motivational value of stimuli (O'Doherty, 2007), whereas portions of anterior cingulate cortex (ACC) are

thought to maintain the average motivational value of actions (Rushworth & Behrens, 2008). Additionally, posterior cingulate cortex (PCC) may be involved in integrating motivational information into prospection (Buckner & Carroll, 2007; Maddock, 1999). Regions of dorsolateral prefrontal cortex (DLPFC) have been implicated in the integration of motivational and executive function processes (Spielberg, Miller, et al., 2011; Chapter 3) and are hypothesized to bias processing in other nodes in the model to be congruent with goals. Finally, an important component of this model in relation to DLPFC is hemispheric laterality. Specifically, left DLFPC is posited to be selectively related to approach motivation, whereas right DLPFC is posited to be selectively related to avoidance motivation. However, research also indicates that there are some regions of DLPFC that instantiate motivational processes more broadly and are not specific to approach or avoidance (Spielberg, Miller, et al., 2011; Chapter 3).

Chapter 4 provided a test of the role of DLPFC in this model. Psychophysiological interactions showed that activation in all nodes in the model (OFC, ACC, and PCC) was more highly correlated with DLPFC when goal pursuit was threatened. Interpreted another way, this study found that task-related activation (activation in response to goal-pursuit being threatened) in all nodes in the model was greater when concurrent DLPFC activation was higher. Thus, this study supports the role of DLFPC in biasing processing in other brain regions to be congruent with goals.

Dysfunction in Model Nodes in Anxiety and Depression

As discussed above, there is evidence of dysfunction associated with anxiety and depression in the psychological processes engaged in goal pursuit. Additionally, there is evidence of dysfunction associated with anxiety and depression in brain areas thought to instantiate these processes.

Hyperactivation in Right DLPFC

Hyperactivation in right DLPFC has been observed in studies of both anxiety and depression. For example, several studies have found an association between depression and greater rightward lateralization in DLPFC (e.g., Herrington et al., 2010). Hyperactivation in right DLPFC has also been reported in individuals with posttraumatic stress disorder when viewing trauma-related stimuli (PTSD; Lindauer et al., 2008; Morey, Petty, Cooper, Labar, & McCarthy, 2008), individuals with panic disorder when viewing panic-related words (van den Heuvel et al., 2005), and individuals with generalized anxiety disorder (GAD) during a worry-provoking situation (Bystritsky et al., 2008). Intervention research indicates that the rightward lateralization of DLPFC that is associated with anxiety and depression has functional significance. In one study, right DLPFC activation in individuals with PTSD when viewing trauma-related imagery was normalized after successful psychotherapy (Lindauer et al., 2008). Additionally, repetitive transcranial magnetic stimulation of right DLPFC in individuals with GAD was associated with a reduction in scores on a measure of anxiety (Bystritsky et al., 2008).

Taken together, these studies indicate that anxiety and depression are associated with hyperactivation in right DLPFC. Further, they suggest that individuals with anxiety and depression are engaging the avoidance motivational system to a greater extent than individuals without these forms of psychopathology, because research has linked rightward lateralization in DLPFC with avoidance motivation (Spielberg, Miller, et al., 2011).

Posterior Cingulate Cortex

Dysfunction in PCC has also been associated with anxiety disorders and depression, although these relationships often emerge in opposite directions. Several studies have found PCC hypoactivation at rest in individuals with depression, which normalizes after treatment (Lozano

et al., 2008; Mayberg, 1997; Mayberg et al., 1999). Bench, Friston, Brown, Frackowiak, and Dolan (1993) found that activation in PCC was positively associated with anxiety symptoms and negatively associated with cognitive impairment in individuals with depression. A number of studies have found hyperactivation of PCC when individuals with anxiety disorders encountered disorder-relevant stimuli (panic disorder, Maddock, Buonocore, Kile, Garrett, 2003; obsessive compulsive disorder, Maltby, Tolin, Worhunsky, Keefe, & Kiehl, 2005; specific phobia, Straube, Mentzel, Glauer, & Miltner, 2004; social phobia, Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004).

In combination, these findings suggest PCC that hyperactivation and hypoactivation are associated with anxiety disorders and depression, respectively. The findings of PCC hypoactivation at rest associated with depression may reflect a lack of spontaneous consideration of future outcomes. In contrast, the findings of PCC hyperactivation suggest that, in the face of threatening stimuli, avoidance-related anticipation is initiated, a process that may be more likely to occur in individuals with an anxiety disorder.

Orbitofrontal Cortex

Studies investigating OFC dysfunction in depression find both hyper- and hypoactivation, depending on the valence of the stimuli. For example, Elliott, Rubinsztein, Sahakian, and Dolan (2002) found more right, lateral OFC activation to sad than happy stimuli in individuals with depression. A meta-analysis of emotional challenge studies conducted on depression also found increased activation in OFC for sad stimuli (Fitzgerald, Laird, Maller, & Daskalakis, 2008), this time in left, posterior OFC (overlapping the area found to be negatively correlated with approach temperament in Spielberg, Miller, et al.. 2011). Additionally, this area of OFC was found to be hypoactive when happy stimuli were used. These findings are consistent with research indicating

overestimation of costs (e.g., Voncken, Bögels, & Peeters, 2007) and underestimation of benefits (e.g., Chentsova-Dutton & Hanley, 2010) in depression.

