DISSERTATION

DISAMBIGUATNG AMBIGUITY: INFLUENCE OF VARIOUS LEVELS OF UNCERTAINTY ON NEURAL SYSTEMS MEDIATING CHOICE

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ABSTRACT

DISAMBIGUATNG AMBIGUITY: INFLUENCE OF VARIOUS LEVELS OF UNCERTAINTY ON NEURAL SYSTEMS MEDIATING CHOICE.

Previous studies have dissociated two types of uncertainty in decision making: risk and ambiguity. However, many of these studies have categorically defined ambiguity as a complete lack of information regarding outcome probabilities, thereby precluding the study of how various neural substrates may acknowledge and track levels of ambiguity. The present study provided a novel paradigm designed to address how decisions are made under varying states of uncertainty, ranging from risk to ambiguity. More important, the present study was designed to address limitations of previous studies looking at decision making under uncertainty: explore neural regions sensitive to hidden but searchable information by parametrically controlling the amount of information hidden from the subject by using different levels of ambiguity manipulations instead of just the one, as used in previous studies, and allowed subjects to freely choose the best option.

Participants were asked to play one of two lotteries, one uncertain and one certain. Throughout the task, the certain lottery offered to participants was always a 100% chance of winning $1. This was contrasted by the uncertain lottery in which various

probabilities of winning (20%, 33%, 50 % or 80%) were combined with different potential gains (2$, 3$, 5$, or 8$) so that expected values ranged from being better, equal or worse than the expected value of the certain lottery. In our lotteries, the probability of winning or losing any given amount of money was indicated along the borders of the wheel, increasing from 0% to 100% in a clockwise direction starting at the 12 o'clock position. For some uncertain lotteries and all certain lotteries, a "dial" explicitly indicated the probability of winning. For some uncertain lotteries, there was no dial to indicate a specific probability. Instead, a blinder that covered a portion of the wheel occluded the dial. This occlusion represented the possible range of percentages in which the actual probability of winning lay. Finally, the blinder covered 15%, 33%, 66%, 80% or 100% of the wheel in order to vary the level of ambiguity. By manipulating the level of ambiguity, we were able to explore neural responses to different types of uncertainty ranging from risk to full ambiguity. Participants completed this task while BOLD contrast images were collected using a 3T MR scanner.

Here, we show that both risk and ambiguity share a common network devoted to uncertainty processing in general. Moreover, we found support for the hypothesis that regions of the DLPFC might subserve contextual analysis when search of hidden information is both necessary and meaningful in order to optimize behavior in a decision making task; activation in the DLPFC peaked when the degraded information could be resolved by additional cognitive processing. Our results help to underscore the importance of studying varying degrees of uncertainty, as we found evidence for different neural responses for intermediate and high levels of ambiguity that are easy to ignore depending on how ambiguity is defined. Additionally, our results help reconcile two

different accounts of brain activity during ambiguous decision making, one suggesting that uncertainty increases linearly and another suggesting ambiguity processing is greater at intermediate levels. The graded coding of uncertainty we reported may reflect a unified neural treatment of risk and ambiguity as limiting cases of a general system evaluating uncertainty mediated by the DLPFC which then recruits different regions of the prefrontal cortex as well as other valuation and learning systems according to the inherent difficulty of a decision.

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CHAPTER 1 - INTRODUCTION

Making decisions is an integral part of everyday life, yet, the parameters that determine our decisions are not fully known. From simple decisions such as what to eat for lunch or which route to take to work to complex decisions such as who to marry or how which stocks to buy, we constantly have to determine what the optimal decision is among a list of seemingly infinite options. Unfortunately, choices can vary greatly in the level of information available to the decision-making agent, as the probability distributions of outcomes for many decisions cannot always be fully known. In some choices, such as gambling on the outcome of a roulette game, probability can be easily determined from relative frequencies, or past outcomes. On the other hand, there are choices in which probabilities are based on incomplete or missing information, such as in deciding whether or not to bring an umbrella in case of rain. In economics, these conditions are termed "risk" and "ambiguity" respectively (Ellsberg, 1961; Knight, 1921), which have been dissociated behaviorally and (very recently) neurally.

This section will focus primarily on decision making under states of ambiguity and how neural correlates associated with this type of uncertainty differ from those associated with other states of uncertainly – mainly risk. We will first discuss different theories of optimal and rational decision making developed in the fields of behavioral economics, then discuss theories of choice behavior under states of uncertainty. Then we will discuss the neural architecture supporting simple decision making and explore the

additional neural structures that are recruited when uncertainty is introduced into a decision making environment. Finally, we will discuss open questions regarding uncertain decision making, and propose a novel task designed to better distinguish between risk and uncertainty.

1.1. Theories of Decision Making

One way to optimize decision making is to make decisions based solely on value. For decades, insights into this evaluation process centered on Expected Value (EV) Theory, first proposed by Blaise Pascal. Pascal (1670/1966) argued that an uninformed agent could make the most optimal choice by treating all available actions as an option. The decision making agent should then rank the desirability of each option by assigning value to it: that is, determine how much the chooser could stand to gain or lose, whether it is money or other incentive, should that option be chosen. Additionally, the decision making agent should assess the probability of obtaining the desired outcome associated with each option. Thus, the optimal choice can be selected from multiple options by simply multiplying the value of each option by the likelihood of the desired outcome occurring (EV = Probability X Value). The chooser simply selects the option with the highest EV. For example, consider a game of chance with two options. The first option is a payoff of $50 if a 5 appears on the roll of a single die and no money if any other number is rolled. The second option is a payoff of $320 if two 5s appear on the roll of two six-sided dice and no money if any other number is rolled. According to Expected Value Theory, option 2 is the better option, since it has an associated EV of 8.8, whereas the first option only has an associated EV of 8.3.

Unfortunately, EV is often a poor predictor of actual choices; people often make choices that have a lower expected value than other options. This is highlighted by the St. Petersburg paradox. This paradox is based on a game of chance in which a player pays a fixed fee to enter a lottery in which a fair coin is repeatedly tossed until "heads" comes up which ends the game and the player wins the pot. The pot starts with $2 and is doubled every trial in which "heads" does not come up so that the pot is $4 on the second trial, $8 on the third and so on. Thus, the payoff depends on the trial at which the first "heads" comes up. First, the player would have to calculate the EV in order to determine how much he should pay to play, which is the sum of the expected payoffs of all the consequences: 1/2 probability of winning $2 on the first trial, 1/4 probability of winning $4 on the second trial, 1/8 probability of winning $8 on the third trial, etc. Since the expected payoff of each possible consequence is $1, and there are an infinite number of them, this sum is an infinite number of dollars. In order to maximize the payoff, the player should enter the game only if the entry fee he pays is less than the expected value. In the case of the St. Petersburg game with infinite EV, any finite price is lower than the EV. Therefore, this means that it should not matter how much the player pays to enter. However, people are only willing to pay a very small fee ($2-$4) to play when offered the choice (Aumann, 1977).

To resolve the St. Petersburg paradox, Daniel Bernoulli (as cited in Glimcher, 2008) postulated that humans do not base decision based solely on a constant value assigned to each option, but rather tend to select the option whose probability distribution has the highest *subjective* value, or utility, compared to all other options. Like Pascal's model of expected value, Bernoulli's model of expected utility (Expected Utility =

Probability X Utility) accounts for the likelihood of any given outcome occurring, but also suggests that personal preference is a powerful decision parameter even when the likelihood of various options is 100% certain. One observation made regarding the St. Petersburg paradox is that it does not take into account how various states of wealth affect choices. Bernoulli argued that money and other incentives diminish in value at higher levels. In other words, a gain of $1000 is worth more to a man with a net worth of $0 than it is to a man whose net worth exceeds $1 million. This principle later became know as the Principle of Decreasing Marginal Utility, which states that value is no longer linear, but "concave", in that each additional good consumed or unit of wealth gained is less satisfying or valuable than the previous one.

Thus, Bernoulli postulated that a more realistic measure of the value of something like money might be better estimated via a logarithmic scale. Similar to using Expected Value Theory, a decision-making agent can make an optimal decision using Expected Utility Theory by determining the probability of a desirable outcome occurring. Rather than multiplying the likelihood of a favorable outcome with a value, Bernoulli suggested that one must first take into consideration total objective wealth of the decision making agent, and then take the log of this number to yield the total "subjective wealth". The decision making agent can then evaluate which option yields the biggest increment to subjective wealth, and choose accordingly. This results in choices that violate Expected Utility Theory. Using the earlier example of the game of chance with two options based on dice rolls (either $50 if a 5 is rolled with one die or $320 if two 5s are rolled with two dice), a person with an initial subjective wealth of $1 would likely choose to bet on the option with lower EV, but higher marginal utility ($50 on the roll of one die) since this

choice represents a lower probability of remaining relatively poor (1/6 chance vs. 1/36 chance).

Bernoulli's theory of expected utility has become very influential in several academic fields studying decision making, including economics and neuroscience, because it converts the various aspects of available options into a single measure that allows for comparison across different dimensions. In other words, utility (subjective value) is what allow us to compare apple to oranges based on personal preference. Furthermore, work by von Neumann and Morgenstern (1947) expanded Expected Utility Theory to account for a wider range of phenomena observed in decision making scenarios. To do so, von Neumann and Morgenstern (1947), and later Savage (1954) proposed a set of axioms that characterize choice behavior when one or more options are available, which include principles such as completeness, transitivity and independence, among others. According to this axiomatic model of decision making, the completeness and transitivity axioms establish that decision making agents can order preferences on an ordinal scale. For example a decision making agent could show he/she obeys the completeness axiom by showing a marked preference for apples compared to oranges, and a preference of oranges to pears. Additionally, the decision making agent could show adherence to the transitivity axiom if one chooses an apple when asked to choose between an apple and a pear. Axioms were included in EU Theory as a simple way to classify a set of behaviors that one should exhibit if one is trying to maximize net utility above all else.

Finally, EU has proven a powerful theory to describe choice behavior because it assumes that the value of different options, as represented by utility, can be ranked on an ordinal

rather than cardinal scale. In our above examples of a decision making agent that prefers apples to oranges to pears, the utility associated with each object is not associated with a particular numerical value. That is to say, one does not necessarily value apples twice as much as oranges, but only half as much as pears. Utility allows for a unit-free way to assess the preference of options during choice. The usefulness of utility becomes more apparent when we introduce a new option, bananas, to the available options. If preference or value was to be ranked cardinally, and the decision making agent now prefers bananas to apples, the scale would have to be regenerated to accommodate the new option.

1.2. Neural Substrates of Decision Making

In order to understand how we make decision under conditions of uncertainty, it is important to understand the basic neural substrates that underlie simple, unambiguous decision making. In most cases, a decision is the act of choosing one option from several discrete options presented to us. We can break down decision making into two separate stages: the valuation stage, where we evaluate the merit of each option and assign an arbitrary level of desirability to it, and a choice stage, where we select the option with the highest value by making overt motor responses. Growing evidence suggests that the basic network responsible for producing choices in humans and non-human primates does in fact involve a two-stage process that is housed in different regions of the brain. Valuation is associated with activity in ventral parts of the frontal cortex and sub-regions of the striatum, whereas choice is associated with activity in lateral prefrontal and parietal cortices.

