CHOOSING OUR WORDS: NEURAL MECHANISMS SUPPORTING COGNITIVE CONTROL DURING LANGUAGE PROCESSING

BY

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ABSTRACT

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Choosing our words: Neural mechanisms supporting cognitive control during language processing

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Abstract: When we speak, we must constantly retrieve and select words in the face of multiple competing alternatives. Previous research has left many questions unanswered about how we achieve these fundamental cognitive control processes. This dissertation contributes to answering these questions at three levels. First, using well-controlled tasks and measures, we ask what specific aspects of language production drive cognitive control demands, as indexed by slower RTs to produce a verbal response. Second, we apply these unconfounded measures to fMRI experiments, to ask what neural substrates support cognitive control during language production. Third, we ask how these brain areas support cognitive control processes, by first simulating possible mechanisms in a neural network model and then empirically testing model predictions using pharmacological and clinical methods. In sum, the dissertation research suggests that cognitive control is needed during language production when responses compete with alternative task-relevant response options (underdetermined selection), compete with prepotent responses (prepotent selection), or are difficult to retrieve from semantic memory (controlled retrieval), and these demands interact both behaviorally and neurally. Shared neural substrates in left ventrolateral prefrontal cortex (VLPFC) support both underdetermined selection and controlled retrieval, while left VLPFC is not activated by prepotent selection demands. In contrast, an area of left dorsolateral prefrontal cortex (DLPFC) is sensitive to both underdetermined and prepotent competition. Neural network simulations suggest that competitive lateral inhibition in VLPFC is key for underdetermined selection, while other mechanisms subserved by VLPFC support controlled retrieval, and top-down biasing from DLPFC is critical for prepotent selection. As predicted by the model, increased inhibition under the GABA agonist midazolam improved selection, while anxiety (linked to reduced GABAergic function) was associated with impaired selection and reduced engagement of left VLPFC during selection. These findings enable a synthesis and reinterpretation of prior evidence, and suggest that language production is affected by both selection and retrieval mechanisms subserved by left VLPFC and DLPFC, and these processes interact in meaningful ways. Better understanding these fundamental aspects of language production may ultimately have implications for better understanding and treating impairments associated with prefrontal damage, as well as anxiety and depression.
DEDICATION

For my parents, who taught me to ask questions, and my teachers, who taught me how to begin looking for the answers.
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CHAPTER 1: GENERAL INTRODUCTION

One of the defining characteristics of human intelligence is that we are able to respond flexibly to the environment. Rather than being tied to habitual responses, we are able to respond to a given environmental context in a wide variety of ways, informed by past experience, current context, and long-term goals. This ability allows us to engage in an almost infinite repertoire of behaviors. Indeed, this capacity for generativity has long been considered definitional for the most human behavior of all: language (Chomsky, 1966; Hauser, Chomsky, & Fitch, 2002). But like all cognitive abilities, it comes at a cost: with the capacity to generate infinite options comes the difficulty of choosing among them. People claim to love the freedom of unlimited choices, but in reality we are often stymied by too many options and disconcerted by not knowing what the outcome of our choices will be. Selecting between multiple options is effortful and time-consuming, whether choosing between fruit jams (Iyengar & Lepper, 2000), retirement plans (Sethi-Iyengar, Huberman, & Jiang, 2004), or medical treatments (Redelmeier & Shafir, 1995). This problem is particularly pervasive during language production, when we must constantly choose words to express a thought (e.g., Badre & Wagner, 2007; Snyder & Munakata, 2008; Thompson-Schill, 2005).

During ordinary language production, words must constantly be retrieved and selected for production in the face of multiple possible alternatives. Even linguists happily discussing the infinite options of language must narrow them down to the one word they are currently saying. For example, when constructing a sentence, a speaker must not only choose the intended message but must also retrieve and select among multiple syntactic structures and words that are all compatible with the intended message. At the same time, the speaker must avoid errors that are not compatible with the intended message but may come automatically to mind based on past
learning or environmental cues. Even healthy adults take longer to respond when (1) it is difficult to retrieve an appropriate response (controlled retrieval), (2) there are multiple possible appropriate responses (underdetermined selection), or (3) a response that is not appropriate in the context competes with relevant responses (prepotent selection). However, for the most part speakers are able to effectively manage these cognitive control demands to speak fluently and with few errors. What mechanisms allow us to do so?

This question can be approached at multiple levels of analysis. Broadly speaking, these approaches can characterized as asking what, where, and how. First, at the behavioral level, we can ask what specific aspects of language production drive cognitive control demands. Second, at the neuroanatomical level, we can ask where in the brain these processes occur. Third, at the mechanistic level, we can ask how these brain areas support cognitive control processes, in terms of specific computational and neural mechanisms. Previous research has made progress in addressing questions at each of these levels, as discussed in the following sections. However, answers to these questions remain incomplete at best; thus, the research presented in this dissertation aims to advance understanding at each of these levels of analysis, as discussed in the final section of the chapter.

**What Aspects of Language Production Drive Cognitive Control Demands?**

**Underdetermined selection vs. controlled retrieval.** Previous research has found that reaction times are longer when there is competition between multiple automatically activated representations (high underdetermined selection demands), which must be resolved in order for the speaker to select a single response for output (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Thompson-Schill & Botvinick, 2006; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). That is, the more possible responses there are, and the less differentiated the activation
pattern across all possible responses, the longer it takes to respond (Thompson-Schill &
Botvinick, 2006). For example, participants are slower to respond when there is high competition
between multiple verb responses in the verb generation task (Nelson, Reuter-Lorenz, Persson,
Sylvester, & Jonides, 2009; Persson et al., 2004; Snyder & Munakata, 2008; Thompson-Schill et
al., 1997), multiple words that could complete a sentence (Allen et al., 2008; Nathaniel-James &
Frith, 2002; Snyder & Munakata, 2008), and multiple names for a picture (e.g., Kan &
Thompson-Schill, 2004; Kan, Kable, Van Scoyoc, Chatterjee, & Thompson-Schill, 2006).

Previous research has also found that reaction times (RTs) are longer when is difficult to
retrieve a response from semantic memory, requiring effortful, controlled retrieval (R. C. Martin
& Cheng, 2006; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). That is, the weaker the
connection between the stimulus and the most accessible response (association strength), the
longer it takes to retrieve a response. For example, in the verb generation task, in which
participants must say a verb associated with each noun stimulus, RTs are longer when the nouns
are only weakly associated with verb responses (R. C. Martin & Cheng, 2006; Snyder &
Munakata, 2008).

Some have argued that only controlled retrieval demands affect response times during
language production. In the verb generation task, RTs for producing a verb in response to a noun
were predicted by association strength (operationalized as the proportion of a norming sample
giving the most common response; i.e., agreement) but not by competition (operationalized as
the ratio of the first to the second most frequent responses in the norming sample; Martin &
Cheng, 2006). However, these results and others (e.g., Badre, Poldrack, Paré-Blagoev, Insler, &
Wagner, 2005; Nathaniel-James & Frith, 2002; Persson et al., 2004; Thompson-Schill et al.,
1997) may reflect operationalizations that confound competition and association strength and
that fail to adequately capture either theoretical construct. First, association strength has been described as an a priori parameter that arises through semantic and linguistic experience (e.g., Wagner et al., 2001); thus, the association strength between any given stimulus and response should be independent of the alternative responses. However, agreement is a proportion measure and, thus, relative to these alternative responses. Consider a noun (e.g., *ball*) with several strongly associated verb responses (e.g., *throw, catch, roll, toss*). If participants in the norming sample spread their responses fairly evenly between them, this item would be (incorrectly) classified as having low association strength, whereas, in fact, it has both high association strength and high competition between alternatives. Second, the measure of competition (ratio) considers only the two most frequent responses, rather than all active representations, but the latter is supported by evidence from other semantic tasks (e.g., Howard, Nickels, Coltheart, & Cole-Virtue, 2006). Thus, the ratio and agreement measures do not fully capture the constructs of competition and association strength, respectively.

In addition, these agreement and ratio measures are strongly correlated, in such a way that conditions differing on one measure differed on the other as well. Attempts have been made to match stimulus sets on one variable (R. C. Martin & Cheng, 2006), but this process can introduce other confounds (Thompson-Schill & Botvinick, 2006). In a behavioral experiment (Snyder & Munakata, 2008), we therefore introduced measures based on latent semantic analyses (LSA) that unconfound retrieval and selection demands, and better capture the underlying theoretical constructs of association strength and competition. LSA is a technique for extracting the similarity of words by analyzing large bodies of text, capturing contextual as well as co-occurrence information (Landauer, Foltz, & Laham, 1998). LSA provides a powerful tool for representing association strength, and thus predicting the degree to which responses are activated
by the presentation of a stimulus. Because LSA association values are absolute, using LSA-based measures eliminates the problems with the relative measures based on norming data, making purer, uncorrelated measures of both association strength and competition possible. Second, we developed a new measure of competition (entropy, computed over LSA association values), which reflects competition between all alternative responses, rather than just the two most active responses. Using previous measures of retrieval demands (agreement) and selection demands (ratio), we replicated the finding that only retrieval demands predict RTs in underdetermined tasks (R. C. Martin & Cheng, 2006). However, the agreement measure of retrieval demands masks the effects of competition. When purer, more theoretically-justified measures of retrieval demands (LSA association strength) and selection demands (LSA entropy) were used, independent effects of each factor on RTs were revealed, suggesting that both selection and retrieval place demands on cognitive control processes. This finding highlights the need for unconfounded measures of association strength and competition, both in studies of neural localization and neural mechanisms, which is a major goal of the dissertation research.

**Prepotent selection.** RTs are also longer when selecting an appropriate response requires over-riding a strongly dominant, but task-inappropriate response. For example, participants are slower to name pictures presented with or after a semantically-related competitor (e.g., de Zubicaray, McMahon, Eastburn, & Pringle, 2006; Maanen, Rijn, & Borst, 2009; Moss, 2005). In addition, one of the most frequently used cognitive control tasks in the literature, the Stroop color-word interference task, also demonstrates that competition from prepotent responses (i.e., the meaning of the word) slows naming of the ink color in which color words are written (e.g., Kane & Engle, 2003; Stroop, 1935). However, previous research has not quantified the amount of prepotent competition in these tasks (e.g., using LSA based measures as described above), or
directly compared prepotent selection to underdetermined selection.

Thus, across language production tasks, there is evidence that responses are slowed when they are not automatically driven by past learning or the environment, and instead must be retrieved and selected from among competing options (prepotent or underdetermined). However, there has been considerable debate in the literature regarding how cognitive control is employed in these situations, both in terms of the neural substrates involved (i.e., where does cognitive control occur?) and the neural and computational mechanisms involved (i.e. how is cognitive control implemented?).

**Where Does Cognitive Control Occur During Language Production?**

Patients with damage to left lateral prefrontal cortex (PFC) often have severe difficulty in relatively unconstrained language contexts. Several patients with left PFC damage have been reported who have severely impaired spontaneous speech and verbal fluency, but preserved naming, repetition and comprehension (Randolph, Braun, Goldberg, & Chase, 1993; G. Robinson & Cipolotti, 2004; G. Robinson, Shallice, & Cipolotti, 2006). Patients with left PFC damage are more impaired on generating verbs for nouns with many associates then with a single strong associate (Thompson-Schill et al., 1998; Tippett, Gendall, Farah, & Thompson-Schill, 2004). This pattern suggests that these patients are able to perform well when the response is well constrained by the stimulus, but experience difficulty when the response is difficult to retrieve or select. Thus, there is broad consensus that less constrained language production tasks are sensitive to prefrontal damage. However, the nature of the cognitive control processes involved, and the role of specific neural substrates, is strongly debated, in part because the dominant theories have not yet been definitively tested.

**Neural substrates supporting controlled retrieval vs. selection.** Three main theories of
the role of PFC in retrieving and selecting verbal responses have been proposed, each focusing on the left ventrolateral PFC (VLPFC; BA 44, 45, 47). According to the selection hypothesis, left VLPFC resolves competition between multiple automatically activated representations to select a single response for output (e.g., Botvinick et al., 2001; Thompson-Schill et al., 1997). The less differentiated the activation pattern across all possible responses, the more difficult it is to resolve the competition and the greater is the activation of left VLPFC (Thompson-Schill & Botvinick, 2006). This hypothesis is supported by neuroimaging evidence that left VLPFC is recruited in situations requiring selection between multiple competing representations. For example, in the verb generation task, left VLPFC is more active when participants generate verbs for nouns with multiple verb associates (e.g., ball, associated with kick, hit, throw, etc.) versus one associate (e.g., scissors, associated with cut; Barch, Braver, Sabb, & Noll, 2000; Nagel, Schumacher, Goebel, & D'Esposito, 2008; Nelson et al., 2009; Persson et al., 2004; Thompson-Schill et al., 1997). In addition, left VLPFC is more active when people name pictures with low versus high name agreement (Kan et al., 2006; Kan & Thompson-Schill, 2004), and generate items from larger categories (e.g., flower) than from smaller categories (e.g., red flower; Tremblay & Gracco, 2006).

In contrast, according to the controlled retrieval hypothesis, left VLPFC retrieves responses from semantic memory when such responses are effortful and require cognitive control (e.g., R. C. Martin & Cheng, 2006; Wagner et al., 2001). Thus, the weaker the connection between the stimulus and the most accessible response (association strength), the more difficult it is to retrieve a response and the greater is the activation of the left VLPFC (e.g., R. C. Martin & Cheng, 2006; Wagner et al., 2001). This hypothesis is supported by evidence that the left VLPFC is recruited when it is necessary to retrieve a weakly associated response. For example, the left
VLPFC is more active when participants generate verbs for nouns with weak versus strong verb associates (Crescentini, Shallice, & Macaluso, 2010), make semantic relatedness judgments about weakly associated (compared with strongly associated) words (Badre et al., 2005; Chou, Booth, Bitan, Burman, Bigio, Cone, Lu, & Cao, 2006a; Chou, Booth, Burman, Bitan, Bigio, Lu, & Cone, 2006b; Chou, Chen, Wu, & Booth, 2009; Wagner et al., 2001), or retrieve information about briefly studied (vs. well-studied) items (Souza, Donohue, & Bunge, 2009; Velanova, Jacoby, & Wheeler, 2003).

Recently, a synthesis of the controlled retrieval and selection hypotheses has been proposed (the two-process account; Badre et al., 2005; Badre & Wagner, 2007; c.f. Gold et al., 2006), positing that the left anterior VLPFC (BA 47) supports controlled retrieval of semantic knowledge from posterior conceptual stores, whereas the left mid-VLPFC (BA 45) supports post-retrieval selection between active representations, irrespective of whether they were retrieved in an automatic or controlled manner. Suggestive evidence is provided by a review of the literature that reported peak coordinates in left anterior or mid-VLPFC in six studies identified as manipulating controlled retrieval and/or selection demands (Badre & Wagner, 2007). This review found that putative selection manipulations tended to activate left mid-VLPFC whereas putative retrieval manipulations tended to activate left anterior VLPFC. However, the purity of the manipulations of selection and retrieval demands in these studies are debatable, as further discussed in Chapter 2. In sum, although each of these theories has been supported by some prior evidence, each has also been challenged by other findings.

**Neural substrates supporting underdetermined selection vs. prepotent selection.** In some cases, selecting an appropriate response requires over-riding a strongly dominant, but task-inappropriate response. Tasks requiring overriding a prepotent response (e.g. Stroop, Wisconsin
Card Sort, and incongruent cue tasks) have been shown to activate the anterior cingulate cortex (ACC) and left VLPFC and DLPFC (Collette, Hogge, Salmon, & Van der Linden, 2006; Liu, Banich, Jacobson, & Tanabe, 2004). By one account (Banich’s cascade model), DLPFC (BA 9/46) maintains abstract representations which provide top-down support for task-relevant representations, biasing the system towards the correct response, while regions of the ACC resolve and evaluate conflict at the response level (Herd, Banich, & O'Reilly, 2006; Milham, Banich, & Barad, 2003). No known study has examined the relation between resolving competition from a prepotent but inappropriate response (prepotent selection), and resolving competition between multiple allowable responses (underdetermined selection). Whether these two forms of selection depend on shared or separate neural substrates has implications for the cascade model and other theories of cognitive control. For example, if shared areas of PFC support both forms of selection, it may suggest that PFC implements selection between competing representations at the item level, rather than between more abstract task-set representations.

How is Cognitive Control Implemented During Language Production?

Possible neural mechanisms. There has thus far been little investigation as to specific mechanisms that may support controlled retrieval and selection of responses. While there are likely many complex mechanisms involved, competitive, inhibitory dynamics among neurons in prefrontal cortical networks likely play a key role in underdetermined selection, while the strength of neural connections may be critical for retrieval and sustained firing of DLPFC cortical networks may be important for prepotent selection.

Competitive lateral inhibition, which is critical for the function of these prefrontal circuits, is carried out by GABAergic interneurons. Cortical representations may be sharpened
through dynamic inhibitory interactions in PFC networks, allowing one representation to be selected. Indirect evidence for a role of GABAergic function in selection is provided by studies linking reduced GABAergic function to anxiety (e.g., Kalueff & Nutt, 2007; Sen et al., 2004; Smoller et al., 2001; Zai, Arnold, Burroughs, Barr, & Richter, 2005), which has in turn been linked to altered left VLPFC activity in the same area involved in underdetermined responding (Engels et al., 2007), as well as intolerance of uncertainty, decision-making problems and indecisiveness (e.g., Ladouceur, Talbot, & Dugas, 1997; Sachdev & Malhi, 2005). Thus, reduced GABAergic function in individuals with high anxiety may lead to impaired selection, as discussed further in Chapters 3 and 4. In addition, the balance between neural excitation and inhibition may be important for selection. Specifically, reduced neural inhibition may impair selection more when neural excitation levels are high, allowing competitors to become more active. Interestingly, emerging evidence links depression to reduced neural excitation (e.g., Hasler et al., 2007; Mitchell & Baker, 2010). These glutamatergic changes may be associated with improved selection (through reduced activation of competitors), leading to the counter-intuitive prediction that comorbid depression may reduce the deleterious effects of anxiety on selection, as discussed further in Chapter 4.

While competitive lateral inhibition may thus be key for underdetermined selection, controlled retrieval may depend on synaptic connectivity strength, both in posterior cortical areas representing semantic knowledge, and within prefrontal circuits. First, associations between cues (e.g., nouns in the verb generation task) and response options (e.g., verbs) arise from previous Hebbian learning during semantic and linguistic experience (Wagner et al., 2001). The weaker the association between a cue and possible responses, instantiated as weak synaptic connections between those representations within semantic networks, the longer it should take to activate a
response, as discussed further in Chapter 3. In addition to this latent mechanism, strong recurrent
connectivity within prefrontal circuits may be a more active mechanism for controlled retrieval,
by boosting the activity level of weakly active representations (e.g., Franks et al., 2011).

Active maintenance of goal representations, through sustained firing in prefrontal neural
circuits, may be critical for prepotent selection. A distinguishing characteristic of PFC is the
ability to maintain sustained neural firing that is robust to delays and interference (e.g., E. K.
Miller & Cohen, 2001). This property allows task goals (e.g., to name the ink color in the Stroop
task) to be maintained throughout the task; these actively maintained representations provide top-
down biasing to support goal-relevant representations, allowing them to be selected over
prepotent competitors (e.g., word reading in the Stroop task; E. K. Miller & Cohen, 2001).
Multiple neural mechanisms may play a role in enabling sustained firing, including: (1) strong
feedback excitation in local circuits (i.e. recurrent connectivity) that supports reverberatory
activity, (2) NMDA glutamate receptor activity, which promote bi-stable, synchronous firing via
their voltage dependency and long decay constant, and (3) intrinsic membrane currents that help
stabilize and maintain firing patterns (see Compte, 2006 for a review). Regardless of the exact
mechanism(s) involved, robust active maintenance of task rules in PFC may be important for
overcoming prepotent competition, as discussed further in Chapter 5.

**Computational models.** A number of biologically-plausible computational models have
been developed which explore possible mechanisms for resolving competition from prepotent
responses (usually through top-down biasing of task-relevant representations, e.g., Badre &
Wagner, 2006; Herd et al., 2006; Morton & Munakata, 2002). For example, in a model of the
Stroop task, a simulated PFC layer actively maintains the task goal of color naming, which
provides top-down, excitatory input to simulated posterior cortical representations of ink color,
boosting their activation level and thus allowing them to out-compete representations of the word meaning (Herd et al., 2006). The ability of PFC to actively maintain task goals has been simulated in several ways, including by implementing recurrent excitatory connections which allow units to remain active in the absence of external input (e.g., Morton & Munakata, 2002), and intrinsic maintenance currents (e.g., Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005). These mechanisms are not mutually exclusive, and may both play an important role in enabling prepotent selection.

Only a few attempts have been made to model underdetermined selection and controlled retrieval from semantic memory. One such attempt models the stem completion task (Botvinick et al., 2001; based on McClelland & Rumelhart, 1981). When a two-letter word stem is presented to the model, it activates multiple representations in the word layer (e.g. FI activates FISH, FIND, FIRE etc.), which compete through inhibitory interconnections between word units. More recently, a small-scale model of verb generation has been proposed (Thompson-Schill & Botvinick, 2006; based on Usher & McClelland, 2001) in which differences in association strength between noun stimuli and verb responses were simulated by varying their connection weights. In the presence of small random initial activation levels, the effect of association strength on cycles to settle depended on the strength of the lateral inhibition between verb responses in a complex manner, suggesting that association strength and competition may interact in interesting and unanticipated ways. In contrast, others have suggested that differences in association strength alone can account for apparent competitive effects (Danker, Gunn, & Anderson, 2008; R. C. Martin & Byrne, 2006).

**Dissertation Summary**

In sum, previous research has left many questions unanswered about the cognitive control
mechanisms that allow us to navigate the potentially overwhelming options involved in the seemingly simple act of speaking. Turning back to the questions at the beginning of the chapter, this dissertation aims to contribute to better understanding the what, where, and how of cognitive control during language production. First, using a well-controlled task and measures that allow us to disentangle selection and retrieval demands, we ask what specific aspects of language production drive cognitive control demands, as indexed by slower RTs to produce a verbal response. Second, we apply these unconfounded measures to fMRI experiments, to ask what neural substrates support selection and retrieval processes during language production. Third, we ask how these brain areas support cognitive control processes, by first simulating possible mechanisms in a neural network model and then empirically testing the predictions from this model using pharmacological and clinical methods.

Chapter 2 reports two experiments that investigated underdetermined selection and retrieval of words from semantic memory in the verb generation task, which allows these cognitive control demands to be precisely quantified and independently manipulated. Participants are presented with noun cues (e.g., ball) and generate verbs to go with them (e.g., throw). Noun stimuli vary in how strongly they are associated with a verb response (e.g., ball has strongly associated verbs, while shelf has only weakly associated verbs), and how much competition there is between multiple verb responses (e.g., ball is associated with multiple verbs, while scissors is only associated with one verb). The results demonstrate strong independent behavioral effects of competition and association strength (Experiment 1), and that shared neural substrates in left VLPFC support both underdetermined selection and controlled retrieval (Experiment 2). In addition, underdetermined selection and retrieval demands interact: behavioral and neural selection costs were greater under low retrieval demands than under high
retrieval demands.

**Chapter 3** explores what mechanisms allow us to retrieve and select among multiple options when speaking. Current psychological theories of selection focus on the importance of cognitive control (e.g., Chapter 2, Snyder & Munakata, 2008) and prefrontal cortical regions (e.g., Chapter 2, Badre & Wagner, 2007; Thompson-Schill, 2005), but do not address questions at the level of specific neural mechanisms. We address these questions by implementing a unified, biologically plausible computational model that implements a version of the verb generation task using the Leabra framework (O'Reilly, 1998; O'Reilly & Munakata, 2000). This framework has been used to successfully model a wide variety of phenomena and make counter-intuitive predictions about human behavior that have later been confirmed (e.g., Frank & O'Reilly, 2006; Shinskey & Munakata, 2005). The model replicates the behavioral effects of retrieval and underdetermined selection demands in humans, and manipulations of competitive inhibition in the VLPFC layer of the model generate novel predictions regarding the effects of reduced GABAergic function associated with anxiety, and increased GABAergic function under GABA agonists, which are then tested empirically in Chapter 4.

**Chapter 4** reports four experiments testing the predictions from the neural network simulations. The key role played by competitive inhibition in the computational model discussed above suggests a role for GABAergic function in underdetermined selection. As predicted by the model, increased inhibition under the GABA agonist midazolam improved selection (Experiment 3), while anxiety (linked to reduced GABAergic function) was associated with impaired selection (Experiments 4 and 6) and reduced engagement of left VLPFC during selection (Experiment 5). These findings are specific to selection and anxiety, as retrieval was not affected (Experiments 3-5), and participants with co-occurring high dysphoria actually show better selection performance than those with high anxiety alone.
Chapter 5 reports an experiment (Experiment 7) designed to cleanly differentiate the neural substrates supporting selection between competing task-relevant responses (underdetermined selection) and selection of a valid response in the face of competition from a non-task-relevant prepotent response (prepotent selection). As in the previous experiments, participants completed a verb generation task, and noun stimuli varied in competition from multiple allowable verb responses (high and low underdetermined competition). Unlike in previous experiments, noun stimuli also systematically varied in the amount of competition from unallowable non-verb responses (high vs. low prepotent competition, e.g. *cat* is strongly associated with *dog*, but *dog* is not an allowable response in the verb generation task). Association strength was matched across conditions. This study allows the neural response to these two forms of competition to be directly compared in the same task for the first time. We find that left VLPFC is sensitive to underdetermined selection demands, but not prepotent selection demands, while an area of left DLPFC is sensitive to both underdetermined and prepotent competition. We explore possible neural mechanisms underlying these responses in an expanded version of the verb generation model, which suggests that top-down biasing from DLPFC is necessary to resolve competition from prepotent responses.

Chapter 6 provides a general discussion and synthesis of the findings, discusses limitations, and outlines future directions. Specifically, Chapter 6 discusses (i) the benefits and limitations of neural network modeling simplifications, (ii) the benefits and limitations of using laboratory language tasks which are well-controlled but lack ecological validity, and (iii) the broader context and implications of the research beyond the domain of language production, including language comprehension and selection in complex real-world domains.
CHAPTER 2: BEHAVIORAL AND NEURAL EFFECTS OF UNDERDETERMINED SELECTION AND RETRIEVAL

There is broad consensus that our ability to respond in less constrained language tasks requires cognitive control and is supported by processes subserved by left ventrolateral prefrontal cortical (VLPFC) regions. However, exactly what cognitive control processes are involved, and what this neural region does to support these fundamental cognitive processes, are strongly debated. As discussed in Chapter 1, three competing theories have been proposed, positing that left VLPFC subserves (1) selection among competing alternatives (e.g., Botvinick et al., 2001; Thompson-Schill, 2005), (2) controlled retrieval from semantic memory (e.g., R. C. Martin & Cheng, 2006; Wagner et al., 2001), or (3) selection and controlled retrieval in different regions of the VLPFC (two-process account; selection in mid-VLPFC and controlled retrieval in anterior VLPFC, e.g., Badre et al., 2005; Badre & Wagner, 2007). While each of these theories has been supported by some prior evidence, each has also been challenged by other findings. Resolving this debate will advance our understanding of language production, in addition to speaking to broader issues about the nature of the functional organization of PFC, and the neural bases for specializations of distinct subregions (e.g., Duncan & Owen, 2000; E. K. Miller, 2000; Petrides, 2005).