Studies of OFC function in anxiety disorders have shown consistent hyperactivation to aversive stimuli. For example, individuals with panic disorder exhibited greater OFC activation when viewing anxiety-related images (Bystritsky et al., 2001). In a study of individuals with social phobia, increased activation was observed when viewing neutral faces that had been paired with a painful stimulus (Veit et al., 2002). In fact, higher activation to the faces was observed even before pairing with shock (after shock pairing, the difference was larger). In addition, in a study with a mixed sample of individuals with GAD or social phobia, a measure of intolerance of uncertainty correlated positively with OFC activation during an uncertain gambling task (Krain et al., 2008). These findings are consistent with research indicating an overestimation of costs in anxiety disorders (e.g., Foa, Franklin, Perry, & Herbert, 1996).

Anterior Cingulate Cortex

Research investigating dysfunction associated with depression in the area of ACC specified in the model has produced mixed results. For example, one study found hypoactivation in ACC at rest (Goldapple et al., 2004), which was normalized after successful cognitive behavioral therapy. In contrast, hyperactivation in ACC has been observed when participants with major depressive disorder viewed sadness-inducing film clips (Beauregard et al., 1998). Since anxiety was not examined in these studies, it is possible that differences in the amount of comorbid anxiety account for the conflicting findings. Another potential explanation is that, when at rest, individuals with depression are not considering goal-directed action (leading to decreased recruitment of ACC), whereas, when sadness is induced, individuals with depression overestimate the costs associated with action (leading to increased recruitment of ACC). Both

hypotheses are consistent with the withdrawal from goal-directed action associated with depression (APA, 2000).

Anxiety has consistently been associated with hyperactivation in the area of ACC under consideration. For example, hyperactivation has been observed when individuals with panic disorder view panic-related words (van den Heuvel et al., 2005), in individuals with PTSD during shock anticipation (Bremner et al., 2005), and in individuals with social phobia in response to negative comments and harsh facial expressions (Amir et al., 2005; Blair et al., 2008; Phan, Fitzgerald, Nathan, & Tancer, 2006). Additionally, anxious apprehension has been shown to interact with ACC activation to predict behavioral deficits in inhibition, such that higher anxious apprehension and ACC hyperactivation together were associated with the longest reaction times during a color word Stroop task (Silton et al., 2011). Hyperactivation in ACC has been shown to normalize after anti-depressant treatment in individuals with social phobia (Kilts et al., 2006). This research suggests that individuals with anxiety disorders overestimate the costs associated with action.

Hyperactivation in Amygdala

Although not included in the model outlined in Chapter 2, amygdala was found in Chapter 4 to be part of the network of brain areas involved in goal pursuit and research suggests that this area exhibits dysfunction in anxiety and depression. Therefore, amygdala was examined in the present study. Amygdala is hypothesized to be involved in the identification of salient stimuli and the enhancement of processing of relevant stimulus features (Pessoa & Adolphs, 2010). Both anxiety and depression have been associated with amygdala hyperactivation (e.g, Engels et al., 2010; Herrington et al., 2010). For example, one study found that depression was associated with hyperactivation in amygdala when participants made ratings of emotionally

arousing stimuli (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). A different study found that amygdala hyperactivation when viewing aversive faces predicted the severity of social phobia (Phan et al., 2006). Thus, there is evidence to suggest dysfunction associated with anxiety and depression is present in the areas included in the proposed model, along with amygdala.

Present Study

Although there is evidence of dysfunction in the areas in the proposed model of goal pursuit associated with anxiety disorders and depression, research has yet to determine whether this dysfunction results from dysfunctional biasing by DLPFC. For example, it is possible that hyperactivation in amygdala in anxiety is due to anxiety being associated with increased recruitment of amygdala by right DLPFC. Thus, the purpose of the present study is to test the hypothesis that anxiety and depression are associated with dysfunctional DLPFC biasing of nodes in the proposed model. Specifically, this study tested whether the relationships between DLPFC areas associated with motivation and brain areas observed to have a condition-dependent relationship with DLPFC in Chapter 4 (i.e., a stronger correlation during incongruent condition than congruent condition) vary as a function of anxiety and depression. In relation to the example above, the present study tested whether the relationship between amygdala and right DLPFC showed a condition-dependent increase as a function of dimensions of anxiety. If found to be true, this would suggest that the amygdala hyperactivation associated with anxiety is due to dysfunctional biasing by right DLPFC.

Experimental Design

In order to examine moderation of model relationships by anxiety and depression, three-way interactions between brain activation in DLPFC clusters, the task contrast of interest

(incongruent vs. congruent), and questionnaire measures of anxious apprehension, anxious arousal, and anhedonic depression were tested.

Hypotheses

Hypotheses for the present study are pictured in Figure 5.1 and summarized below.

Anxious Apprehension. Given that anxious apprehension has been associated with avoidance motivation (Spielberg, Heller, et al., 2011) and overestimation of potential costs (Berenbaum, Thompson, & Pomerantz, 2007), recruitment of OFC and ACC by the DLPFC cluster associated with avoidance temperament in Spielberg, Miller, et al. (2011) was hypothesized to increase as levels of anxious apprehension increase. Additionally, anxious apprehension was hypothesized to interfere with engagement of imagery processes when moderation by motivational systems is needed (i.e., when task demands are high), because anxious apprehension has been associated with decreased levels of imagery, even at rest (Borkovec & Inz, 1990). Therefore, recruitment of PCC by the DLPFC cluster associated with avoidance temperament was hypothesized to decrease as anxious apprehension increased. Anxious apprehension has been associated with increased salience of threat stimuli (MacLeod & Rutherford, 2004). Therefore, recruitment of amygdala by the DLPFC cluster associated with avoidance motivation was hypothesized to increase as anxious apprehension increased. Finally, because anxious apprehension has exhibited a weak and inconsistent relationship with approach motivation (Spielberg, Heller, et al., 2011), relationships with the DLPFC area associated with approach were not expected to be moderated by anxious apprehension.