1.2.1. Valuation

As stated previously, most theories of decision making require a valuation stage in which the various dimensions of a single option are converted into a single dimension which can then be associated with a subjective value. It is this measure of value that serves as a sort of common currency that allows us to compare seemingly different choices. Several studies have found that activity in the orbitofrontal cortex (OFC) and striatum is positively correlated with behavioral measures of value. Refer to Table 1 for a list of studies looking at neural correlates of valuation.

Some of the first studies to demonstrate value-related activity in the brain were carried out using single-unit recordings in the OFC of non-human primates. Thorpe et al. (1983) found that the response of specific neurons in the OFC to a visual stimuli depended on whether the previous stimuli was associated with a reward (apple juice) or no reward (saline). Similar findings were reported by Rolls and colleagues (1989) who reported increased activity in OFC neurons associated with gustatory stimuli that could be modulated by varying hunger and satiety. Importantly, this modulation of activity was not found in primary gustatory cortex, suggesting that activation reported in the OFC was associated with stimuli associated with a rudimentary value function and not just sensory processing. These findings have since been replicated in studies using advanced recording techniques and experimental paradigms (Roesch & Olson, 2005; Wallis, 2007).

Although these classical studies demonstrate that neurons in the OFC can encode simple forms of value or preference, these experiments were devoid of choice; the animals in these studies only passively attended to stimuli. More concrete evidence of

preference-based value in the OFC came from studies in which animals were allowed to freely choose based on preference. For example, Padoa-Schioppa and Assad (2006) demonstrated that a small population of neurons in the OFC encoded subjective value. In this experiment, monkeys were presented with pairs of different types of juice in varying amounts. The experimenters found that when the two stimuli were presented in equal amounts, monkeys chose based on subjective preference, and that monkeys chose the less-preferred juice only when it was offered in sufficiently large amounts. Based on this pattern, experimenters were able to infer the value of each type of juice and calculate the amount of juice needed so that each type of juice would be chosen equally often. Cell recordings were found to match the various assignments of value in each monkey, and the firing patterns reported were independent of the spatial arrangement of the stimuli and of the motor response made by each animal (Padoa-Schioppa & Assad, 2006).

Finally, it is important to note that value signals observed in the OFC represent *absolute* value rather than *relative* value. Again Padoa-Schioppa and Assad (2008) recorded activity from a population of OFC neurons in monkeys performing a choice preference task in which subjects were offered the option to drink different types of juice. Padoa-Schioppa and Assad (2008) demonstrated that activity in the OFC is "menu invariant"; as patterns of the OFC neurons showed consistent firing associated with specific stimuli and matched behavioral responses. This finding is important, in that it demonstrates that even neurons in certain regions of the brain obey axioms. In this study, the firing pattern in OFC neurons was consistent with the transitivity axiom: a neuron that encoded the value of grape juice did so in the same manner whether the other option was apple juice or water (Padoa-Schioppa & Assad, 2008).

These findings showing value-related signals in the OFC have also been replicated in humans using various methods of neuroimaging, providing converging evidence that the OFC is crucial for the calculation of value. Though it is always difficult to exactly match the neural substrates of choice across human and animal models, there is strong agreement between regions observed to be active using electrophysiological recordings in animals and neuroimaging in humans, leading us to believe we are discussing directly homologous structures. As in animal studies, value-related signals in the OFC have been observed in the absence of choice, and activity is consistent with tracking or predicting objects and outcomes associated with high value and/or reward (Knutson & Cooper, 2005; J. O'Doherty et al., 2004). More importantly, in studies which directly compared conditions of passive stimulus presentation and choice, activity in the OFC was associated with trials in which subjects were allowed to choose based on preference (Arana et al., 2003).

Mirroring animal work, several studies have been conducted on preference based value signals in the OFC. For example, Plassman and colleagues (2007) showed food-deprived participants various images of food while inside an fMRI scanner. Subjects were then asked to bid hypothetical money for the right to eat one of these foods based on preference. Thus, the value of each food item was inferred by the amount of money subjects were willing to pay to acquire and consume each item. A positive correlation was found between the subjective valuation of the food items and BOLD activity in the OFC (Plassmann et al., 2007). Similarly, Hare and colleagues (2008, 2009) performed a similar set of studies in which hungry subjects were given a monetary budget that they could spend on various food items they wanted to eat. These studies again showed

activity in the OFC was associated with the valuation of individual items, and not due to other possible signals, such as outcome and reinforcement values (Hare, Camerer, & Rangel, 2009; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008).

Finally, studies using human subjects with damage to the OFC show that value computation is impaired across various tasks. However, many of the studies looking at human lesions have investigated valuation and decision making in the brain using the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994). The IGT requires subjects to search for monetary rewards by selecting cards from among several decks. The proportion of winning cards within each deck is varied and subjects learn through exploration which are the "good" decks that pay the most over a period of time and which are the "bad" decks that are associated with losing money, essentially forming a 4-armed bandit task (a task in which each "arm" represents an independent lottery with its own reward schedule). Using the IGT, Bechara and colleagues (1994) demonstrated that while healthy subjects were able to make successful choices by choosing the good decks and avoiding the bad ones, one particular patient with damage to the ventromedial prefrontal cortex was not able to distinguish optimal from suboptimal choices. Although previously discussed studies have used the anatomical term OFC, the ventromedial prefrontal cortex as discussed by human lesion studies includes the same regions of cortex often referred to as the OFC, such as medial Broadmann's areas (BA) 10, 11, 12, and the lower BA 24, 25 and 32. Consequently, this study provided some of the first data in humans indicating that the ventromedial prefrontal cortex is crucial for valuation; patients with ventromedial prefrontal cortex damage fail to place a higher value on certain decks. Subsequently, more studies have been carried out using patients with

ventromedial prefrontal cortex lesions and have replicated these initial findings showing sub-optimal decision making in the Iowa Gambling Task (Bechara, Damasio, & Damasio, 2000; Bechara, Damasio, Damasio, & Lee, 1999; Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, Tranel, & Damasio, 2000), the ultimatum game (Koenigs & Tranel, 2007), and fail to show any consistent patterns of valuation in other choice preference tasks (Fellows, 2006; Fellows & Farah, 2007).

In addition to the OFC, regions of the striatum have also been shown to play a role in valuation of choices during decision making. In one such study, monkeys were taught to associate lever turns, either to the right or left, with varying amounts of fruit juice. The firing patterns of neurons in the putamen seemed to track the value of actions; neurons that tracked the value of a turn in either direction would always exhibit a consistent response, even if the animal chose a different direction associated with a larger reward (Samejima, Ueda, Doya, & Kimura, 2005). This finding implies that neurons in the striatum are capable of encoding value to a certain extent, and that the value encoded is also absolute and not relative, like the menu-invariant value signals in the OFC. In a more recent study by Lau and Glimcher (2008), monkeys were required to perform an occulomotor choice task in order to receive reward dependant upon the different reward schedules for each stimulus. In this study, monkeys displayed the ability to adjust saccadic movements such that the proportion of their responses to each stimulus matched the relative magnitude of reward associated with each stimulus based on the reward schedules; animals responded more often to stimuli that had achieved higher value via a more generous reward schedule and responded significantly less to stimuli that had acquired a lower value. More importantly, their recordings from neurons within the

caudate closely resembled the pattern of activity reported by Padoa-Schioppa and Assad (2006, 2008) in the OFC and Samejima and colleagues (2005) in the putamen. Since then, striatal activity consistent with these findings has been demonstrated in other studies using different paradigms and species (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Kable & Glimcher, 2007; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001; McClure, Li et al., 2004; Tom, Fox, Trepel, & Poldrack, 2007; Waelti, Dickinson, & Schultz, 2001).

Taken together, the findings mentioned above indicate that regions of the striatum are involved in the computation of value. However, most of the activity in the striatum may not be directly attributed to the process of assigning subjective value *per se*, but rather learning the value of objects and choices. In many experiments using both animals and humans, subjects have to learn the value of different actions throughout the course of the experiment. Many times, this must occur in situations in which the consequences of each action cannot be communicated verbally. Overwhelming evidence suggests that dopaminergic neurons in the midbrain encode a teaching signal that can be used to learn the subjective value of actions (see Schultz, 2002 for review). In particular, the ventral striatum has been typically associated with dopamine-dependent learning and reward processing -- unexpected reward particularly. In the reinforcement learning framework, dopamine activity signals reward prediction error in which a reward that is better than expected will elicit a phasic burst of dopamine, a fully expected reward elicits no activity, and a reward that is worse than expected will produce a depression of dopaminergic firing (Schultz, Dayan, & Montague, 1997). Moreover, the prediction error response is sensitive to the time of reward delivery, meaning that a delayed reward will produce a

depression at the original time of reward delivery and a shift in activation towards the new time of reward. Overall, this suggests that reward prediction error is used as a teaching signal by cells within the ventral striatum, which we will briefly discuss.

More recent studies have explored the reward prediction error hypothesis using a variety of experimental paradigms and have provided solid support for Schultz and colleagues (1997) work. For example, Bayer and Glimcher (2005) recorded from dopaminergic neurons in the ventral striatum while monkeys performed an occulomotor (saccade) task. In this experiment, monkeys were rewarded for making specific saccadic movements. However, the reward associated with each moment varied in a continuous manner from trial-to-trial, so that even the same movement executed in succession did not necessarily result in equal reward. Bayer and Glimcher (2005) found that dopaminergic firing rates in the ventral striatum were linearly related to a previously modeled reward prediction error. Additionally, studies investigating the reinforcement properties of dopamine have demonstrated that when conditioned cues predict rewards with different magnitudes or probabilities, the observed dopamine response also scales with magnitude and probability, which is expected if dopamine activity in this region of the striatum truly represents a cue-elicited prediction error (Fiorillo, Tobler, & Schultz, 2003; Tobler, Fiorillo, & Schultz, 2005). Similar electrophysiological studies using non-human primates have demonstrated that if different cues predict rewards after different delays, the cue-elicited response decreases as the delay-to-reward increases, consistent with a prediction that incorporates discounting of future rewards (Fiorillo, Newsome, & Schultz, 2008; Kobayashi & Schultz, 2008; Roesch, Calu, & Schoenbaum, 2007).

Despite the large body of work investigating the reinforcement learning hypothesis in animals, there is little direct evidence regarding the activity of dopaminergic neurons in humans. This lack of evidence is mostly attributed to the spatial resolution in many of the available neuroimaging methods and the size of the various dopamine-producing regions of the midbrain. However, several studies have been successful in using functional magnetic resonance imaging (fMRI) to show reward prediction error-related signals in targets of the dopaminergic neurons, mainly the ventral striatum (McClure, Li et al., 2004; J. P. O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). All these studies are in agreement with previous animal work and help highlight the ventral striatum's role in reinforcement learning (Berns et al., 2001; McClure et al., 2003). Recent advancements in neuroimaging have allowed us to obtain more direct evidence from dopamine-producing regions of the midbrain by using smaller voxel sizes and different normalization procedures (D'Ardenne et al., 2008). In these studies, BOLD activity in the ventral tegmental area (VTA) has been reported to be significantly correlated with positive, but not negative, reward prediction errors.