Suggestive evidence in favor of the two-process account comes from a recent review, which found that putative selection manipulations tended to activate left mid-VLPFC, while putative retrieval manipulations tended to activate left anterior-VLPFC (Badre & Wagner, 2007). However, the purity of the manipulations of selection and retrieval demands in these studies are debatable. For example, one of the included studies found that mid-VLPFC was more active for task-switch than task-repeat trials (Badre & Wagner, 2006), with the need to switch
characterized as solely a manipulation of selection demands (because the old and new task rules compete, Badre & Wagner, 2007). However, many theories of task-switching argue that switching also requires retrieving the new rule from memory (e.g., Altmann & Gray, 2008; Miyake, 2004). Thus, while this evidence could be interpreted as consistent with the two-process account, it could be re-interpreted as consistent with other accounts as well.

Relatively few studies have directly tested this two-process account by manipulating selection and retrieval demands within the same experiment, and those studies have yielded inconsistent results. Only one study has found evidence suggesting differential responses to retrieval and selection demands in left anterior and mid-VLPFC, respectively: in a lexical decision task, left anterior-VLPFC was more active for unprimed (thus harder to retrieve) than primed (easier to retrieve) words, while mid-VLPFC was more active for words preceded by an unrelated prime (presumably introducing competition) than unprimed words (Gold et al., 2006). However, region x condition interactions were not tested; thus, it is not clear if there is a full dissociation between these regions (as opposed to them supporting similar processes, with one contrast just failing to reach significance within each region, for example).

Three other experiments provide mixed results, finding selection or controlled retrieval in one or both regions of left VLPFC. In one experiment, participants decided which of two words was semantically related to a probe word: left anterior-VLPFC was specifically sensitive to the probe-target association strength (retrieval demand), while both left anterior and mid-VLPFC were more active when participants had to make a judgment based on a specific semantic feature (e.g., color, high selection demand) versus overall similarity (low selection demand; Badre et al., 2005). Likewise, in a task in which participants retrieved meanings of street signs, left anterior-VLPFC was more active for newly learned (high retrieval demand) than well-learned (low
retrieval demand) meanings, while left mid-VLPFC was sensitive to both retrieval demands and selection demands (one versus two sign meanings, Souza et al., 2009). Finally, in the verb generation task and a noun generation variant (Crescentini et al., 2010), manipulations of controlled retrieval and selection were interpreted as yielding, but did not clearly indicate, a dissociation between mid and anterior VLPFC. Specifically, although left mid-VLPFC was sensitive to selection demands and left anterior-VLPFC was sensitive to retrieval demands, each region also showed trends for sensitivity to the other demand, and region x condition interactions were either non-significant (verb generation task) or not tested (noun generation task). Moreover, the manipulation of retrieval demands seemed problematic, yielding effects in the noun generation task in the opposite direction from predictions (with greater activation in VLPFC when retrieval demands were low), and yielding no effects in the whole-brain analysis. Thus, the results are difficult to interpret and do not clearly indicate a dissociation between mid and anterior VLPFC.

Given this conflicting and inconclusive evidence, the debate about these fundamental cognitive processes, and the neural substrates that subserve them, is unresolved. In the current studies we use measures of selection and retrieval demand based on LSA (Snyder & Munakata, 2008 see Chapter 1), which allow us to examine these processes and their interaction in a way that was not previously possible. These purer, more theoretically justified measures of retrieval demands (LSA strength) and selection demands (LSA entropy) allow the effects of selection and retrieval demands to be unconfounded. Moreover, this design allowed us to examine interactions between selection and retrieval demands, something prior studies had been unable to do, as it was not possible to create a full 2 x 2 design with previously used measures of competition and association strength (Crescentini et al., 2010; R. C. Martin & Cheng, 2006). By using
unconfounded LSA-based measures of competition and association strength, and a full 2 x 2 design, we are able to test for main and interactive effects of underdetermined selection and retrieval demands on behavior (Experiment 1) and brain activity (Experiment 2) for the first time. We demonstrate that both underdetermined selection and controlled retrieval slow responding and activate the same regions of left VLPFC, contrary to previous theories. Moreover, selection and controlled retrieval interact behaviorally and in left VLPFC, with larger selection effects when retrieval demands are low.

**Experiment 1: Basic Behavioral Effects of Underdetermined Selection and Retrieval Demands**

**Method**

**Participants.** Participants were 85 young adults from the University of Colorado Boulder community who spoke English as a first language. An additional eight participants were excluded for not following task directions (n = 4), self-reported reading disorders (n = 2), and equipment failure (n = 2). All participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado Institutional Review Board.

**Design and stimuli.** Verb generation stimuli were 100 nouns in a 2 x 2 design: high and low retrieval demand (association strength between nouns and possible verb responses) crossed with high and low selection demand (degree of competition among alternative responses; Figure 2.1A). Association strength and competition were calculated as in Snyder & Munakata (2008), using latent semantic analysis (Landauer et al., 1998). The “general reading up to first-year college” corpus was used, and a term-to-term (nouns to verbs) comparison was used to obtain the LSA cosine (association strength) between the nouns and all verb responses generated by two or more participants in the norming sample. Association strength was calculated as the average of three measures: (i) the strongest LSA cosine, (ii) the LSA cosine for the most frequent response
given by the norming sample, and (iii) a weighted average of the LSA cosines for all verb responses given by the norming sample. Competition was defined as entropy \( H = -\sum (p(i) \ln p(i)) \), where \( p(i) \) is the cosine between the stimulus and each alternative response, divided by the sum of LSA cosines among all alternative responses. Therefore, entropy is 0 when there is only one response (e.g., the cosine is 1), and increases as additional responses are equally associated with the stimuli (Snyder & Munakata, 2008). Nouns with high association strength (with both high and low competition) were drawn from our previous work (Snyder & Munakata, 2008).

Because nouns with low association strength (with high or low competition) were not available from previous studies, they were selected from a large set of nouns normed for this study by a separate sample of participants \( n = 50 \). High and low association strength conditions were matched on LSA entropy, while high and low competition conditions were matched on association strength, allowing unconfounded effects of each variable to be assessed.

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1 One might ask whether association strength can truly be measured (or exist) independent of competition (e.g., Anderson & Reder, 1999). For example, if when a word occurs in the text corpus it represents a case in which the word’s synonyms were not used, does it decrease the association strengths of the synonyms with the co-occurring words in the text? This “push-pull” relationship between measures of association strength and competition would occur if our measures were based only on the co-occurrence of items in the text corpus, and if alternative responses in our high selection demand conditions were mutually exclusive across paragraphs of text, but neither is the case. The association strength estimates derived from LSA are not simple contiguity frequencies, co-occurrence counts, or correlations in usage (Landauer et al., 1998). Rather, they capture contextual information (the “latent” part of the semantic analysis), such that words can be strongly associated even if they never directly co-occur together, so long as they occur in contexts with similar meanings (Landauer et al., 1998). That is, LSA can accurately estimate the association strength between word pairs never observed together, by fitting them simultaneously in a higher-dimensional semantic space (Landauer & Dumais, 1997). In addition, alternative responses in the high selection demand conditions are not generally mutually exclusive synonyms but rather multiple actions associated with the noun. For example, talking about a cat purring in one sentence of a paragraph does not preclude talking about it licking in another sentence (or even within the same sentence), and since LSA learns associations over paragraphs rather than relying on simple contiguity, it would learn the association between cat and each of these verbs. Thus, our LSA-based measures do not involve an inherent trade-off such that nouns with multiple alternative verb responses have lower association strengths.
**Task and procedure.** Participants were instructed to say the first verb that came to mind when presented with a noun (e.g., *meow* or *feed* for *cat*), and were given an example and eight practice trials before completing the task. A fixation-cross appeared for 500 ms, followed by a noun. Participants responded by speaking into a microphone that recorded voice-triggered reaction times (RTs), and advanced the computer to the next trial. Trial order was randomized for each participant.

**Statistical methods.** When the microphone was accidentally triggered (e.g., by a cough) or an error made (a non-verb), the trial was eliminated from analysis. The data were trimmed to remove trials with RTs less than 200 ms or greater than three SDs above each participant’s mean. RTs were natural log transformed to normalize the data. Data were analyzed with a $2 \times 2$ repeated-measures ANOVA.

**Results**

There were significant main effects of both selection demand and retrieval demand. Specifically, RTs were longer in the high selection demand (log RT $M=7.70$, $SE=0.03$) than low selection demand conditions (log RT $M=7.53$, $SE=0.03$; $F(1,82)=215.9$, $p<0.001$), and longer in the high retrieval demand (log RT $M=7.78$, $SE=0.04$) than low retrieval demand (log RT $M=7.45$, $SE=0.03$) conditions ($F(1,82)=387.9$, $p<0.001$) (Figure 2.1 B). In addition, there was a significant interaction between selection and retrieval demands: selection costs were greater under low retrieval demands (log RT difference $M=0.20$, $SE=0.02$) than under high retrieval demands (log RT difference $M=0.13$, $SE=0.02$; $F(1,82)=12.1$, $p=0.001$; Figure 2.1 C).
**Figure 2.1.** Experiment 1 design and basic behavioral findings for the verb generation task. (A) Verb generation task design with example items. Selection demand (high versus low competition) is crossed with retrieval demand (high versus low association strength). Nouns in the high selection demand conditions have multiple possible verb responses, while nouns in the low selection demand conditions have few possible verb responses (quantified as the LSA entropy, see Methods). Nouns in the high retrieval demand conditions have only weakly associated verb responses, while nouns in the low retrieval demand conditions have strongly associated verb responses (quantified as the LSA cosine, see Methods). High and low selection demand conditions are matched on retrieval demand, and high and low retrieval demand conditions are matched on selection demand, allowing the effects of each to be examined. (B) Participants take longer to generate a response when retrieval demands are high and when selection demands are high. (C) Selection costs (RT difference between high and low selection demand conditions) are greater when retrieval demands are low than when they are high. All error bars are SEs.

**Experiment 2: Neural Substrates Supporting Underdetermined Selection and Retrieval**

**Method**

**Participants.** Eighteen healthy, right-handed, young adults (9 women) from the University of Colorado community participated in this study. Three additional subjects participated but were excluded from analysis due to excessively high error rates (>25%).
addition, one outlier was excluded from analysis. All subjects were native English speakers, had no history of neurological conditions or head injury, and were not taking any psychoactive medication. Subjects gave informed consent and were treated in accordance with procedures approved by the University of Colorado Institutional Review Board.

**Design and stimuli.** The verb generation task design and stimuli were the same as those in Experiment 1, except that the task was adapted for fMRI by fixing the timing of each trial and adding fixation trials to optimize the design (see Procedure).

**Procedure.** The verb generation task was administered as in Experiment 1. Subjects were given an example and eight practice trials prior to entering the scanner, and were reminded of the instructions prior to beginning the task. During image acquisition, subjects completed 25 trials in each condition, for a total of 100 trials. On each trial, subjects viewed a fixation point for 500 ms, followed by a noun cue for 3500 ms, and respond by saying a verb associated with the noun. Verbal responses are collected with a fiber-optic noise-canceling microphone (Optoacoustics Ltd., Or-Yehuda, Israel) via a procedure that has been found to minimize head motion (Barch, Sabb, Carter, Braver, & Noll, 1999). A rapid event-related paradigm was used: the sequence was optimized using Optseq (surfer.nmr.mgh.harvard.edu/fswiki/optseq2), including 50 null events (fixations) with a log jitter to maximize power. Presentation of items from each condition was intermixed, with first-order counterbalancing. Within-condition, item order was randomized across subjects. Data were acquired in one functional run, lasting about 9 minutes.

**Image acquisition and processing.** Data were acquired with a 3T GE Signal whole-body MRI scanner at the University of Colorado Health Sciences Center, using T2*-weighted echo,

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2 This subject showed an unusual pattern, with much higher activation in mid-VLPFC in the easiest experimental condition (low competition and high association strength Cook’s D $z=2.75$). The pattern of results remained the same when this subject was included, although power was slightly reduced.
echo-planer imaging (EPI; TR= 2000 ms, TE= 32 ms, flip angle= 70°). Functional data were collected in a single run of 258 EPI volumes, each consisting of 32 4 mm-thick slices (gap=0 mm, field-of-view (FOV)=220 mm, in-plane matrix= 64 x 64, in-plane resolution= 3.44 x 3.44 mm²), angled parallel to the AC-PC line. Prior to the functional run, high-resolution T1-weighted 3D IR-SPGR full head anatomical images were acquired along the coronal plane (TR=9 ms, TE=2 ms, flip angle=10°, inversion time=500 ms; 220 mm FOV, 256 x 256 matrix, 0.87 mm x 0.87 mm in-plane resolution, 124 slices, 1.7-mm slice thickness). The scanner was equipped with a standard head coil and participants’ heads were secured with moldable pillows to minimize head motion. Stimuli were displayed through fiber-optic goggles and participants responding by speaking into a fiber-optic noise-canceling microphone (Optoacoustics Ltd., Or-Yehuda, Israel) positioned directly above the mouth. All participants met our criteria for minimal head motion (< 2 mm translation/2° rotation in any direction).

Image pre-processing and analysis were largely conducted with FSL (FMRIB’s Software Library). After discarding the first six volumes of the run to allow the MR signal to reach steady state, the remaining images in each participant’s time series were motion corrected using MCFLIRT (Jenkinson & Smith, 2001), and non-brain voxels removed using BET. Images in the data series were spatially smoothed with a 3D Gaussian kernel (FWHM = 8 mm), intensity normalized for all volumes by the same factor, and high-pass filtered to remove high-frequency noise (σ=100 sec) was applied. After statistical analysis for each participant’s time series, the statistical maps (reflecting each participant’s response in each condition) were normalized into the common MNI-152 stereotaxic space, using FLIRT (FMRIB’s Linear Image Registration Tool, Jenkinson, Bannister, Brady, & Smith, 2002) before random effect group analyses were performed. Subsequent statistical analyses were conducted using FEAT (FMRIB’s Easy
Analysis Tool). GLM analyses of the fMRI time series data were conducted, then subjected to group-level random effects analysis.

**Results**

**Behavioral results.** Reaction time (RT) data were analyzed with a 2 x 2 repeated-measures ANOVA. Replicating Experiment 1, participants were slowed by greater competition (greater selection demand, $F(1,16)=119.16$, $p<.001$) and lower association strength (greater retrieval demand, $F(1,16)=578.80$, $p<.001$). Specifically, RTs were longer in the high competition (log RT M=7.70, SE=.02) than low competition (log RT M=7.62, SE=.02) conditions, and longer in the low association strength (log RT M=7.72, SE=.02) than high association strength (log RT M=7.60, SE=.02) conditions. Also consistent with previous results, the effects of competition (selection costs) were numerically higher under high association strength (low retrieval demands; log RT difference M=.10, SE=.01) than under low association strength (high retrieval demands; log RT difference M=.07, SE=.01), although the interaction did not reach significance given the small number of subjects ($F(1,16)=1.82$, $p=.197$).

**Left VLPFC region of interest analyses.** Region of interest (ROI) analyses were conducted for the key regions hypothesized to play a role in controlled retrieval and selection: left anterior-VLPFC and left mid-VLPFC. Spherical ROIs were defined around the mean coordinates identified in Badre and Wagner (2007) for left anterior-VLPFC (-48, 30, -6) and left mid-VLPFC (-50, 25, 14), with a radius of 10 mm (Figure 2.2 A).

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3 These ROIs were chosen because they represent the mean coordinates from six previous studies of selection and controlled retrieval, and are thus likely to be more reliable than coordinates from any individual study. To confirm that the results were not specific to the choice of ROI coordinates, additional analyses were conducted with anatomically defined ROIs for anterior-VLPFC (left inferior gyrus pars orbitalis) and mid-VLPFC (left inferior gyrus pars triangularis), and yielded the same pattern of results. We therefore report only the coordinate-based ROIs, which represent a stronger test of the two-process account.
Activation for each condition versus fixation baseline within each ROI was extracted for each participant and subjected to a 2 x 2 x 2 (competition x association strength x region) repeated measures ANOVA. There was a significant main effect of competition (selection demand), with greater activation in the high competition than low competition conditions ($F(1,16)= 15.32, p=.001$), and a significant main effect of association strength (retrieval demands).
demand), with greater activation in the low association strength than high association strength conditions \((F(1,16)= 21.53, p<.001)\). There was also a significant competition x association strength interaction: effects of competition were greatest when association strength was high (low retrieval demand; \(F(1,16)= 4.68, p=.046\)). There was no main effect of region \((F(1,16)= 0.27, p=.6)\). Importantly, there were no interactions with region (region x competition \(F(1,16)= 0.72, p=.4\); region x association strength \(F(1,16)= 0.95, p=.3\); region x competition x association strength \(F(1,16)= 0.09, p=.8\)).

Within each VLPFC ROI, main effects of competition and association strength were significant and the interaction between competition and association strength was marginal, as confirmed by \(2 \times 2\) (competition x association strength ANOVAS run for anterior and mid-VLPFC ROIs separately (anterior VLPFC: competition \(F(1,16)= 8.47, p=.01\), association strength \(F(1,16)= 16.11, p=.001\), competition x association strength interaction \(F(1,16)= 3.60, p=.076\); mid VLPFC: competition \(F(1,16)= 14.92, p=.001\), association strength \(F(1,16)= 22.39, p<.001\), competition x association strength interaction \(F(1,16)= 4.39, p=.052\). Thus, the left anterior and mid-VLPFC ROIs showed similar patterns of activity (Figure 2.2).

**Whole brain analysis.** In addition, exploratory whole-brain analyses were conducted for the following key contrasts: (1) high vs. low association strength, collapsing across levels of competition (controlled retrieval), (2) high vs. low competition, collapsing across levels of association (selection), (3) high vs. low competition with high association strength (selection with low retrieval demand), and (4) high vs. low competition with low association strength (selection with high retrieval demand; see Table 2.1, Figure 2.3).

In addition to mid (BA 45) and anterior (BA 47) left VLPFC, both competition and association strength manipulations engaged a larger frontal network, prominently including the
pre-supplementary motor area (pre-SMA) in the superior frontal gyrus and right VLPFC. As in the ROI analysis, competition effects are most apparent when association strength is high (retrieval demands are low). The association strength manipulation additionally recruited a wide network of other medial and lateral PFC areas. In addition, both competition and association strength manipulations activated posterior cortical areas, including temporal and occipital cortex.

**Figure 2.3.** Experiment 2 exploratory whole brain analysis activation. In addition to left VLPFC, both association strength (retrieval demand; A) and competition (selection demand) with high association strength (low retrieval demand; B) activate wider prefrontal networks, whereas competition with low association strength (high retrieval demand; C) activates medial frontal cortex (p < .05, two-tailed). A conjunction analysis confirms that association strength and competition with high association strength manipulations activate shared areas of left VLPFC and anterior cingulate/pre-SMA (D). Thus, prefrontal areas recruited by association strength manipulations (retrieval demand) are also recruited by competition manipulations (selection demand), even when association strength is high (retrieval demands are low). See Table 1 for all significant areas of activation in the whole-brain random effects analysis.
Table 2.1
Experiment 2 Peak Voxel Coordinates, Anatomical Locations, and Approximate Brodmann’s Areas from Exploratory Whole-Brain Random Effects Analysis

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Region</th>
<th>BA</th>
<th>Max Z</th>
<th>No. of voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection (high competition &gt; low competition, collapsing across levels of association strength)</td>
<td>Superior frontal gyrus (L)</td>
<td>6</td>
<td>3.30</td>
<td>181</td>
<td>-6</td>
<td>16</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (VLPFC) (L)</td>
<td>45</td>
<td>3.24</td>
<td>127</td>
<td>-44</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (VLPFC) (L)</td>
<td>47</td>
<td>3.07</td>
<td>103</td>
<td>-30</td>
<td>26</td>
<td>-16</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (VLPFC) (R)</td>
<td>47</td>
<td>2.98</td>
<td>59</td>
<td>36</td>
<td>28</td>
<td>-12</td>
</tr>
<tr>
<td></td>
<td>Medial frontal gyrus (R)</td>
<td>10</td>
<td>2.88</td>
<td>33</td>
<td>10</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Middle temporal gyrus (L)</td>
<td>21</td>
<td>3.00</td>
<td>41</td>
<td>-66</td>
<td>-28</td>
<td>-6</td>
</tr>
<tr>
<td></td>
<td>Middle temporal gyrus (R)</td>
<td>21</td>
<td>3.15</td>
<td>36</td>
<td>56</td>
<td>10</td>
<td>-36</td>
</tr>
<tr>
<td></td>
<td>Inferior occipital gyrus (R)</td>
<td>17</td>
<td>3.01</td>
<td>42</td>
<td>16</td>
<td>-92</td>
<td>-8</td>
</tr>
<tr>
<td></td>
<td>Lingual gyrus (L)</td>
<td>18</td>
<td>3.09</td>
<td>63</td>
<td>-14</td>
<td>-92</td>
<td>-14</td>
</tr>
<tr>
<td>Selection w/ Low Retrieval Demands (high competition/high association strength &gt; low competition/high association strength)</td>
<td>Inferior frontal gyrus (VLPFC) (L)</td>
<td>45</td>
<td>3.18</td>
<td>362</td>
<td>-42</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus (L)</td>
<td>6</td>
<td>3.17</td>
<td>245</td>
<td>-6</td>
<td>14</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (R)</td>
<td>47</td>
<td>3.23</td>
<td>68</td>
<td>42</td>
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<td>Parahippocampal gyrus (R)</td>
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<td>3.03</td>
<td>94</td>
<td>16</td>
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<td>-16</td>
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<td>Inferior temporal gyrus (L)</td>
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<td>75</td>
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<td>-4</td>
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<td></td>
<td>Middle temporal gyrus (L)</td>
<td>21</td>
<td>2.93</td>
<td>53</td>
<td>-68</td>
<td>-30</td>
<td>-4</td>
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<tr>
<td></td>
<td>Superior temporal gyrus (L)</td>
<td>38</td>
<td>3.23</td>
<td>254</td>
<td>-42</td>
<td>24</td>
<td>-26</td>
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<tr>
<td></td>
<td>Brainstem</td>
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<td>-30</td>
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<td>Brainstem</td>
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<td>-34</td>
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<tr>
<td>Selection w/ High Retrieval Demands (high competition/low association strength &gt; low competition/low association strength)</td>
<td>Medial frontal gyrus</td>
<td>10</td>
<td>2.80</td>
<td>29</td>
<td>10</td>
<td>54</td>
<td>18</td>
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</tbody>
</table>

Retrieval (low association strength> high association strength, collapsing across levels of competition) | Large left/medial frontal cluster: | 5.38 | 11947 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Local maxima*</td>
<td>Superior frontal gyrus (L)</td>
<td>6</td>
<td>5.38</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus (R)</td>
<td>6</td>
<td>3.70</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus (L)</td>
<td>8</td>
<td>4.53</td>
</tr>
<tr>
<td></td>
<td>Anterior cingulate (L)</td>
<td>32</td>
<td>3.09</td>
</tr>
<tr>
<td></td>
<td>Anterior cingulate (R)</td>
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<td>3.03</td>
</tr>
<tr>
<td></td>
<td>Cingulate gyrus (L)</td>
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<td>Middle frontal gyrus (L)</td>
<td>11</td>
<td>2.90</td>
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<td></td>
<td>Medial frontal gyrus (L)</td>
<td>6</td>
<td>5.03</td>
</tr>
<tr>
<td></td>
<td>Medial frontal gyrus (L)</td>
<td>8</td>
<td>2.94</td>
</tr>
</tbody>
</table>
Insula (L) | 13 | 3.77 | -48 | 12 | 2
---|---|---|---|---|---
Large right frontal cluster: | | | | |
Local maxima*: | | | | |
Inferior frontal gyrus (VLPFC) (R) | 45 | 2.85 | 60 | 20 | 6
Inferior frontal gyrus (VLPFC) (R) | 47 | 3.91 | 52 | 26 | -6
Middle frontal gyrus (R) | 11 | 2.68 | 40 | 40 | -20
Superior frontal gyrus (L) | 10 | 3.98 | 978 | -26 | 46 | 24
Superior frontal gyrus (R) | 9 | 3.29 | 364 | 30 | 52 | 32
Middle frontal gyrus (R) | 6 | 3.35 | 80 | 50 | 6 | 44
Middle frontal gyrus (R) | 11 | 2.93 | 36 | 44 | 50 | -18
Superior frontal gyrus (R) | 10 | 3.15 | 26 | 26 | 62 | -12
Middle frontal gyrus (R) | 8 | 2.94 | 20 | 44 | 26 | 42
Large posterior cortical cluster: | | | | |
Local maxima*: | | | | |
Cuneus (R) | 17 | 2.76 | 20 | -76 | 2
Lingual gyrus (L) | 17 | 4.12 | -16 | -94 | -12
Lingual gyrus (L) | 18 | 4.08 | -2 | -96 | -18
Lingual gyrus (R) | 18 | 4.28 | 14 | -88 | -16
Middle occipital gyrus (L) | 19 | 3.86 | -26 | -84 | 18
Middle occipital gyrus (R) | 19 | 3.38 | 30 | -84 | 10
Middle temporal gyrus (L) | 21 | 3.94 | -56 | -48 | -2
Superior temporal gyrus (L) | 22 | 2.69 | -66 | -60 | 12
Precuneus (R) | 31 | 3.56 | 30 | -76 | 14
Fusiform gyrus (L) | 37 | 3.31 | -48 | -66 | -22
Superior temporal gyrus (R) | 22 | 2.90 | 28 | 34 | -56 | 16
Middle temporal gyrus (R) | 21 | 2.72 | 20 | 52 | -26 | -10
Precuneus (R) | 7 | 3.20 | 26 | 4 | -84 | 44
Fusiform gyrus (R) | 37 | 2.93 | 20 | 36 | -52 | -26

Note. All clusters z>2.58, p<.01, two-tailed. BA= Brodmann’s area, L= left, R=right.
* When there was more than one local maximum in the same BA and hemisphere, the peak with the highest maximum Z is reported.

Discussion

Experiments 1 and 2 used LSA-based measures to unconfound competition and association strength, which revealed main and interactive effects of underdetermined selection and retrieval demands on RTs and activation of left VLPFC. Specifically, RTs were slowed and left VLPFC was more active when there was high competition between alternative responses (revealing an effect of underdetermined selection demand), and when possible responses were weakly associated with the noun cue (revealing an effect of retrieval demand). Moreover,
selection and controlled retrieval interact, with RTs and activation of left VLPFC increasing with greater demands on selection, when retrieval demands are low. When retrieval demands are high, selection demands resulted in a smaller RT cost and did not modulate the observed activation of VLPFC. It is possible that when retrieval demands are high, selection costs may be partially offset by the advantage multiple responses confer on retrieval (see Chapter 3). Thus, it may be impossible to observe an effect of selection demands if retrieval demands are high, potentially explaining the null results for selection manipulations in some previous studies. This finding also suggests that future studies investigating selection processes should seek to minimize retrieval demands in order to increase power for observing selection effects.