Anxious Arousal. Although anxious arousal has been associated with greater avoidance motivation, it has not been associated with overestimation of costs (Berenbaum et al., 2007). Therefore, anxious arousal was not expected to moderate recruitment of ACC and OFC by the

DLPFC area associated with avoidance. There is some evidence that imagery ability is positively correlated with somatic anxiety and sympathetic hyperarousal (e.g., Cook, Melamed, Cuthbert, McNeil, & Lang, 1988; Miller et al., 1987). Therefore, recruitment of PCC by the DLPFC cluster associated with avoidance temperament was hypothesized to increase as anxious arousal increases. Anxious arousal has been associated with increased detection of potentially salient stimuli (Nitschke, Heller, & Miller, 2000), and recruitment of amygdala by the DLPFC cluster associated with avoidance was anticipated to increase as anxious arousal increases. Based on the weak and inconsistent relationship between anxious arousal and approach motivation, anxious arousal was not expected to moderate relationships with the DLPFC area associated with approach.

Anhedonic Depression. Research associates anhedonic depression with decreased levels of approach temperament (Spielberg, Heller, et al. 2011) and underestimates of benefit (e.g., Chentsova-Dutton & Hanley, 2010). Consequently, recruitment of OFC and ACC by the DLPFC cluster associated with approach temperament was hypothesized to decrease as anhedonic depression increases. Anhedonic depression has also been associated with increased levels of avoidance temperament (Spielberg, Heller, et al. 2011) and overestimates of cost (Voncken et al., 2007), which suggests that recruitment of OFC and ACC by the DLPFC cluster associated with avoidance temperament should decrease as anhedonic depression increases. Additionally, research indicates that depression is associated with decreased levels of pleasant imagery and increased levels of unpleasant imagery (Holmes, Lang, Moulds, & Steele, 2008; Patel et al., 2007). Therefore, recruitment of PCC by the DLPFC cluster associated with approach temperament was hypothesized to decrease as anhedonic depression increases, whereas recruitment of PCC by the DLPFC cluster associated with avoidance was hypothesized to

decrease as anhedonic depression increases. Finally, depression has been associated with decreased salience of appetitive stimuli (Henriques & Davidson, 2000). Consequently, recruitment of amygdala by the DLPFC cluster associated with approach was hypothesized to decrease as anhedonic depression increases.

Methods

The present study used the Study 1 sample from Chapter 4. One individual from that sample was not included in the present study, because psychopathology questionnaire data were not available. Stimuli, experimental design, data collection, data reduction, and preprocessing are described in Chapter 4.

Questionnaires

The 16-item Penn State Worry Questionnaire (PSWQ) was used to assess anxious apprehension. For this questionnaire, participants rated how characteristic (1 = not at all, 5 = very typical) each item was of them. Participants completed a 39 item portion of the Mood and Anxiety Symptom Questionnaire (MASQ) that provided two scales, the Anxious Arousal scale (MASQ-AA), consisting of 17 items, and the Anhedonic Depression scale (MASQ-AD), consisting of 22 items. For both MASQ scales, participants rated how much they experienced each item during the previous week (1 = not at all, 5 = extremely). Two subscales of the MASQ-AD were examined, given evidence indicating that they reflect different sub-facets of anhedonic depression (e.g., Nitschke et al., 2001; Spielberg, Heller, et al. 2011). These were the Loss of Interest subscale (MASQ-AD-LI) and the Low Positive Affect subscale (MASQ-AD-LP).

fMRI Data Processing

Three-way psychophysiological interaction analyses were performed with FLAME (FMRIB's Local Analysis of Mixed Effects) using the two-way interaction β maps created in

Chapter 4. Instead of entering the interaction maps into a t-test (as done in Chapter 4), the interaction maps were entered as dependent variables into a group-level regression, with PSWQ, MASQ-AA, MASQ-AD-LI, and MASQ-AD-LP as between-subject predictors. Three regressions were conducted, one for each DLPFC cluster. For each regression analysis, each predictor yielded a per-voxel effect-size parameter estimate (β) map representing the unique variance associated with that predictor. As done in Chapter 4, t-tests were conducted on the β maps and converted to z-scores to determine the significance of the β's. For β's in which an a priori hypothesis was made, 1-tailed t-tests were used. For all other β's, 2-tailed t-tests were used.

Monte Carlo simulations via AFNI's AlphaSim program were used to estimate the overall significance level for thresholding the 3D functional z-map image (Ward, 2000). These simulations provided the appropriate cluster size, which, in combination with an individual voxel z-threshold of $p = 0.05$, gave an overall two-tailed family-wise error rate of 0.05. Four masks of a priori regions of interest were used to limit the number of voxels under consideration. Specifically, these masks were of 1) ventral prefrontal cortex (including OFC; cluster threshold = 1,131 mm^3), 2) anterior cingulate cortex (cluster threshold = 702 mm^3), 3) posterior cingulate cortex (cluster threshold = 741 mm^3), and 4) amygdala (cluster threshold = 390 mm^3).

Results

Table 9 lists clusters where the psychopathology dimensions moderated the relationship between the area listed and the DLPFC clusters.

Anxious Apprehension

In line with hypotheses, PSWQ was associated with increased recruitment of right agranular and middle OFC by the right DLPFC cluster associated with avoidance temperament,

pictured in Figure 5.2B. Unexpectedly, PSWQ was also associated with increased recruitment of right middle and left lateral and middle OFC by the left DLPFC cluster associated with approach temperament, illustrated in Figure 5.2A. PSWQ was not associated with differential recruitment in any of the other brain areas examined.