Beyond neuroimaging, some studies have successfully obtained direct recordings from populations of midbrain neurons in humans (Zaghloul et al., 2009). Zaghloul and colleagues (2009) were the first to report electrophysiological recordings in human substantia nigra during learning. These investigators recorded neuronal activity while individuals with Parkinson's disease underwent surgery to place electrodes for deep brain stimulation therapy. Subjects had to learn which of two options provided a greater probability of a hypothetical monetary reward, and their choices were fit with a reward prediction model. In the subset of neurons that were thought to be dopaminergic, they

found an increase in firing rate for unexpected positive outcomes, relative to unexpected negative outcomes, while the firing rates for expected outcomes did not differ (Zaghloul et al., 2009). Such an encoding of unexpected rewards is again consistent with the reward prediction error hypothesis.

Using patients with neurological conditions has also provided insights as to how the midbrain dopamine system helps in reinforcement learning. For example, Pessiglione and colleagues (2006) demonstrated a causal role for dopaminergic signaling in both learning and striatal BOLD prediction error signals. During an instrumental learning paradigm, they tested subjects who had received L-DOPA (a dopamine precursor), haloperidol (a dopamine receptor antagonist), or placebo (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). Consistent with other findings from Parkinson's patients (Frank, Seeberger, & O'Reilly R, 2004), L-DOPA (compared to haloperidol) improved learning to select a more rewarding option, but did not affect learning to avoid a more punishing option. In addition, the BOLD reward prediction error in the striatum was larger for the L-DOPA group than for the haloperidol group, and differences in this response, when incorporated into a reinforcement learning model, could account for differences in the speed of learning across groups.

1.2.2. Choice

After computing and learning value in a manner that allows different options to be compared on the same scale, one must still select the most desirable or appropriate option from the set of available alternatives. Although it is well understood that the motor system is necessarily involved in choice as a physical response typically signifies choice,

the following section will instead focus on the cognitive processes associated with the selection of an optimal option that precede motor execution. Like the previous section on the neural substrates of valuation, the following section will focus heavily on studies using electrophysiological recordings of neurons in non-human primates. Although there exist studies on the neural correlates of choice in humans, the saccadic control system in non-human primates has been extensively studied and mapped for decades, and has provided the most detailed model of sensory-motor control we have to date (Glimcher, 2003; Gold & Shadlen, 2007). Additionally, electrophysiological recordings in animals allows us to invasively study the decision making network in a manner not possible with humans. Overall, the data suggest that regions of the parietal cortex and dorsolateral prefrontal cortex play a role in helping select the best choice. Table 2 lists empirical studies that highlight the neural architecture of choice selection.

Traditionally, the parietal cortex has been associated with linking sensory signals with motor commands as well as supplementary sensory processing and guiding attention processes (Colby, Duhamel, & Goldberg, 1996; Gnadt & Andersen, 1988). The notion that regions of the parietal cortex could also potentially bias action came from studies carried out by Basso and Wurtz (1998) and Dorris and Munoz (1998), who found evidence using non-human primates suggesting that a winner-take-all computation occurred in the colliculus, in which the patterns of activity in the collicular neurons effectively selected one movement from the two options for execution (Basso & Wurtz, 1997; Dorris & Munoz, 1998). These studies indicated that if the probability that a saccade would yield a reward was increased, firing rates associated with that saccade

increased, and if the probability that a saccade would yield a reward was decreased, then the firing rate was decreased.

Based on these findings, Platt and Glimcher (1999) recoded in a region of the parietal cortex, the lateral intra-parietal area (LIP), down-stream of the colliculus in the visuomotor system. Platt and Glimcher (1999) systematically manipulated the expected value of specific saccadic movements by either altering the probability or the magnitude of reward yielded by making a movement oriented towards a specific target, which were cued by the color of a fixation stimulus. They found that firing rates in the LIP before the collicular burst occurred were a nearly linear function of both magnitude and probability of reward, suggesting that these pre-movement signals encode the subjective value of movements. In a second study, Platt and Glimcher (1999) repeated the previous experiment with one major change: the monkeys were not given an overt visual cue to initiate a specific movement. Behaviorally, the frequency of the monkeys' responses proportionally matched the expected value of each movement so that monkeys made significantly more high value movements than low value ones. Again, the firing patterns of neurons in the LIP also matched expected value. Given these experiments by Platt and Glimcher, it is plausible that the LIP plays a role in the selection of highly rewarding actions based on the value computations carried out in the OFC and striatum.

Many subsequent studies have since been carried out that support the conclusion that the LIP plays a large role in biasing decisions based on value. This body of work includes studies demonstrating that various manipulations that increase and decrease the subjective value of a given saccade also modulate increases and decreases in the firing rate of neurons within this region of the parietal cortex in non-human primates (Dorris &

Glimcher, 2004; Janssen & Shadlen, 2005; S. Kim, Hwang, & Lee, 2008; Leon & Shadlen, 1999, 2003; Wallis, 2007; Yang & Shadlen, 2007). More importantly, the LIP has been shown to track small fluctuations of value over time, suggesting that activity in the LIP is dynamic and varies according to environmental demands. For example, Sugrue and colleagues (2004) recorded activity in the LIP in an unstable decision making environment using a foraging task. In this study, the likelihood of reward associated with each of two stimuli fluctuated over time based on preceding response made, and monkeys were free to choose the stimulus most appealing to them. This led monkeys to match the rate of choosing each target to the relative reward probabilities of each stimulus over both short and long time scales. Electrical activity in LIP neurons associated with selecting a particular target was significantly correlated with the history of relative reward, indicating that more recent trials were weighted more (Sugrue, Corrado, & Newsome, 2004). Similarly, Dorris and Glimcher (2004) found using a similar foraging task that LIP neurons reflected a value weight in which the activity of individual LIP neurons was modulated by the relative value of an option compared to similar options in preceding trials. Together, these results suggest that decisions may be formed in the LIP by scaling neuronal responses according to expected value, and action selection depends critically on the modulation of neurons to reach a certain threshold.

This threshold model of action selection has been also been demonstrated in similar perceptual decision making studies. In a series of studies, Shadlen and colleagues (1996, 2001) used an ambiguous visual stimulus to indicate which of two saccades would yield a reward, and the monkey was reinforced if he made the indicated saccade (Shadlen, Britten, Newsome, & Movshon, 1996; Shadlen & Newsome, 2001).

Researchers found that the activity of LIP neurons in the decision-making process resembled an accumulation signal, in which the firing rate of LIP neurons increased prior to the selection of a particular action. Subsequent studies have also demonstrated similar dynamics of this decision making process. During these kinds of perceptual decision-making tasks the firing rates of LIP neurons show the similar pattern of neuronal firing increase as the evidence that a saccade into the response field will be rewarded accumulates, and once firing rates cross a maximal threshold a saccade is initiated (Churchland et al., 2008; Roitman and Shadlen, 2002). A closely related series of studies also shows a similar pattern of neuronal firing in the frontal eye fields, and lead to the similar conclusion where the most appropriate or desired option or behavior is the one that reaches a certain threshold the fastest (Gold & Shadlen, 2000; J. N. Kim & Shadlen, 1999).

In humans, perceptual decision making tasks have also been used to demonstrate that certain regions of the parietal cortex are involved in action/choice selection. However, it should be noted that there is no LIP in the human brain. Rather, the presumed human homologue of the primate LIP is considered to be the intraparietal sulcus (IPS), including middle IPS. For example, Ploran and colleagues (2007) found specific regions of the parietal lobe showed increased BOLD activity that was characteristic of an evidence accumulation function. Using a perceptual decision making task, subjects were presented with a series of visual stimuli which, as an ensemble, corresponded to a specific motor response. Subjects were encouraged to make a response as quickly as they had reached a decision as to what the required motor response was. Increased activity was reported in the IPS beginning with the presentation of a stimulus,

which continued to increase as subsequent stimuli were presented until a decision was made. Once a decision had been reached, activity in the IPS sharply decreased to baseline levels. This pattern was notably different from a more tonic activation reported in regions of the prefrontal cortex also involved in decision making or regions of the striatum that showed an increase in activity after a decision was made (Ploran et al., 2007). Numerous other studies have also shown that the increased rate of neural activity in the IPS of humans matches that of the LIP in non-human primates, which may represent the accumulation of sensory evidence as one reaches a specific decision (Astafiev et al., 2003; Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006; Ho, Brown, & Serences, 2009; James & Gauthier, 2006; Noppeney, Ostwald, & Werner, 2010; Philiastides & Sajda, 2007; Ploran, Tremel, Nelson, & Wheeler, 2011; Sereno, Pitzalis, & Martinez, 2001; Stark & Zohary, 2008; Tosoni, Galati, Romani, & Corbetta, 2008; Wheeler, Petersen, Nelson, Ploran, & Velanova, 2008).

Along with the parietal cortex, several lines of evidence indicate that the dorsolateral prefrontal cortex (DLPFC) also plays a role in the decision making process. Traditionally, the DLPFC has been associated with a wide range of cognitive processes such as working memory (R. Levy & Goldman-Rakic, 2000; Petrides, 2000), cognitive control (Milham, Banich, & Barad, 2003; Miller, 2000; Miller & Cohen, 2001; Wallis & Miller, 2003) and emotional regulation (Delgado, Gillis, & Phelps, 2008; Ochsner & Gross, 2005). In addition, there is now evidence that DLPFC activity changes according to whether or not a reward is expected in a given state in simple decision making tasks (Kobayashi, Lauwereyns, Koizumi, Sakagami, & Hikosaka, 2002; Leon & Shadlen, 1999; Watanabe, 1996). These findings suggest that the DLPFC plays an important role

in decision making by encoding a particular state, along with the desirability of the outcome expected when the decision-making agent is in the same state (Lee, Rushworth, Walton, Watanabe, & Sakagami, 2007). For a task that demonstrates this phenomenon that better approximates decision making in the real world outside of a laboratory setting, researchers have employed games such as the matching pennies game. In this mixed-strategy game, one player attempts to match the sides of a coin with that of a fellow player or computer. If the two sides match, the player keeps both coins, whereas the player loses the coin if both sides do not match. The results from these experiments closely mirror previous studies investigating DLPFC function during choice and decision making. Activity of many neurons in the DLPFC was reported to correspond not only the upcoming choice, but also the choices made in the previous trials; activity of the DLPFC neurons during the feedback period was correlated to whether or not a choice was rewarded in previous trials (Barraclough, Conroy, & Lee, 2004; Seo, Barraclough, & Lee, 2007). These findings suggests that the activity in the DLPFC might be influenced by reward history and therefore by the context in which a particular reward was delivered or omitted and match similar studies looking at prefrontal cortex function and decision making (Camus et al., 2009; Domenech & Dreher, 2010; Forstmann et al., 2008; Hanes & Schall, 1996; J. N. Kim & Shadlen, 1999; S. Kim et al., 2008; Mullette-Gillman, Detwiler, Winecoff, Dobbins, & Huettel, 2011).