Critically, in the current study both mid and anterior VLPFC show nearly identical profiles, with no significant interactions between region and any task condition. Thus, the same regions of left VLPFC support both selection and controlled retrieval, and these processes interact. These results challenge previous accounts, and may help to explain mixed findings in the prior literature. Previous studies of selection and retrieval during language production used response-frequency based measures that were highly correlated, such that conditions differing on one measure also differed on the other, confounding retrieval and selection demands. Two recent studies attempted to address this problem by creating high and low selection demand conditions matched on retrieval demand, and high and low retrieval demand conditions matched on selection demand (Crescentini et al., 2010; R. C. Martin & Chang, 2006). However, attempting to separate highly collinear variables in this way tends to produce severe restrictions of range and thus low power and manipulation failures. Indeed, a re-analysis of Martin & Cheng’s (2006) conditions with LSA-based measures revealed that the high and low selection demand conditions did not actually differ in competition (while the high and low retrieval demand conditions did
differ in association strength), likely explaining the failure to find an effect of selection demand in this study (Snyder & Munakata, 2008). It is likely that a similar manipulation failure occurred for retrieval demands in Crescentini et al. (2010), given the failure to find an effect of retrieval demand in the whole-brain analysis, and unexpected results in the ROI analyses (greater VLPFC activation in the low retrieval demand condition for the noun-generation task). Thus, previous attempts to disentangle the effects of selection and retrieval demands have proved unsatisfactory. Using LSA-based measures to disentangle these factors, the results of the current study challenge previous theories that posit a single role of left VLPFC in either selection or retrieval, or a functional dissociation between mid and anterior VLPFC.

Given that the current study found that shared neural substrates in VLPFC responded to both selection and retrieval demands, one could argue that these manipulations might affect a single process rather than separate selection and controlled retrieval processes (e.g., J. R. Anderson & Reder, 1999). For example, it has been proposed that VLPFC activity is determined by a single memory activation value, which depends on the association strength between cues and items in memory, such that when multiple items are associated with the memory cue, the association strength of each is weakened by competition (Danker et al., 2008). Items with lower activation values are retrieved more slowly and require more control (and thus more VLPFC activity) than those with higher activation values (Danker et al., 2008).

While this account is consistent with results presented here, other evidence indicates that selection and controlled retrieval processes are separable (but interacting) at the level of neural mechanisms, as discussed in Chapters 3 and 4. Specifically, as predicted by a neural network

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4 A formal re-analysis with LSA-based measures cannot be carried out because the tasks were in Italian, for which there is currently no LSA corpus.
model of the verb generation task, selection and retrieval processes can be dissociated through
the effects of neural inhibition (Experiments 3-6). Thus, rather than favoring a single-process
account, we posit that the same areas of left VLPFC support both selection and controlled
retrieval through partially dissociable neural mechanisms.

Future work along (at least) three lines is needed to fully understand selection and
retrieval processes for verbal as well as non-verbal material. First, although mid and anterior
VLPFC both contribute to selection and retrieval, they could potentially act on different types of
representations of the same stimuli. For example, several theories posit a rostral-caudal gradient
in PFC, with representations becoming increasingly abstract in more anterior areas (e.g., Badre,
2008; Petrides, 2005). Thus, it is possible that anterior-VLPFC retrieves and selects among more
abstract semantic representations of the response options, while mid-VLPFC acts on less abstract
(e.g., lexical) representations of the same responses. This possibility could be tested in future
studies that manipulate the abstractness of the relevant representations. Second, the current study
focused exclusively on selection and controlled retrieval during language production, and future
work is needed to determine whether these findings extend to other domains.

Finally, while we have focused here on the role of left VLPFC, both selection and
retrieval processes clearly tap a larger network of brain areas, including other prefrontal regions
and posterior cortical areas involved in representing semantic knowledge. Of particular interest,
posterior dorsal anterior cingulate cortex extending into the pre-supplementary motor area
(pdACC/pre-SMA) was robustly activated by both selection and retrieval demands. In the
cascade model (e.g., Banich, 2009; Milham & Banich, 2005), this region is involved in guiding
responding when earlier prefrontal processing areas have failed to exert adequate top-down
control (see Silton et al., 2010 for ERP evidence). While this model was developed based on
evidence from the Stroop task and focused on interactions with dorsolateral PFC (rather than VLPFC), pdACC/pre-SMA may play a similar role during language production, as a final stage of control when left VLPFC has not been fully effective in retrieving or selecting words. Future research could test this possibility by investigating the temporal dynamics of the activation of left VLPFC and pdACC/pre-SMA, potentially through combined ERP/fMRI studies.

In sum, the findings of the current study enable a synthesis and reinterpretation of prior evidence, and suggest that the ability to respond in language tasks requiring cognitive control is affected by both selection and retrieval mechanisms subserved by left VLPFC, and these processes interact in meaningful ways. Better understanding these fundamental aspects of language production may ultimately have implications for better understanding and treating language impairments associated with VLPFC damage, as well as more subtle deficits associated with psychopathology (e.g., anxiety, Chapter 4). Finally, beyond the domain of language, these findings may have broader implications for understanding the functional organization of prefrontal cortex by illustrating how what have been conceptualized as distinct cognitive processes can be supported by shared neural substrates.
CHAPTER 3: COMPUTATIONAL MECHANISMS FOR UNDERDETERMINED SELECTION AND CONTROLLED RETRIEVAL

What mechanisms allow us to retrieve and select among multiple options when speaking? Current psychological theories of controlled retrieval and selection focus on the importance of cognitive control (Snyder & Munakata, 2008) and prefrontal cortical regions (e.g., Badre & Wagner, 2007; Barch et al., 2000; Thompson-Schill, 2005), but do not address questions at the level of specific neural mechanisms. Likewise, Experiments 1 and 2 (Chapter 2) demonstrated that selection and retrieval slow responses and activate left VLPFC, but do not address the specific mechanisms within VLPFC that may support these processes. We address these questions by implementing a unified, biologically plausible computational model of the verb generation task, and testing its predictions about both brain and behavior (Chapter 4). Our model simulates and provides a framework for understanding these findings. The model uses a powerful framework that simulates the electrophysiological properties of neurons and can use networks of such neurons to simulate human behavior, including language and cognitive control.

Our model demonstrates how competitive, inhibitory dynamics among neurons in prefrontal cortical networks (Herd et al., 2006) support selection between alternatives. Specifically, these competitive dynamics serve to sharpen cognitive representations by amplifying activity in the most active, task-relevant, representations (e.g., the most appropriate word to complete a sentence) and suppressing competing representations (e.g., for the many other word possibilities). A tenet of the model is that these critical dynamics occur via inhibitory, GABAergic interneurons (Bagary et al., 2000; Jansen et al., 2006; Phillips & Silverstein, 2003). Our model demonstrates how reduced GABAergic function can lead to reduced competitive dynamics in prefrontal cortical networks, allowing non-winning competitors (alternative
responses that are not selected) to become more active and to compete over a longer period, which impairs selection. Conversely, increased GABAergic function leads to lower and briefer activation of these competitors and to improvements in selection. These basic mechanisms provide a unified framework for understanding how we make choices in language, to a degree of precision that allows us to test (and confirm) predictions through neuropharmacological manipulation, links to psychopathology, and levels of brain activity, as discussed in Chapter 4.

**Neural Network Model**

The model implements a version of the verb generation task in a biologically-plausible neural network using the Leabra framework (O'Reilly, 1998; O'Reilly & Munakata, 2000) as implemented in Emergent (grey.colorado.edu/emergent). Details of the Leabra modeling framework are given in the Appendix. The model contains layers (simulated brain areas) that simulate the following: (i) presentation of noun stimuli, (ii) activation of associated verb responses in the posterior cortex, (iii) selection of responses in the VLPFC, and (iv) output of a response (Figure 3.1 A). The strength of connections between nouns and associated verb responses and between alternative verb responses were set according to the known association strengths observed in humans (Landauer et al., 1998); these connections support spreading activation between related semantic representations like that observed in posterior cortex. Simulated neurons in the posterior cortex layer then activate verb representations in the VLPFC layer, which implements competitive lateral inhibition, selecting one response for output.

**Verb Generation Model**

Table 3.1 lists parameter values, nearly all of which are at their default settings. These same parameters and equations have been used to simulate more than 40 different models (O'Reilly & Munakata, 2000). Thus, the model can be viewed as an instantiation of a systematic
modeling framework using standardized mechanisms, instead of constructing new mechanisms for each model. Model development and testing proceeded in two phases. First, the specifics of the basic model were shaped to capture the basic pattern of behavioral data (main effects of selection and retrieval demands, and an interaction). Second, to simulate increased and decreased competitive lateral inhibition, only the parameter of interest (kWTA) was manipulated, whereas all other parameters remained unchanged. Each phase is detailed in the simulation section below.

Table 3.1

Parameters for Neural Network Model Simulations

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<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
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<td>$g_i$</td>
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<td>$g_e$</td>
<td>1.0</td>
</tr>
<tr>
<td>$V_{rest}$</td>
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<td>$\Theta$</td>
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<tr>
<td>$\tau$</td>
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<td>$\varepsilon$</td>
<td>.01</td>
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<tr>
<td>$\gamma$</td>
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</tbody>
</table>

*Note. See equations in Appendix for explanation of parameters. All are standard default parameters except for those with an * (see Footnote 5).*

**Input layer.** The input layer consisted of four units, representing the average noun for each of the four conditions used: low competition/high association strength, high competition/high association strength, low competition/low association strength, and high competition/low association strength conditions. The weights between these input units and their verb response units in the posterior cortex layer were set as a function of LSA cosines, averaged across all items in the corresponding condition of Experiment 1. The weights between the input units and their verb response units in the posterior cortex layer, and between alternative verb response units in the posterior cortex layer, were set to the average LSA-based association strength measures for each condition of Experiment 1, scaled to 75%. This scaling served to ground the arbitrary units of LSA cosines so that the balance between selection and retrieval difficulty in the model matched the basic human data, allowing the effects of inhibitory
manipulations to be tested. LSA cosines were obtained using the “general reading up to first-year college” topic space (Landauer & Dumais, 1997). The two high competition condition units each project to six verb units in the posterior cortex layer (reflecting the average number verb associates in the human task for these conditions), whereas the two low competition condition units each project to one verb unit in the posterior cortex layer, reflecting the conditions in the behavioral experiments.

**Posterior cortex layer: Spreading semantic activation.** The posterior cortex layer contains one unit for each alternative verb response (six units each for the high competition conditions, one unit each for the low competition conditions, for a total of 14 units).\(^5\) We view these verb responses as being represented in a distributed manner across multiple posterior cortical areas (e.g., visual features in visual association areas, auditory features in auditory association areas, and semantic processing in lateral temporal lobes, as in Patterson, Nestor, & Rogers, 2007). Units in the high competition conditions have lateral connections to one another, set according to the average LSA cosines between each pair of verb associates in that condition in the human task. Thus, the posterior cortex layer simulates spreading semantic activation in posterior cortex. Each posterior cortex layer unit projects to one unit in the VLPFC layer and one unit in the output layer.

**VLPFC: Implementing selection.** The VLPFC layer contains one unit for each alternative verb response, as in the posterior cortex layer: six units each for each high

---

\(^5\) Because this is a small, localist network, the gain parameter on the noisy x/x+1 activation function was reduced to 50, nvar = 0.05 (variance of the Gaussian noise kernel), and the leak current was set to 0.21. kWTA was set to average maximum point inhibition, kWTA pt = 0.2 (which determines how far between the average and maximum activation inhibition is set), pct = 0.375 (desired level of activity over entire layer, note that this level is set to allow all six units in the high-competition conditions to become active).
competition condition and one unit for each low competition condition. VLPFC units are recurrently connected to themselves, and project back to their respective posterior cortex layer units, and to their output units. The VLPFC layer implements selection through strong kWTA competitive inhibition (kWTA average inhibition = 2). Leabra uses a kWTA function to achieve inhibitory competition among units within a layer (area). The kWTA function computes a uniform level of inhibitory current for all units in the layer, such that the k+1th most excited unit within a layer is below its firing threshold, whereas the kth is above threshold. Activation dynamics similar to those produced by the kWTA function have been shown to result from simulated inhibitory interneurons that project both feedforward and feedback inhibition (O’Reilly & Munakata, 2000). Thus, although the kWTA function is somewhat biologically implausible in its implementation (e.g., requiring global information about activation states and using sorting mechanisms), it provides a computationally effective approximation to biologically plausible inhibitory dynamics. In simulations of selection effects, the level of kWTA inhibition was manipulated by adjusting the kWTA pt parameter (which determines how far between k and k+1 inhibition is set) between 0.62 and 0.68.

Model Simulations

To explore potential mechanisms involved in controlled retrieval and selection, model parameters were first adjusted to simulate the basic behavioral effects in the verb generation task: independent effects of selection and retrieval demands and an interaction between these two

---

For simplicity, we model verb representations in VLPFC as direct copies from posterior cortex. Although PFC representations may be more abstract (Badre & Wagner, 2007) and more dynamic (Cohen & Miller, 2001) than posterior cortical representations, our investigation focuses on the mechanisms of selection that operate over these representations, regardless of their particular form. The strength of the recurrent VLPFC connections was set to 0.90 for all simulations. As in the posterior cortex layer, gain of the noisy x/x+1 activation function was set to 50, nvar = 0.05, and leak current to 0.21.
factors. Vm trial noise was added (Gaussian distribution with M = 0, var = 0.00005) and 85 simulations were run (equaling the number of participants in Experiment 1). To test the effects of decreased neural inhibition, the kWTA pt parameter in the VLPFC layer was reduced from 0.66 to 0.62 in increments of 0.01, and 30 simulations were run at each level. To test the effect of increased neural inhibition, the kWTA pt parameter in the VLPFC layer was increased from 0.66 to 0.68 in increments of 0.01, and 30 simulations were run at each level.

**Model Simulation Results**

As in human participants, the model generates longer settling times (cycles to generate a response) when retrieval demands are high (low association strength) than when retrieval demands are low (high association strength), with an average retrieval cost of 33.5 cycles (Figure 2B). Also as in human participants, the model produces longer settling times in the high selection demand (high competition) compared with low selection demand (low competition) conditions, with an average selection cost of 22.6 cycles (Figure 2B). The model also produces the interaction found in human data: selection costs are higher when retrieval demands are low (26.0 cycles) than when retrieval demands are high (19.2 cycles; Figure 2C).

---

A simple manual search was conducted over (i) gain (between 20 and 100) and variance (between 0.02 and 0.05) of the noisy x/x +1 activation function, (ii) the leak current (between 0.1 and 0.25), (iii) recurrent connection strength in the VLPFC layer (from 0.85 to 1), and (iv) the kWTA pt parameter (which determines how far between k and k+1 inhibition is set) in the VLPFC layer (between 0.6 and 0.8) to achieve a qualitative match to results. The basic pattern of results (independent effects of selection and retrieval demands) was never violated within this set of parameters. The kWTA pt parameter was set to 0.66 in the VLPFC layer, and all other parameters were set as described above for each layer.
Reducing kWTA inhibition increases selection costs, while increasing kWTA inhibition reduces selection costs, with these effects being more robust when retrieval demands are low.

Specifically, reducing inhibition increases selection costs to a greater degree under low retrieval demand than under high retrieval demand, and increasing inhibition reduces selection costs only under low retrieval demand. In contrast, neural inhibition does not affect retrieval processes. The full pattern of model simulations is provided in Figure 3.2 and Table 3.2. Figure 3.3 shows network dynamics, plotting changes in activation of VLPFC units over time for each condition and at standard, increased, and reduced inhibition levels.\(^8\)

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\(^8\) Note that because the model uses kWTA to mathematically calculate inhibition, rather than including separate inhibitory units, the activation level of the layer represents only the excitatory activity, not the total neural activity of the simulated brain region, and thus should not be the basis of predicting fMRI BOLD signal.
The effects of retrieval demands, selection demands, and inhibition can be understood in terms of the activation dynamics of units in the VLPFC layer. Figure 3.3 illustrates the following: (i) retrieval demands affect the onset of VLPFC unit activations, with units starting to become active later under high retrieval demands, because the reduced connection strengths into posterior cortex lead units to become activated more slowly there; (ii) selection demands affect the slope and asymptote of VLPFC unit activations, with units becoming active more gradually and reaching a lower asymptote under high selection demands, because of the competition from alternative responses; and (iii) manipulations of inhibition in VLPFC affect selection processes, as indexed by their effects on the slope and asymptote (but not onset) of unit activations for the winners, with reduced inhibition leading to prolonged activation of alternative responses. These activation graphs also convey the basis for the interaction between retrieval and selection demands: When retrieval demands are low so the onset to activating options is fast, increases in
selection demands decrease the slope and asymptote of unit activations as units compete. In contrast, when retrieval demands are high so the onset to activating options is slow, increases in selection demands not only decrease the slope and asymptote of unit activations as units compete, but also speed the onset of activation via spreading activation from competitors.

Table 3.2. 
Response Times (Cycles to Settle) Across Network Manipulations of Competitive Inhibition (kWTA pt).

<table>
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<th>Inhibition Level (kWTA pt)</th>
<th>.68</th>
<th>.67</th>
<th>.66</th>
<th>.65</th>
<th>.64</th>
<th>.63</th>
<th>.62</th>
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<tr>
<td>Low Retrieval Demand</td>
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<td>63.2</td>
<td>63.0</td>
<td>63.1</td>
<td>63.3</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Low Retrieval Demand</td>
<td>83.6</td>
<td>83.9</td>
<td>88.6</td>
<td>95.9</td>
<td>108.1</td>
<td>124.7</td>
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<td>Low Selection Demand/</td>
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</tr>
<tr>
<td>High Retrieval Demand</td>
<td>99.9</td>
<td>100.1</td>
<td>100.0</td>
<td>100.2</td>
<td>100.2</td>
<td>100.0</td>
<td>99.5</td>
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<td>High Selection Demand/</td>
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</tr>
<tr>
<td>High Retrieval Demand</td>
<td>118.7</td>
<td>119.1</td>
<td>118.7</td>
<td>119.2</td>
<td>120.3</td>
<td>128.6</td>
<td>140.2</td>
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<tr>
<td>Selection Cost with</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low Retrieval Demand</td>
<td>20.2</td>
<td>20.7</td>
<td>25.6</td>
<td>32.8</td>
<td>44.8</td>
<td>60.1</td>
<td>76.8</td>
</tr>
<tr>
<td>Selection Cost with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Retrieval Demand</td>
<td>18.7</td>
<td>19.1</td>
<td>18.7</td>
<td>19.0</td>
<td>20.1</td>
<td>28.6</td>
<td>40.7</td>
</tr>
<tr>
<td>Overall Selection Cost</td>
<td>19.5</td>
<td>19.9</td>
<td>22.1</td>
<td>25.9</td>
<td>32.5</td>
<td>44.9</td>
<td>58.7</td>
</tr>
</tbody>
</table>

Note. An inhibition level of .66 served as the baseline based on qualitative fits with basic behavioral results. From there, decreases in inhibition (simulating the effects of anxiety) led to increased response times when selection demand was high, while increases in inhibition (simulating the effects of midazolam) led to reduced response times when selection demand was high and retrieval demand was low.

The lack of effect of inhibition on retrieval costs can be understood most clearly when selection demands are low. In this case, there is one associated response and thus no spreading activation. Retrieval is directly governed by the synaptic weights (association strengths) between the noun stimulus and the associated verb response in the posterior cortex layer; weaker weights cause a slower buildup of activation, requiring more time to reach the threshold for generating a response. Thus, competitive neural inhibition does not affect retrieval when selection demands are low. In contrast, when selection demands are high, increasing inhibition speeds processing under both low and high retrieval demand, by allowing the target response to win the competition with alternative responses more rapidly. Although retrieval cost (the difference
between high and low retrieval demand conditions) does increase as inhibition increases when selection demands are high, this increase arises because increases to inhibition speed the resolution of the competition even more when retrieval demands are low than when retrieval demands are high (the interaction between retrieval and selection demands), not because increased inhibition slows processing more with high than with low retrieval demand.

**Figure 3.3.** Activity of VLPFC units in each simulation condition. Selection demands and inhibition affect the slope and height of activations, with more competitors leading to a slower rise and lower asymptote for winning units (A), and reduced inhibition leading to higher and prolonged activation of competitors (B). When selection demands are low, competitive neural inhibition does not affect network dynamics; winner trajectories across different levels of inhibition overlap with the single trajectories shown. Retrieval demands affect the onset of VLPFC unit activations, with units starting to become active later under high retrieval demands, because the reduced connection strengths into posterior cortex lead units to become activated more slowly. When retrieval demands are high, increases in selection demands also speed the onset of winner activation via spreading activation from competitors in posterior cortex. Activity is plotted in terms of the product of unit activation and net input, to capture differences in synaptic drive (net input) and effects of inhibition on activation.
Discussion

Like people, the model takes longer to respond when retrieval or selection demands are high. The effects of retrieval demand are a direct consequence of the strength of the synaptic weights between a stimulus and its response representation in the posterior cortex layer (Wagner et al., 2001); weaker weights cause a slower buildup of activation, requiring more time to reach the threshold for generating a response. Selection demand increases when multiple alternative responses become simultaneously active and competition must be resolved to select a single response. In the model, this resolution is accomplished through strong lateral inhibition in the VLPFC layer, simulating the effects of GABAergic interneurons.

In addition, the model replicates the interaction between selection and retrieval demands found in Experiments 1 and 2, and provides insight into why such an interaction occurs. When responses are easily retrieved, activating multiple responses serves only to generate competition, imposing a large selection cost. However, when it is difficult to retrieve any response, activating multiple responses aids retrieval, as spreading activation between these weakly associated alternatives (e.g., between hold and store when generating a response for shelf) boosts their activation levels. Thus, when retrieval demands are high, selection costs are partially offset by the advantage multiple responses confer on retrieval.

Manipulations of competitive inhibition in the VLPFC layer of the model enabled us to generate novel predictions regarding the effects of reduced and increased GABAergic function, which are tested empirically in Chapter 4. These simulations showed that competitive inhibition is critical for selection between competing alternatives, and that the effect of competitive inhibition on selection is modulated by retrieval demands. Decreasing competitive inhibition impairs selection, whereas increasing competitive inhibition improves selection. These effects of
competitive inhibition on selection are more robust when retrieval demands are low. When retrieval demands are high, increased neural inhibition increases competitive dynamics that support selection, but also reduces spreading activation that aids retrieval, leading to weaker effects. In contrast, changes in competitive inhibition do not affect retrieval when selection demands are low (i.e., there is one associated response and thus no spreading activation).

The simulations predict that reduced neural inhibition, associated with anxiety, will impair selection and associated VLPFC activity (Buzsáki, Kaila, & Raichle, 2007; Logothetis, 2008 Chapter 4), whereas increased neural inhibition under the GABA agonist midazolam will improve selection (Chapter 4). These effects may be more apparent when retrieval demands are low. In addition, retrieval should not be affected by changes in neural inhibition when selection demands are low. These predictions were supported in empirical investigations, as discussed in Chapter 4.
CHAPTER 4: BEHAVIORAL TESTS OF NEURAL NETWORK PREDICTIONS

The key role played by competitive inhibition in the neural network model discussed in Chapter 3 suggests a role for GABAergic function in selection. These simulations demonstrate how reduced GABAergic function can lead to reduced competitive dynamics in prefrontal cortical networks. This allows stronger representations of competitors, which causes impairments in selection, but not retrieval, of responses. Conversely, the model predicts that increased inhibition should improve selection when retrieval demands are low. These predictions were tested in four experiments.

We tested the prediction that increased neural inhibition should improve selection in Experiment 3, a double-blind, placebo-controlled study in which participants completed the verb generation task after injection of the GABA agonist midazolam as compared with a saline control in two counterbalanced sessions. Midazolam is a benzodiazepine that potentiates the binding of GABA to GABA-A receptors throughout the brain (Reinsel et al., 2000). Clinically, it is frequently used for conscious sedation during medical procedures, and to treat anxiety (Hirshman, Passannante, & Arndt, 2001). Experimentally, even at non-sedating doses, midazolam produces a dense but temporary anterograde amnesia, which is believed to arise from impairment of encoding and consolidation of episodic memories in the hippocampus (Hirshman et al., 2001). Suggestive evidence relevant to the current investigation includes the findings that left prefrontal cortical regions are also affected by midazolam (Bagary et al., 2000; Jansen et al., 2006; Reinsel et al., 2000), whereas retrieval from semantic memory is unimpaired (Hirshman et al., 2001); however, the effects of midazolam on selection have not previously been investigated.

We tested the prediction that decreased inhibition should be associated with impaired selection in Experiment 4, and with impaired recruitment of VLPFC during selection in
Experiment 5. These experiments examined the relation between trait anxiety (linked to reduced GABAergic function) and behavioral and neural underdetermined selection and controlled retrieval effects during verb generation. People with anxiety disorders find coping with too many options particularly difficult, and struggle with decision-making problems (e.g., Sachdev & Malhi, 2005), indecisiveness (e.g., Abramowitz, 1998), and intolerance of uncertainty (e.g., Starcevic & Berle, 2006). Whereas decision-making deficits in persons with anxiety have previously been shown in complex or affective tasks, our model predicts that selection deficits that lie at the core of these problems should be observed even in a simple language production task, whereas other cognitive processes should remain intact.

Reduced GABAergic function has been linked to anxiety disorders and increased trait anxiety. First, drugs that increase GABA transmission (e.g., benzodiazepines, tiagabine, neurosteroids) have powerful anxiolytic effects, while drugs that decrease GABA transmission precipitate anxiety (for reviews see Lydiard, 2003; Möhler, 2012). Second, magnetic resonance spectroscopy and PET evidence demonstrates that anxiety is associated with reduced GABA levels (Goddard et al., 2001; Pollack, Jensen, Simon, Kaufman, & Renshaw, 2008; Streeter et al., 2010; but see, Hasler et al., 2009) and receptor binding (Hasler et al., 2008), and an experimental manipulation of anxiety decreased prefrontal GABA levels (Hasler, van der Veen, Grillon, Drevets, & Shen, 2010). Third, a number of polymorphisms in genes coding for components of the GABAergic system are associated with anxiety (Arias et al., 2012; Hettema et al., 2006; Sen et al., 2004; Smoller et al., 2001; Thoeringer et al., 2007; Unschuld et al., 2009; Zai et al., 2005). Thus, we tested the prediction that reduced neural inhibition in anxiety would be associated with impaired selection. Experiment 5 investigates the effects of anxiety on neural activity during selection and retrieval. As reported in Chapter 2 (Experiment 2), left VLPFC is
activated during selection. Thus, we predicted that anxious apprehension would correlate with left VLPFC activity during selection.