Anxious Arousal

Supporting present hypotheses, MASQ-AA was associated with increased recruitment of left amygdala by the right DLPFC cluster associated with avoidance temperament, illustrated in Figure 5.2D. Unexpectedly, MASQ-AA was also associated with decreased recruitment of dACC by the left DLPFC cluster associated with approach temperament, pictured in Figure 5.2C. MASQ-AA was not associated with differential recruitment in any of the other brain areas examined.

Anhedonic Depression – Loss of Interest

In line with hypotheses, MASQ-AD-LI was associated with increased recruitment of posterior dACC by the right DLPFC cluster associated with avoidance temperament, pictured in Figure 5.2E. MASQ-AD-LI was not associated with differential recruitment in any of the other brain areas examined.

Anhedonic Depression – Low Positive Affect

MASQ-AD-LP was not associated with differential recruitment in any of the brain areas examined.

Discussion

The findings of the present study suggest that observed dysfunction in brain areas associated with goal pursuit in anxiety and depression is due, at least in part, to dysfunctional recruitment by regions of DLPFC associated with trait motivation. Additionally, the present

findings indicate some specificity, in that dimensions of anxiety and anhedonic depression were associated with dysfunctional biasing by DLPFC in different brain regions. Specifically, anxious apprehension was associated with increased recruitment of regions of OFC by both DLPFC clusters. Anxious arousal was associated with increased recruitment of amygdala by the right DLPFC cluster associated with avoidance and decreased recruitment of dACC by the left DLPFC cluster associated with approach. Finally, the loss of interest sub-facet of anhedonic depression was associated with increased recruitment of dACC by the right DLPFC cluster associated with avoidance. No effects were found for the low positive affect sub-facet of anhedonic depression, nor was either of the sub-facets associated with differential recruitment by the left DLPFC cluster associated with approach.

Present findings indicate that the hyperactivation in OFC that has been observed in individuals with pathological anxiety (e.g., Bystritsky et al., 2001; Veit et al., 2002) may be due to increased top-down recruitment by DLPFC. Anxious apprehension was associated with increased recruitment of OFC for both of the DLPFC clusters examined in the present study, whereas only the right DLPFC cluster associated with avoidance temperament was expected to show this finding. This suggests that anxious apprehension is associated with increased assessment of the value of stimuli, independent of the type of goal (approach or avoidance). This is consistent with evidence that hyperactivation in OFC associated with anxiety is related to uncertainty (Krain et al., 2008), which is important for both approach and avoidance goals. Future research should investigate potential dysfunction associated with anxious apprehension in the estimates of value related to both approach and avoidance goals, and, if present, whether this dysfunction is moderated by the level of uncertainty. Present findings also suggest that the hyperactivation of OFC observed in anxiety is due to symptoms of anxious apprehension, rather

than anxious arousal, which was not associated with increased recruitment by DLPFC in the present study. This is consistent with evidence that anxious apprehension, and not anxious arousal, is associated with overestimation of costs (Berenbaum et al., 2007).

Present findings also suggest that the hyperactivation in amygdala that has been observed in individuals with anxiety (e.g., Engels et al., 2010; Phan et al., 2006) is due to increased top-down recruitment by regions of right DLPFC associated with avoidance motivation. This effect was found only for anxious arousal, suggesting that amygdala hyperactivation observed in individuals with pathological anxiety is specific to symptoms of anxious arousal. Hyper-recruitment of amygdala by right DLPFC is consistent with research suggesting that anxious arousal is associated with hyperactivation in a system involved in responding to threat that includes right DLPFC and amygdala (Nitschke et al., 2000).

Unexpectedly, anxious arousal was also associated with decreased recruitment of dACC by the left DLPFC cluster associated with approach motivation. This finding suggests that, during the planning of actions related to approach goals, anxious arousal is associated with decreased reliance on information regarding the average value of these actions. Instead, anxious arousal may be associated with a reliance on more stereotyped action plans associated with emotion, specifically fear (e.g., fight, flight). This is consistent with research indicating that anxious arousal is a major component of Panic Disorder (Brown, Chorpita, & Barlow, 1998), which is associated with hyperactivation of physiological responses related to fear (Gorman, Kent, Sullivan, & Coplan, 2004). Future research should test whether anxious apprehension is associated with deficits in the efficient planning of actions, especially when information related to potential threats is present.

Consistent with present hypotheses, the loss of interest sub-facet of anhedonic depression was associated with stronger recruitment of dACC by the DLPFC cluster associated with avoidance motivation. This suggests that the hyperactivation of ACC associated with depression is due to increased recruitment by right DLPFC. This finding was present only for the loss of interest sub-facet of anhedonic depression, which is consistent with research indicating that this sub-facet has a greater relationship with avoidance motivation than the low positive affect sub-facet (Spielberg, Heller, et al., 2011).

Neither sub-facet of depression moderated recruitment of the brain areas examined by the left DLPFC cluster associated with approach motivation, which is inconsistent with present hypotheses. This result may be due to a number of factors. First, the present task may not have induced approach motivation to the degree necessary to observe differential recruitment by left DLPFC, which would be consistent with the fact that the task used in the present study relied on inhibition of responses, which is often associated with avoidance motivation, rather than approach motivation (e.g., Gray, 1994). Another possible explanation is that the dysfunction in approach-related goal pursuit observed in depression may not be due to dysfunctional biasing by DLPFC. Rather, DLPFC may bias other brain areas appropriately, but these areas are dysfunctional for other reasons.

In summary, present findings suggest that dysfunction associated with anxious apprehension and anhedonic depression in the neural processes involved in the estimation of costs is due, at least in part, to dysfunction in top-down biasing by DLPFC. Present findings indicate that dysfunction associated with anxious arousal in the neural processes involved in the identification of salience is also due to dysfunctional top-down biasing by DLPFC. Additionally, present findings suggest that anxious arousal is associated with dysfunction in the efficient

planning of actions related to approach goals. Finally, present findings indicate that dysfunction associated with anhedonic depression in brain areas involved in pursuing approach goals may not be due to dysfunctional biasing by DLPFC, in contrast to present hypotheses.