Besides maintaining information of previous reward state that can influence current choices, the DLPFC, like the LIP/IPS, appears to also be involved in helping influence choice based on value calculated elsewhere (presumably the striatum and OFC). As previously stated, specific regions of the parietal cortex seem to play a key

role in mediating choice based on value. However, evidence suggests that the DLPFC may play a similar role during decision making tasks. That is, activity in the DLPFC shows an increase prior to a decision or selection/execution of a choice that sharply drops off once a decision is made (Ivanoff, Branning, & Marois, 2008; Kayser, Buchsbaum, Erickson, & D'Esposito, 2009; van Veen, Krug, & Carter, 2008). This indicates that there exists a fronto-parietal network that mediates choice based on subjective value. Heekeren and colleagues (2004) demonstrated in a perceptual decision making task that the DLPFC helps integrate choice signals in the parietal cortex with other sensory cues. In their experiment, Heekeren and colleagues (2004) asked human subjects to categorize images as either houses or faces. The images were clear on half of the trials, but were masked by noise on the remaining trials. Researchers found that the DLPFC was more active when the decision was easy (e.g. not distorted). Additionally, DLPFC activity was greater on trials for which the sensory evidence was substantial (clear images) than on trials for which the sensory evidence was weak (Heekeren, Marrett, Bandettini, & Ungerleider, 2004). This finding is important, in that it directly matches patterns of activity reported in the parietal cortex (Roitman & Shadlen, 2002; Shadlen et al., 1996; Shadlen & Newsome, 2001). Based on these lines of evidence, the DLPFC seems to have an integrative role in decision making, in which it links decision making outcomes from previous trials with selection strategies for the upcoming choice in a given trial.

One important observation that must be noted is that unlike firing rates in OFC and striatum, firing rates in LIP and IPS (and presumably other frontal-parietal regions involved in choice rather than valuation such as the DLPFC) are not "menu-invariant." This suggests an important distinction between activity in the parietal cortex and activity

in the OFC and striatum. Orbitofrontal and striatal neurons appear to encode absolute (and hence transitive) subjective values. Parietal neurons, presumably using a normalization mechanism like the one studied in visual cortex (Heeger, 1992), transform absolute values into relative values in order to maximize the differences between all available options before a choice is selected.

1.3. Decision Making Under Uncertainty

Two-step models of decision making that assume separate stages for valuation and choice can be adequate for studying simple decisions; however, they often ignore the fact that decisions made by both humans and animals can be modulated by environmental and intrinsic variables. These decision variables include reward magnitude (Delgado, Locke, Stenger, & Fiez, 2003), reward quality, various needs or motivational states (Balleine, 2005; Balleine & Killcross, 2006), time spent (Niv, Daw, Joel, & Dayan, 2007), time remaining (Kable & Glimcher, 2007; Schweighofer et al., 2006), and uncertainty. Additionally, decision variables can also independently influence decision making or be transformed or combined with any number of other variables. One common, and important factor across decision variables is that they are subjective, and express the decision making agent's estimation of the attractiveness of the available options. Essentially, these extraneous factors constitute the very idea of what economists call utility. Though it is important to acknowledge other decision variables, an in-depth discussion of each is outside the scope of this section, and we will instead focus on how uncertainty modulates choice behavior.

Given its ubiquitous nature in decision making, uncertainty presents a special problem in the study of decision making across several areas of research. A wide range of studies throughout the past decades have confirmed that uncertainty contributes crucially to the valuation of options during decision making in such diverse situations as animals engaging in foraging, making medical diagnoses, buying into stock markets, and companies pricing insurance (Bossaerts & Plott, 2004; McNamara & Houston, 1980; Pauker & Kassirer, 1980; Real, 1991). Therefore, one must evaluate both the values, as well as the uncertainty associated with the options in order to make optimal decisions. As pointed out at the beginning of this chapter, choices can vary greatly in the level of information available to us at any given time, as the probability distributions of outcomes for many decisions cannot always be fully known. In the following sections we will explore differences in uncertainty, using Knight's (1921) definitions of "risk" and "ambiguity".

1.3.1. Risk

Risk is a type of uncertainty that Knight (1921) defined as "knowable" uncertainty. That is, the probability of a given outcome that is less than certain is available to the decision making agent. Risk is often discussed in terms of risk aversion, which is a well-documented phenomenon that describes subjects' dislike for risky choices given safe alternatives, and usually leads to sub-optimal choices (e.g. taking a sure bet that has lower EV or subjective utility rather than betting on an uncertain outcome). Generally, people tend to be risk seeking for large gains and risk-averse for large loses. This is similar to evidence showing people overweight large probabilities

and underweight small probabilities, leading people to place disproportionate attention on the best and worst possible outcomes. For example, buying insurance *and* playing the lottery at the same time (Kahneman & Tversky, 1979; Quiggin, 1982). However, the observation of risk-seeking for gains behavior reverses when gains and loses are small, leading people to be risk averse for gains and risk seeking for losses (Tversky & Kahneman, 1991).

Previous research reveals another interesting phenomenon associated with decision making under states of uncertainty: risk aversion is inherently intertwined with loss aversion. Like risk aversion, loss aversion is the observation that when given the option people will take measures to avoid a loss rather than seek a gain (Tversky & Kahneman, 1981). Tversky and Kahneman proposed loss aversion as an explanation for the "endowment effect," in which people place a higher value on a good that they own than on an identical good that they do not own (Kahneman, Knetsch, & Thaler, 1990). Tversky and Kahneman demonstrated the effects of framing on decision making by asking subjects to imagine that the United States is preparing for the outbreak of an unusual Asian disease expected to kill 600 people. Participants were asked to choose between two pairs of programs to address the problem. In the gain condition, participants were told that if they chose option A, 200 people would be saved. If subjects chose option B, there is a 1/3 probability that 600 people would be saved and a 2/3 probability that no one would be saved. In the loss condition, participants were told that if they chose option C, 400 people would die. If they chose option D, there was a 1/3 probability that nobody would die and a 2/3 probability that 600 people would die. Most people presented with these decisions preferred option A to B and option D to C, which is

surprising because option A is identical to option C, and B to D, just framed differently (Tversky & Kahneman, 1981). Combined with risk aversion, loss aversion can help to explain various phenomena that can be described as being risk averse, such as the tendency to reject symmetric bets, the preference for investing in bonds over stocks, and the tendency to hold on to depreciating property such as stocks and houses (Benartzi & Thaler, 1995; Genovese & Mayer, 2001; Gneezy & Potters, 1997).

Recently, the focus of research dealing with risky decision making has been on finding regions of the brain that code specifically for risk. Neurally, the coding of risk-related signals in humans is similar to the activity of dopamine neurons recorded across various species of non-human mammals performing various instrumental learning tasks. These studies demonstrate that dopamine neurons can encode two very different pieces of information about reward outcomes, and these separate signals operate along different time scales. One signal is associated with a phasic burst of activity at the onset of the stimulus, and is thought to carry information about reward value prediction and error. A second signal gradually increases from the time the stimulus is removed and then ends prior to the delivery of the reward; it is thought to encode reward risk (Fiorillo et al., 2003; Tobler et al., 2005). Fiorillo and colleagues (2003) found that when reward magnitude was held constant and reward probability ranged from 0 to 1, the risk signal followed an inverted U function: It peaked when reward probability was 0.5, when there was the highest chances of either obtaining or missing a reward. This slow dopamine risk signal is then believed to provide an input to brain structures dealing with the assessment of risk.

In humans, there is a similar distinction between reward prediction and risk assessment in regions heavily influenced by dopamine activity. To investigate the risk response in humans, Tobler and colleagues (2007) used the same manipulation of reward probability as in Fiorillo et al. ($p = 0, 0.25, 0.5, 0.75$, and 1), and found activity in the orbitofrontal cortex modulated by risk that was negatively correlated with individual measures of risk aversion. Additionally, work by Preuschoff et al. (2006) found activity in the striatum, midbrain, anterior insula and subregions of the medial orbitofrontal cortex that matched the slow, risk-related response reported in animals. Together, these studies were some of the first to indicate the possibility of two distinct neural signals, a fast reward-related signal and a slower risk-related signal, underlying choice behavior (Preuschoff, Bossaerts, & Quartz, 2006; Tobler, O'Doherty, Dolan, & Schultz, 2007). However, it is possible that these two signals overlapped in these studies given the slow nature of the BOLD response compared to the millisecond resolution available with single-cell recording. In addition to these regions, there are several regions that are reported to be increasingly active in risky situations, but it is not known if the activity reported in these regions reflects a pure risk signal. For example, the insula is often implicated in risk processing (Huettel, Stowe, Gordon, Warner, & Platt, 2006; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Preuschoff, Quartz, & Bossaerts, 2008) along with regions in the posterior parietal lobe (Huettel, Song, & McCarthy, 2005; Platt & Glimcher, 1999).

1.3.2. Ambiguity

Unlike decisions under risk, in decisions under ambiguity information regarding the probability of specific outcomes is unavailable. Knight (1921) defined ambiguity as "immeasurable uncertainty." Due to ambiguity's similarity to risk, people often show behavior similar to risk aversion; that is, people prefer options with certain probabilities to options with ambiguous probabilities, even when these choices contradict expected utility theory predictions (Heath & Tversky, 1991; Lauriola & Levin, 2001). The phenomenon of ambiguity aversion was first described by Daniel Ellsberg (1961), who argued that people treat ambiguous probabilities differently from unambiguous ones, using a hypothetical experiment. Here Ellsberg asked readers to imagine being presented with two urns, each containing a mixture of red and black balls. Urn 1 contains 100 red and black balls, but in an unknown ratio. Urn 2 contains exactly 50 red and 50 black balls. Drawing a ball of a designated color from an urn wins $100. Ellsberg argued that people should be indifferent between betting on red or black from Urn I, which implies that they believe that each has a 50% chance of occurring. Similarly, people should indifferent to betting on red or black from Urn II, which has the equivalent interpretation. However, most people prefer betting on red from Urn II to betting on red from Urn I and betting on black from Urn II to betting on black from Urn I, which cannot occur unless people hold distinct and asymmetrical probabilities for each event (Ellsberg, 1961). This can be taken as evidence for ambiguity aversion that cannot be accounted for in expected utility theory; however, it should be noted that this phenomenon occurs only when the task permits comparison of the ambiguous option to another option with more explicit information regarding reward outcome (Fox & Tversky, 1995).

Although ambiguity aversion has received much attention since Ellsberg's seminal work in 1961, the explanation for the anomaly has itself remained ambiguous. Many explanations have been proposed, but can be divided into three major classes. One type of explanation assumes that people react pessimistically to ambiguous probabilities, as if they assume that when the odds are unknown they will be stacked against the decision maker; this is also known as a sense of incompetence (Heath & Tversky, 1991). Ellsberg himself offered such an account. A second class of explanation assumes comparative ignorance, where subjects weigh heavily the information that they do not know when compared to a choice with more information (Fox & Tversky, 1995). A third explanation assumes that ambiguity aversion arises when the subject believes he is playing against an informed opponent (such as the experimenter) who could observe the choices made by the subject (Kühberger & Perner, 2003).

Curley, Yates and Abrams (1986) tested several proposed explanations behaviorally using the Ellsberg paradox. They found that even participants who said the ambiguous urn could not be biased against them were still ambiguity-averse, suggesting ambiguity aversion is not driven by pessimism about a "hostile" generation of outcomes. The authors also found that ambiguity aversion was uncorrelated with risk aversion, casting doubt on the second class of explanations discussed above. Finally, Curley et al. (1986) found that participants were significantly more ambiguity-averse when they were told that the chosen gamble would be played and the urn's contents revealed in front of other participants than when the gamble was resolved privately. The authors thus surmised that ambiguity aversion is due to social presentation concerns. However, their findings offer a limited explanation of ambiguity aversion.