Finally, Experiment 6 extends Experiment 4 to a more clinically relevant high anxiety sample and investigates the effects of co-occurring depressive symptoms (dysphoria). Anxiety and depression frequently co-occur: approximately 40% of individuals with anxiety disorders also have major depressive disorder (MDD) and 60% of individuals with MDD also have an anxiety disorder (Rodriguez et al., 2004) with many others experiencing high subclinical levels of anxiety (Hranov, 2007). Comorbid anxiety and depression often produce worse outcomes than either alone, including more severe symptoms, worse psychosocial function, and poorer treatment response (Gorman, 1996). Some research also suggests comorbidity can exacerbate cognitive deficits. For example, anxiety and depression are each associated with deficits in executive function (EF; for reviews, see Castaneda, Tuulio-Henriksson, & Marttunen, 2008; M. A. Rogers et al., 2004). Co-occurring anxiety and depression may have additive effects on EF deficits. For example, patients with comorbid MDD and anxiety disorders had worse EF than either patients with MDD alone or healthy control participants, who did not differ (Basso et al., 2007; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011). Similarly, co-occurring dysphoria contributed to greater EF impairments in patients with obsessive compulsive disorder (Aycicegi, Dinn, Harris, & Erkmen, 2003; Moritz et al., 2001).

However, anxiety and depression are also associated with distinct profiles of symptoms (e.g., Watson, 2009), neuroanatomy (van Tol et al., 2010), and neurochemistry (e.g., Hasler et al., 2007; Phan et al., 2005). In fact, some evidence suggests that they can have opposite effects on brain and behavior. For example, anxiety is associated with a greater visual attentional bias towards the right hemisphere (left visual field), and dysphoria with greater bias towards the left
hemisphere; these asymmetries only become apparent when controlling for comorbidity (J. Keller et al., 2000). Similarly, dysphoria is associated with opposite patterns of activity in several brain regions during an emotional Stroop task, depending on the presence of co-occurring anxiety (although there were no behavioral differences; Engels et al., 2010). Finally, participants with social anxiety disorder alone generally had reduced performance on EF tasks under social stress compared to non-stress baseline, whereas those with comorbid social anxiety and depression generally improved their performance under social stress. However, the performance of the latter group was never significantly better than that of the social anxiety only group (Graver & White, 2007).

Given these distinct mechanisms and effects, it is possible that in some cases anxiety and depression could counteract each other. That is, the neurobiological changes associated with these syndromes could effectively cancel each other out, leading to better cognitive performance for individuals with co-occurring anxiety and dysphoria than those with elevated anxiety alone. To our knowledge this has never been demonstrated. We examine this issue in the context of cognitive control during language production; specifically, in Experiment 5 we test the possibility that anxiety interacts with dysphoria to predict performance in selection among competing options.

**Experiment 3: Increased Inhibition Under Midazolam Improves Underdetermined Selection**

**Method**

**Subjects.** Participants were 24 young adults. One additional participant was excluded for not completing the second session. Participants were pre-screened for the below exclusion criteria before being scheduled for the study. Participants were excluded if they had a serious
physical or mental illness, were taking any medication, consumed more than one alcoholic drink per day, had a history of drug abuse or tested positive for any drug or alcohol, or had an allergy to benzyl alcohol or other benzodiazepines. In addition, female participants were excluded if they were pregnant or breastfeeding.

**Materials and measures.** The verb generation task was identical to that in Experiments 1 and 2, except that the stimulus set was divided at random into two lists (with an additional 50 filler items), counterbalanced across sessions and drug conditions.

**Procedure.** All participants were tested at the Clinical Translation Research Center (CTRC) at the University of Colorado Boulder. Participants were required to abstain from food for at least 4 hours, and liquids for at least 2 hours, before testing, to minimize the risks of nausea and vomiting (rare side effects of midazolam). Upon arriving at the CTRC, participants were greeted by the experimenter who issued the informed consent, and teaching sheets to ensure that participants understood the procedures and complied with all pre- and post experimental safety precautions. Participants who passed the initial screening had a medical history and physical performed by a physician. Participants were weighed and females were given pregnancy tests at the beginning of each session. A blood sample was taken for the pregnancy test and for a toxicology screen to measure the presence of legal and illegal drugs that might interfere with participants’ mental abilities and/ or adversely interact with midazolam. A breathalyzer test was also given to assess potential alcohol intoxication.

All drug administration and monitoring procedures were carried out by a CTRC nurse. If a participant received a midazolam injection in the first session, that individual received a saline injection in the second session and vice versa. Order of these injections was counterbalanced across participants. Session order for each participant was provided to the pharmacist and
physician by an investigator not involved in data acquisition or analysis and kept sealed until the participant had completed both sessions. An IV catheter was inserted and the participant was administered an injection of either 0.03 mg/kg body weight of midazolam diluted to a total volume of 10 mL or 10 mL saline. The injection was given over 2 min, with a maximum dose of 2.5 mg (thus, maximum weight of participants was limited to 83 kg). Participants were monitored as if they were undergoing a diagnostic procedure under conscious sedation. Respiratory rate, arterial oxygen saturation, and electrocardiograms were continuously monitored and blood pressure was monitored every 15 min.

Participants first completed a task for an unrelated experiment with pictures. Participants began the verb generation task an average of 34 min after the injection was administered (range, 25–45 min), and completed the task in an average of 8 min (range, 5–15 min.). In addition, to verify that drug effects were still present during the verb generation task, participants studied a list of 10 words (first names and city names, counterbalanced) for 5 s each, immediately before and after the verb generation task, and were tested on their free-recall the following day.

At the end of the session, participants were offered a meal prepared by the CTRC nutritionist to further ensure their wellbeing. Participants were not allowed to drive home (and were required to arrange a ride with a family member or friend), and agreed not to drive, drink alcohol, or operate dangerous machinery until the morning after the infusion.

**Data analysis.** Verb generation data were processed as in Experiment 1. Data were analyzed with a 2 (drug condition) × 2 (verb generation selection) × 2 (verb generation retrieval) repeated-measures ANOVA. Four outliers with negative selection and/or retrieval effects under saline were excluded from analysis, as in Experiment 1, because it is difficult to interpret drug
effects in cases in which there is a clear manipulation failure.⁹

Results

Drug manipulation check. There was no correlation between selection and retrieval
costs and time since injection (ps > 0.5). Participants’ next-day free recall was significantly
impaired under midazolam compared with saline solution, both for names studied before the verb
generation task (10.5% vs. 32% correct, t(19) = 4.56, p < 0.001) and after the verb generation
task (15% vs. 31% correct, t(19) = 4.56, p < 0.001). Thus, drug effects were still robust at the
time the verb generation task was completed.

Verb generation. Descriptive statistics are given in Table 4.1 and ANCOVA results in
Table 4.2. There was an interaction between drug condition, selection demand, and retrieval
demand (F(1,19) = 5.67, p = 0.028). As predicted, when retrieval demands were low, midazolam
improved selection (with selection costs lower under midazolam, z-transformed RT diff. M =
0.15, SE = 0.06; RT diff. 267 ms, than under saline, z-transformed RT diff. M = 0.37, SE = 0.07;
RT diff. 355 ms; t(19) = −2.95, p = 0.008), when retrieval demands were high (t(19) = 1.05, p =
0.3) (Figure 4.1 and Table 4.2). Also as predicted, there was no effect of midazolam on retrieval
when selection demands were low (t(19) = −0.53, p = 0.6). Effects were not due to overall
response slowing: there was no effect of midazolam on grand mean reaction time in the verb
generation task (t(19) = 1.42, p = 0.2); furthermore, any non-significant differences in grand
mean reaction time between conditions were controlled for in these analyses by z transforming
the data within-subjects.

⁹ Including these subjects does not change the overall pattern of results; the significant
three-way interaction becomes marginally significant (p = 0.06), and all other significant effects
remain significant.
Simulated Selection Cost (Z Model Cycle Diff., +/- SE)

Figure 4.1. Experiment 3: Effect of increased neural inhibition. (A) Model predictions. Increased neural inhibition (simulating GABA agonist drugs) improves selection (i.e., reduces selection cost) only when retrieval demands are low. As there is no a prior reason for assigning a specific inhibition level to the midazolam effect size tested in Experiment 3, the highest (.68) level was chosen to contrast with the standard level of inhibition (.66) as it provided best qualitative match to the data; the full pattern of model simulations is discussed in Chapter 3. (B) Empirical results. Midazolam improves selection only when retrieval demands are low. RTs are z transformed to remove baseline differences between conditions. All error bars are SEs.

Table 4.1

Experiment 3: Descriptive Statistics for Saline and Midazolam Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Saline</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Back-</td>
<td>Standardized</td>
</tr>
<tr>
<td></td>
<td>transformed</td>
<td>Mean (z)</td>
</tr>
<tr>
<td></td>
<td>Mean (ms)</td>
<td>SE</td>
</tr>
<tr>
<td>Low Selection/Low Retrieval</td>
<td>1249</td>
<td>51</td>
</tr>
<tr>
<td>High Selection/Low Retrieval</td>
<td>1604</td>
<td>99</td>
</tr>
<tr>
<td>High Retrieval/Low Selection</td>
<td>1669</td>
<td>103</td>
</tr>
<tr>
<td>High Retrieval/High Selection</td>
<td>1920</td>
<td>160</td>
</tr>
</tbody>
</table>

Note. Means and standard errors (in milliseconds, back transformed from log RT data), and z-transformed means and standard errors, for each condition.
Table 4.2
Experiment 3: Repeated Measures ANOVA for Midazolam Effects

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>0.00</td>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
<td>.97</td>
</tr>
<tr>
<td>Error</td>
<td>0.74</td>
<td>19</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection Demand</td>
<td>1.86</td>
<td>1</td>
<td>1.86</td>
<td>34.70</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Error</td>
<td>1.02</td>
<td>19</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrieval Demand</td>
<td>8.27</td>
<td>1</td>
<td>8.27</td>
<td>69.32</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Error</td>
<td>2.27</td>
<td>19</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug x Selection Demand</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td>0.21</td>
<td>.65</td>
</tr>
<tr>
<td>Error</td>
<td>1.31</td>
<td>19</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug x Retrieval Demand</td>
<td>0.15</td>
<td>1</td>
<td>0.15</td>
<td>1.71</td>
<td>.21</td>
</tr>
<tr>
<td>Error</td>
<td>1.67</td>
<td>19</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection Demand x Retrieval Demand</td>
<td>0.08</td>
<td>1</td>
<td>0.08</td>
<td>1.78</td>
<td>.20</td>
</tr>
<tr>
<td>Error</td>
<td>0.88</td>
<td>19</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug x Selection Demand x Retrieval Demand</td>
<td>0.36</td>
<td>1</td>
<td>0.36</td>
<td>5.67</td>
<td>.03*</td>
</tr>
<tr>
<td>Error</td>
<td>1.19</td>
<td>19</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. * Significant effect (p<.05)

Experiment 4: Anxiety is Associated with Impaired Underdetermined Selection

Method

Participants. Sixty of the participants in Experiment 1 also completed anxiety and depression measures in Experiment 4. All participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado Institutional Review Board.

Materials and procedure. Participants completed the verb generation task as described in Experiment 1 (Chapter 2). Participants then completed four standardized questionnaires to assess anxious apprehension: (1) NEO Five Factor Inventory (NEO-FFI) neuroticism subscale

10 Anxious apprehension is characterized by worry and verbal rumination; these persistent worries are focused on immediate or future perceived threats, and may include personal and emotional threats to self, physical health, competence at work, or general world problems (e.g., Engels et al., 2007; Heller, Nitchke, Etienne, & Miller, 1997). These worries are mentally rehearsed repeatedly without being resolved, are difficult to dismiss (e.g., Mathews, 1990), and may be accompanied by restlessness, fatigue, and muscle tension (e.g., Nitschke, Heller, Palmieri, & Miller, 1999). Because obsessive compulsive disorder and generalized anxiety disorder are most characterized by anxious apprehension (e.g., Nitschke et al., 1999) and most consistently linked to deficits in cognitive control and prefrontal function (e.g., Engels et al., 2007; Olley, Malhi, & Sachdev, 2007) and polymorphisms in the GABAergic system (e.g., Zai et al., 2005), this study focuses on anxious apprehension.
(Costa & McCrae, 1992), (2) Lehrer Woolfolk Anxiety Symptom Questionnaire cognitive factor (Ferrari & McCown, 1994; Lehrer & Woolfolk, 1982; Sachdev & Malhi, 2005), (3) Penn State Worry Questionnaire (PSWQ, T. J. Meyer, Miller, Metzger, & Borkovec, 1990), and (4) Behavioral Inhibition Scale/Behavioral Activation Scale (Carver & White, 1994) Behavioral Inhibition subscale.

These questionnaires were combined into a summary score: A principal components analysis was performed on the scores from the anxious apprehension measures. All four measures loaded strongly onto a single component (BIS = 0.80, NEO-n = 0.83, LASQ = 0.84, PSWQ = 0.87), explaining 69.6% of the variance. Latent factor scores for each participant were thus extracted to provide a composite of shared variance across anxious apprehension measures while eliminating error variance specific to each measure. In addition, participants completed the Mood and Anxiety Symptom Questionnaire (MASQ, Watson & Weber, 1995) to control for depression and anxious arousal symptoms.

**Data analysis.** Verb generation data were processed as in the previous experiments. Participants were classified as high or low anxious apprehension using a median split on the anxious apprehension factor scores (see Results for converging results from a continuous analysis). Two outliers with negative selection and/or retrieval effects were excluded from analysis, because the basic effects of the task manipulations are very robust, occurring for the vast majority of subjects, making it difficult to interpret individual differences in cases in which there is a clear manipulation failure. With the inclusion of these subjects, all significant effects remain significant. Data were analyzed with a 2 (anxiety) × 2 (verb generation selection) × 2 (verb generation retrieval) mixed factorial ANOVA.

**Results**
Descriptive statistics are presented in Table 4.3 and ANOVA results in Table 4.4. As predicted, participants higher in anxiety had larger selection costs (z-transformed RT diff. M = 0.37, SE = 0.03; RT diff. 421 ms) than lower-anxiety participants (z-transformed RT diff. M = 0.26, SE = 0.03; RT diff. 269 ms; F(1, 57) = 6.32 p = 0.015; Figure 4.2 B), but the retrieval costs were equivalent across the groups (F(1, 57) = 0.72, p = 0.4). The effect of anxious apprehension on selection did not interact with retrieval demand (p = 0.4), that is, the effects of anxiety on selection are not reliably greater when retrieval demands are high. Anxiety also does not affect the interaction between selection and retrieval, and the model predictions do not significantly differ from the human behavior (Figure 4.2 A). The effect of anxious apprehension on selection remained significant controlling for anxious arousal and depression (F(1, 55) = 4.21, p = 0.045).

Table 4.3

Experiment 4: Descriptive Statistics for the High and Low Anxiety Groups

<table>
<thead>
<tr>
<th>Condition</th>
<th>Low Anxious Apprehension (n=30)</th>
<th>High Anxious Apprehension (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Back-transformed Mean (ms)</td>
<td>SE</td>
</tr>
<tr>
<td>Low Selection/ Low Retrieval</td>
<td>1556</td>
<td>80</td>
</tr>
<tr>
<td>High Selection/ Low Retrieval</td>
<td>1863</td>
<td>96</td>
</tr>
<tr>
<td>High Retrieval/ Low Selection</td>
<td>2186</td>
<td>136</td>
</tr>
<tr>
<td>High Retrieval/ High Selection</td>
<td>2416</td>
<td>176</td>
</tr>
</tbody>
</table>

Note. Descriptive statistics for the high and low anxiety groups (median split) in Experiment 4: Means and standard errors (in milliseconds, back transformed from log RT data), and z-transformed means and standard errors, for each condition.

Although the difference between selection costs when retrieval demands are high vs. low appear larger for low anxiety participants (Figure 4.2 B) than in the model (Figure 4.2 A), these effects are not significantly different. The standard-inhibition (low-anxiety) model produces a selection cost for high retrieval demand conditions of 18.7, and a selection cost for low retrieval demand conditions of 25.6, giving a ratio of 73%. This ratio is, by design, similar to the ratio between these selection effects in the full behavioral sample. For the low anxiety participants, this ratio between the two selection effects is numerically smaller (ratio = 49%), but not significantly different from that of the model (one-sample t(29) = −1.16, p = 0.3). Thus, across the low-anxiety model and subjects, greater selection costs are observed under low retrieval demand than high retrieval demand.
Figure 4.2. Experiment 4: Effects of reduced neural inhibition (A) Model predictions: Reduced competitive neural inhibition in the VLPFC layer, simulating increasing anxiety, impairs selection (i.e., increases selection cost) under high and low retrieval demands, and suggests that effects of anxiety on selection may be most robust under low retrieval demands. As there is no a priori reason for assigning specific inhibition levels in the model to the anxiety effect, the lowest (0.62) level of inhibition were chosen to contrast with the standard level of inhibition (0.66), as it provided best qualitative match to the data (see Chapter 3 for the full pattern of model simulations). (B) Empirical results. Higher anxiety participants show impaired selection under high and low retrieval demands. All error bars are SEs.

Table 4.4

Experiment 4: Mixed Factorial ANOVA for Anxious Apprehension Effects

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious Apprehension</td>
<td>0.01</td>
<td>1</td>
<td>0.01</td>
<td>0.03</td>
<td>.86</td>
</tr>
<tr>
<td>Error</td>
<td>0.21</td>
<td>57</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection Demand</td>
<td>5.85</td>
<td>1</td>
<td>5.85</td>
<td>223.20</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Anxious Apprehension x Selection Demand</td>
<td>0.17</td>
<td>1</td>
<td>0.17</td>
<td>6.32</td>
<td>.02*</td>
</tr>
<tr>
<td>Error</td>
<td>1.49</td>
<td>57</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrieval Demand</td>
<td>21.33</td>
<td>1</td>
<td>21.33</td>
<td>478.35</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Anxious Apprehension x Retrieval Demand</td>
<td>0.32</td>
<td>1</td>
<td>0.32</td>
<td>0.72</td>
<td>.40</td>
</tr>
<tr>
<td>Error</td>
<td>2.54</td>
<td>57</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection Demand x Retrieval Demand</td>
<td>0.30</td>
<td>1</td>
<td>0.30</td>
<td>10.19</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Anxious Apprehension x Selection Demand x Retrieval Demand</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td>0.71</td>
<td>.40</td>
</tr>
<tr>
<td>Error</td>
<td>1.67</td>
<td>57</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. * Significant effect (p<.05)
Effects of anxious apprehension were also apparent using a continuous measure of anxiety. For all continuous analyses, outliers were excluded for which the absolute value of DfBeta (the change in the standardized regression coefficient resulting from excluding that case) exceeded $2/\sqrt{N}$. This resulted in the exclusion of no more than four cases from any analysis.

There was a significant positive correlation between anxious apprehension and selection costs (high competition – low competition RTs): Participants with higher levels of anxious apprehension were more slowed by competition ($r = 0.35, n = 55, p = 0.008$, two-tailed). This effect remained significant controlling for anxious arousal and depression ($r(51) = 0.36, p = 0.008$). Examining selection costs under high and low retrieval demands separately the difference between these correlations is not significant ($r = 0.33, p=0.014, n=56 \text{ vs. } r=0.15, p=0.3, n=54$, Fisher $z= 0.98, p = 0.3$). Thus, the effect of anxious apprehension on selection is not significantly modulated by retrieval demands. Also as predicted, there was no correlation between anxious apprehension and retrieval cost (low association strength – high association strength; $r = 0.05, n = 56, p = 0.7$ two-tailed, controlling for anxious arousal and depression $r(52) = 0.07, p = 0.6$).

The difference between the correlations of anxious apprehension with selection and retrieval costs is significant at the one-tailed level (Fisher $z = 1.65, p = 0.05$, one-tailed).

**Experiment 5: Anxiety is Associated with Reduced VLPFC Activity During Underdetermined Selection**

**Method**

**Participants.** The participants in Experiment 2 also completed anxiety and depression measures in Experiment 5. All participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado Institutional Review Board.

**Materials and procedure.** Participants completed the verb generation task during fMRI
scanning as described in Experiment 2. After completing the scanning session, participants completed the PSWQ to assess anxious apprehension, as well as the MASQ to control for anxious arousal and depression symptoms.

**Data analysis.** fMRI data were analyzed as described in Experiment 2. Percent signal change for each contrast was extracted from the anatomical left VLPFC ROI (Figure 4.3 A) for each subject and correlated with the questionnaire scores.

**Results**

As predicted, left VLPFC activity correlated with anxious apprehension during selection when retrieval demands were low ($r=-.66, p=.004, n=17$; Figure 4.3 B), but not during retrieval ($r=-.05, p=.9, n=17$).\(^{12}\) Increased anxiety predicts reduced VLPFC recruitment during selection for both the mid-VLPFC (pars triangularis, $r = −0.56, p = 0.024, n = 16$) and anterior-VLPFC (pars orbitalis $r = −0.60, p = 0.008, n = 18$), and these correlations do not differ from each other (Fisher’s $z = 0.16, p = 0.9$). These findings suggest high anxiety participants fail to adequately engage VLPFC when they must select between competing options. The correlation remained significant controlling for depression and anxious arousal ($r(13) = −0.61, p = 0.017$). There was no correlation between anxious apprehension and VLPFC activity when retrieval demands were high (high selection demand/high retrieval demand vs. low selection demand/ high retrieval demand).

\(^{12}\) Predicting how anxiety will affect VLPFC activity using fMRI requires translating reduced neural inhibition into the hemodynamic response measured by BOLD activation. This translation is far from straight forward, as outlined below. Thus, the key prediction for testing our model is that anxiety will affect BOLD activation in VLPFC during selection. There is clear evidence that purely inhibitory inputs can lead to an increased hemodynamic response (e.g., Hershey, et al., 2003; Peyron et al., 1994). The increased hemodynamic response with increased inhibition probably arises because, although there are fewer inhibitory than excitatory neurons, neural inhibition can be more metabolically costly than excitation (for a review see Buzsáki, Kaila, & Raichle, 2007). This and other evidence has led prominent researchers in fMRI methods to argue persuasively that it should never be assumed that fMRI BOLD signal reflects excitation rather than inhibition or a mixture of both (e.g., Logothetis, 2008).
demand, \( r = 0.309, p = 0.2, n = 18 \).

![Engagement of left VLPFC during selection, as a function of anxiety. (A) Anatomically defined region of interest (mid and anterior left VLPFC, shown in blue). (B) Higher anxiety participants showed reduced engagement of VLPFC during selection under low retrieval demands, which may reflect reduced activity of GABAergic interneurons.](image)

To ensure that the correlation between left VLPFC activity and anxious apprehension during selection when retrieval demands are low is not a general effect of anxiety on fMRI BOLD signal during selection, we tested the correlation in two other regions that are implicated the verb generation task: the posterior middle temporal gyrus (association cortex implicated in semantic representations) and precentral gyrus (premotor cortex implicated in speech production). There was no correlation between anxious apprehension and activity during selection when retrieval demands are low in posterior middle temporal gyrus \( (r = 0.24, p = 0.4, n = 17) \) or premotor cortex \( (r = 0.02, p = 0.9, n = 18) \).
**Experiment 6: Dysphoria Can Counteract Selection Deficits Associated with Anxiety**

**Method**

**Participants.** Participants were 110 native English-speaking young adults (61% female) from the University of Colorado Boulder, divided into three groups: 45 high anxiety/high dysphoria, 34 high anxiety/low dysphoria, and 31 low anxiety/low dysphoria.\(^\text{13}\) Participants were selected based on PSWQ scores. The distribution of PSWQ scores for the students completing the pre-screening process closely matched previously published norms (e.g., Gillis, Haaga, & Ford, 1995). Participants scoring in the top and bottom quartiles (>48 = high anxiety, <33 = low anxiety, from Gillis et al., 1995) were invited to participate. The cut score we used for classifying participants into the high anxiety groups (>48) is slightly higher than the cut score recommended by Behar, Alcaine, Zuellig, and Borkovec (2003) for screening for generalized anxiety disorder in non-clinical samples. High and low dysphoria groups were determined based on the Beck Depression Inventory – Second Edition (BDI-II, Beck, Steer, & Brown, 1996), a 21-item scale evaluating current symptoms of depression (≤12 = low dysphoria, >12 = high dysphoria). The cut score we used for classifying participants into the high dysphoria group (>12) is the recommended cut score for screening for depression in non-clinical samples (Kendall, Hollon, Beck, Hammen, & Ingram, 1987 adjusted from BDI-IA to BDI-II based on Beck et al., 1996).

Participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado Boulder Institutional Review Board.

**Materials and procedure.** Participants completed three tasks that assessed selection abilities to yield a composite score: verb generation, blocked cyclic naming, and sentence

\(^{13}\) No low anxiety/high dysphoria group was included because such individuals are extremely rare, as anxiety typically precedes and accompanies depression (e.g., Hranov, 2007).
completion. In each, RTs were recorded using a voice-activated microphone. Responses were also audio-recorded and transcribed to remove error trials. In addition, participants completed a choice RT task and the North American Adult Reading Test (NAART), to control for psychomotor speed and IQ, respectively.

**Verb generation.** Verb generation was administered as in the previous experiments. Stimuli were 25 nouns in two conditions: high competition with many possible verb responses (e.g., *cat*, associated with *purr, lick, meow* etc.) and low competition with few possible verb responses (e.g., *scissors*, associated with *cut*). Participants saw nouns one at a time and stated the first verb that came to mind (something the noun does or something that could be done with the noun). Data were excluded for seven participants due to failure to follow task directions (>25% errors).

**Blocked cyclic naming.** Participants repeatedly named 16 pictures as quickly as possible in two conditions: homogenous blocks of pictures from the same category (e.g., *bed, table, bench, crib*), and mixed blocks with each picture from a different category (e.g., *lion, pajamas, bench, car*). The homogenous condition creates high competition among responses due to spreading semantic activation, whereas the mixed condition has low competition (e.g., Schnur, Schwartz, Brecher, & Hodgson, 2006). Participants completed eight blocks, each with four pictures repeated six times in different orders. The same pictures appeared in both conditions. Data were missing for one participant due to equipment failure.

**Sentence completion.** Sentence completion was administered as in Snyder and Munakata (2008). Stimuli were sentences with the final word omitted, with 50 sentences each in two conditions: high competition with many possible endings (e.g., *There is something grand about the _____*), and low competition with few possible endings (e.g., *He mailed the letter without*
Participants read sentences silently as they appeared in segments of 1-2 words (to control reading speed) then said a word aloud to complete the sentence. The final segment always contained one word and the blank. Data were missing for one participant due to equipment failure.

**NAART.** The NAART is a well-established IQ estimate (Uttl, 2002). Participants read 60 irregular words aloud, which increased in difficulty (e.g., debt to sidereal). Estimated full scale IQ was calculated from the number of incorrect pronunciations (Uttl, 2002). One participant did not complete the NAART due to experimenter error.

**Choice RT.** Participants pressed buttons with their left and right hands as fast as possible when presented with left or right pointing triangles. Data were missing for three participants due to equipment failure.