Strengths and Limitations

The present study benefitted from a large sample for the fMRI literature. Additionally, the present study carefully measured dimensions of both anxiety and depression, which are often not examined in the same study. The present approach diminishes the likelihood that findings are confounded by high levels of co-occurrence among anxiety and depression. Further, the present study used an empirically-based method of selecting seed clusters in DLPFC associated with approach and avoidance motivation.

As with any study, there are a number of limitations that must be considered when interpreting the findings. Specifically, the present study used correlational methods that cannot determine causality. Therefore, although the present study interpreted the findings as DLPFC biasing other brain regions involved in goal pursuit, it is possible that the relationship occurs in the opposite direction or is bidirectional. Consequently, future research should employ methods that can better determine causality (e.g., Granger causality analysis, Granger, 1969), which would be important for determining the roles different nodes in the proposed network have for goal pursuit and understanding how these relationships may be dysfunctional in pathological anxiety and depression. Additionally, the present study relied on the use of a canonical hemodynamic response function to estimate the shape and latency of the hemodynamic response. However, it is possible that psychopathology is associated with differences in latency of the response. For example, it is possible that anxious arousal is associated with an increase in latency of the hemodynamic response in dACC, rather than being associated with a lack of recruitment

by DLPFC. Future research should examine potential differences in the latency of the hemodynamic response associated with anxiety and depression to determine whether there are differences in communication between areas of the network or whether the present findings are due to latency differences in the hemodynamic response that make it appear that connectivity differences are present.

In spite of these limitations, the present study provides novel insight into potential causes of dysfunction in brain areas associated with goal pursuit in anxiety and depression. Specifically, the present study suggests that dysfunction in brain areas associated with goal pursuit observed in anxiety and depression is due, in part, to dysfunction in top-down biasing by areas of DLPFC associated with motivation. Therefore, research attempting to develop interventions that target this dysfunction may be better served by attempting to ameliorate dysfunctional biasing by DLPFC.

Table 9

Brain Areas Exhibiting Moderation by Psychopathology

Region	Direction of Effect	Cluster Size (mm^3)	Mean z-value	Location X	Location Y	Location Z
Anxious Apprehension						
L DLPFC Associated with Approach Temperament						
L lateral/middle OFC (BA 11/47)	Positive	3,276	2.38	-37	40	-12
R middle OFC (BA 11/47)	Positive	1,204	2.43	27	28	-20
R DLPFC Associated with Avoidance Temperament						
R agranular/middle OFC (BA 11/47)	Positive	1,619	1.97	26	23	-20
Anxious Arousal						
L DLPFC Associated with Approach Temperament						
M dACC (BA 24/32)	Negative	2,584	-2.30	0	25	25
R DLPFC Associated with Avoidance Temperament						
L amygdala	Positive	503	2.12	-27	2	-22
Anhedonic Depression – Loss of Interest						
L DLPFC Associated with Approach Temperament						
—	—	—	—	—	—	—
R DLPFC Associated with Avoidance Temperament						
M dACC (BA 24)	Positive	940	2.00	0	9	30
Anhedonic Depression – Low Positive Affect						
L DLPFC Associated with Approach Temperament						
—	—	—	—	—	—	—
R DLPFC Associated with Avoidance Temperament						
—	—	—	—	—	—	—

Table 9 con't

Note. L = left. R = right. M = medial. DLPFC = dorsolateral prefrontal cortex. OFC = orbitofrontal cortex. dACC = dorsal anterior cingulate cortex. BA = Brodmann's Area. Location = coordinates are for the maximum z-value and are for MNI152 2009 space, with the x axis moving from left to right. Direction of Effect: Positive = stronger relationship between DLPFC and cluster as psychopathology score is greater. Negative = weaker relationship between DLPFC and cluster as psychopathology score is greater.