Neurally, decisions under ambiguity have been demonstrated to recruit certain neural regions also activated by risky decision making, including the medial prefrontal cortex, amygdala and striatum (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Kuhnen & Knutson, 2005; I. Levy, Snell, Nelson, Rustichini, & Glimcher, 2010). Given the similarity of risk and ambiguity as two types of uncertainty, it is reasonable that there should exist a common network for processing uncertainty. To distinguish between risk and ambiguity, Hsu et al developed tasks that presented different amounts of information for choices across separate conditions, most notably: 1) a card game, in which the uncertain option involved either a risky gamble (known probabilities) or an ambiguous option (unknown probabilities), and 2) a knowledge estimation game, in which the uncertain options involved events and facts that fell along a spectrum from risk to ambiguity, such as temperature judgments for more (risk) or less well-known cities (ambiguous) (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005). Hsu and colleagues (2005) found that activation in areas of the orbitofrontal cortex, amygdala and dorsomedial prefrontal cortex (DMPFC) was positively correlated with ambiguity. In addition, this study found that striatal activation was negatively correlated with ambiguity (but positively correlated with risk) and operated on a slower time course compared to those of the orbitofrontal cortex or amygdala (Hsu et al., 2005).

A similar study was conducted that looked at both risky and ambiguous decisions within the same task (Huettel et al., 2006). In their study, Huettel and colleagues (2006) showed areas in the lateral prefrontal cortex (specifically the posterior inferior frontal gyrus) were activated for ambiguous choices and not risky ones. Alternately, risk was shown to activate regions of the ventral striatum and parietal cortex (Huettel et al., 2006).

Further studies looking at neural differences of risk and ambiguity processing have also corroborated these findings; increased activation in the posterior inferior frontal gyrus and amygdala for ambiguity, and increased activation in the striatum and posterior parietal cortex for risky choices (Huettel et al., 2006; Krain, Wison, Arbuckle, Castellanos, & Milham, 2006; Rustichini, Dickhaut, Ghirardato, Smith, & Pardo, 2005).

1.4. Aims

Despite studies contrasting decision making under conditions of either risk or ambiguity, it is still unclear whether these types of uncertainty are two distinct processes or one process operating along a qualitative continuum, given the lack of data for decisions made under states of partial ambiguity. Additionally, there is also a lingering question regarding which neural structures mediate a transition from ambiguity to risk processing that occurs in a constantly changing environment, and how they may interact and function in relation to one another. The proposed study is aimed at exploring neural activity associated with decision making in states of partial ambiguity in both cortical and sub-cortical regions.

The patterns of neural activation discussed above for both risk and ambiguity certainly suggest that these two types of uncertainty may be coded differently in the brain. On one hand, some brain structures show stronger BOLD responses to ambiguous compared with risky gambles, such as in parts of frontal cortex (Hsu et al., 2005; I. Levy et al., 2010). If levels of activation are influenced by the level of uncertainty within the same regions, that would be consistent with the notion of a continuum in uncertainty between ambiguity and risk. On the other hand, there are brain structures that show

distinct patterns of activation for risk and ambiguity, mainly the striatum and parietal cortex for risk, and orbitofrontal cortex, dorsolateral prefrontal cortex and amygdala for ambiguity (Hsu et al., 2005; Huettel et al., 2006). This dissociation is consistent with the idea that these regions process risk and ambiguity as qualitatively different and distinct phenomena.

The studies mentioned above (i.e. Hsu et al., 2005; Huettel et al., 2006) have made significant breakthroughs in understanding the neural processing of uncertainty in decision making. Unfortunately, previously mentioned findings contrasting risk and ambiguity are limited by the fact that ambiguity has been categorically defined as an all-or-none variable; that is, ambiguity has been typically been presented to subjects as a complete lack of information regarding reward probabilities. Although this treatment of ambiguity has proven powerful in identifying mutually exclusive neural substrates mediating different types of uncertainty, it precludes the study of decision making across varying amounts of ambiguity. Moreover, it can be argued that one rarely experiences real-life situations where information regarding the probability of reward is an absolute unknown; therefore, it is important to also investigate neural responses associated with "partial" ambiguity.

In a recent study, Bach and colleagues (2009) designed a decision-free task that introduced partially ambiguous states. In this task, human subjects were trained via Pavlovian conditioning to associate a painful electric shock to the hand (US) with visual patterns (a series of triangles and squares) representing various types of uncertainty (CS): risk, ambiguity, and ignorance. In the risk condition, the color of the border surrounding the stimuli indicated different probabilities of receiving the shock (P = 0.25, 0.50, 0.75).

In the ambiguous condition, the same CS was used, except the frame around the CS was gray, signaling to the participants that ambiguity was added to the previously learned risky CS configurations. Through the addition of this noise, the US probability was only partially predictable according to the previously learned CS–US contingencies (based on the arrangement of the stimuli). In the third condition called "ignorance," a completely new set of CSs were used and each CS was presented infrequently to avoid full learning of the outcome contingencies; thus the subjects remained ignorant of the probabilities of the shock (Bach, Seymour, & Dolan, 2009).

Bach and colleagues (2009) found an increase in activation in the dorosolateral prefrontal cortex and posterior parietal cortex for the partially ambiguous condition compared to the risk and ignorance conditions. Activation for risk and ignorance was limited, but similar for both conditions. This finding corroborates findings of Huettel and colleagues (2006), but the study by Bach and colleagues also found that the dorosolateral prefrontal cortex was active for risk. This work by Bach et al (2009) is extremely valuable because it measures neural responses to uncertainty without the confound of choice/motor responses. More importantly, this study provides insight as to *how* varying degrees of uncertainty are processed within prefrontal and parietal cortices (as opposed to just *where*). With this in mind, it is possible that regions associated with ambiguity, especially the posterior inferior frontal gyrus are more likely involved in extracting tractable information from learning context; however, this novel concept requires further study.

If regions of the brain are sensitive to hidden but searchable information masked by uncertainty, it can be further tested by parametrically controlling the amount of

information provided to subjects. This study aims to extend Bach and colleagues' (2009) study by introducing a novel paradigm that relies on varying levels of ambiguity to study the underlying neural processes of choice behavior. To date, no previous study has shown a parametric modulation of the hemodynamic response associated with different levels of uncertainty in the same task. Though Levy and colleagues (2010) used 3 levels of ambiguity, their study focused exclusively on isolating neural signals related to utility functions in the ventrolateral prefrontal cortex. This study is intended to address the limitations of Hsu et al. (2005) and Huettel et al. (2006), in which we will ask subjects to make simple economic decisions under different levels of either risk or ambiguity while we measure neural activity using functional magnetic resonance imaging (fMRI).

1.5. Predictions

1.5.1. Neural Activity Associated With High Levels of Uncertainty

Based on the previous discussion of neural regions involved in decision making and specific studies investigating decision making in states of uncertainty mentioned above, we can make tentative predictions regarding patterns of activity as uncertainty increases. First, we are interested in the activity in the DLPFC. Not only is this region of the prefrontal cortex linked to value-based choice, but also this is the main region that showed increased activation for ambiguity in previous studies (Bach et al, 2009; 2011; Huettel et al., 2006, Hsu et al., 2005). Additionally, this region of the DLPFC (referred to as the posterior inferior frontal gyrus by both Bach and colleagues (2009) and Huettel and colleagues (2006)) is implicated in cognitive control and executive function (Sakagami & Watanabe, 2007; Tanji, Shima, & Mushiake, 2007). We hypothesize that if

the DLPFC reflects an increased search for tractable contextual information, then we should see a pattern very similar to that of Bach et al., (2010), where our 0% and 100% ambiguity conditions should elicit little activity in the posterior inferior frontal gyrus, whereas other levels of ambiguity (15, 33, 66 or 80%) should be associated with an increase in the posterior inferior frontal gyrus. According to this hypothesis, "easy" decisions with either too much or not enough information should be mediated by simple sensorimotor activation and not require too much intervention from the DLPFC. However, as decisions become "harder" the DLPFC should provide supplemental processing along with activity in premotor areas for intermediate levels of ambiguity as the demands to extract contextual information increase.

Although not previously discussed, the anterior insula should also see an increase in activity as ambiguity increases. Insula activation occurs in a wide variety of tasks and conditions. There is, however, an emerging consensus that insula activation is frequently associated with aversive states, such as a potential loss resulting from a risky decision (Paulus et al., 2003). While there is no existing theory of insular activation in decision making, several studies have found greater activation in the insula for decisions involving uncertainty when compared to certain choices (Huettel et al., 2005; Krain et al., 2006); therefore, we expect to see insula activation for high levels of uncertainty in our categorical analysis.

1.5.2. Neural Activity Associated With Valuation of Choices

Because many studies investigating valuation processes in the brain have not included conditions of uncertainty, this study is in a unique position to explore how the

brain assigns value to choices in various states of uncertainty. We hypothesize that uncertainty modulates activity in neural regions associated with value in a manner that value-related activity is decreased as a function of increased uncertainty. As discussed previously, cross-species evidence shows that the orbitofrontal cortex is one of the neural regions responsible for assigning subjective value to stimuli (i.e. Padoa-Schioppa & Assad, 2006; Plassman, O'Doherty, & Rangel, 2007). Given these results, we would expect the orbitofrontal cortex to be recruited for trials that allow for subjects to develop clear preferences; the OFC should show a graded response that is greater for ambiguity-free trials and decreases for fully ambiguous trials. Previously, greater activity has been shown for risk than ambiguity in the orbitofrontal cortex (Huettel et al., 2005), and this activation is correlated with individual measures of risk aversion (Tobler et al., 2007).

Another region linked to value related processing is the dorsal striatum; the dorsal striatum has been reported to signal both value and risk in specific populations of dopaminergic neurons. Within the putamen, activity has been shown to be associated with value representations of actions. More specifically, activity in the putamen has been shown to 1) code for subjective value for actions, regardless if they're executed or not, 2) code for the actual response, and 3) code for the experienced subjective value of a choice once a response has been made (Lau & Glimcher, 2008). Within the caudate, there is also evidence that this region supports representations of value for specific actions, in conjunction with regions linked to frontal eye fields (Samejima et al., 2005). Additionally, Hsu and colleagues (2005) found that regions of the caudate were sensitive to EV. These findings suggest that we would expect to see greater activation for trials in which it was advantageous to choose the variable lottery. Additionally, this would be

reflected in a categorical contrast (Advantageous > Disadvantageous) showing greater activity in the dorsal striatum for trials in which it was optimal to choose the variable lottery.

Along with the orbitofrontal cortex, the superior parietal cortex has long been implicated in mediating value-based responses in decision making tasks (Churchland, Kiani, & Shandlen, 2008; Wang, 2008), especially regions of the superior parietal lobule extending to the precuneus (Broadmann's Area 7). While certain studies report parietal activation for decisions involving low ambiguity (i.e. Huettel et al., 2005), there is evidence to suggest that highly ambiguous decisions also recruit this region (Krain et al., 2006). Thus, we expect to observe increased activation in the posterior parietal lobe for low levels of ambiguity, where expected value can potentially be calculated, as opposed to trials with greater ambiguity. Here, Knight's (1921) notion of immeasurable risk seems to be reflected in BA 7; the parietal lobe is sensitive to tractable information.