**Data Analysis.** Incorrect responses (e.g., non-verbs in verb generation) and microphone errors (e.g., failing to trigger) were excluded. RTs <200 ms, >10,000 ms, or greater than three standard deviations above the participant’s mean RT were trimmed. RTs were log transformed to remove skew and z-transformed within subjects to remove baseline differences in RT. For the verb generation, blocked cyclic naming, and sentence completion tasks, selection cost was calculated as the z RT difference between the high competition and low competition conditions. Selection costs for each task were z-transformed across subjects and averaged into the primary measure of interest, the selection composite score. Composite scores that aggregate results across multiple tasks provide a more accurate and reliable measure of the intended EF than single tasks, because the non-executive task requirements specific to each task (e.g., visual processing of pictures in blocked cyclic naming vs. sentence reading in the sentence completion task) have less influence (Miyake, Emerson, & Friedman, 2000a; Miyake et al., 2000b; van Eerde, 2003).
Outlier analyses were conducted (Cook’s D >3 SD above the mean, two rounds), resulting in exclusion of no more than seven outliers from any analysis.

Data were analyzed with analyses of covariance (ANCOVAs) testing the effect of group (high anxiety/high dysphoria, high anxiety/low dysphoria, and low anxiety/low dysphoria) on selection composite scores (and on selection cost for each task), controlling for NAART and choice RT. Planned pairwise comparisons were conducted between the low anxiety/low dysphoria group and each of the high anxiety groups, and between the two high anxiety groups.

**Results**

Descriptive statistics are presented in Tables 4.5 and 4.6, and ANCOVA results in Table 4.7 and Figure 4.4.

**Anxiety and dysphoria.** PSWQ and BDI-II descriptive statistics for each group are reported in Table 4.5. The mean PSWQ scores for the high anxiety groups are above the 90th percentile (Gillis et al., 1995) and similar to levels reported for participants with anxiety disorders (e.g., T. A. Brown, Antony, & Barlow, 1992; Starcevic et al., 2007). The mean BDI-II score for the high dysphoria group would be considered moderate depression symptom severity in a clinical sample (Beck et al., 1996) and meets or exceeds that reported for college student samples with diagnosed mood disorders (Shean & Baldwin, 2008) or seeking treatment (Sprinkle et al., 2002). Thus, although the high anxiety and high dysphoria groups were not clinically diagnosed, their self-reported levels of anxious apprehension and depression are likely of clinical significance.

**IQ and psychomotor speed.** There were no significant group differences on NAART or choice RT (Table 4.5); however, NAART marginally predicted selection composite scores and choice RT significantly predicted blocked cyclic naming (Table 4.7), so these variables were
controlled for as covariates in all analyses.

**Table 4.5**

*Experiment 6 Descriptive Statistics for Clinical Questionnaires and Control Measures*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SE</th>
<th>Pairwise Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSWQ</td>
<td>HA/LD</td>
<td>34</td>
<td>58.29</td>
<td>1.04</td>
<td>HA/LD&gt;LA/LD (p&lt;.01, d=6.01)</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>44</td>
<td>63.84</td>
<td>1.23</td>
<td>HA/HD&gt;LA/LD (p&lt;.01, d=5.46)</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>31</td>
<td>26.71</td>
<td>0.79</td>
<td>HA/LD&lt;HA/HD (p&lt;.01, d=0.77)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>HA/LD</td>
<td>34</td>
<td>6.79</td>
<td>0.50</td>
<td>HA/LD&gt;LA/LD (p&lt;0.01, d=0.84)</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>44</td>
<td>21.75</td>
<td>1.31</td>
<td>HA/HD&gt;LA/LD (p&lt;.01, d=2.54)</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>31</td>
<td>4.29</td>
<td>0.56</td>
<td>HA/LD&lt;HA/HD (p&lt;.01, d=2.19)</td>
</tr>
<tr>
<td>NAART IQ</td>
<td>HA/LD</td>
<td>33</td>
<td>109.31</td>
<td>1.10</td>
<td>HA/LD=LA/LD (p=0.27, d=0.28)</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>44</td>
<td>107.93</td>
<td>0.92</td>
<td>HA/HD=LA/LD (p=0.76, d=0.07)</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>31</td>
<td>107.47</td>
<td>1.23</td>
<td>HA/HD=HA/HD (p=0.34, d=0.23)</td>
</tr>
<tr>
<td>Choice RT</td>
<td>HA/LD</td>
<td>34</td>
<td>5.82</td>
<td>0.02</td>
<td>HA/LD=LA/LD (p=.68, d=.09)</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>42</td>
<td>5.85</td>
<td>0.01</td>
<td>HA/HD=LA/LD (p=.30, d=.24)</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>30</td>
<td>5.83</td>
<td>0.02</td>
<td>HA/LD=HA/HD (p=.17, d=.33)</td>
</tr>
</tbody>
</table>

*Note. PSWQ = Penn State Worry Questionnaire; BDI-II = Beck Depression Inventory—Second Edition; NAART = North American Adult Reading Test; HA/LD = High anxiety/low dysphoria group; HA/HD = High anxiety/high dysphoria group; LA/LD = Low anxiety/low dysphoria group.*

**Selection.** For the primary measure of interest, selection composite scores, there was a significant effect of group (Table 4.7). Pairwise comparisons demonstrated that anxiety is associated with impaired selection: High anxiety/low dysphoria participants had significantly larger selection costs (i.e., worse performance) than low anxiety/low dysphoria participants. However, comorbid dysphoria counteracted the effects of anxiety: High anxiety/high dysphoria participants had significantly smaller selection costs than high anxiety/low dysphoria participants, and did not differ from the low anxiety participants.
Table 4.6
Experiment 6 Descriptive Statistics for Selection Measures

<table>
<thead>
<tr>
<th>Task</th>
<th>Group</th>
<th>n</th>
<th>Observed Mean</th>
<th>SE</th>
<th>Estimated Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Composite Score</td>
<td>HA/LD</td>
<td>31</td>
<td>0.29</td>
<td>0.10</td>
<td>0.27</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>40</td>
<td>-0.01</td>
<td>0.10</td>
<td>-0.01</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>28</td>
<td>-0.18</td>
<td>0.08</td>
<td>-0.16</td>
<td>0.11</td>
</tr>
<tr>
<td>Verb Generation</td>
<td>HA/LD</td>
<td>28</td>
<td>0.50</td>
<td>0.04</td>
<td>0.51</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>38</td>
<td>0.33</td>
<td>0.04</td>
<td>0.33</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>29</td>
<td>0.37</td>
<td>0.04</td>
<td>0.37</td>
<td>0.04</td>
</tr>
<tr>
<td>Sentence Completion</td>
<td>HA/LD</td>
<td>32</td>
<td>0.79</td>
<td>0.03</td>
<td>0.79</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>37</td>
<td>0.82</td>
<td>0.03</td>
<td>0.82</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>28</td>
<td>0.70</td>
<td>0.03</td>
<td>0.70</td>
<td>0.03</td>
</tr>
<tr>
<td>Blocked Cyclical Naming</td>
<td>HA/LD</td>
<td>32</td>
<td>0.18</td>
<td>0.03</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>HA/HD</td>
<td>40</td>
<td>0.14</td>
<td>0.02</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>LA/LD</td>
<td>29</td>
<td>0.08</td>
<td>0.03</td>
<td>0.08</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note. HA/LD = High anxiety/low dysphoria group; HA/HD = High anxiety/high dysphoria group; LA/LD = Low anxiety/low dysphoria group.  
1High–Low Selection Condition z reaction time.  
2Estimated marginal means from ANCOVA controlling for NAART and choice RT.

For all individual selection tasks, there were significant effects of group. As with selection composite scores, high anxiety/low dysphoria participants had significantly larger selection costs than low anxiety/low dysphoria participants on all individual selection tasks. As with selection composite scores, high anxiety/high dysphoria participants had significantly smaller selection costs than high anxiety/low dysphoria participants on verb generation, and marginally smaller selection costs on blocked cyclic naming. With comorbid dysphoria, the association between anxiety and impaired selection was evident only on sentence completion: compared to low anxiety participants, high anxiety/high dysphoria participants had significantly larger selection costs on sentence completion, with no significant difference between the two high anxiety groups.  

Consistent with previous findings (e.g., Starcevic et al., 2007), the high anxiety group with co-occurring dysphoria had somewhat higher PSWQ scores than the high anxiety/low dysphoria group (Table 4.5). However, the same pattern of results held for analyses including a subset of high anxiety/high dysphoria participants closely matched to high anxiety/low dysphoria participants on PSWQ scores, although power was reduced. Thus, the full sample was included in all analyses.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Predictor</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Pairwise Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Composite Score</td>
<td>Group</td>
<td>2.81</td>
<td>2</td>
<td>1.40</td>
<td>4.44</td>
<td>.01</td>
<td>HA/LD&gt;LA/LD (p=.01, d=0.75)</td>
</tr>
<tr>
<td></td>
<td>NAART</td>
<td>0.98</td>
<td>1</td>
<td>0.98</td>
<td>3.09</td>
<td>.08</td>
<td>HA/HD=LA/LD (p=.30, d=0.26)</td>
</tr>
<tr>
<td></td>
<td>Choice RT</td>
<td>0.27</td>
<td>1</td>
<td>0.27</td>
<td>0.84</td>
<td>.36</td>
<td>HA/LD&gt;HA/HD (p=.04, d=0.50)</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>29.73</td>
<td>94</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verb Generation</td>
<td>Group</td>
<td>0.49</td>
<td>2</td>
<td>0.25</td>
<td>4.49</td>
<td>.01</td>
<td>HA/LD&gt;LA/LD (p=.04, d=0.58)</td>
</tr>
<tr>
<td></td>
<td>NAART</td>
<td>0.00</td>
<td>1</td>
<td>0.00</td>
<td>0.06</td>
<td>.81</td>
<td>HA/HD=LA/LD (p=.45, d=-0.17)</td>
</tr>
<tr>
<td></td>
<td>Choice RT</td>
<td>0.03</td>
<td>1</td>
<td>0.03</td>
<td>0.50</td>
<td>.48</td>
<td>HA/LD&gt;HA/HD (p&lt;.01, d=0.70)</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>4.89</td>
<td>89</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sentence Completion</td>
<td>Group</td>
<td>0.24</td>
<td>2</td>
<td>0.12</td>
<td>4.32</td>
<td>.02</td>
<td>HA/LD&gt;LA/LD (p=.04, d=0.55)</td>
</tr>
<tr>
<td></td>
<td>NAART</td>
<td>0.01</td>
<td>1</td>
<td>0.01</td>
<td>0.20</td>
<td>.66</td>
<td>HA/HD&gt;LA/LD (p=.01, d=0.70)</td>
</tr>
<tr>
<td></td>
<td>Choice RT</td>
<td>0.05</td>
<td>1</td>
<td>0.05</td>
<td>1.81</td>
<td>.18</td>
<td>HA/LD=HA/HD (p=.49, d=-0.17)</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>2.40</td>
<td>92</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blocked Cyclic Naming</td>
<td>Group</td>
<td>0.18</td>
<td>2</td>
<td>0.09</td>
<td>4.15</td>
<td>.02</td>
<td>HA/LD&gt;LA/LD (p=.01, d=0.66)</td>
</tr>
<tr>
<td></td>
<td>NAART</td>
<td>0.00</td>
<td>1</td>
<td>0.00</td>
<td>0.06</td>
<td>.81</td>
<td>HA/HD=LA/LD (p=.19, d=0.34)</td>
</tr>
<tr>
<td></td>
<td>Choice RT</td>
<td>0.18</td>
<td>1</td>
<td>0.18</td>
<td>8.14</td>
<td>.01</td>
<td>HA/LD&gt;HA/HD (p=.09, d=-0.40)</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>2.08</td>
<td>96</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. HA/LD = High anxiety/low dysphoria group; HA/HD = High anxiety/high dysphoria group; LA/LD = Low anxiety/low dysphoria group.
Discussion

The current studies demonstrate that competitive neural inhibition, via GABAergic interneurons in prefrontal circuits, likely plays an important role in selecting among alternatives during language processing. As predicted by neural network simulations (Chapter 3), selection is improved under the drug midazolam (which increases GABAergic function, Experiment 3) whereas anxiety (linked with reduced GABAergic function) is associated with impaired selection (Experiments 4 and 6), and reduced VLPFC function during selection (Experiment 5).15

Although GABA agonists are widely used to treat the affective symptoms of anxiety disorders

15 Of note, retrieval is unaffected by GABAergic function; instead, other mechanisms (e.g., sustained neuronal activation, enabled by recurrent connections in PFC networks) may support retrieval of weakly active representations.
(for reviews see Lydiard, 2003; Möhler, 2012), we demonstrate that midazolam improves the cognitive process of selection in a nonclinical population, suggesting that GABA agonists may also be effective in treating the cognitive control and decision-making deficits in anxiety disorders.

Importantly, Experiment 6 demonstrates that high anxiety participants without comorbid depressive symptoms (dysphoria) show impaired selection, supporting the findings of Experiment 4 and extending them to people with more highly elevated anxiety symptoms and to additional tasks. Counterintuitively, compared to participants with high anxiety alone, those with co-occurring anxiety and dysphoria showed better selection, as indexed by a composite measure of three selection tasks. This finding is in contrast to theories suggesting that co-occurring anxiety and depression lead to more pronounced EF deficits than either disorder alone (e.g., Basso et al., 2007), but is in accord with previous evidence for opposing changes in brain and behavior associated with anxiety and depression in other domains (e.g., J. Keller et al., 2000). Experiment 6 shows for the first time that dysphoria counteracts the effects of anxiety on one aspect of EF: selection among competing options.

Although this study cannot directly address the reasons for this effect, one intriguing possibility is that anxiety and depression may be related to opposing changes in neural activity in prefrontal areas critical for selection. Specifically, while anxiety is associated with reduced GABAergic function, depression may be associated with reduced function of the major excitatory neurotransmitter glutamate (e.g., Hasler et al., 2007; Mitchell & Baker, 2010). As a proof-of-concept, additional neural network simulations were conducted with the ‘high anxiety’ (low inhibition, kWTA=0.62) model described in Chapter 3, in which the level of simulated neural excitation in the VLPFC layer was reduced (Figure 4.5). These simulations suggest that

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16 Reduced GABA is also found in patients with MDD, who nearly always also have high anxiety (e.g., Hasler et al., 2007; Kalueff & Nutt, 2007), but reduced glutamate is not associated with anxiety (Phan et al., 2005).
reduced glutamatergic function can improve selection by reducing activation of competing responses. Thus, reduced glutamatergic function in individuals with co-occurring anxiety and dysphoria could counteract the effects of reduced GABAergic function associated with anxiety, leading to improvements in selection. This theory makes predictions that should be tested by future research: for example, co-occurring dysphoria should improve performance only on tasks requiring competitive inhibition, such as selection, and should harm performance on tasks requiring neural excitation, such as working memory maintenance.

![Graph showing selection cost as a function of VLPFC excitation](image)

**Figure 4.5.** Neural network simulations of selection as a function of VLPFC excitation. Levels of neural excitation in the VLPFC layer of the ‘high anxiety’ (kWTA=.62) model described in Chapter 3 were systematically reduced to simulate possible reduced glutamatergic function associated with depression. Reducing excitation below the default level (e=1) led to a reduction in selection costs, simulating the effect of co-occurring dysphoria on the verb generation task in Experiment 6.

One alternative possibility is that dysphoric individuals who are able to cope with their depressive symptoms effectively enough to attend college might have better pre-existing cognitive function, which both allows them to attend college despite their dysphoria and to do well on selection tasks. However, high and low dysphoria participants did not perform any better than low dysphoria participants on IQ or psychomotor speed tasks, suggesting the groups did not differ in general intellectual function or motivation. Nonetheless, the possibility cannot be ruled out that dysphoric college students are self-selected for high EF in particular. Future research
with community samples can address this question.

Another question concerns the reason for the dissociation between the sentence completion task and the other selection tasks in Experiment 6. Namely, the two high anxiety groups were equally impaired on the sentence completion task, whereas only the high anxiety/low dysphoria group was impaired on the verb generation and blocked cyclic naming tasks. Although there are several differences between the tasks, one key feature that differentiates sentence completion is timing. In contrast to the other tasks, sentence completion stimuli are presented incrementally to control reading pace. Thus, competing responses may be active well before the participant is allowed to respond (e.g., DeLong, Urbach, & Kutas, 2005). If individuals with high dysphoria have lower levels of neural excitation, this pacing may allow time for activation levels to slowly build, negating the benefit of reduced competitor activation associated with low glutamate levels. This explanation could be investigated in future studies that manipulate timing across selection tasks.

Although many questions thus remain to be answered, these findings shed light on why choosing among many options can be difficult for anyone, and why it can be paralyzing for people with anxiety. Our modeling and empirical work suggest that the reduced GABAergic function associated with anxiety leads to impaired competitive neural inhibition and contributes to difficulty in selection. In sum, we confirm that increasing GABAergic function (under midazolam) improves selection, while anxiety is associated with a robust and specific impairment in selection among competing options, and co-occurring dysphoria may counteract these effects. This counterintuitive effect of co-occurring dysphoria could potentially explain mixed evidence for EF deficits associated with anxiety (Castaneda et al., 2008), because previous studies may have varied in the levels of co-occurring dysphoria experienced by their anxious participants, as well as the sensitivity of their tasks to the effects of dysphoria. Our results emphasize the need to control for co-occurrence and consider the ways that anxiety and
depression may interact to affect selection and EF more broadly. Further, our results suggest that specific neural mechanisms associated with individual EF processes may be affected differently by anxiety and depression. Future research is needed to investigate these mechanisms and explore the implications for understanding and ameliorating impairments in daily functioning associated with these common mental health problems.
CHAPTER 5: NEURAL SUBSTRATES AND MECHANISMS SUPPORTING UNDETERMINED VERSUS PREPOTENT SELECTION

Thus far, we have focused on cases where there is competition among multiple valid response options (e.g., multiple verb associates in the verb generation task; *underdetermined selection demand*). However, in some cases, selecting an appropriate response requires over-riding a strongly dominant, but inappropriate response (*prepotent selection demand*), such as over-riding the habit of taking the usual route home when you need to stop at the store instead. Prepotent selection demands are also common during language production, such as when we must avoid using a word that is more familiar but incorrect (e.g., calling a spatula a spoon) or not appropriate in the current context (e.g., a New Yorker calling the Metro the Subway in D.C., or more consequentially, one researcher continuing to refer to his wife as his girlfriend after their marriage (M. C. Anderson & Levy, 2007). This raises an important limitation to the selection mechanism proposed in our neural network model (Chapter 3). Namely, competitive lateral inhibition among response options will always result in selection of the response that is most active in the VLPFC layer. When there is competition among multiple valid task responses this mechanism is sufficient. However, when there is competition from task-inappropriate responses (e.g., non-verbs in the verb generation task), this mechanism would allow these task-inappropriate responses to win the competition if they are more strongly activated than task-relevant responses. Yet healthy adults generally make relatively few errors on tasks involving prepotent selection (e.g., Stroop). How are we able to over-ride such prepotent responses to make a task-appropriate response?

Some previous accounts propose that VLPFC plays a role in both underdetermined and prepotent selection. Specifically, Thompson-Schill and colleagues have proposed that “Both of
these situations (underdetermined representations and prepotent representations) can induce conflict among active representations in working memory that require top-down intervention…We suggest that this intervention comes in the form of a modulatory signal from prefrontal cortex [left VLPFC] that aids in selection of appropriate representations” (Thompson-Schill, 2005, pp. 177-178) (c.f., Botvinick et al., 2001). In this model, the pattern of activation across response possibilities is a function both of the stimulus and of the task representation, such that the stimulus initially induces a pattern of activation resembling the pattern of activation in a free association task, and this pattern is then modulated by a control signal that increases activation of task-relevant responses and decreases the activation of task-irrelevant responses (Thompson-Schill & Botvinick, 2006). They propose that left VLPFC is the source of this control signal, but note that this mechanism does not require any particular localization.

Indeed, others have assigned this role not to VLPFC, but to dorsolateral prefrontal cortex (DLPFC). Specifically, several frameworks propose that portions of DLPFC maintain abstract representations of the task goal, which provide top-down support for task-relevant representations, biasing the system towards the correct response (e.g., Banich, 2009; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Herd et al., 2006; Milham et al., 2003; E. K. Miller & Cohen, 2001; Munakata et al., 2011). For example, the cascade model (e.g., Banich, 2009) predicts that left VLPFC will be sensitive to prepotent competition only if task-set maintenance and top-down biasing from DLPFC is inadequate to prevent activation of non-task-relevant representations (e.g., Herd et al., 2006), while other models predict that left VLPFC will play a role in resolving competition between any active representations, including those that are not task-relevant (e.g., Thompson-Schill & Botvinick, 2006).

Regardless of the source (VLPFC or DLPFC), boosting the activation level of task-
relevant responses could enable them to subsequently out-compete prepotent responses via competitive lateral inhibition in VLPFC. Thus, lateral inhibition in VLPFC alone may be sufficient for underdetermined selection, while prepotent selection may require active maintenance of task goals to bias competition towards task-relevant responses. Experiment 7 tests this possibility by directly contrasting underdetermined and prepotent selection demands within the same task for the first time. We find that participants are slowed, and activation in an area of left DLPFC is increased, by both underdetermined and prepotent competition, while left VLPFC is sensitive to underdetermined selection demands, but not prepotent selection demands.

A secondary aim of Experiment 7 was to further explore differences in neural activity associated with anxiety and depressive symptoms. Experiment 5 (Chapter 4) found that anxiety was associated with reduced VLPFC activation during underdetermined selection, suggesting that individuals higher in anxiety fail to adequately recruit VLPFC inhibitory mechanisms when there is competition among task-relevant responses. Experiment 7 replicates this finding and extends it to prepotent competition. Depressive symptoms were also associated with reduced VLPFC and DLPFC activation, during both prepotent and underdetermined selection, inconsistent with Experiment 5 but consistent with previous findings of prefrontal hypoactivity associated with depression (e.g., Elliott et al., 1997; Engels et al., 2010; Järnum et al., 2011; Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003).

We explore possible neural mechanisms underlying these group and individual differences effects in a modified version of the verb generation model. To simulate the effects of competition from prepotent responses (non-verb competitors in the verb generation task), units representing non-verb competitors were added to the posterior cortex and VLPFC layers, and a DLPFC layer was added which maintains the task set (i.e., generate verbs) during high-
competition conditions and provides top-down support for relevant verb responses. The model replicates the behavioral results of Experiment 7 and suggests that top-down biasing from DLPFC is necessary to resolve competition from prepotent responses, but may contribute to underdetermined competition by making all task-relevant responses more active. Moreover, this trade-off, whereby DLPFC input improves prepotent selection but impairs underdetermined selection, interacts with the level of competitive inhibition in VLPFC.

**Experiment 7: Differentiating Prefrontal Responses to Underdetermined and Prepotent Selection Demands**

**Method**

**Participants.** Nineteen healthy, right-handed, young adults (11 women) from the University of Colorado community participated in this study. Four additional subjects participated but were excluded due to excessive movement during fMRI scanning (> 2 mm). All participants were native English speakers, had no history of neurological conditions or head injury, and were not taking any psychoactive medication. Participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado Institutional Review Board.

**Design and stimuli.** Stimuli were 100 nouns in a 2 x 2 design (Figure 5.1) crossing underdetermined selection demand (high vs. low underdetermined competition) with prepotent selection demand (high vs. low prepotent competition), with 25 trials/condition for a total of 100 trials. Because nouns with high prepotent competition were not available from previous studies, they were selected from a large set of nouns normed for this study by a separate sample of participants (n = 49). In the high prepotent competition condition, task-inappropriate non-verb responses (generated by two or more participants in a free-association norming sample) are
significantly more strongly associated with the noun stimuli than task-appropriate verb responses (based on higher LSA cosine), whereas in the low prepotent competition condition the reverse is true. High vs. low underdetermined competition is defined as in the previous experiments (Chapters 2 and 4). All conditions were matched on retrieval demands (calculated as described in Chapters 2 and 4).

**Procedure.** Participants were instructed to generate the first verb that came to mind when presented with a noun stimulus (e.g., *cat*). The verb could be either something the noun does (e.g., *meow*), or something you do with it (e.g., *feed*). Participants were given an example and eight practice trials prior to entering the scanner, and were reminded of the instructions prior to beginning the task. During image acquisition, participants completed 25 trials in each condition, for a total of 100 trials. On each trial, participants viewed a fixation point for 500 ms, followed by a noun cue for 3500 ms, and responded by saying a verb associated with the noun. Verbal responses were collected with a fiber-optic noise-canceling microphone (Optoacoustics Ltd., Or-Yehuda, Israel) via a procedure that has been found to minimize head motion (Barch, Sabb, Carter, Braver, & Noll, 1999). A blocked paradigm was used to encourage participants to maintain cognitive control during the high-demand conditions and reduce control during the low-demand conditions. Participants completed 5 blocks of 5 trials each per condition, plus 11 baseline fixation blocks, for a total of 31 blocks lasting 20 seconds each. Blocks were presented in two counterbalanced orders across participants. Within-condition, item order was randomized across subjects. Data were acquired in one functional run, lasting about 10.5 minutes. At an earlier behavioral testing session, participants completed the PSWQ to assess anxious apprehension, as well as the MASQ to control for anxious arousal and depressive symptoms, as part of a larger battery of measures. One participant declined to complete the PSWQ.
**Image acquisition and processing.** Data were acquired with a 3T Siemens Magnetom TrioTim whole-body MRI scanner at the University of Colorado Boulder, using T2*-weighted echo, echo-planer imaging (EPI; TR= 2000 ms, TE= 29 ms, flip angle= 75°). Functional data were collected in a single run of 316 EPI volumes, each consisting of 28 ascending 4 mm thick slices (gap=1 mm, filed-of-view (FOV)=220 mm, in-plane matrix= 64 x 64, in-plane resolution= 3.4 x 3.4 mm²), angled parallel to the inferior surface of the orbital frontal cortex. Prior to the

**Figure 5.1** Experiment 7 design and behavioral results. (A) Verb generation task design with example items. Underdetermined selection demand (high versus low competition among possible verb responses) is crossed with prepotent selection demand (high versus low competition from non-verb associates). Nouns in the high underdetermined selection demand conditions have multiple possible verb responses, while nouns in the low underdetermined selection demand conditions have few possible verb responses (quantified as the LSA entropy, see Methods). Nouns in the high prepotent selection demand conditions have strong non-verb associates, while nouns in the low prepotent selection demand conditions have stronger verb than non-verb associates (quantified as the LSA cosine, see Methods). All conditions are matched on retrieval demand. (B) Participants take longer to respond when there is competition among verb responses (underdetermined selection) or competition from prepotent non-verb responses (prepotent selection), and these factors interact (see Results)
functional run, high-resolution 3D multiecho MPRAGE full head anatomical images were acquired along the transverse plane (TR=2530 ms, TE1=1.64 ms, TE2=3.50 ms, TE3= 5.36 ms, TE4=7.22 ms, TE5= 9.08 ms, flip angle=7°, inversion time=1200 ms; 220 mm FOV, 256 x 256 matrix, 1 mm x 1 mm in-plane resolution, 192 slices, 1 mm slice thickness). The scanner was equipped with a standard head coil and participants’ heads were secured with moldable pillows to minimize head motion. Stimuli were displayed on a screen and participants responding by speaking into a fiber-optic noise-canceling microphone (Optoacoustics Ltd., Or-Yehuda, Israel) positioned directly above the mouth. All participants included in the analyses met our criteria for minimal head motion (< 2 mm translation/2° rotation in any direction).