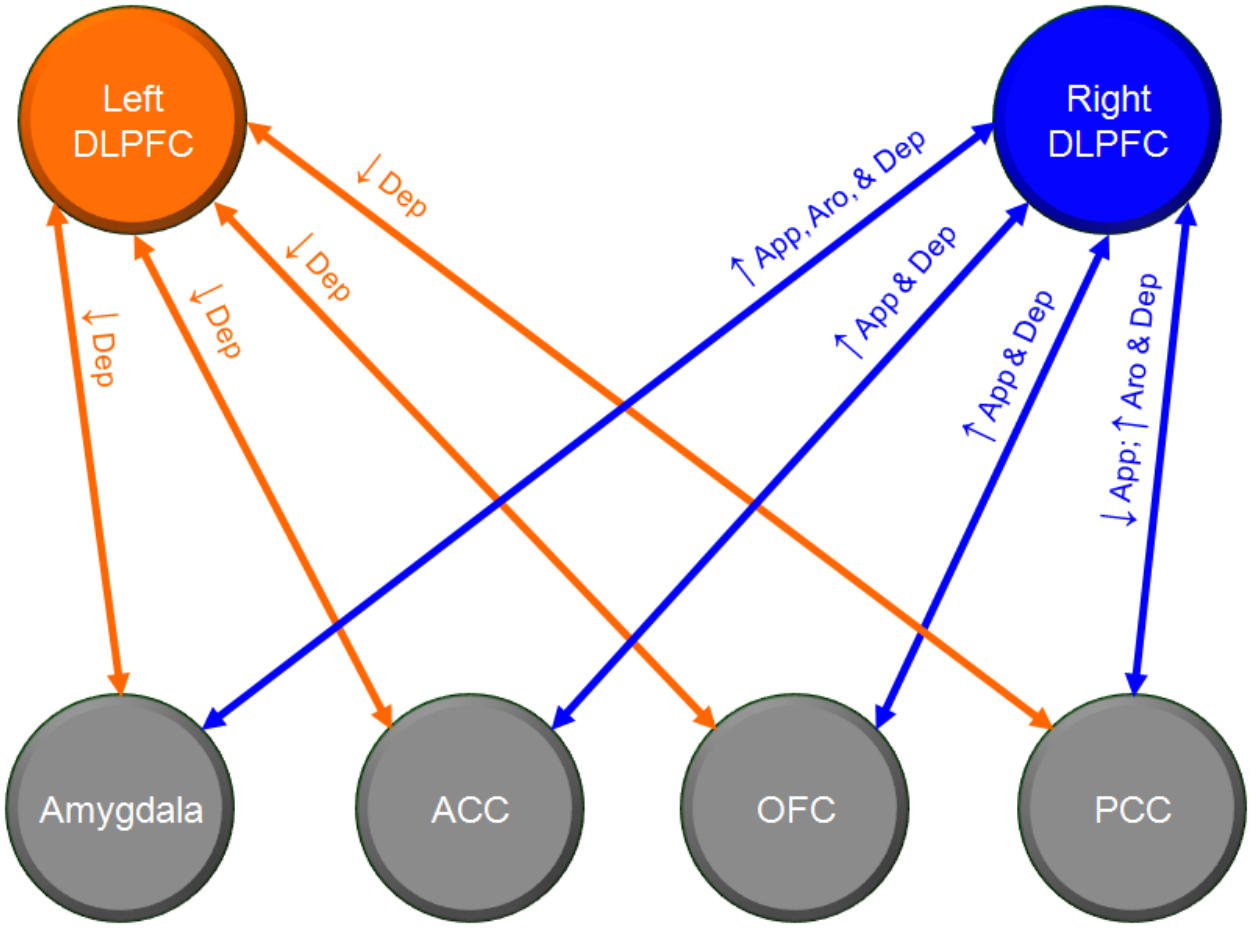

Figure 5.1. Predicted moderation of model relationships by anxiety and depression. ↑ = hypothesized increase in relationship strength when questionnaire scores are greater. ↓ = hypothesized decrease in relationship strength when questionnaire scores are greater. App = anxious apprehension, Aro = anxious arousal, and Dep = anhedonic depression. DLPFC = dorsolateral prefrontal cortex. ACC = anterior cingulate cortex. OFC = orbitofrontal cortex. PCC = posterior cingulate cortex.