Finally, we expect to see value-related activity in dorsal regions of the dorsal medial prefrontal cortex, including the anterior cingulate gyrus. Like the insula, we did not discuss this region at length as activity in the dorsal medial prefrontal cortex has been typically associated with various processes, not just decision making. Levy et al. (2010) report that dorsal medial prefrontal cortex was activated when they looked at subjective value signals associated with both risky and ambiguous decisions, suggesting that this region may be part of a common system for mediating uncertain decisions. However, previous studies have reported this region as being sensitive to expectation of reward (Knutson, Fong, Bennett, Adams, & Hommer, 2003). Given the dopaminergic inputs into the dorsal medial prefrontal cortex, activity in the dorsal medial prefrontal cortex

should be greater when anticipating reward and lower for conditions in which the expectation of reward is unclear. Similarly, Xue et al. (2009) reports increased activity in the ventromedial prefrontal cortex was associated with prediction of rewarding outcomes. These studies suggest that we could expect to see a linear decrease in activation in ventral regions of the dorsal medial prefrontal cortex as the amount of ambiguity in a given lottery grows, with greatest activation for ambiguity-free trials where information is explicit and more definite reward predictions can be made, and lower levels of activity for fully ambiguous trials where there is no information regarding reward probability on which to base an expectation. Additionally, Knutson et al. (2005) also found that the ventromedial prefrontal cortex was sensitive to EV, suggesting that there could potentially be a scaling of activation in the ventromedial prefrontal cortex associated with our EV manipulation. We expect to see greater activation for trials in which it is advantageous to choose the variable lottery and the least amount of activation for trials in which it is disadvantageous to play the variable lottery.

1.5.3. Neural Activity Associated With Monetary Gains and Losses

Activity in the ventral striatum is highly linked to value-related processes, as discussed earlier. However, our paradigm is not well suited for investigating valuation in the ventral striatum in detail such as in the work of Fiorillo et al. (2003), Tobler et al. (2005; 2007) and Preuschoff et al. (2006). Instead, we can look at this regions response to the receipt of various types of rewards, as this region is typically associated with dopamine-dependent learning and reward processing, particularly unexpected rewards (Berns et al., 2001; McClure et al., 2003). In the reinforcement learning framework,

dopamine activity signals reward prediction error in which a reward that is better than expected will elicit a phasic burst of dopamine, a fully expected reward elicits no activity, and a reward that is worse than expected will produce a depression of dopaminergic firing (Schultz, 2002). Thus, we should expect to see increased activity in the ventral striatum associated with winning money but not losing money. Given this region's affinity to respond to deviations from expectation, we can also expect to see increased activity in the ventral striatum for unexpected wins (e.g. money won via the variable lottery) compared to expected wins (money won via the safe lottery).

CHAPTER 2 - METHODS

2.1. Participants

fMRI participants included 14 normal, right-handed adults (age range = 22-36, mean age = 26.8 years) recruited from the Colorado State University (Fort Collins, CO) and School of Medicine, University of Colorado, Denver, (Aurora, CO) communities. We based our exclusion criteria on studies of cognitive aging showing that frontal lobe development is complete in the early 20s and begins to decline in the late 20s (see Hedden & Gabrieli, 2004). All participants were fluent speakers of English and were screened for a history of neurological and psychiatric disorders, and contraindications to MRI (i.e. no metallic implants, no claustrophobia, head size compatible with RF coil). Additionally, participants were screened for uncertainty preference by using a shortened version of our task, in order to exclude potential subjects who showed either too much or too little uncertainty preference. For this study we excluded participants who exhibited increased uncertainty preference and chose to play the variable lottery 75% of the time or those who displayed too much uncertainty aversion and played the uncertain lottery less than 20% of the time. The Colorado State University institutional review board approved the experimental protocol, and written informed consent was obtained from all subjects.

2.2. Task

In this experiment, participants performed a simple, two-alternative, forced-choice gambling task. In this task, subjects were asked to choose to play one of two lotteries: one variable lottery that was always presented, and a constant, or reference, lottery that was not presented. The construction of the stimuli was crucial so that the variable lottery varied in the amount of information, or ambiguity, it represented. First, each lottery circle was associated with an outcome (in this case, the amount of money that could be either won or lost) presented in the center of the circle. The probability of winning the specified amount of money was represented on the outer edge of the circle, which started at 0% in the 12 o'clock position and increased to 100% in a clockwise direction. A "dial" was then used to indicate a specific probability of winning the specified amount of money (Figure 1a); however, this dial was hidden from view on certain trials. The size of the occlusion hiding the dial varied in size to occlude 15%, 33%, 66%, 80% or 100% of the lottery circle (Figure 1b).

Subjects were told that although they could not see the dial, the dial was hidden somewhere inside the occlusion, thereby representing a range of probabilities. By occluding the actual probability of winning, information needed to calculate expected value was incomplete, introducing ambiguity, per the classical economic definition, to choice. This manipulation allowed us to have trials in which there was no ambiguity (risk) as well as trials in which there was full ambiguity within the same task, as in Hsu et al. (2005) and Huettel et al. (2006). More importantly, this allowed us to more carefully manipulate ambiguity and examine behavioral and neural responses to parametrically increasing levels of uncertainty.

Finally, the amount of money and probability of winning on the variable lottery was combined so that it varied in terms of expected value in relation to the constant lottery, which was 100% chance of winning $1.00 (EV = 1). On certain trials, the variable lottery was constructed in a manner where the expected value of the variable lottery was greater than the certain lottery, making these trials ambiguity advantageous (AA trials). These included: 33% chance of winning $5 and 50% chance of winning $3 (EV = 1.55). On specific trials, the certain lottery had a higher expected value than the variable lottery making these trials ambiguity disadvantageous (AD trials). These included: 20% chance of winning $3 and 33% chance of winning $2 (EV = .66). Finally, some trials were set up in a manner in which the expected value of the variable lottery matched the expected value of the constant lottery (EQ trials). These included: 20% chance of winning $5, 33% chance of winning $3, or 50% chance of winning $2. Including trials in which expected value was equal was a crucial part of this study, since they provide a quick, simple and objective measure of uncertainty sensitivity without explicitly modeling behavior. In this task, trials were balanced so that each manipulation of EV was equally represented: 1/3 trials AA, 1/3 trials AD and 1/3 trials EQ.

Subjects were compensated at a base rate of $25 USD/hour. Subjects were also given the opportunity to add to their total pay based on performance. Before the scanning session, subjects were asked to choose 12 numbers between 1 and 180 (the number of trials in the study, unbeknownst to the subject) and told that certain trials would be chosen at random to be played for real money. After the scan, subjects were informed that these numbers corresponded to a specific trial number, and they would receive the cumulative sum of their winnings from these trials as additional pay. Choosing a limited

number of trials to play for real money was necessary because playing each and every trial for real money would have become unfeasibly expensive. This payment mechanism ensured that subjects treated every trial as if they would be paid according to the outcome of that trial because they did not know they had already chosen in advance which trials would be real. Providing real monetary incentive was a key part of this study given evidence that shows subjects can behave differently when they are making real decisions for real money versus when they are making "as-if" decisions that have no financial impact on their lives (Smith & Walker, 1993).

For analysis, experimental trials were broken into conditions on the basis of ambiguity level of the variable lottery, yielding 6 conditions: 0% ambiguity (*a0*), 15% ambiguity (*a15*), 33% ambiguity (*a33*), 66% ambiguity (*a66*), 80% ambiguity (*a80*) and 100% ambiguity (*a100*). Each ambiguity condition was presented for 30 trials. Trials were also separated into conditions based on the expected value of the variable lottery in comparison to the constant lottery, yielding 3 conditions: ambiguity advantageous (*Adv*), ambiguity disadvantageous (*Disadv*) and neutral trials. Adding to these three conditions of EV, we further separated our data based on whether or not subjects chose to play the variable lottery (*Uncert*) or play the constant lottery (*Cert*) yielding 6 possible conditions: *Adv-Uncert, Adv-Cert, Neutral-Uncert, Neutral-Cert, Disadv-Uncert and Disadv-Cert*. Finally, we divided our data according to the outcome of the lottery so that we could compare trials in which subjects won or lost money, and then further subdivided the wins depending on the type of lottery the money came from to compare expected and unexpected wins.

2.3. Design

For this task, subjects performed 180 trials, divided evenly into 3 scans (60 trials per scan). In our pilot studies, we were able to obtain significant behavioral results with as little as 120 trials; however, we only included three ambiguity conditions for most of these pilot studies. On each trial, the variable lottery was presented for 5 s, during which participants were required to make a response whether they chose to play the displayed lottery, or if they wanted to play the certain (not shown) lottery. Following the response, there was a short, 1.5 s window before participants were given feedback as to the outcome of their choice (either winning or losing $2, $3, or $5 dollars) for 1.5 s. After feedback, a jittered inter-trial interval, ranging between 2 s and 10 s randomly sampled from a geometric distribution, was presented. This experiment used a rapid event-related fMRI design. Trials were arranged pseudo-randomly to control for any sequential effects, and 'null' jittered ITI provided a measure of baseline activation (Bandettini, 2007; Donaldson, 2004). All timing elements in this study summed up so that total trial length was limited to multiples of the TR, (i.e. 2 s, 4 s, etc), so as to keep trial onset synchronized with TR onset. In total, the task required approximately 40 minutes of scanning time.

In order to make the task fMRI compatible, visual stimuli were presented to participants using magnet-compatible goggles (Resonance Technology Inc., Los Angeles, CA). A computer running E-Prime experiment software (Psychology Software Tools Inc., Pittsburg, PA) was used to control stimulus presentation and interface with a magnet compatible response box. Earplugs were provided to protect the participants' hearing.

Head movement was minimized using a custom-fitted head holder, consisting of polyurethane foam beads inflated to tightly mold around the head and neck.

2.4. fMRI image acquisition

Images were obtained on a research-dedicated 3.0T whole-body MRI scanner (GE Healthcare, Milwaukee, WI) located on the campus of the University of Colorado Health Sciences Center, Aurora, CO. The scanner was equipped with an 8-channel, high-resolution phased array head coil using GE's Array Spatial Sensitivity Encoding Technique (ASSET) software. A trial scan of whole-brain EPI was acquired before the functional scans. Functional images were reconstructed from 31+5 axial oblique slices obtained using a T2*-weighted, volume-selective z-shim pulse sequence (TR, 2000 ms; TE, 26 ms; FA, 77°; FOV, 220-mm; 64*64 matrix; 4.0-mm slices; no inter-slice gap) adapted from the EPI-Gradient-Echo sequence. The z-shim pulse sequence was developed to address signal loss in neural regions adjacent to air cavities, such as the OFC. This protocol acquires additional volumes with a compensation gradient that are then combined with the original volume data to compensate for regions of signal dropout. Recently, Du and colleagues (2007) developed a sequence that minimized signal dropout in the OFC, in which the z-shim compensation is applied only to volumes that show significant signal loss, thereby substantially decreasing scanning time (Du, Dalwani, Wylie, Claus, & Tregellas, 2007). Echo-planar images from the initial trial scan were used to determine the number and location of the z-shim slices in which the OFC showed intermediate or severe SFG signal loss. Overall, five continuous slice locations were typically sufficient to cover the regions affected by the susceptibility artifacts.