Image pre-processing and analysis were conducted with FSL (FMRIB’s Software Library). After discarding the first five volumes of the run to allow the MR signal to reach steady state, the remaining images in each participant’s time series were motion corrected using MCFLIRT (Jenkinson, 2001), and non-brain voxels removed using BET. Images in the data series were spatially smoothed with a 3D Gaussian kernel (FWHM = 8 mm), intensity normalized for all volumes by the same factor, and high-pass filtered to remove high-frequency noise (σ=120 sec) was applied. After statistical analysis for each participant’s time series, the statistical maps (reflecting each participant’s response in each condition) were normalized into the common MNI-152 stereotaxic space, using FLIRT (FMRIB’s Linear Image Registration Tool, Jenkinson, Bannister, Brady, & Smith, 2002) before random effect group analyses were performed. Subsequent statistical analyses were conducted using FEAT (FMRIB’s Easy Analysis Tool). GLM analyses of the fMRI time series data were conducted, then subjected to group-level random effects analysis.
Results

**Behavioral results.** RT data were analyzed with a 2 x 2 repeated-measures ANOVA. Replicating Experiment 1, participants were slowed by greater competition among possible verb responses (greater underdetermined selection demand, $F(1,17)=80.37, p<.001$). Participants were also slowed by competition from prepotent non-verb associates (greater prepotent selection demand, $F(1,17)=8.37, p=.01$). Specifically, RTs were longer in the high underdetermined competition (log RT M=7.40, SE=.03) than low underdetermined competition (log RT M=7.26, SE=.02) conditions, and longer in the high prepotent competition (log RT M=7.34, SE=.03) than low prepotent competition (log RT M=7.32, SE=.02) conditions. In addition, there was a significant interaction between prepotent and underdetermined competition ($F(1,17)=5.91, p=.026$). Specifically, the effect of prepotent competition was greater when underdetermined competition was low (log RT difference M=.06, SE=.02) than when underdetermined competition was high (log RT difference M=-.01, SE=.01), and the effect of underdetermined competition was greater when prepotent competition was low (log RT difference M=.17, SE=.02) than when prepotent competition was high (log RT difference M=.10, SE=.02).

**Whole brain analysis.** Whole-brain analyses were conducted for the following key contrasts: (1) underdetermined selection demand main effect (high vs. low underdetermined competition, collapsing across levels of prepotent competition) and (2) simple effect (high vs. low underdetermined competition, with low levels of prepotent competition), (3) prepotent selection demand main effect (high vs. low prepotent competition, collapsing across levels of underdetermined competition) and (4) simple effect (high vs. low prepotent competition, at low levels of underdetermined competition). As predicted, underdetermined selection engaged a large area of left VLPFC (left inferior frontal gyrus, centered on BA 47), while prepotent selection
engaged left DLPFC (left middle frontal gyrus, centered on BA 9; Table 5.1 and Figure 5.2). In addition, underdetermined selection engaged the pre-cingulate/supplementary motor area in the superior frontal gyrus, the middle temporal gyrus, and the cerebellum (Table 5.1).

Table 5.1
Experiment 7 Peak Voxel Coordinates, Anatomical Locations, and Approximate Brodmann’s Areas from Whole-Brain Random Effects Analysis

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Region</th>
<th>BA</th>
<th>Max Z</th>
<th>No. of Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underdetermined Selection</td>
<td>Inferior Frontal Gyrus (L)</td>
<td>47</td>
<td>4.51</td>
<td>3493</td>
<td>-42</td>
<td>32</td>
<td>-8</td>
</tr>
<tr>
<td></td>
<td>Superior Frontal Gyrus (L)</td>
<td>8</td>
<td>3.29</td>
<td>439</td>
<td>-6</td>
<td>16</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Middle Temporal Gyrus (L)</td>
<td>21</td>
<td>3.64</td>
<td>219</td>
<td>-58</td>
<td>-54</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cerebellum Posterior Lobe (R)</td>
<td>NA</td>
<td>4.08</td>
<td>3676</td>
<td>34</td>
<td>-60</td>
<td>-32</td>
</tr>
<tr>
<td></td>
<td>Cerebellum Posterior Lobe (L)</td>
<td>NA</td>
<td>3.18</td>
<td>190</td>
<td>-32</td>
<td>-58</td>
<td>-34</td>
</tr>
<tr>
<td></td>
<td>Caudate (R)</td>
<td>NA</td>
<td>3.29</td>
<td>368</td>
<td>20</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Precuneus (R)</td>
<td>7</td>
<td>-3.94</td>
<td>1951</td>
<td>6</td>
<td>-64</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Superior Temporal Gyrus (R)</td>
<td>39</td>
<td>-3.24</td>
<td>456</td>
<td>48</td>
<td>-58</td>
<td>22</td>
</tr>
<tr>
<td>Main Effect</td>
<td>Inferior Frontal Gyrus (L)</td>
<td>45</td>
<td>4.02</td>
<td>721</td>
<td>-30</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Precentral Gyrus (L)</td>
<td>9</td>
<td>3.35</td>
<td>168</td>
<td>-38</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Cerebellum Posterior Lobe (R)</td>
<td>NA</td>
<td>3.47</td>
<td>231</td>
<td>36</td>
<td>-66</td>
<td>-36</td>
</tr>
<tr>
<td>Simple Effect</td>
<td>Inferior Frontal Gyrus (L)</td>
<td>45</td>
<td>4.02</td>
<td>721</td>
<td>-30</td>
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<td>3.35</td>
<td>168</td>
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<td>3.47</td>
<td>231</td>
<td>36</td>
<td>-66</td>
<td>-36</td>
</tr>
</tbody>
</table>

Note. All clusters z>2.58, minimum cluster size=154 voxels, p<.01, two-tailed. BA= Brodmann’s area, L= left, R=right.

To further explore the profile of activation in key left VLPFC and DLPFC clusters, spherical ROIs (radius =10 mm) were created around their peak coordinates. Activation of each condition versus fixation baseline for each peak ROI is presented in Figure 5.2, and the opposite contrast was tested in each (i.e. the prepotent competition contrast in the ROI defined around the underdetermined competition peak in VLPFC, and the underdetermined competition contrast in the ROI defined around the prepotent competition peak in DLPFC).

In the VLPFC ROI defined as showing a significant underdetermined selection response in the whole-brain analysis, there was no effect of prepotent competition (t(18)=0.27, p=.79).

The pattern of activation across the four conditions versus baseline revealed similarly high activation levels for the two high underdetermined competition conditions (high
underdetermined/high prepotent, high underdetermined/low prepotent) and similarly lower activation for the two low underdetermined competition conditions (low underdetermined/high prepotent, low underdetermined/low prepotent). In contrast, in the DLPFC ROI defined as showing a significant prepotent selection response in the whole-brain analysis, there was also a significant effect of underdetermined competition ($t(18) = 3.35, p = .004$). The pattern of activation across the four conditions versus baseline revealed similarly high activation levels for the three high competition conditions (high underdetermined/high prepotent, high underdetermined/low prepotent, and low underdetermined/high prepotent) and lower activation for the low competition condition (low underdetermined/low prepotent).
A priori left VLPFC region of interest analyses. A priori region of interest (ROI) analyses were conducted for the left VLPFC ROIs implicated in underdetermined selection in Experiment 2: left anterior-VLPFC and left mid-VLPFC. ROIs were identical to those in Experiment 2. First, an anatomical ROI consisting of left inferior frontal gyrus pars triangularis and pars orbitalis (mid and anterior VLPFC) was defined using the Harvard–Oxford Cortical Structures (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) and Duvernoy atlases (Duvernoy, 1999). Second, spherical ROIs were defined around the mean coordinates identified in Badre and Wagner (2007) for left anterior-VLPFC (-48, 30, -6) and left mid-VLPFC (-50, 25,
14), with a radius of 10 mm. Activation for each condition versus fixation baseline within each ROI was extracted for each participant and subjected to a 2 x 2 (underdetermined selection demand x prepotent selection demand) repeated measures ANOVA. Outliers with Cook’s d > 3 SD above the mean were excluded; this led to the exclusion of no more than three participants from any analysis. The significance of all effects remained the same with these outliers included.

For the anatomically-defined left VLPFC ROI (Figure 5.3), there was a significant main effect of underdetermined selection demand, with greater activation in the high underdetermined competition than low underdetermined competition conditions \((F(1,17)= 19.35, p<.001)\). There was no significant effect of prepotent competition \((F(1,17)= 0.16, p=.70)\), and no interaction between underdetermined and prepotent competition \((F(1,17)= 0.05, p=.82)\).

For the spherical ROIs, a 2 x 2 x 2 (underdetermined competition x prepotent competition x region) repeated measures ANOVA again revealed a significant effect of underdetermined selection demand, with greater activation in the high underdetermined competition than low underdetermined competition conditions \((F(1,16)= 24.68, p<.001)\). There was no significant effect of prepotent competition \((F(1,16)= 0.04, p=.85)\), and no interaction between underdetermined and prepotent competition \((F(1,16)= 0.07, p=.79)\). There was no main effect of region \((F(1,16)= 1.41, p=.25)\), and no interactions between prepotent competition and region \((F(1,16)= 0.03, p=.86)\) or region x prepotent competition x underdetermined competition \(F(1,16)= 2.63, p=.12\). There was a marginal underdetermined competition x region interaction \((F(1,16)= 4.09, p=.060)\), with a larger effect of underdetermined competition in anterior-VLPFC than mid-VLPFC (Figure 5.4).Within each VLPFC ROI, mid and anterior VLPFC showed the same pattern of results: significant effects of underdetermined selection demand (mid-VLPFC, \(F(1,18)= 24.90, p<.001\); anterior-VLPFC, \(F(1,16)= 21.06, p<.001\)), with no effect of prepotent
selection demand (mid-VLPFC, $F(1,18)= 0.26, p=.61$; anterior-VLPFC, $F(1,16)= 0.01, p=.93$),
or interaction (mid-VLPFC, $F(1,18)= 1.04, p=.32$; anterior-VLPFC, $F(1,16)= 0.05, p=.83$).

Figure 5.3 Experiment 7 anatomical VLPFC ROI. (A) Anatomically defined region of interest (mid and anterior left VLPFC, shown in blue. (B) The VLPFC is sensitive to underdetermined selection demand but not prepotent selection demands.
Left DLPFC region of interest analyses. First, an anatomical ROI consisting of left middle frontal gyrus (MFG) was defined using the Harvard–Oxford Cortical Structures (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) and Duvernoy atlases (Duvernoy, 1999). Second, a spherical ROI was defined around the mean coordinates identified in a meta-analysis of Stroop fMRI studies (Nee, Wager, & Jonides, 2007) for DLPFC ($-42$, $16$, $28$) with a radius of $10$ mm. The Stroop contrast was chosen because the Stroop task is the most widely used task involving competition from prepotent verbal responses. Activation for each condition
versus fixation baseline within each ROI was extracted for each participant and subjected to a 2 x 2 (underdetermined selection demand x prepotent selection demand) repeated measures ANOVA. Outliers with Cook’s $d > 3$ SD above the mean were excluded; this led to the exclusion of no more than three participants from any analysis.

For the anatomical left MFG ROI, there were no significant effects (underdetermined selection demand, $F(1,15)= 1.41, p=.25$, prepotent selection demand $F(1,15)= 0.37, p=.55$, interaction $F(1,15)= 1.48, p=.24$). This can be understood in reference to the whole-brain analysis, which demonstrated activation for prepotent selection demands only in a specific area of DLPFC.

**Figure 5.5** Experiment 7 DLPFC ROI activation. (A) The ROI was defined in left DLPFC based on a Stroop meta-analysis (Nee et al., 2007), as the Stoop task involves prepotent competition. (B) This area of DLPFC is sensitive to both prepotent and underdetermined selection demands, with similar activation levels for the three high-competition conditions.
portion of the left MFG, rather than the gyrus as a whole. For the Stroop meta-analysis spherical ROI (Figure 5.5), there was a significant main effect of prepotent selection demand, with greater activation in the high prepotent competition than low prepotent competition conditions \((F(1,15)=6.38, p=.023)\). There was also a significant main effect of underdetermined selection demand, with greater activation in the high underdetermined competition than low underdetermined competition conditions \((F(1,15)=9.64, p=.007)\). There was a significant interaction between underdetermined and prepotent competition \((F(1,15)=7.22, p=.017)\), such that the effect of prepotent competition was larger when underdetermined competition was low.

**Correlations with anxiety and depression.**

**Whole brain.** Z-transformed PSWQ and MASQ-D scores were entered as covariates in higher-level GLM analyses to test for correlations between brain activation, anxious apprehension, and anhedonic depression. There were no correlations between PSWQ or MASQ-D and the main effects of prepotent or underdetermined competition. However, there were multiple brain areas that correlated negatively with PSWQ and MASQ-D scores in the simple effects contrasts: prepotent selection with low underdetermined selection demands and underdetermined selection with low prepotent selection demands (Table 5.2). In sum, both anxious apprehension and anhedonic depression symptoms were associated with reduced activation in anterior cingulate cortex and multiple posterior cortical and subcortical areas during underdetermined selection, and a subset of these areas also showed negative correlations during prepotent selection. In addition, anhedonic depression (but not anxious apprehension) was associated with decreased activation in areas of DLPFC during both underdetermined and prepotent selection.
Table 5.2

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Region</th>
<th>BA</th>
<th>Max Z</th>
<th>No. of Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
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<tr>
<td>Underdetermined Selection (with low Prepotent Selection Demands):</td>
<td>Anterior Cingulate (L)</td>
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<td>321</td>
<td>2</td>
<td>48</td>
<td>-2</td>
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<tr>
<td></td>
<td>Inferior Frontal Gyrus (R)</td>
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<td>-3.53</td>
<td>229</td>
<td>50</td>
<td>24</td>
<td>20</td>
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<tr>
<td></td>
<td>Parahippocampal Gyrus (L)</td>
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<td>-4.11</td>
<td>2590</td>
<td>-32</td>
<td>-36</td>
<td>-30</td>
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<tr>
<td></td>
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<td>-3.74</td>
<td>1588</td>
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<td>-46</td>
<td>-14</td>
</tr>
<tr>
<td></td>
<td>Postcentral Gyrus (R)</td>
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<td>-3.45</td>
<td>721</td>
<td>54</td>
<td>-28</td>
<td>36</td>
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<tr>
<td></td>
<td>Inferior Parietal Lobule (R)</td>
<td>40</td>
<td>-3.34</td>
<td>352</td>
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<td>42</td>
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<td></td>
<td>Insula (R)</td>
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<td>-3.33</td>
<td>208</td>
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<td>-44</td>
<td>24</td>
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<tr>
<td></td>
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<td>1517</td>
<td>-54</td>
<td>-4</td>
<td>-8</td>
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<td>Superior Temporal Gyrus (R)</td>
<td>38</td>
<td>-3.72</td>
<td>172</td>
<td>64</td>
<td>10</td>
<td>-14</td>
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<tr>
<td></td>
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<td>-54</td>
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<td>-2</td>
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<td></td>
<td>Cerebellum Posterior Lobe (R)</td>
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<td>-42</td>
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<td>Caudate (L)</td>
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<td>-12</td>
<td>16</td>
<td>10</td>
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<td>Negative Correlation with Anxious Apprehension (PSWQ)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlling for MASQ-D</td>
<td>Precuneus (L)</td>
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<td>-3.86</td>
<td>182</td>
<td>-4</td>
<td>-84</td>
<td>52</td>
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<td></td>
<td>Precuneus (R)</td>
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<td>-66</td>
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<td>Parahippocampal Gyrus (R)</td>
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<td>-3.37</td>
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<td>-46</td>
<td>-14</td>
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<td>Superior Temporal Gyrus (L)</td>
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<td>-3.41</td>
<td>154</td>
<td>-34</td>
<td>14</td>
<td>-36</td>
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</tbody>
</table>

Figure 5.6 Experiment 7 whole brain correlations with anxiety and depression. (A) Negative correlations with anxious apprehension. (B) Negative correlations with anhedonic depression. Both correlate negatively with activation during both underdetermined selection (blue) and prepotent selection (green) in a number of brain regions (see Table 5.2).
### Table: Correlation Magnitudes

<table>
<thead>
<tr>
<th>Region (L)</th>
<th>Z-Score</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
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<tr>
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<tr>
<td>Middle Frontal Gyrus (L)</td>
<td>10</td>
<td>-3.87 1169 -8 48 -4</td>
</tr>
<tr>
<td>Middle Frontal Gyrus (R)</td>
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<td>-3.57 220 38 42 8</td>
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<tr>
<td>Middle Temporal Gyrus (R)</td>
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<td>-3.27 168 68 -2 -20</td>
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</table>

**Negative Correlation with Anhedonic Depression (MASQ-D)**

<table>
<thead>
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<th>Region (L)</th>
<th>Z-Score</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle Frontal Gyrus (L)</td>
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<tr>
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<td>40</td>
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<td>Inferior Parietal Lobule (R)</td>
<td>40</td>
<td>-3.48 514 38 -54 58</td>
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**Controlling for PSWQ**

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<th>MNI Coordinates</th>
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<tr>
<td>Middle Temporal Gyrus (L)</td>
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**Prepotent Selection (w/ low Underdetermined Selection Demands):**

<table>
<thead>
<tr>
<th>Region (L)</th>
<th>Z-Score</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cingulate (L)</td>
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<td>Middle Occipital Gyrus (L)</td>
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<td>Precuneus (L)</td>
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<td>Cuneus (L)</td>
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<td>-3.35 184 38 6 -22</td>
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<td>Cerebellum Posterior Lobe (L)</td>
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<td>-3.32 245 -22 -48 -56</td>
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</table>

**Controlling for MASQ-D**

<table>
<thead>
<tr>
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<th>MNI Coordinates</th>
</tr>
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<tr>
<td>Superior Frontal Gyrus (L)</td>
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<td>Insula (L)</td>
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<td>Precuneus (R)</td>
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<tr>
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<td>-3.85 387 62 -34 30</td>
</tr>
<tr>
<td>Superior Temporal Gyrus (R)</td>
<td>22</td>
<td>-3.96 260 62 -8 4</td>
</tr>
</tbody>
</table>

**Negative Correlation with Anxious Apprehension (PSWQ)**

<table>
<thead>
<tr>
<th>Region (L)</th>
<th>Z-Score</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior Parietal Lobule (L)</td>
<td>40</td>
<td>-3.59 256 -52 -46 46</td>
</tr>
</tbody>
</table>

**Note.** All clusters z>2.58, minimum cluster size=154 voxels, p<.01, two-tailed. BA=Brodmann’s area, L= left, R=right.

**ROIs.** We further tested correlations within VLPFC and DLPFC ROIs (described above).

To limit multiple-comparisons, we only examined the simple effects contrasts that emerged in the whole-brain correlation analyses.

**VLPFC.** Correlations for the anatomical VLPFC ROI\(^{17}\) are shown in Figure 5.7. There

\(^{17}\) For the anterior VLPFC and mid VLPFC spherical ROIs, there were similar negative correlations as for the anatomical VLPFC ROI, although correlations with the PSWQ did not reach significance, potentially due to reduced power from the smaller volume of the ROIs. Correlation magnitudes for the mid and anterior ROIs were similar to each other.
were significant negative correlations between activation during underdetermined selection (simple effect contrast) and both anxious apprehension (PSWQ; $r = -.48, p = .049, n = 18$; controlling for MASQ-D $r(14) = -.32, p = .2$, controlling for MASQ-A, $r(14) = -.43, p = .10$) and anhedonic depression (MADQ-D; $r = -.73, p < .001, n = 19$; controlling for PSWQ $r(15) = -.63, p = .01$, controlling for MASQ-A, $r(16) = -.78, p < .001$). There were also significant negative correlations between activation during prepotent selection (simple effects contrast) and both anxious apprehension (PSWQ; $r = -.56, p = .019, n = 17$; controlling for MASQ-D $r(14) = -.48, p = .057$, controlling for MASQ-A, $r(14) = -.42, p = .10$) and anhedonic depression (MADQ-D; $r = -.54, p = .018, n = 19$, controlling for PSWQ $r(15) = -.37, p = .14$, controlling for MASQ-A, $r(16) = -.56, p = .017$).

**Figure 5.7.** Experiment 7 engagement of left VLPFC during selection, as a function of anxiety and depression. Anxiety (PSWQ, A-B) and depression (MASQ-D, C-D) both correlate negatively with activation in the left VLPFC ROI during underdetermined (A, C) and prepotent (B, D) selection.
DLPFC. Correlations for the Stroop meta-analysis spherical ROI\textsuperscript{18} are shown in Figure 5.8. There were significant negative correlations between activation during prepotent selection (simple effects contrast) and both anxious apprehension (PSWQ; $r = -.50$, $p = .040$, $n = 17$; controlling for MASQ-D $r(14) = -.33$, $p = .2$, controlling for MASQ-A, $r(13) = -.52$, $p = .040$) and anhedonic depression (MADQ-D; $r = -.77$, $p < .001$, $n = 17$; controlling for PSWQ $r(13) = -.73$, $p = .002$, controlling for MASQ-A, $r(14) = -.77$, $p < .001$). There was a marginally significant negative correlation between activation during underdetermined selection (simple effects contrast) and anhedonic depression ($r = -.47$, $p = .056$, $n = 17$; controlling for PSWQ $r(13) = -.26$, $p = .3$), controlling for MASQ-A, $r(14) = -.49$, $p = .055$). The correlation with anxious apprehension was not significant ($r = -.29$, $p = .2$, $n = 18$; controlling for MASQ-D $r(15) = -.09$, $p = .7$, controlling for MASQ-A, $r(15) = -.19$, $p = .5$).

**Figure 5.8.** Experiment 7 engagement of left DLPFC during selection, as a function of depression. Depression (MASQ-D correlates negatively with activation in the left DLPFC ROI during underdetermined (A) and prepotent (B) selection.

\textsuperscript{18} Correlations were not tested for the anatomical left MFG ROI since it did not exhibit significant group effects of the task manipulations.
Discussion

Multiple accounts suggest that there is a prefrontal control mechanism that biases competition towards task-relevant responses, but accounts differ as to the source of that control signal: DLPFC (e.g., Banich, 2009) or VLPFC (e.g., Thompson-Schill, 2006). Experiment 7 suggests that an area of left DLPFC is the key source of the control process that supports prepotent selection. Specifically, an area of left DLPFC was sensitive to both underdetermined and prepotent selection demands, suggesting that it becomes active whenever competition is high. In contrast, left VLPFC was only activated across the group during underdetermined selection. This suggests that it cannot be the source of the control signal that biases competition towards task-relevant responses, although it may be sensitive to prepotent competition when top-down cognitive control is inadequate (as evidenced by correlations between activity during prepotent selection and psychopathology).

Both anxious apprehension and anhedonic depression symptoms were associated with reduced activation during both prepotent and underdetermined selection in VLPFC, anterior cingulate cortex and multiple posterior cortical and subcortical areas. The negative correlation with anxious apprehension in VLPFC replicates the finding of Experiment 5, and extends it to prepotent competition. However, unlike in Experiment 5, anhedonic depression symptoms also correlated negatively with VLPFC activity during selection. What might account for this discrepancy? One possibility is that correlations with depression symptoms may only occur when the task context requires or encourages maintenance of task goals in DLPFC. A meta-analysis of the previous literature suggests that depression is associated with broad impairments in executive function (Snyder, 2012), consistent with a deficit in a general executive function ability.
hypothesized to be the ability to actively maintain task goals (Friedman et al., 2008). Notably, in Experiment 7 anhedonic depression symptoms (but not anxious apprehension) were also associated with decreased DLPFC activation during selection, suggesting reduced DLPFC task-set maintenance. This experiment may have encouraged maintenance of task goals, and thus revealed correlations with depression symptoms, because it included prepotent competition and used a blocked design to promote sustained control, unlike Experiment 5, which did not involve prepotent competition and used an event-related design.

Thus, it is possible that reduced VLPFC activation may be associated with anxiety and depression for different reasons. Namely, anxiety may be associated with reduced recruitment of inhibitory activity to resolve competition within the VLPFC, while depression may be associated with reduced excitatory input from DLPFC. Since fMRI BOLD signal reflects a combination of excitatory and inhibitory neural activity (e.g., Buzsáki et al., 2007), both of these factors could result in reduced BOLD signal. Future research is needed to test this possibility, and better characterize the specific profile of neural differences and cognitive control deficits associated with anxiety and depression.

Several additional questions also remain. First, prepotent competition slows RTS, but does not activate VLPFC across the group. What might account for this apparent discrepancy? Second, the area of left DLPFC sensitive to prepotent competition was also sensitive to underdetermined competition. Previous theories have posited that this area is involved in maintaining task goals to bias competition towards task-relevant responses. Thus, it is not clear what role left DLPFC may play in underdetermined selection (where competition is among task-relevant responses), and how it may differ from the role of VLPFC in underdetermined selection. While the current study cannot fully address these questions, our neural network simulations
explore possible answers and generate predictions for future empirical research.

Computational Mechanisms for Prepotent Selection

**Extension of Verb Generation Model**

The verb generation neural network model described in Chapter 3 was extended to explore what neural mechanism subserved by DLPFC might support prepotent selection. Specifically, the model tests the theory that input from DLPFC to task-relevant responses in VLPFC can enable them to out-compete prepotent responses (e.g., Banich, 2009; Miller & Cohen, 2001; Munakata et al., 2011). The model further allows us to explore how this DLPFC mechanism might affect underdetermined selection (given that DLPFC was also sensitive to underdetermined competition in Experiment 7), and how it might interact with the competitive lateral inhibition mechanism in VLPFC, which was key to underdetermined selection in the earlier version of the model. We thus adapted the model to simulate prepotent competition by (a) adding units representing non-verb competitors to the posterior cortex and VLPFC layers, and (b) adding a DLPFC layer (Figure 5.9 A). These changes to the model are detailed below. Unless otherwise noted, all other aspects of the model are identical to those in the previous version of the model described in Chapter 3.

**Input layer.** The input layer consisted of four units, representing the average noun for each of the four conditions used: low underdetermined competition/low prepotent competition, high underdetermined competition/low prepotent competition, low underdetermined competition/high prepotent competition, and high underdetermined competition/high prepotent competition. As in the previous version of the model, the weights between these input units and their response units in the posterior cortex layer were set as a function of LSA cosines, averaged across all items in the corresponding condition of Experiment 7 and scaled to 75%. As in the
previous version of the model, the two high underdetermined competition condition input units each project to six verb response units in the posterior cortex layer, while the two low underdetermined competition units each project to one verb response unit in posterior cortex. To model prepotent competition, the two high prepotent competition condition input units also projected to non-verb competitor units in posterior cortex, representing the strongest non-verb associate in each condition (as described in Experiment 7 methods). In addition, each input unit projects to the DLPFC layer, with the strength of the connection scaled according to the relative activation levels of the DLPFC in Experiment 7, as discussed further in the DLPFC layer section.