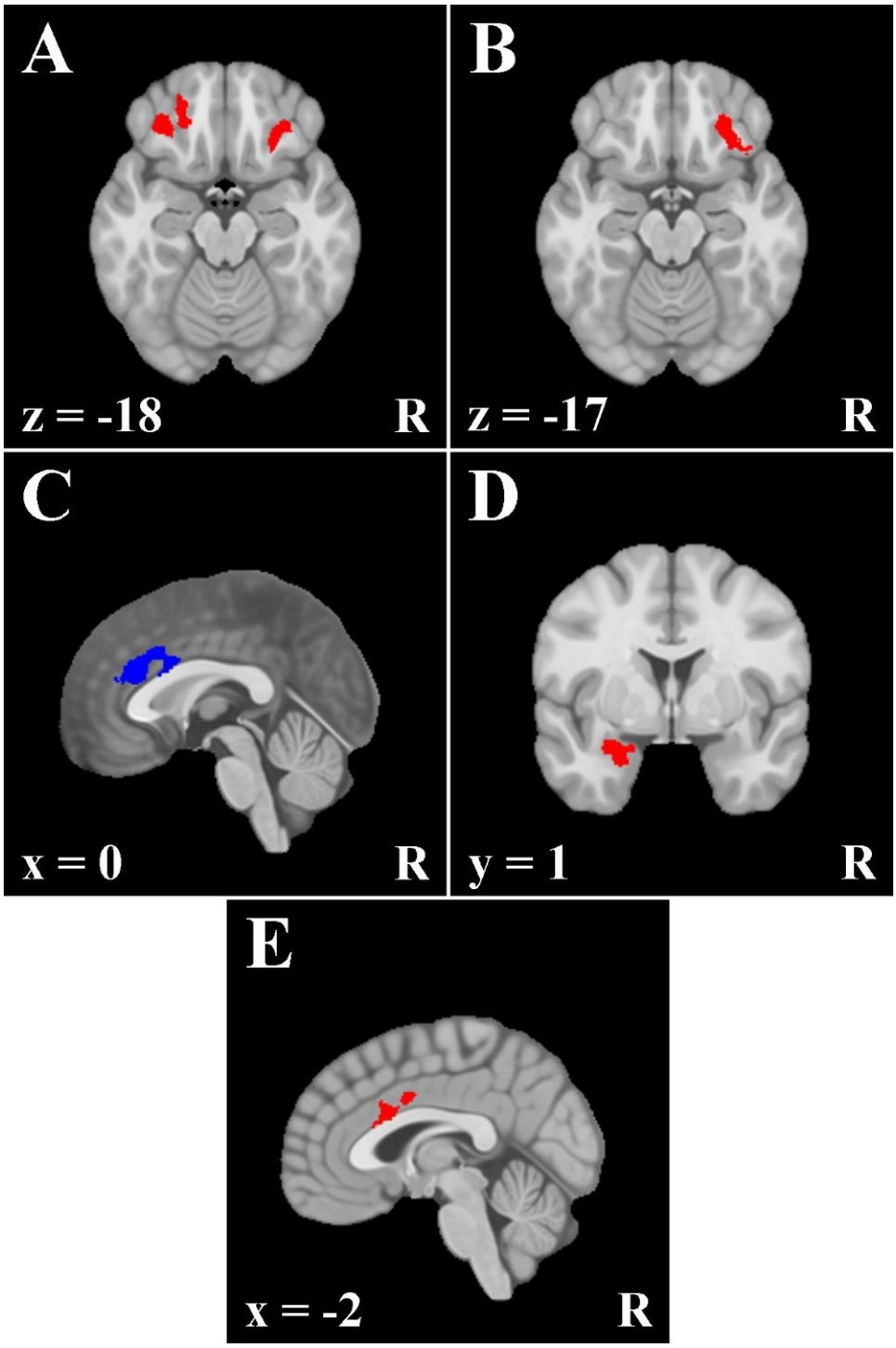

Figure 5.2: Brain Areas Exhibiting Moderation by Psychopathology.

R = right. x, y, and z = coordinates in MNI 2009a space. A = anxious apprehension associated with stronger condition dependent connectivity between bilateral orbitofrontal cortex and left

dorsolateral prefrontal cortex. B = anxious apprehension associated with stronger condition dependent connectivity between right orbitofrontal cortex and right dorsolateral prefrontal cortex. C = anxious arousal associated with weaker condition dependent connectivity between dorsal anterior cingulate and left dorsolateral prefrontal cortex. D = anxious arousal associated with stronger condition dependent connectivity between left amygdala and right dorsolateral prefrontal cortex. E = anhedonic depression loss of interest associated with stronger condition dependent connectivity between dorsal anterior cingulate and right dorsolateral prefrontal cortex.

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CHAPTER 6

GENERAL DISCUSSION

The present dissertation proposed a model of the neural instantiation of approach and avoidance motivation and tested several aspects this model. First, Chapter 2 reviewed and integrated research suggesting that 1) approach motivation and avoidance motivation are preferentially associated with left and right superior-lateral prefrontal cortex, respectively, 2) the levels of hierarchical approach and avoidance motivation can be mapped onto a proposed abstraction gradient running anterior-posterior in superior-lateral prefrontal cortex, 3) orbitofrontal cortex (OFC) maintains stimulus value information, 4) anterior cingulate cortex (ACC) maintains action value information, and 5) posterior cingulate cortex (PCC) is involved with the incorporation of motivational information into memory used to anticipate future outcomes. Based on reviewed research, a model was proposed in which these brain areas function as a network in which OFC, ACC, and PCC provide value-related information to superior-lateral PFC, particularly dorsolateral prefrontal cortex (DLPFC). The role of DLPFC in this model is to integrate motivational and executive function processes and bias processing in other brain areas to be congruent with goals.

Chapter 3 provided a test of a number of aspects of the model, including the hypothesis that regions of DLPFC are involved in integrating motivational and executive function information, the hypothesis that OFC, ACC, and PCC are involved in maintaining goal pursuit, and the hypothesis that regions of DLPFC related to trait motivation are differentially sensitive to stimulus valence. Chapter 4 provided a test of the hypothesis that DLPFC is involved in top-down biasing of other nodes in the model to be congruent with goals. Lastly, Chapter 5 provided a test of the hypothesis that dysfunction associated with anxiety and depression in nodes in the

model proposed in Chapter 2 is due to dysfunctional biasing by regions of DLPFC associated with trait motivation.

Implications for the Model of Approach and Avoidance

The findings reported in Chapters 3, 4, and 5 have a number of implications for the model of the neural instantiation of approach and avoidance motivation presented in Chapter 2. First, Chapters 3 and 4 provide support for several aspects of the model. Specifically, Chapter 3 supports the hypothesis that dorsolateral prefrontal cortex (DLPFC) is involved in integrating motivational and executive function processes, because it largely replicated the findings of Spielberg et al. (2011) but with a different type of distracting information threatening goal pursuit. Additionally, Chapter 3 provides support for the inclusion of orbitofrontal cortex (OFC), anterior cingulate (ACC), and posterior cingulate (PCC) as nodes in the model, because activation in these regions was also found to be moderated by approach and avoidance temperament when goal pursuit was threatened.

Chapter 4 provides support for the hypothesis that DLPFC provides top-down biasing of nodes in the model to be congruent with goals, because activation in DLPFC was more highly correlated with activation in model nodes when goal pursuit was threatened. It should be noted that interpretation of the findings of Chapter 4 should be qualified by the fact that the analysis strategy used was correlational in nature and cannot determine causality or direction of influence. Chapter 4 also provides support for the inclusion of OFC, ACC, and PCC as nodes in the model, given that connectivity with DLPFC was found for all of these regions. The fact that the findings of Chapter 4 were replicated in two independent samples drawn from different populations indicates that these findings are reliable. Overall, Chapter 4 provides support for the hypothesis that the brain regions incorporated in the model proposed in Chapter 2 function as a network.

The findings of Chapters 3 and 4 also provide information that can be used to refine the model proposed in Chapter 2. First, the findings of Chapter 3 suggest that regions of DLPFC associated with approach and avoidance temperament are not differentially sensitive to the valence of stimuli, at least when these stimuli are not relevant to the goal being pursued. This is important, because differential sensitivity to valence is an important aspect of conceptualizations of approach and avoidance motivation (e.g., Elliot & Thrash, 2002). Thus, the findings of Chapter 3 raise questions regarding the role of DLPFC in the model, particularly the proposal that different regions of DLPFC are differentially sensitive to approach- and avoidance-related goals. However, the findings of Chapter 3 leave open the possibility that regions of DLPFC associated with trait motivation will be differentially sensitive to the valence of stimuli when these stimuli are directly relevant to the goal being pursued or are related to a competing goal. Thus, it remains possible that these regions of DLPFC are differentially sensitive to approach- and avoidance-related goals. Future research in which the valence of the goal object itself is manipulated would provide a test of this hypothesis.