Anatomical images were then collected using a T1-weighted SPGR sequence (minimal TR; TE, 3.95 ms; TI, 950 ms; FA, 10°; FOV, 220-mm; 256*256 coronal matrix; 166 1.2-mm slices). This set of structural images was used to verify proper slice selection and to determine the sites of functional activation, (i.e., voxels that were found to be significantly activated during the functional scan were overlaid on the high-resolution structural images). Finally, functional data from the inferior cerebellum was not collected because it was necessary to adjust slice acquisition angle and the field of view (FOV) to obtain the best possible signal-to-noise ratio in the frontal lobe.

2.5. fMRI Image Analysis

Before preprocessing, functional images with and without z-shim compensation were combined using MatLab (The Mathworks, Inc. Houston, TX) using a specially written z-shim toolbox. The intensity in the composite images was multiplied by a factor of 1.33 to reduce signal discontinuity between image sets (Du et al., 2007).

Image analysis was performed using BrainVoyager QX V1.10 (Brain Innovation, Maastricht, The Netherlands). Functional data was first subjected to preprocessing, consisting of 1) three dimensional motion correction using trilinear interpolation, 2) slice scan time correction using cubic spline interpolation, 3) temporal data filtering with a high-pass filter of 3 cycles in the time course and 4) linear trend removal. Each subject's high-resolution anatomical image was then normalized to the Tailarach & Tournoux (1998) brain template. The normalization process consisted of two steps: an initial rigid body translation into the AC-PC plane, followed by an elastic deformation into the standard space performed on 12 individual sub-volumes. The resulting set of

transformations was applied to the subject's functional image volumes to form volume time course representations to be used in subsequent statistical analyses. Finally, the volume time course representations were spatially smoothed using a Gaussian kernel, full-width at half maximum (FWHM) of 4.0 mm.

In order to identify brain regions that showed significant signal changes in response to a task demands, imaging data was analyzed using two main statistical methods. Although many techniques have been developed, most analysis approaches for fMRI have been integrated into the general linear model (GLM) framework (Friston, Frith, Frackowiak, & Turner, 1995). First, a whole brain analysis was performed to identify striatal and cortical regions involved in decision making under risk and ambiguity by separating trials into separate conditions based on level of ambiguity (risk (a0), partial ambiguity (a15, a33, a66, and a80), or complete ambiguity (a100)), and then using the general linear model (GLM) provided by Brain Voyager QX. In the GLM model, the amplitude for each time point of the BOLD response can be estimated, resulting in an approximation of the shape of the BOLD response for each event type. Additionally, we used parametrically weighted predictors to model the effects of ambiguity within the GLM (Buchel, Holmes, Rees, & Friston, 1998). We assigned weights to each ambiguity condition and then convolving the resulting boxcar functions with our BOLD data. Different functions were used to fit our data based on various levels of uncertainty. First, we fit a linear function that placed greater weight on higher levels of ambiguity, so that trials with zero ambiguity were associated with a weight of 0 and trials with full ambiguity were associated with a weight of 1. Additionally, we tested parabolic “inverted U” function that weighted intermediate levels of ambiguity greater.

Trials with zero and full ambiguity were assigned a weight of 0, trials with 15% ambiguity were assigned a weigh of .5. Trials with 33% and 66% ambiguity were assigned a weight of .9. Trials with 80% ambiguity were assigned a weight of .6, slightly higher than a15 trials. A weight of 1 was not used, as it would correspond to trials with 50% ambiguity not present in the study. Finally, for comparison purposes we tested functions in which predictor weights were chosen at random.

This study controlled for multiple comparisons using the cluster-size thresholding procedure developed by Forman et al. (1995) extended to 3D maps, and implemented in the Brain Voyager Cluster Threshold plug-in (Goebel, Esposito, & Formisano, 2006). An initial map was formed using an uncorrected p value of $p < .005$. The minimum cluster size (based on an alpha level of .05) was then set by MonteCarlo simulation using 1000 iterations, simulating the stochastic process of image generation. Afterwards, spatial correlations between neighboring voxels were calculated, before voxel intensity thresholds were finally calculated and the corrected map was formed and displayed.

CHAPTER 3 - RESULTS

3.1. Behavioral Results

In order to quantify behavior as a function of uncertainty, choices were defined in terms of the proportion of trials in which subjects chose to play the variable lottery, rather than defining behavior based on the outcome (as monetary gains or losses) of each trial. First, we separated trials according to expected value, in order to determine whether or not subjects could, in fact, determine a "good" lottery (advantageous trials in which EV > 1) from a "bad" lottery (disadvantageous trials in which EV < 1). A one-way analysis of variance (ANOVA) with factors of EV (Advantageous, Neutral and Disadvantageous) revealed a main effect of EV ($F_{(2,39)} = 15.56$; $p < 0.001$). As shown in Figure 2, post hoc tests using a Games-Howell correction revealed that subjects chose to play the variable (uncertain) lottery when its EV was greater than the constant lottery significantly more than when the variable lottery was equal in EV to the constant lottery ($p < .05$) or when the variable lottery was lower in EV compared to the safe lottery ($p < .05$). Additionally, our data show that when subjects decided to play the variable lottery, they did so significantly more when the variable lottery was equal in EV to the constant than when the variable lottery was lower in EV compared to the safe lottery ($p < .05$).

As shown in Figure 3, we also separated trials according to the amount of ambiguity indicated in the variable lottery in order to determine the effect of various amounts of ambiguity on choice behavior. A one-way ANOVA with ambiguity level as a

factor (0%, 15%, 33%, 66%, 80%, 100%) revealed no significant differences in choice behavior across the various different levels of ambiguity. A single sample t-test against .50 shows that overall, subjects showed avoidance of all types of uncertainty, regardless of whether it was risk or full ambiguity.

We then separated trials according to EV and level of ambiguity. A 3 (EV) x 6 (ambiguity level) repeated measures ANOVA showed a main effect of EV ($F_{(1.23,15.92)}$ = 48.82; $p < 0.001$) and a significant interaction of EV and level of ambiguity ($F_{(4.18,54.31)}$ = 13.50; $p < 0.001$). Maluchy's test indicated that the assumption of sphericity had been violated for EV, ambiguity and the EV by ambiguity interaction (chi-square = 12.03, 62.05, and 80.43 respectively), which required us to adjust degrees of freedom using a Greenhouse–Geisser estimate of sphericity (epsilon = 0.61, 0.41 and 0.42 respectively). Further analysis via a one-way ANOVA with ambiguity as a factor for advantageous trials revealed significant differences in responses associated with different levels of ambiguity ($F_{(5,78)}$ = 2.96; p = 0.02). As shown in Figure 4, post hoc tests using a Bonferroni correction showed that subjects chose the variable lottery significantly less in trials with 100% ambiguity compared to trials with 30% (p = .01) and 80% (p = .04) ambiguity. Similarly, a one-way ANOVA for disadvantageous trials using ambiguity as a factor also showed significant differences in choice behavior ($F_{(5,78)}$ = 6.43; $p < 0.001$). Although Levene's test indicated that variances were not homogeneous for this group, both Welch and Brown-Forsythe tests showed significant differences in responses across different ambiguity levels. Post hoc tests using a Games-Howell correction revealed that subjects chose the variable lottery significantly more in trials with 100% ambiguity

compared to trials with 0% or 15% ambiguity as shown in Figure 4. No significant differences were found for neutral trials when broken down by ambiguity levels.

Finally, we compared behavioral data from our pre-test session and the scanning session to determine whether or not choice behavior significantly differed between sessions. A 2 (session) X 6 (ambiguity level) repeated measures ANOVA showed a main effect of session ($F_{(1,13)} = 14.44$; $p = 0.002$), but no main effect of ambiguity or significant interaction. Additionally, a 2 (session) X 3 (expected value) repeated measures ANOVA showed a main effect of session ($F_{(1,13)} = 10.30$; $p = 0.007$), a main effect of EV ($F_{(1.36,17.64)} = 53.81$; $p < 0.001$), and no significant interaction. Again, Maluchy's test indicated that the assumption of sphericity had been violated for EV (chi-square = 7.72), so degrees of freedom were adjusted using a Greenhouse–Geisser estimate of sphericity (epsilon = 0.68). For both pre-testing and scanning sessions, post hoc tests using a Bonferroni correction revealed that when subjects chose the variable lottery, they did so significantly more in advantageous trials than neutral ($p < .05$) or disadvantageous trials($p < .05$), and selected the variable lottery more for neutral trials compared to disadvantageous trials ($p < .05$). Overall, these results suggest that subjects' choices were more conservative during the scanning session than they were during our pre-test session.

3.2. Functional, Whole-brain Analysis

3.2.1. Uncertain vs. Certain Choices

To examine the overall pattern of neural activity associated with uncertainty, we combined all trials in which subjects chose to play the variable lottery, regardless of

outcome and contrasted that against trials in which subjects chose to play the safe lottery (*Uncertain* > *Certain*). Using this contrast, we observed increased activity associated with uncertain choices bilaterally in the insula, superior parietal cortex, and DMPFC. We also observed increased activity in the right supplementary motor area and right frontal pole.

Furthermore, we decided to examine different types of uncertainty (risk or ambiguity) by comparing each type against all other trials. For example, we compared trials with very little to no uncertainty (a0 + a15) trials against all other levels of ambiguity (a33, a66, a80, a100). We found regions of increased modulation bilaterally in the putamen and insula and primary motor cortex, posterior parietal lobe and superior cuneus. Alternately, we compared trials with high levels of ambiguity (a80 + a100) with trials with low ambiguity (a0, a15, a33, a66) in an attempt to simulate previous studies' treatment of ambiguity as a complete lack of information. Here, we find increased activations associated with high levels of ambiguity bilaterally in the premotor cortex, left superior parietal cortex, including intraparietal sulcus, and left anterior cingulate gyrus. Additionally, we find bilateral modulation of activity in the amygdala as well as left parahippocampal gyrus. See Table 3 for a full list of activated regions. and Figure 5

3.2.3. Risk vs. Ambiguity

Next, we were interested in exploring differences in neural activity associated with specific types of uncertainty, categorically defined as risk or ambiguity in previous papers. First, we compared trials with 100% ambiguity (a100 trials) against trials with 0% ambiguity (a0 trials) resulting in our *a100* > *a0* contrast. Using this contrast, we

observed increased activity associated with high levels of ambiguity in the left DLPFC, right putamen, right head of the caudate, left intraparietal sulcus, and bilateral activation in the premotor. Additionally, we expanded this previous contrast to include more trials at either range of the uncertainty spectrum. We compared trials with high levels of ambiguity (a80 + a100) to trials with low levels of ambiguity (a0 + a15) resulting in our *a100 + a80 > a0 +a15* contrast. As shown in Figure 6, we observed clusters of increased activation associated with high ambiguity bilaterally in the putamen extending into the insula, DLPFC and both frontal poles. Overall, the pattern we found in both the *a100 >a0* and *a100 + a80 > a0 +a15* contrasts were similar, but the latter contrast resulted in more robust and symmetrical patterns of activity, likely due to the inclusion of a larger number of trials. See Table 4 for a full list of activated regions.