**Posterior cortex layer.** The posterior cortex layer contains one unit for each alternative verb response (six units each for the high competition conditions, one unit each for the low competition conditions) as in the previous version of the model, plus two non-verb competitor units (one each for the two high prepotent competition conditions). As in the previous version of the model, verb response units in the high underdetermined conditions have lateral connections to one another. In addition, the non-verb competitor units in the high prepotent competition conditions have lateral connections to the verb response units. All lateral connection strengths are set according to the LSA association values, as described in Chapter 3. Thus, the posterior cortex layer simulates spreading semantic activation in posterior cortex. Each posterior cortex layer unit projects to one unit in the VLPFC layer and one unit in the output layer.

**VLPFC layer.** The VLPFC layer contains one unit for each alternative verb response, as in the previous version of the model, plus two non-verb competitor units as in the posterior cortex layer. Units compete through kWTA inhibition, as described in Chapter 3, with the kWTA parameter set to the standard inhibition level used in the previous version of the model (.66) to fit the group behavioral data, then manipulated to the low (.62) and high (.68) inhibition levels to
test effects of competitive inhibition in the new model version. As in the previous version of the model, VLPFC units are recurrently connected to themselves, and project back to their respective posterior cortex layer units, and to their output units. In addition, VLPFC verb response units receive input from the DLPFC layer, as described in the next section. All parameters are the same as in the previous version of the model, with the exception of the recurrent connection strength, which was reduced to .60 to prevent over-activation of the layer given the additional inputs form the new DLPFC layer.

**DLPFC layer.** The main addition to the model is a DLPFC layer, which provides top-down support for task-relevant verb responses. For simplicity, the DLPFC layer contains a single unit, simulating populations of neurons in DLPFC that represent the task goal (i.e., to say verbs). Again for simplicity in the model, the DLPFC is activated directly from the input, with weights scaled according to the activation pattern of the DLPFC ROI in Experiment 7 (.3 for the three high competition conditions and .2 for the low competition condition). In the brain, the DLPFC may instead be activated by other brain areas which detect conflict or competition, such as the ACC (e.g., Barch et al., 2000).

The DLPFC then activates verb, but not non-verb, response units in the VLPFC layer. To prevent verbs not associated with the current noun input from becoming activated (which would be akin to thought disorder or hallucination), the code was modified such that only verb units that were already becoming active (due to input from the posterior cortex layer) received added excitatory input from the DLPFC. This mechanism simulates the role of voltage-gated N-methyl-D-aspartate (NMDA) receptors, which are highly concentrated in PFC (Phillips & Silverstein,
Specifically, at each cycle (time-step) of the settling process, the DLPFC unit activation level was multiplied by a weight term (ranging from .003 to .007 to simulate different levels of DLPFC function, as discussed in the next section) and added to the existing activation level of all VLPFC verb units with activation levels >0.

**Model Simulations.** To explore potential mechanisms involved in underdetermined and prepotent selection, model parameters were first adjusted to simulate the basic behavioral effects in the verb generation task: independent effects of underdetermined and prepotent selection demands and an interaction between these two factors.\(^\text{20}\) Vm trial noise was added (Gaussian distribution with M = 0, var = 0.00005) and 30 simulations were run at each of five levels of DLPFC input (DLPFC pt. = .003-.007). To test the effects of decreased neural inhibition, the kWTA pt parameter in the VLPFC layer was reduced from 0.66 to 0.62, and 30 simulations were again run at each level of DLPFC input. To test the effect of increased neural inhibition, the kWTA pt parameter in the VLPFC layer was increased from 0.66 to 0.68, and 30 simulations were again run at each level of DLPFC input.

---

\(^{19}\) NMDA receptors have binding sites for both glutamate and Mg\(^{2+}\); at membrane potentials more negative than \(-50\) mV, the concentration of Mg\(^{2+}\) in the extracellular fluid virtually abolishes ion flux through the NMDA receptor channels, even in the presence of glutamate. Thus, at resting membrane potentials (-70 mV), the activation of NMDA receptors causes little current change, even when glutamate is bound to the receptor. As the membrane potential becomes less negative (e.g. due to glutamate binding at AMPA receptors), the affinity of Mg\(^{2+}\) for its binding site decreases, and ionic current can pass through the channel. Thus, NMDA receptors are thought to act as coincidence detectors that sense simultaneous, repetitive activity at a number of adjacent synapses (since multiple synapses must be simultaneously active to raise membrane potential sufficiently).

\(^{20}\) A simple manual search was conducted over (i) recurrent connection strength in the VLPFC layer (from 0.5 to 1) and (ii) the DLPFC wt parameter (from .001 to .1) to achieve a qualitative match to results, while keeping all other parameters identical to those in the previous version of the model (Chapter 3). The basic pattern of results (independent effects of underdetermined and prepotent selection demands) was never violated within this set of parameters.
Model Simulation Results

Model response times and VLPFC activation dynamics at the standard parameter settings (DLPFC pt.=.005, VLPFC kWTA=.66) are shown in Figure 5.9 B and C respectively. As in human participants, the model generates longer settling times (cycles to generate a response) when underdetermined selection demands are high (many possible verb responses) than when underdetermined selection costs are low (few possible verb responses), with an average underdetermined selection cost of 7.2 cycles. Also as in human participants, the model produces longer settling times in the high prepotent selection demand (strong non-verb competitor) compared with low prepotent selection demand (weak non-verb competitor) conditions, with an average selection cost of 4.5 cycles. The model also produces the interaction found in human data: prepotent selection costs are higher when underdetermined selection demands are low (12.2 cycles) than when underdetermined selection demands are high (2.3 cycles).
Figure 5.9. Expanded neural network model. (A) Network architecture, with added non-verb competitor units in the posterior cortex and VLPFC layers to simulate prepotent competition, and a new DLPFC layer that provides top-down support for relevant verb responses in the VLPFC to test this mechanism for prepotent selection. (B) Model simulates human RTs, showing effects of underdetermined and prepotent competition and their interaction. (C) Activation of the VLPFC units in each simulation condition. Both underdetermined and prepotent selection demands delay and reduce activation of winning verb responses (thin solid lines), due to competition from alternative responses (thick and dashed lines). Activation of non-verb competitors in the high prepotent competition conditions is reduced by top-down biasing from the DLPFC, which boosts activation of verb responses, helping them to outcompete non-verbs. LULP= low underdetermined competition/low prepotent competition, HULP= high underdetermined competition/low prepotent competition, LUHP= low underdetermined competition/high prepotent competition, HUHP= high underdetermined competition/high prepotent competition.
The effects of underdetermined and prepotent selection demands can be understood in terms of the activation dynamics of units in the VLPFC layer. Figure 5.9 C illustrates three key effects. First, both types of selection demands affect the slope and asymptote of VLPFC unit activations, with units becoming active more gradually and reaching a lower asymptote under high selection demands, because of the competition from alternative responses. The magnitude of these effects is consistent with the order of RTs in the human data (compare solid lines). Second, both verb and non-verb competitors become active in the VLPFC, but non-verb competitors have lower asymptotes and are active for a shorter period of time than verb competitors (compare thick to dashed lines), even though they are more strongly activated in the posterior cortex. This reflects the influence of top-down biasing from the DLPFC, which boosts activation of verbs, but not non-verbs. Finally, verb competitors have a lower slope and asymptote in the presence of non-verb competitors than in their absence (compare light blue and dark blue thick lines) and non-verb competitors likewise have a lower slope and asymptote in the presence of verb competitors than in their absence (compare dark blue and dark purple dashed lines), replicating the interaction found in the human RT data. This reflects the fact that verb and non-verb competitors also compete with one another, and thus suppress one another.

The effects of DLPFC top-down biasing of VLPFC are illustrated in Figure 5.10. Under normal levels of VLPFC competitive lateral inhibition (5.10 A), when DLPFC influence is inadequate (below .003) non-verb responses win the competition— that is, the model reliably makes non-verb errors. As the amount of DLPFC activation of VLPFC verb units increases, model response times in the high prepotent competition conditions decrease, as verb units are able to more easily out-compete non-verb competitors. However, as DLPFC influence increases, model response times in the high underdetermined/ low prepotent competition condition
increase, as DLPFC input increases activation of all verb responses, thus increasing competition among them.

The model simulations also make the novel prediction that individual differences in DLPFC and VLPFC function should affect the relative order of behavioral effects across conditions, and not just their magnitude. Specifically, the model produces a cross-over interaction between the two high prepotent competition conditions, whereby at the lowest levels of DLPFC input the low underdetermined/high prepotent condition is slowest, and at higher levels of DLPFC input the high underdetermined/high prepotent condition is slowest. This pattern reflects the fact that spreading activation among verb responses in posterior cortex (which boosts verb activation) and competition between verb and non-verb competitors can help verb responses out-compete non-verb responses when DLPFC input is weak. However, when DLPFC input is strong, minimizing prepotent selection demands, having multiple active verb responses only serves to increase underdetermined selection demands, slowing responding.

These patterns interact with the level of competitive lateral inhibition within the VLPFC layer. When inhibition is decreased (5.10 B), both the positive and negative effects of DLPFC biasing are exaggerated. Specifically, at low levels of DLPFC input, prepotent selection costs are increased; indeed, at the lowest level of DLPFC input (.003), the model is unable to resolve competition between non-verb competitors and verb responses in the high prepotent competition conditions, and fails to settle on a response. Conversely, at higher levels of DLPFC input, underdetermined selection costs are increased, and at the highest level of DLPFC input (.007), the model is unable to resolve competition among verb responses, and fails to settle on a response. Increasing VLPFC competitive lateral inhibition (5.10 C) has the opposite effects: reducing the negative effects of low DLPFC input on prepotent selection and high DLPFC input
on underdetermined selection.

Figure 5.10. Effects of DLPFC top-down biasing and VLPFC competitive lateral inhibition. (A) As DLPFC input increases, increasing activation of possible verb responses, response times in the high prepotent competition conditions decrease (verbs more easily out-compete non-verbs), but underdetermined competition increases (there is more competition among verbs). This pattern is stronger when VLPFC competitive inhibition is reduced (B) and weaker when VLPFC inhibition is increased (C).
General Discussion

All competition is not alike. Our previous neural network simulations (Chapter 3) suggest that resolving competition from prepotent responses that are not task-relevant (e.g., non-verbs in the verb generation task; prepotent selection) must depend on partly dissociable neural mechanisms from resolving competition among task-relevant responses (e.g., possible verb responses; underdetermined selection). Namely, unbiased competitive lateral inhibition in VLPFC may be sufficient for underdetermined selection, but would allow prepotent competitors to win. Thus, Experiment 7 and the associated neural network simulations in the current chapter were designed to explore the neural substrates and mechanisms that allow us to resist prepotent responses in favor of more weakly associated but task-relevant responses.

Experiment 7 directly contrasted underdetermined and prepotent selection demands within the same task for the first time. The results support unique roles for left VLPFC and DLPFC in resolving prepotent and underdetermined competition. Left VLPFC was more active when underdetermined selection demands were high, replicating the findings of Experiment 2. Also replicating the findings of Experiment 2, both anterior and mid-VLPFC were sensitive to underdetermined selection demands, and, if anything, anterior VLPFC showed a larger underdetermined selection response, counter to the two-process account (Badre & Wagner, 2007). However, left VLPFC was not more active when prepotent selection demands were high. In contrast, an area of left DLPFC (middle frontal gyrus, BA 9, in the vicinity of the inferior frontal junction) was more active in both high prepotent and high underdetermined selection demand conditions. Based on these results and our neural network simulations, we propose that left DLPFC and VLPFC implement different neural mechanisms, which interact to affect prepotent and underdetermined selection.
The results of Experiment 7 are consistent with the cascade model, which posits that portions of DLPFC provide top-down support for task-relevant representations when there is high prepotent competition (e.g., Banich, 2009; Herd et al., 2006; Milham et al., 2003). We thus expanded the previous version of the neural network model to operationalize a version of this conceptual model. The expanded model includes a DLPFC layer that increases activation of task-relevant responses, but not task-irrelevant competitors, in the VLPFC layer. (This mechanism is also similar to that proposed by Thompson-Schill and colleagues (Thompson-Schill, 2005), although the current data do not support their speculation that VLPFC itself is the source of the mechanism that biases competition). When individuals detect increased competition, they may attempt to increase control by more strongly maintaining the task goals in left DLPFC, which in turn boosts activation of task-relevant responses in left VLPFC. When the competition arises from prepotent but task-irrelevant responses, top-down biasing from DLPFC is essential: it allows initially weaker task-relevant responses to become more active and thus out-compete the formerly stronger task-irrelevant responses. When DLPFC input to VLPFC is too weak, the model makes errors, generating the prepotent response rather than the a task-relevant response, as do patients with left prefrontal damage (e.g., Jefferies, 2006; Noonan, Jefferies, Corbett, & Ralph, 2009).

However, as with many cognitive and neural processes, there is an inherent trade-off: when competition arises between multiple task-relevant responses (underdetermined selection), such top-down biasing may actually impair performance, since DLPFC boosts the activation of all task-relevant responses, increasing competition among them. Thus, in the model the best overall performance is obtained with a moderate level of DLPFC input to VLPFC, consistent with the inverted U-shaped curves found for the relation between cognition and many neural
processes. Ideally given this trade-off, DLPFC top-down biasing would only be engaged when prepotent selection demands are high, but not when underdetermined selection demands are high. Counter to this ideal, we found that the area of left DLPFC sensitive to prepotent selection demands was also sensitive to underdetermined selection demands. There are two broad possibilities for this discrepancy. First, brain mechanisms may not be ideal. It is possible that individuals cannot successfully detect the source of competition, and instead simply detect that competition in general, or even cognitive control demands more broadly, have increased. In a task context in which these increased demands often involve prepotent competition, more strongly maintaining the task goal whenever the going gets tough is a reasonable strategy. Second, the model mechanism may not be ideal. The model provides equal input to all task-relevant responses that are active in the VLPFC layer, thus increasing competition among them. However, it is possible that in the brain there are mechanisms to weight the amount of DLPFC input by the activity level of the VLPFC neurons, such that only the most highly active representations are boosted. Future animal research is needed to examine the specificity of the inputs from DLPFC to VLPFC to determine if the amount of excitatory input from DLPFC depends on the current activity level of postsynaptic neurons in VLPFC, and if so, what mechanisms support this scaling.

In either case, the modeling simulations are informative: either there is an inverted U-shaped function of DLPFC biasing, or the biasing mechanism must be more complex. The potential downsides of top-down excitation are best illustrated by an informative early failure of a version of the model that implemented the simplest possible version of this mechanism. The DLPFC layer, as it was first implemented, simply provided top-down excitation to all verb units in the VLPFC layer. This leads to diffuse excitation of all verb representations, including those
that are not associated with the current noun stimulus (akin to thought disorder), and massively increasing competition among them. While this may seem obvious in retrospect, it has not been noted by any of the previous conceptual models, which have assumed that a simple DLPFC mechanism providing top-down support for task-relevant representations should always improve performance. The model demonstrates that this is not the case, and at minimum it is necessary to restrict DLPFC input to those response representations that are already active in VLPFC, due to bottom-up activation from posterior cortex.

The model achieves this with a simple mechanism that limits DLPFC input to those units with activation levels above zero. In the brain, a similar mechanism may be partly achieved by NMDA receptors. Because they are voltage-dependent, activation of NMDA receptors allows neurons which are already to active become more so, while relatively quiet cells remain blockaded, increasing the signal-to-noise ratio (Phillips & Silverstein, 2003). Thus, NMDA synapses may play a crucial role in biased competition between neural representations, because their voltage-dependent properties can selectively boost activation of relevant responses without increasing noise by activating neurons which are not already active (Raffone, Murre, & Wolters, 2003; G. Robinson, Shallice, Bozzali, & Cipolotti, 2010). Interestingly, NMDA hypofunction has been linked to schizophrenia and other psychotic disorders, as well as drug-induced psychosis (e.g., Bubeníková-Valešová, Horáček, Vrajová, & Höschl, 2008; Harrison & Weinberger, 2004). These conditions are in turn all characterized by formal thought disorder and abnormal use of language, characterized by loose associations, tangentiality, and inability to adhere to a topic (Neill et al., 2011; e.g., Niznikiewicz, Mittal, Nestor, & McCarley, 2010). This is reminiscent of the problems demonstrated in the model without the NMDA-like mechanism, in which inappropriate responses became activated and interfered with the ability to select an
appropriate response. Future research testing prepotent and underdetermined selection abilities in individuals with psychotic disorders or under NMDA-antagonists (e.g., ketamine) might thus clarify the possible role of NMDA receptor function in formal thought disorder.

In sum, the model and neuroimaging evidence are consistent with the view that left DLPFC plays a key role in increasing activation of task-relevant representations in left VLPFC, and that this top-down support must be limited to already active representations, perhaps via an NMDA receptor mechanism. In contrast, the results are not consistent with the proposal that VLPFC is itself the source of the control signal that biases competition towards task-relevant responses (Thompson-Schill & Botvinick, 2006), although the VLPFC may still be sensitive to prepotent competition when top-down biasing is inadequate to quickly reduce the activation of prepotent competitors (e.g., Herd et al., 2006). Specifically, we suggest that all associated responses (both task relevant and irrelevant) then compete in VLPFC, with input from DLPFC biasing competition in favor of the task-relevant responses (because they are now more active, and thus send more inhibition than they receive).

The cascade model predicts that left VLPFC will be sensitive to prepotent competition only if task-set maintenance and top-down biasing from DLPFC is inadequate to prevent activation of non-task-relevant representations (e.g., Herd et al., 2006), either because task demands are too high or because cognitive control is impaired. When DLPFC input is adequate, prepotent competitors may become only briefly and/or weakly active in VLPFC, and so may not drive VLPFC BOLD signal. Consistent with this model, left VLPFC was not sensitive to prepotent competition at the group level, but VLPFC activation during prepotent selection did correlate with anxiety and depression, suggesting that VLPFC may be sensitive to prepotent competition when cognitive control is compromised.
In sum, the findings of the current study and neural network simulations suggest that all competition is not alike: prepotent and underdetermined selection rely on partly dissociable neural substrates and mechanisms. Specifically, an area of left DLPFC (rather than VLPFC as some suggested) is sensitive to both prepotent and underdetermined competition, and may be critical for providing top-down support for task-relevant responses, enabling them to subsequently out-compete prepotent responses via competitive lateral inhibition in left VLPFC. However, this process comes at a cost, as too much top-down support may increase competition among task-relevant responses, increasing underdetermined selection demands. In addition, we replicated our previous finding that anxiety is associated with reduced VLPFC activation during selection, and extended it to show that in the current study anxiety and depressive symptoms were both associated with prefrontal hypoactivity (along with a larger neural network) during both prepotent and underdetermined selection. Better understanding how these processes and brain areas interact during language production may ultimately have implications for better understanding and treating impairments associated with prefrontal damage, as well as anxiety and depression. For example, strategies or interventions that improve prepotent selection (e.g., increasing task goal maintenance) may be detrimental to underdetermined selection. Finally, beyond the domain of language, these findings may have broader implications for understanding the organization of prefrontal cortex and fundamental trade-offs between excitatory and inhibitory neural mechanisms supporting cognitive control.
CHAPTER 6: GENERAL DISCUSSION

When we speak, we must constantly retrieve and select words in the face of multiple competing alternatives. How do we achieve these fundamental cognitive control processes? This dissertation aims to contribute to answering this question at three levels: *what* specific aspects of language production drive cognitive control demands, *where* in the brain these processes occur, and *how* these brain areas support cognitive control during language production. We investigated selection and retrieval of words from semantic memory in language production tasks that allowed these demands to be precisely quantified and independently manipulated. Retrieval demand (which is higher when association strength is lower) and selection demand (which is higher when competition is higher) were based on LSA, allowing the effects of each to be unconfounded, behaviorally, neurally, and mechanistically.

First, what specific aspects of language production drive cognitive control demands? Behaviorally, participants were slower to respond when there was high underdetermined selection demand (competition among task-relevant responses), high prepotent selection demand (competition from prepotent but task-inappropriate responses), or high retrieval demand (low association strength between cues and responses; Experiments 1 and 7). In addition, these demands interact. Underdetermined selection costs were greater under low retrieval demands than under high retrieval demands. Likewise, prepotent selection costs were greater when underdetermined competition was low.

Second, where in the brain do these processes occur? Using unconfounded LSA measures allows retrieval and selection to be fully disentangled for the first time in neuroimaging studies. Results indicated that shared neural substrates in left VLPFC support both underdetermined selection and controlled retrieval, with no dissociation between mid and anterior regions.
(Experiment 2). These results are contrary to previous accounts positing a single role for left VLPFC or a functional dissociation between anterior and mid VLPFC. Moreover, consistent with the behavioral findings in Experiment 1, selection and retrieval demands interacted in left VLPFC, such that selection effects were greatest when retrieval demands were low. While left VLPFC was sensitive to underdetermined selection demands, it was not activated by prepotent selection demands (Experiment 7). In contrast, an area of left DLPFC was sensitive to both underdetermined and prepotent selection demands. These findings enable a synthesis and reinterpretation of prior evidence, and suggest that the ability to respond in less constrained language tasks is affected by both selection and retrieval mechanisms subserved by left VLPFC and DLPFC, and these processes interact in meaningful ways.

Finally, how these brain areas support these cognitive control processes during language production? Neural network modeling provides a valuable tool for investigating the mechanisms underlying selection and retrieval. The neural mechanisms involved in these processes have not yet been extensively investigated, and are almost certainly complex and multitudinous. However, computational modeling, conducted iteratively with empirical research, has proved fruitful in beginning to identify candidate mechanisms. In our verb generation model, retrieval demands are a direct consequence of the strength of the synaptic weights between stimuli and their response representations in the posterior cortex layer; weaker weights cause a slower buildup of activation, requiring more time to reach the threshold for generating a response. Selection demands arise when multiple alternative responses become simultaneously active and competition must be resolved in order to select a single response. In the model, this resolution is accomplished through strong lateral inhibition in the VLPFC layer, simulating the effects of GABAergic interneurons.
We tested the predicted effects of increased neural inhibition in a double-blind, placebo controlled study (Experiment 3) in which participants completed the verb generation task after injection of the GABA agonist midazolam as compared to a saline control. As predicted, when retrieval demands were low, midazolam improved selection, while there was no effect of midazolam on retrieval when selection demands were low. We tested the predicted effects of reduced neural inhibition in three experiments. In a behavioral study (Experiment 4) we examined the relation between trait anxiety (linked to reduced GABAergic function) and selection and controlled retrieval effects during verb generation. As predicted, participants higher in anxiety had larger selection costs than lower-anxiety participants, but not larger retrieval costs. In addition, left VLPFC activity correlated with trait anxiety during selection when retrieval demands were low, but not during retrieval (Experiment 5). These findings suggest high anxiety participants fail to adequately engage VLPFC when they must select between competing options. Thus, reduced GABAergic function (in anxiety) is associated with deficits in selection, while increased GABAergic function (under midazolam) improves selection.

Finally, Experiment 6 was designed to extend this research to a more clinically-relevant high anxiety sample and tests the generalizability of previous findings across tasks. In addition, anxiety and depression frequently co-occur, such that the effects of one may exacerbate the effects of the other. However, anxiety and depression also have distinct profiles of symptoms, neuroanatomy, and neurochemistry, such that the effects of one could potentially counteract the effects of the other. Confirming the findings of Experiment 3, participants with high anxiety alone showed impairments in selection relative to low anxiety participants across three selection tasks. However, those with high anxiety and co-occurring high dysphoria showed better selection performance than those with high anxiety alone. These results demonstrate for the first time that
co-occurring psychiatric symptoms counterintuitively lead to better performance on a cognitive task. Neural network simulations suggested a possible explanation for this counterintuitive finding: decreased neural excitation (linked to depression) weakens the representations of competitors, aiding selection.

Using the approach of conducting computational modeling iteratively with empirical research, we expanded the model based on our prepotent selection findings (Experiment 7). To simulate the effects of competition from prepotent responses (non-verb competitors in the verb generation task), units representing non-verb competitors were added to the posterior cortex and VLPFC layers, and a DLPFC layer was added which maintains the task set (i.e., generate verbs) during high-competition conditions and provides top-down support for relevant verb responses. The model suggests that top-down biasing from DLPFC is necessary to resolve competition from prepotent responses, but may contribute to underdetermined competition by making all task-relevant responses more active. Moreover, this trade-off between prepotent and underdetermined selection interacts with the level of competitive inhibition in VLPFC.

In sum, cognitive control is needed during language production when responses compete with alternative task-relevant response options, compete with prepotent responses, or are difficult to retrieve from semantic memory, and these demands interact both behaviorally and neurally. Neuroimaging and neural network modeling evidence suggests that competitive lateral inhibition subserved by left VLPFC is key for underdetermined selection, while other mechanisms subserved by VLPFC support controlled retrieval, and top-down biasing from left DLPFC is critical for selection when there is prepotent competition. The following sections discuss the strengths and limitations of work, and outline future directions and broader implications. Specifically, the remainder of the chapter discusses (i) the benefits and limitations of neural
network modeling simplifications, (ii) the benefits and limitations of using laboratory language tasks which are well-controlled but lack ecological validity, and (iii) the broader context and implications of the research beyond the domain of language production, including language comprehension and selection in complex real-world domains.

**Neural Network Model Simplifications: Benefits and Limitations**

Even good models are, by definition, simplified versions of reality. Our neural network model of the verb generation task is a highly simplified one, simulating only a few key brain areas and mechanisms, rather than attempting to include all the neural substrates and mechanisms that likely participate in this task in the human brain. Such simplifications are necessary, not only from a practical perspective (we don’t know enough, or have enough computing power, to simulate an entire human brain in detail), but to serve the fundamental purpose of most modeling—which is to take something intractably complex (e.g., the human brain) and make specific aspects of its function tractable to study. Of course it is open for debate how much, and what kind, of simplification is ideal (O'Reilly & Munakata, 2000). Arguably, there is no more one right approach to modeling than there is one right experimental approach: in both cases the best approach depends on the scientific questions to be answered and the current state of knowledge in the field.

In our case, given the potentially confounding complexity of the cognitive processes of interest and the paucity of previous knowledge of the mechanisms involved, we elected to keep the model simple. Doing so allowed us to isolate and understand specific mechanisms in a way that enabled us to successfully make and test empirical predictions. Of course, keeping the model simple comes at the price of not simulating some aspects of brain function that may also be important for cognitive control during language production. Specifically, our model makes
simplifications both in terms of the mechanisms involved in selection and retrieval, and the ways in which responses are represented in the network; the benefits and limitations of these simplifications, and ways in which the model could be expanded in the future, are discussed below.

Additional Mechanisms

We have focused on two key mechanisms affecting selection, (competitive lateral inhibition in VLPFC for underdetermined selection and top-down biasing from DLPFC for prepotent selection) and one key mechanism affecting retrieval (synaptic connection strength). Focusing on these mechanisms and manipulating them independently allowed us to understand their function in a way which might not be possible in a more complex model with multiple free parameters, and enabled us to make empirical predictions that were supported. However, we do not claim that these are the only mechanisms supporting selection and retrieval. Indeed, several other aspects of prefrontal function are likely to play a role.