The findings of Chapter 3 also suggest that amygdala and basal ganglia (BG) should be added as nodes in the model, because activation in these areas was found to be moderated by trait motivation when goal pursuit was threatened. The findings of Chapter 4 support the inclusion of these areas in the model, given that activation in these areas was more strongly correlated with activation in DLPFC areas associated with trait motivation when goal pursuit was threatened. Thus, it appears that the model should be expanded to include these areas.

The findings of Chapters 3 and 4 also indicate the involvement of a network of brain areas that has been hypothesized to be involved in using past memories to imagine potential future scenarios (i.e., prospection). Prospection is important for goal pursuit, because it can

improve the selection of goals or goal-pursuit actions by providing more information to use in the decision-making process (Buckner & Carroll, 2007). This appears to be especially important when selecting between goals that the individual has not already encountered directly or when planning the actions necessary to attain a goal in situations in which the individual has not previously pursued a goal in this manner successfully. Among the brain areas thought to be involved in prospection are PCC, which is already part of the proposed model, and genual ACC. Genual ACC was found to be moderated by trait motivation in Chapter 3 and to show increased connectivity with DLPFC when goal pursuit was threatened in Chapter 4, providing support for the inclusion of this area in the model.

The findings of Chapter 5 also have implications for the model proposed in Chapter 2, although of a different type. Specifically, Chapter 5 provides support for the hypothesis that the proposed model can be used as a framework in which to attempt to better understand the dysfunction in goal pursuit observed in pathological anxiety and depression. The findings of Chapter 5 suggest that some of the dysfunction associated with pathological anxiety and depression observed in brain areas involved in goal pursuit, and with the psychological processes instantiated therein, is due to dysfunction in biasing by regions of DLPFC associated with trait approach and avoidance motivation. In summary, the findings of Chapters 3 and 4 provide support for several aspects of the model and provide further refinement, and the findings of Chapter 5 provide support for the utility of the model in improving the understanding of dysfunction associated with pathological anxiety and depression.

Implications for Pathological Anxiety and Depression

The findings of Chapters 3, 4, and 5 have a number of implications for psychopathology. As discussed above, Chapters 3 and 4 provide evidence that the proposed model functions as a

network in which DLPFC is involved in top-down biasing of other brain areas, and Chapter 5 indicates that this biasing is dysfunctional in anxiety and depression. Thus, some of the dysfunction in goal pursuit observed in pathological anxiety and depression appears to be due to dysfunction in the proper coordination of the brain areas involved, rather than, or in addition to, dysfunction specific to the processes occurring in those areas.

The findings of Chapter 5 also suggest that a large portion of the dysfunction in goal pursuit associated with anxiety and depression is not due to dysfunctional biasing by DLPFC, because a number of the hypotheses were not supported. Although the absence of a significant effect in a sample does not entail the absence of that effect in the population, several aspects of the present research suggest that a different avenue of exploration may prove more fruitful. This includes the fact that the sample used in Chapter 5 was substantial and the complete absence of significant moderation by either sub-facet of depression of connectivity with the left DLPFC area associated with approach motivation.

A number of alternative explanations for the dysfunction associated with depression in the psychological and neural processes involved in the pursuit of approach goals are possible. First, dysfunction may be localized to one psychological process or brain area, rather than being associated with the interaction between processes or brain areas. Alternatively, it is possible that there is dysfunction in the influence of one of the nodes in the network (aside from DLPFC) on the other nodes. For example, one of the proposed roles for BG is integrating information from nodes in the model (among other brain regions) and feeding this information back to influence ongoing processing (Haber, 2009). Thus, it is possible that dysfunction in BG impacts other nodes in the model through this feedback process. This could be an important factor in the

maintenance of pathological anxiety and depression, because this feedback loop could maintain and reinforce dysfunctional processing.

A third potential explanation for dysfunction associated with depression is the presence of dysfunctional biasing by a brain area not already included in the model. One promising candidate is subgenual ACC, which projects to a number of areas including OFC, amygdala, and other regions of ACC (Hamani et al., 2011). Depression has been associated with hyperactivation in this area (e.g., Drevets et al., 1997), and successful treatment has been associated with normalization of activation (e.g., Nobler et al., 2001). Additionally, high-frequency deep brain stimulation of subgenual ACC has been associated with remission of treatment-resistant depression, and this remission is also associated with normalization of activation in brain areas that receive projections from subgenual ACC (Lozano et al., 2008). Thus, subgenual ACC appears to be an excellent candidate area to explain dysfunction associated with depression in brain areas involved in goal pursuit.

However, there is some evidence that dysfunction in subgenual ACC may be due to dysfunctional biasing by DLPFC. Research indicates that hyperactivation in subgenual ACC is sometimes accompanied by hypoactivation in DLPFC (Mayberg, 2003). Additionally, Chapter 4 provided evidence that subgenual ACC exhibits greater connectivity with the left DLPFC cluster associated with approach when goal pursuit is threatened. Therefore, it is possible that the effect of dysfunctional biasing by left DLPFC is mediated by subgenual ACC.

In summary, the present dissertation provides insight into the neural instantiation of approach and avoidance motivation and the specific roles of different brain areas in goal pursuit. Further, the present dissertation suggests an explanation for a portion of the dysfunction

associated with pathological anxiety and depression in goal pursuit and provides a framework for future research to use to determine other sources of dysfunction.

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