First, dopamine (DA) may also contribute to selection. DA is known to play an important role in increasing the signal-to-noise ratio of activation patterns (Nicola, Hopf, & Hjelmstad, 2004; O'Donnell, 2003; Rolls, Loh, Deco, & Winterer, 2008; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Specifically, moderate levels of D1 activation appear to enhance prefrontal signal-to-noise (Vijayraghavan et al., 2007), because they increase activity of strongly active neurons by enhancing NMDA receptor postsynaptic currents (Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001), while reducing activity of weakly active neurons by decreasing AMPA receptor postsynaptic currents (Seamans et al., 2001) and increasing activity of GABAergic interneurons (e.g., Seamans, Gorelova, Durstewitz, & Yang, 2001). Thus, prefrontal DA could play a role in selection by increasing the activation level of winning
representations relative to the activation level of competitors, and potentially enhanced competitive lateral inhibition by increasing the intrinsic excitability of GABAergic interneurons (e.g., Seamans et al., 2001). This possibility is supported by the finding that increasing DA (via L-Dopa) reduces priming from weakly associated words, but not strongly associated words, suggesting more focused semantic network activation (Kischka et al., 1996). In addition, there is some evidence that serotonin may play a similar role in enhancing contrast in activation levels (Zhang & Arsenault, 2005). The potential roles of dopamine and serotonin in selection among competing options is an important area for future modeling and empirical research, especially given that they are implemented in multiple clinical and neurological disorders.

Second, the architecture and connectivity of prefrontal circuits may also play an important role in cognitive control. Though it was not the focus of our simulations, our model suggests that recurrent connectivity in VLPFC can enhance both underdetermined selection and retrieval. While the effects of lateral inhibition are specific to selection, both selection and controlled retrieval are supported by strong recurrent connections in the VLPFC layer that boost weakly active representations and sharpen the contrast between activation levels of competitors. This mechanism is neurally plausible, as pyramidal cells within small areas of cortex are recurrently connected to each other (e.g., Markram, Lübke, Frotscher, Roth, & Sakmann, 1997; Morishima & Kawaguchi, 2006), and these excitatory recurrent interactions induce persistent, self-sustaining, activity (e.g., Morita, Kalra, Aihara, & Robinson, 2008; Stern, Kincaid, & Wilson, 1997). Further exploring the role of VLPFC recurrent connectivity in supporting selection and retrieval is an important area for future research. First, previous models have suggested that increases in recurrent connection strength during development may support increases in cognitive control in young children (e.g., Morton & Munakata, 2002), which has
implications for understanding the development of selection and retrieval processes. Second, active VLPFC mechanisms supporting controlled retrieval have not been well specified by our or other previous accounts, and recurrent excitation is a good candidate for such a mechanism. Lastly, our revised model suggests that when there is strong input from DLPFC, too much recurrent connectivity in VLPFC can cause runaway excitation. Future research could test for such trade-offs between within-VLPFC and DLPFC-to-VLPFC connectivity.

In addition, connectivity between prefrontal brain regions is likely to be critical for enabling DLPFC to increase its activity level when competition is high. The model did not simulate this competition detection process; instead, we directly activated the DLPFC layer from the input, based in the fMRI DLPFC activation levels. We made this simplification in order to most cleanly test how the pattern of activation observed in the empirical study would affect model behavior, providing insights into how DLPFC and VLPFC mechanisms may interact. However, future models could be expanded to include a more neurally-plausible mechanism for competition detection. For example, several theories have posited a role for the dorsal anterior cingulate cortex in detecting competition (e.g., Barch et al., 2000; Botvinick et al., 2001), detecting cognitive control demands more broadly (e.g., Badre & Wagner, 2004), and/or evaluating responses (e.g., Banich, 2009; Egner, 2011). While its exact role(s) remains a topic of debate, these theories generally agree that the dorsal anterior cingulate signals DLPFC to increase top-down control. Such a mechanism could be incorporated into future models of the verb generation task, as it has been in previous computational models (Botvinick et al., 2001).

Nature of Representations

The model also makes several simplifications regarding the nature of response representations in the brain. First, representations of response options in the model are localist:
that is, there is only one unit representing each response, rather than a distributed pattern across multiple units. In contrast, nearly all current theories of semantic memory posit that semantic representations are distributed over a wide neural network, with specific sensory and motor features stored in their corresponding sensory and motor cortical areas (see A. Martin, 2007 for a review). Thus, the localist representations in the posterior cortex layer of the model are clearly a simplification. Each response unit in the model can be thought of as representing the sum of activity across all the neurons representing that concept in the brain. Alternately, the posterior cortex layer in the model could be thought of as representing the anterior temporal lobes, which have been posited to serve as an amodal convergence zone or hub for semantic memory (Fasolo, Hertwig, Huber, & Ludwig, 2009; Patterson et al., 2007). Since the goal of the model is to understand the mechanisms supporting cognitive control during language production, rather than semantic memory in all its richness, this simplification seems justified. However, future modeling efforts with more distributed semantic knowledge representations might provide additional insights into the origins of the associations between words (captured by LSA association strength in the model). For example, in addition to previous linguistic experience, overlap in semantic features between response options could also contribute to competition.

Second, representations of response options in the VLPFC layer of the model are direct copies of those in the posterior cortex layer. In contrast, many theories of prefrontal function propose that prefrontal representations are more abstract than those in posterior cortex (e.g., Badre, 2008; Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Christoff, Keramatian, Gordon, Smith, & Mädler, 2009; Muhammad, Wallis, & Miller, 2006; Wallis, Anderson, & Miller, 2001). Because representations are localist throughout the model, this difference in abstraction between posterior and prefrontal cortex is not captured. We believe this simplification is not critical for
understanding cognitive control during language production, as the same basic excitatory and inhibitory dynamics are likely to occur between neurons, regardless of the type of representations involved. However, it may be useful for future models to manipulate the nature of prefrontal representations, for example to gain insight into how increasingly abstract representations in VLPFC (e.g., as children develop more abstract category representations) may reduce selection demands (Snyder & Munakata, 2010).

**Experimental Task Simplifications: Benefits and Limitations**

Experimental tasks can also be thought of as models—models of more complex activities in the real world. As with computational models, there is a trade-off between interpretability and ecological validity. All of the experiments reported here used well-controlled, but rather artificial, language production tasks (such as generating a verb to go with a noun, outside of any sentence or broader context), which have both benefits and limitations. We chose to use these tasks because they allow us to precisely and independently manipulate our factors of interest, while eliminating other demands that would influence performance during more naturalistic language production. Thus, as for the model simplifications discussed above, using simple, well-controlled tasks is essential to our ability to interpret patterns of behavior and neural activity in terms of specific cognitive control mechanisms. On the other hand, these results are only useful if they provide insight into actual human behavior outside the lab. Demands for selection and retrieval are infinitely more complex during everyday language production, with words embedded in sentences (complete with syntactic structures), and sentences embedded in a broader narrative, discourse, and real-world context. In short, actual communication involves a sea of dynamically changing associations and active representations. Despite this complexity, there is evidence that the same neural substrates that support selection and retrieval in laboratory
tasks are also critical for cognitive control during more ecologically valid tasks and everyday language production.

First, neuroimaging studies in healthy participants demonstrate that left VLPFC is activated by narrative speech production (e.g., telling a story based on a series of pictures or an autobiographical memory) to a greater degree than more constrained language tasks (e.g., counting, reciting nursery rhymes, or briefly describing pictures; Awad, Warren, Scott, Turkheimer, & Wise, 2007; Blank, Scott, Murphy, Warburton, & Wise, 2002; Braun, Guillemin, Hosey, & Varga, 2001; Horwitz et al., 2003; O'Reilly & Munakata, 2000; Troiani et al., 2008). This suggests that the same left VLPFC area engaged by selection and controlled retrieval in our verb generation task is also engaged by naturalistic speech production, which is likely to impose strong selection and retrieval demands.

Second, and more definitively, damage to left VLPFC significantly impairs everyday language use in ways that are consistent with deficits in selection and controlled retrieval. Left VLPFC damage produces dynamic aphasia: severe reductions in spontaneous speech, especially when long narratives are required, with preserved reading, repetition, and naming (Luria, 1970; see A. Martin, 2007 for a review; G. Robinson et al., 2010). Further testing of these patients on laboratory tasks, such as sentence completion, suggests that they are severely impaired only when there is competition among multiple response options, with normal performance when competition is low (see Patterson et al., 2007 for a review; G. Robinson et al., 2006; 2010; G. Robinson, Blair, & Cipolotti, 1998). Importantly, patients’ selection deficits on these laboratory tasks predict their spontaneous speech rates, suggesting that the same mechanisms supporting selection in laboratory tasks are critical for normal narrative speech (e.g., Badre, 2008; Christoff et al., 2009; Muhammad et al., 2006; G. Robinson et al., 2010; Wallis et al., 2001).
Important areas for future research include investigating the prepotent selection and controlled retrieval during normal narrative speech. Based on our research, we would also predict that patients with left VLPFC damage would also have impaired controlled retrieval, while patients with left DLPFC damage should have impaired prepotent selection. While some evidence from the verb generation task supports this prediction (R. C. Martin & Cheng, 2006), this study did not cleanly separate retrieval and selection demands, and additional research is needed to link these deficits to word finding difficulties during spontaneous speech. Patients with damage to left DLPFC show marked impairments on laboratory prepotent selection tasks (e.g., in the Stroop task; Alexander, Stuss, Picton, Shallice, & Gillingham, 2007), but research is needed to link these deficits to performance during more naturalistic language production. In sum, there is emerging evidence that the same neural mechanisms supporting underdetermined selection during laboratory tasks are critical for the ability to generate normal narrative speech, while more research is needed on prepotent selection and controlled retrieval during naturalistic language production.

**Broader Context and Implications**

While current research focused on cognitive control during language production, it may have implications for other domains. Specifically, similar mechanisms may be important for cognitive control during language comprehension, and for selection in complex real-world domains. Our findings and model make testable predications and suggest future directions for exploring these potential links across domains.

**Beyond language production: Cognitive Control During Language Comprehension**

Until recently most theories characterized the role of left prefrontal cortex in language almost entirely in terms of production. However, there is growing evidence that similar
prefrontal cognitive control mechanisms may be involved in language comprehension as well. Specifically, it has been proposed that selection demands arise during comprehension when automatically activated linguistic (e.g., phonological, syntactic, and semantic) and sensory (e.g., referential context) information does not converge on a single correct characterization of the input (Novick, Trueswell, & Thompson-Schill, 2005).

Competition within and across channels of information during comprehension activates left prefrontal cortex, just as selection among competing responses during language production does. For example, left VLPFC is more active during comprehension of: (1) words with many phonological competitors (many words starting with the same phonemes, e.g., monkey) compared to those with few (Zhuang, Randall, Stamatakis, Marslen-Wilson, & Tyler, 2011), (2) words with multiple meanings (e.g., bank) than a single meaning (e.g., Bedny, McGill, & Thompson-Schill, 2008; Rodd, Longe, Randall, & Tyler, 2010; Zempleni, Renken, Hoeks, Hoogduin, & Stowe, 2007), and (3) sentences where semantic plausibility conflicts with syntax (e.g., The thief kept the policeman in the police station; e.g., Ye & Zhou, 2009). Competition can also occur during sentence comprehension as new information conflicts with the initial syntactic parse of the sentence. For example, in the sentence The man accepted the money could not be spent yet, the beginning of the sentence activates one representation (the money as direct object), which is in conflict with the information received later in the sentence (Novick et al., 2005). Comprehension of such garden-path sentences activates both left VLPFC (Fiebach, Vos, & Friederici, 2004; Mason, Just, Keller, & Carpenter, 2003; Novais-Santos et al., 2007; Rodd et al., 2010) and left DLPFC (Novais-Santos et al., 2007), and was impaired in a patient with a left VLPFC lesion (Novick, Kan, Trueswell, & Thompson-Schill, 2009).

Given the shared neural substrates between selection during language production and
comprehension, it seems likely that the same mechanisms are also involved, but this has not been directly investigated. Our model makes several predictions that could be tested by future research. First, factors that influence neural inhibition should affect competition resolution during comprehension as well as production (e.g., anxiety should be associated with impaired performance on the high competition conditions of the comprehension tasks described above). Second, since shared neural substrates in left VLPFC support both selection and retrieval (Experiment 2), left VLPFC may be engaged by retrieval demands during comprehension as well as production (e.g., comprehending words that are less strongly associated with the sentence context). Finally, left DLPFC should play an important role in overcoming prepotent competition during comprehension, such as when a subordinate word meaning must be selected over a dominate one (e.g., bank as river bank, rather than money bank) based on a task-set or context held in working memory (e.g., a proceeding sentence which mentioned a river).

**Beyond Language: Selection in Complex Real-World Domains**

**The tyranny of choice.** Language is not the only domain in which we are faced with the need to select among competing options. Indeed, Tversky and Shafir (1992, p. 358) begin their seminal paper by stating that “the experience of conflict is the price one pays for the freedom to choose.” Consider that the average U.S. supermarket has 275 types of cereal (Botti & Iyengar, 2006). When we stand indecisively in a long aisle full of cereals trying to select one, we are arguably experiencing the effects of underdetermined competition, and if we choose the frosted flakes over the bran flakes, we are arguably succumbing to prepotent competition. Yet intuitive as these effects of competition seem, competition plays no role in traditional theories of rational choice, which assume that more options are always better because they increase the chance of maximizing utility for each person (Tversky & Shafir, 1992). While rational choice theory
predominated until recently in economics, political science, and consumer studies, evidence has mounted that competition does affect decision-making in all of these domains, and that having more options is not always better. Interestingly, people seem to have little insight into the downside of choice, as they often predict that having more options will lead to better performance and more positive emotions, when in fact the opposite is true (Botti & Hsee, 2010).

When people are faced with too many options, they may use suboptimal heuristics to reduce the number of alternatives (e.g., Tversky & Kahneman, 1974), make a decision they regret (Fasolo et al., 2009; Haynes, 2009; F. Huber, Köcher, Vogel, & Meyer, 2012; Iyengar, Wells, & Schwartz, 2006; Iyengar & Lepper, 2000; Redelmeier & Shafir, 1995; Reutskaja & Hogarth, 2009; B. Schwartz, 2004; Sethi-Iyengar et al., 2004), or delay making a decision altogether (e.g., Dhar, 1997; Redelmeier & Shafir, 1995; Sethi-Iyengar et al., 2004), often with negative consequences. For example, the more retirement plans that employees must choose among, the less likely they are to join any plan at all (Sethi-Iyengar et al., 2004). Likewise, when physicians are asked to choose between two similar pain medications, they are less likely to prescribe either (Redelmeier & Shafir, 1995).

In these complex decision-making tasks, choice-overload increases when there are many options (e.g., Iyengar & Lepper, 2000; Redelmeier & Shafir, 1995; Reutskaja & Hogarth, 2009; Sethi-Iyengar et al., 2004), especially when options are similar (Dhar, 1997; Fasolo et al., 2009; Tversky & Shafir, 1992). Similarly, in language production we and others have found that the difficulty of selecting among words increases as the number of alternatives (e.g., Desmond, Gabrieli, & Glover, 1998) and similarity of activation levels across alternatives (e.g., Dissertation experiments, Snyder & Munakata, 2008; Thompson-Schill & Botvinick, 2006) increase. Thus, similar selection demands seem to make choice difficult, whether the choice is
between words or cereals. Indeed, some evidence suggests that selection among complex real-world options may rely on shared resources with cognitive control during language production: participants who first performed the Stroop task were subsequently impaired in their ability to select among jobs or computers (Pocheptsova, Amir, Dhar, & Baumeister, 2009). In addition rejecting real-world temptations (e.g., tasty but unhealthy foods) activates similar regions of prefrontal cortex as avoiding prepotent competitors in the Stroop task, although self-control over real-world temptations is likely to involve many additional processes such as valuation and affect regulation (see Coutlee, 2012 for a review).

Thus, it seems possible that some shared mechanisms support selection across domains, while complex real-world decision-making likely taps additional mechanisms. However, potential mechanistic links between selection across domains have not been directly tested. Future research is needed to establish whether there are shared neural substrates and individual differences (e.g., correlations between selection costs) across selection tasks in different domains. Future research could also investigate whether selection in other domains depends on similar mechanisms as selection during language production, by testing predictions from our model. For example, our model predicts that increasing neural inhibition (e.g., with midazolam) should also improve selection among consumer products or other real-world options, while individuals with reduced neural inhibition should experience more difficulty with such decision-making. Indeed, some evidence suggests that individuals with anxiety experience high levels of indecisiveness and intolerance of uncertainty when faced with such decisions in daily life.

**Anxiety, indecisiveness, and intolerance of uncertainty.** Indecisiveness and procrastination are associated with anxiety, particularly anxious apprehension (worry) and obsessive compulsive disorder (OCD, which is characterized by high levels of anxious
apprehension; Milgram & Tenne, 2000; Rassin, Muris, Franken, Smit, & Wong, 2006; Stöber & Joormann, 2001). Like those experiencing choice overload, individuals with high anxiety or OCD often delay or avoid making decisions, (Ferrari & McCown, 1994; Sachdev & Malhi, 2005; van Eerde, 2003), even when there are negative consequences of such procrastination. For example, trait anxiety in high school students is strongly associated with indecisiveness, which in turn predicts later failure to commit to a major in college (Germeijs & Verschueren, 2010; Germeijs, Verschueren, & Soenens, 2006).

Indecisiveness is also closely linked to another hallmark of anxiety, intolerance of uncertainty (IU; e.g., Rassin et al., 2006). IU is characterized by distress and avoidance when faced by the uncertainty or unpredictability of everyday events, especially when a negative event may occur (e.g., Dugas, Gosselin, & Ladouceur, 2001; Schienle, Köchel, Ebner, Reishofer, & Schäfer, 2010). This aversive response to uncertainty often includes *uncertainty paralysis*, the inability to act or make a decision in an uncertain situation, a construct closely linked to indecisiveness (Berenbaum, Bredemeier, & Thompson, 2008). Individuals high in IU find possible negative events unacceptable, even when they are very unlikely to occur (Ladouceur et al., 1997), and over-estimate the likelihood of negative events (Bredemeier & Berenbaum, 2008). Thus, it seems possible that IU is linked to an inability to select an appropriate representation of likely event outcomes, such that unlikely possibilities remain active. While there is no direct evidence that selection impairments are related to IU, several suggestive factors may motivate future research.

First, both impaired selection and IU are specifically linked to anxious apprehension (characterized by excessive worry). IU strongly predicts anxious apprehension, including the anxiety disorders most characterized by anxious apprehension (generalized anxiety disorder,
obsessive compulsive disorder, and social anxiety disorder; e.g., Boelen & Reijntjes, 2009; Gentes & Ruscio, 2011; Starcevic & Berle, 2006), and worry in non-clinical samples (e.g., Buhr & Dugas, 2006; Dugas et al., 2001; Fergus & Wu, 2011). Moreover, this relation appears to be somewhat specific to anxious apprehension, as IU is only weakly related to anxious arousal (panic symptoms; Dugas et al., 2001) or depression (Fergus & Wu, 2011; but see, Gentes & Ruscio, 2011). Second, IU is associated with reduced prefrontal activation during anticipation of an uncertain negative stimulus (including in left DLPFC and anterior cingulate), suggesting that individuals high in IU may have difficulty exerting cognitive control in uncertain situations (Schienle et al., 2010). Finally, individuals high in IU have been found to require more information before making a decision when outcomes are uncertain (Ladouceur et al., 1997), suggesting that IU may be related to slowed decision-making.

Thus, it is possible that difficulty selecting among competing representations could play a role in indecisiveness and procrastination, and also in making uncertain situations highly aversive, due to the difficulty of selecting appropriate courses of action and outcome representations. Understanding the mechanisms involved in these phenomena is important because decisional procrastination can interfere with the ability to achieve major life goals, while IU not only leads to avoiding many potentially positive experiences, but may actually promote the maintenance or increase of anxiety. Specifically, for individuals high in IU, daily stressors lead to increased anxiety symptoms over time, while individuals low in IU appear to be buffered against the effects of stress (C. Y. Chen & Hong, 2010). Future research is needed to determine whether impaired selection on simple non-affective tasks, such as language production tasks, predicts indecisiveness, procrastination, and IU, beyond what is predicted by anxiety alone, and what causal role this may play in the development or maintenance of anxiety.
Conclusions

Humans are able to engage in an almost infinite repertoire of behaviors, but this ability comes at a cost: “Freedom of choice is a two-edged sword, for just on the other side of liberation sits chaos and paralysis” (B. Schwartz, 2000, p. 87). Most of the time, most of us are able to keep on the right side of the line: We manage, with only a little effort, to stop at the store instead of automatically continuing home, choose a box of bran flakes to put in our cart, and chat fluently with the friend we run into in the checkout line. For the last, and perhaps for the first two as well, we can thank cognitive control mechanisms supported by our left lateral prefrontal cortex. Although we are normally able to successfully deploy these mechanisms to retrieve responses and select between competing representations, this ability is compromised in a wide variety of clinical disorders and in patients with prefrontal damage. Better understanding these fundamental aspects of language production may ultimately have implications for better understanding and treating these deficits, and for helping all of us navigate the tyranny of choice we face in every sentence we speak and every decision we make.


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APPENDIX: NEURAL NETWORK MODEL LEABRA FRAMEWORK

Pseudocode

The pseudocode for Leabra (32) is given here, showing exactly how the pieces of the algorithm described in more detail in the subsequent sections fit together.

Outer loop: Iterate over events (trials) within an epoch. For each event:

(1) At start of settling, for all units:
   a. Initialize all state variables (activation, v_m, etc).
   b. Apply external patterns (clamp input).

(2) During each cycle of settling, for all non-clamped units:
   a. Compute excitatory net input (g_e(t) or η_j, eq 3).
   b. Compute kWTA inhibition for each layer, based on g_e^Θ (eq 7):
      i. Sort units into two groups based on g_i^Θ: top k and remaining k+1 to n.
      ii. If basic, find k and k+1th highest; if avg-based, compute avg of 1 → k & k = 1 → n.
      iii. Set inhibitory conductance g_i from s_k^Θ and g_{k+1}^Θ (eq 6).
   c. Compute point-neuron activation combining excitatory input & inhibition (eq 1).

(3) After settling, for all units: Record final settling activations (y_j).

Point Neuron Activation Function. Leabra uses a point neuron activation function that models the electrophysiological properties of real neurons, while simplifying their geometry to a single point. This function is nearly as simple computationally as the standard sigmoidal activation function, but the more biologically-based implementation makes it considerably easier
to model inhibitory competition, as described below. Further, using this function enables cognitive models to be more easily related to more physiologically detailed simulations, thereby facilitating bridge-building between biology and cognition.

The membrane potential $V_m$ is updated as a function of ionic conductances $g$ with reversal (driving) potentials $E$ as follows:

$$\Delta V_m(t) = \tau \sum_c g_c(t) \bar{g}_c (E_c - V_m(t))$$

with 3 channels ($c$) corresponding to: $e$ excitatory input; $l$ leak current; $i$ inhibitory input.

Following electrophysiological convention, the overall conductance is decomposed into a time-varying component $g_c(t)$ computed as a function of the dynamic state of the network, and a constant $\bar{g}_c$ that controls the relative influence of the different conductances. The equilibrium potential can be written in a simplified form by setting the excitatory driving potential ($E_e$) to 1 and the leak and inhibitory driving potentials ($E_l$ and $E_i$) to 0:

$$V_m^e = \frac{g_e \bar{g}_e}{g_e + g_l \bar{g}_l + g_i \bar{g}_i}$$

which shows that the neuron is computing a balance between excitation and the opposing forces of leak and inhibition. This equilibrium form of the equation can be understood in terms of a Bayesian decision-making framework (32). The excitatory net input/conductance $g_e(t)$ or $\eta_j$ is computed as the proportion of open excitatory channels as a function of sending activations times the weight values:

$$\eta_j = g_e(t) = \left< x_i w_{ij} \right> = \frac{1}{n} \sum_i x_i w_{ij}$$

The inhibitory conductance is computed via the kWTA function described in the next section, and leak is a constant.
Activation communicated to other cells \((y_j)\) is a thresholded \((\Theta)\) sigmoidal function of the membrane potential with gain parameter \(\gamma\):

\[
y_j(t) = \frac{1}{1 + \frac{1}{\gamma[V_m(t) - \Theta]_+}}
\]  

where \([x]_+\) is a threshold function that returns 0 if \(x<0\) and \(x\) if \(x>0\). Note that if it returns 0, we assume \(y_j(t) = 0\), to avoid dividing by 0. As it is, this function has a very sharp threshold, which interferes with graded learning mechanisms (e.g., gradient descent). To produce a less discontinuous deterministic function with a softer threshold, the function is convolved with a Gaussian noise kernel \((\mu = 0, \sigma = .01)\), which reflects the intrinsic processing noise of biological neurons:

\[
y_j^*(x) = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi}\sigma} e^{-z^2/(2\sigma^2)} y_j(z - x) dz
\]

where \(x\) represents the \([V_m(t) - \Theta]_+\) value, and \(y_j^*(x)\) is the noise-convolved activation for that value. In the simulation, this function is implemented using a numerical lookup table.

**k-Winners-Take-All Inhibition.** Leabra uses a kWTA function to achieve inhibitory competition among units within a layer (area). The kWTA function computes a uniform level of inhibitory current for all units in the layer, such that the \(k+1\)th most excited unit within a layer is below its firing threshold, while the \(k\)th is above threshold. Activation dynamics similar to those produced by the kWTA function have been shown to result from simulated inhibitory interneurons that project both feedforward and feedback inhibition (32). Thus, although the kWTA function is somewhat biologically implausible in its implementation (e.g., requiring global information about activation states and using sorting mechanisms), it provides a
computationally effective approximation to biologically plausible inhibitory dynamics.

KWTA is computed via a uniform level of inhibitory current for all units in the layer as follows:

$$g_i = g^\Theta_{k+1} + q(g^\Theta_k - g^\Theta_{k+1})$$  \hspace{1cm} (6)

where $0 < q < 1$ is a parameter for setting the inhibition between the upper bound of $g^\Theta_k$ and the lower bound of $g^\Theta_{k+1}$ These boundary inhibition values are computed as a function of the level of inhibition necessary to keep a unit right at threshold:

$$g^\Theta_i = \frac{g^*_e g_e (E_e - \Theta) + g_l g_l (E_l - \Theta)}{\Theta - E_i}$$  \hspace{1cm} (7)

where $g^*_e$ is the excitatory net input without the bias weight contribution --- this allows the bias weights to override the kWTA constraint. In the average-based kWTA version, $g^\Theta_k$ is the average $g^\Theta_i$ value for the top $k$ most excited units, and $g^\Theta_{k+1}$ is the average of $g^\Theta_i$ for the remaining $n-k$ units. This version allows for more flexibility in the actual number of units active depending on the nature of the activation distribution in the layer and the value of the $q$ parameter (which is typically between .5 and .7 depending on the level of sparseness in the layer, with a standard default value of .6).