3.2.2. Wins vs. Losses

We examined the general pattern of activation associated with either winning or losing money. Here, our main contrast compared trials in which subjects gained money, regardless if they chose to play the uncertain or safe lottery, against trials in which subjects lost money. We observed increased activity bilaterally in the ventral striatum, as shown in Figure 7, hippocampus, superior temporal gyrus, posterior cingulate gyrus and cuneus, as well as right body of the caudate, left intraparietal sulcus, left orbitofrontal cortex and left DLPFC. Additionally, we found modulation of activity associated with losing money in the right insula, right frontal pole, right dorsomedial prefrontal cortex, and right middle temporal gyrus, right posterior parietal cortex and right inferior temporal gyrus.

Next, we looked more closely at wins, and separated them according to reward expectancy so that trials in which the outcome was uncertain (unexpected wins) were contrasted against trials in which the outcome was certain (expected wins). This contrast revealed that unexpected wins recruited many of the regions typically defined as the fronto-parietal decision-making network discussed in the first chapter, including intraparietal sulcus, posterior cingulate, superior colliculi, orbitofrontal cortex, DLPFC and primary motor cortex. Additionally, we observed increased activity in the putamen and body/tail of the caudate, left head of the caudate and bilateral insula. The only active region associated with expected feedback was the ventromedial prefrontal cortex/orbitofrontal cortex. Because this task did not allow for a condition in which the subjects were ever faced with a certain loss, we did not look at differences between expected and unexpected losses. See Table 5 for a full list of activated regions.

3.2.4. Expected Value

Like our behavioral analysis, we were interested in investigating neural responses associated with "good" versus "bad" responses. Thus, we separated trials according to our expected value manipulation. Here, we compared trials in which the expected value of the variable lottery was greater than that of the safe, or constant, lottery against trials in which the expected value of the variable lottery was lower than that of the constant lottery *(Adv > Disadv)*. We observed activation bilaterally in pre-motor cortex, superior parietal cortex, and insula. Additionally, we observed increased activity in the left DLPFC. Finally, we observed increased modulation in the left ventromedial prefrontal cortex associated with making disadvantageous choices.

Next, we compared types of trials according to EV and what type of lottery subjects chose to play. For example, we compared trials in which subjects chose the variable lottery over the constant lottery for only advantageous trials (*Uncertain Adv > Certain Adv*). Based on this contrast, we observed bilateral activation throughout the lateral orbitofrontal cortex, posterior cingulate and frontal poles, as shown in Figure 8a. Additionally, we observed increased activation in regions of the right DLPFC, right dorsal medial prefrontal cortex, right posterior parietal lobe, and left tail of the caudate. Increased activity associated with choosing the constant lottery for advantageous trials was observed bilaterally in the motor cortex, left hippocampus and right parahippocampal gyrus. Conversely, we also examined trials in which subjects chose the variable lottery over the constant lottery for only disadvantageous trials (*Uncertain Disadv > Certain Disadv*). Using this contrast, we observed increased activation throughout the anterior insula, frontal poles and posterior parietal cortex, as shown in Figure 8b. See Table 6 for a full list of activated regions.

3.3. Parametric Whole-Brain Analysis

Table 7 shows a complete list of activated regions associated with each parametric model.

3.3.1. Linear Scaling of Uncertainty

In our first parametric analysis, we used our original manipulation of ambiguity as a model in which greater weights were assigned to trials associated with high levels of ambiguity. In order to examine neural regions that are characterized with increased processing as uncertainty increases, risk trials (trials with no ambiguity) were not

weighted, whereas trials with complete ambiguity were given the maximum weight of one (Figure 9a). We observed regions of the anterior insula and DLPFC in both hemispheres that showed increased activation. Additionally, we found activity in the right putamen and head of the caudate, and left intraparietal sulcus, was consistent with this parametric manipulation.

3.3.2. Parabolic Scaling of Uncertainty

For this analysis, we based our parametric weighs on previous research suggesting that the frontal cortex should be more active for trials with intermediate levels of ambiguity (Bach et al., 2009). Here, we did not assign weights to either conditions of risk or complete ambiguity, but assigned increased weights to trials with intermediate levels of ambiguity instead. We found areas of increased activation that matched this function bilaterally in the DLPFC (Figure 9b), premotor cortex, intraparietal sulcus, posterior parietal cortex, and putamen. Additionally, we observed increased activity consistent with an inverted-U function in the left insula, and left body of the caudate.

3.3.3. Random Scaling of Uncertainty

Finally, we decided to examine if any neural region would show activity consistent with a function in which parametric weights were randomly assigned. Surprisingly, we found regions of increased activity bilaterally in the anterior putamen as well as a small region of modulated activity in the left primary motor strip.

CHAPTER 4 - DISCUSSION

4.1. Summary

The present study demonstrated changes in regional brain activation as a function of varying levels of uncertainty. First, we identified a set of brain regions that showed an increase in activation in response to increased uncertainty compared to situations of low uncertainty. We demonstrated that both risk and ambiguity modulate activation in a subset of regions generally activated by economic decision making: the DLPFC, IPS and anterior insula. More importantly, we demonstrated that ambiguity processing in regions of the prefrontal cortex does not necessarily scale linearly with the level of ambiguity, but rather the inherent difficulty of the decision. We found novel evidence to suggest that while activity in the DLPFC is sufficient for the successful processing of contextual information during uncertain decision making, recruitment of anterior regions of the prefrontal cortex is maximal during conditions of partial ambiguity. Finally, we showed that learning and valuation processes are modulated by expectancy and uncertainty; activity in regions related to the valuation of stimuli or options increased in situations where the decision making environment was uncertain.

4.1.1. Risk vs. Ambiguity

Although our study makes use of a novel paradigm to manipulate ambiguity, it is not unique in its aim of comparing different forms of uncertainty within a decision

making context. Previous research, ranging from behavioral economics to more recent cognitive neuroscience studies of decision making, has put forth the idea that risk and ambiguity are two distinct forms of uncertainty linked with activity in different regions of the brain. For example, a study conducted by Smith and colleagues (2002) explored brain activity as a function of making either ambiguous or risky decisions and found qualitative and quantitative differences between decisions made under risk and decisions made under ambiguity. Specifically, they found that the effects of monetary domain (either winning or losing money) modulated activity in the VMPFC more under risky conditions than under ambiguous conditions, and that these decisions made under risk do not recruit regions of the lateral frontal lobe active during ambiguous decisions (Smith et al., 2002). These results were important in the field of neuroeconomics for two main reasons. First, they served as evidence that the theories of rational decision making developed by behavioral economists could also be used to successfully predict brain activity along with behavior. More importantly, they provided solid evidence for Knight's (1921) theory of uncertainty, which proposed separate types of uncertainty.

Unfortunately, data from more recent studies do not match these previous results in which there is a marked difference in activation patterns across the brain for risk and ambiguity. For example, Huettel and colleagues (2006) conducted a study that manipulated both risk and ambiguity and compared these conditions against a control condition with no uncertainty. Here, Huettel and colleagues (2006) found that risk and ambiguity share many of the same neural substrates. However, they did find a notable difference between risk and ambiguity when they correlated individual measures of either risk or ambiguity preference with activity in several regions of interest throughout the

brain. In particular, Huettel and colleagues (2006) found that regions of the prefrontal cortex, DLPC (-41,18,26) especially, were highly correlated with ambiguity preference whereas regions of the posterior parietal cortex and IPS were instead correlated with individual risk preferences.

Similarly, our current data do not support previous conclusions that risk and ambiguity are two distinct processes mediated by separate and dissociable neural substrates. Overall, we reported a clear effect of uncertainty, where many regions previously associated with either risk or ambiguity were active for all levels of uncertainty. First, we observed this pattern when we simply compared all trials in which subjects chose to play the risky lottery over the safe lottery. Here we note that regions of the DLPFC, anterior insula and IPS were recruited for uncertainty processing in general. Second, we note that these regions remained significantly active when we individually compared either risk (0% ambiguity) against all other conditions or ambiguity (100% ambiguity) compared against other conditions. Finally, we observed that activity in regions such as the anterior insula and DLPFC remained elevated when lotteries associated with high levels of uncertainty were directly compared to trials in which lotteries had little or no uncertainty. Together, these results suggest that there is a general network for uncertainty processing, and risk or ambiguity are treated as a single type of uncertainty along one continuum.

Although we observed a different pattern of activation in these regions compared to Hsu et al (2005) and Huettel et al. (2006), it is important to note that our study was not focused on correlating specific behavioral measures of uncertainty preference with neural activation, but rather to observe potential changes in neural activation as a function of

increased uncertainty in a simple decision making task. Given our particular paradigm, it was difficult to directly infer participants' attitudes towards risk and ambiguity as parameters derived from formalized neuroeconomic models that incorporate individual risk and ambiguity preferences. That said, our results do not offer contradictory evidence, but rather complement these earlier studies by supplementing information regarding choice behavior in states of partial uncertainty. We fully acknowledge that provided more sophisticated measures of individual risk or ambiguity preference like the ones used in these studies, it is possible that more nuanced effects could be identified.

4.1.2. Ambiguity and the DLPFC

Our manipulation of ambiguity allowed us to more carefully explore neural responses to varying levels of uncertainty ranging from risk to ambiguity. One of our hypotheses was that specific regions of the lateral prefrontal cortex are not necessarily involved in uncertainty processing or ambiguity detection, but rather mediate a search for contextual information in environments where information regarding outcome probability is degraded, which describes making decisions under states of uncertainty.

First, we regressed our BOLD data against a function in which ambiguity processing was assumed to increase in a linear fashion in order to explore if any cortical regions behaved in this manner, and found that the activity in a specific region of the DLPFC conformed to this model. This was the same region we found to be active for uncertainty processing in general, and the same region, the inferior posterior frontal gyrus, other studies have previously associated with ambiguity processing (Bach et al., 2009; Huettel et al., 2006). This result is certainly consistent with studies suggesting that

cognitive processes related to ambiguity or uncertainty processing increase linearly. However, we also regressed BOLD data against a model that put a greater emphasis on intermediate levels of ambiguity, as proposed by Bach and colleagues (2009), and found that not only were the same regions of DLPFC active under this kind of model, but that regions of the posterior parietal cortex, premotor cortex and anterior prefrontal cortex were also active. This pattern of results is consistent with claims that activity associated with ambiguity processing in the DLPFC is greater only for intermediate levels of uncertainty.

The prefrontal cortex has long been associated with executive functions such as planning (Lee et al., 2007; Tanji et al., 2007; Sakagami and Watanabe, 2007), abstract reasoning, working memory and cognitive control. Because of this wide range of functions attributed to the prefrontal cortex, it is understandable that this functional heterogeneity is reflected in the architecture of the prefrontal cortex. One popular framework of frontal lobe function suggests that the prefrontal cortex is organized in a hierarchical manner in which different regions support various aspects of cognitive control (Koechlin & Summerfield, 2007). In this framework illustrated in Figure 11, contextual control (maintenance of task rules and structure) is associated with posterior regions, whereas episodic control (maintenance of information in a temporal domain) is associated with activity in more anterior regions. In other words, as task demands increase or tasks become more complex, regions of the prefrontal cortex can be recruited in a posterior to anterior fashion to provide the necessary neural processing. For example, Koechlin and colleagues compared task cuing, which was presumed to be primarily contextual, and response cuing, which was presumed to be primarily episodic

(Koechlin et al., 2003). Activation to the contextual cuing was observed in posterior lateral prefrontal cortex. Similarly, Brass and von Cramon (2004), investigated regions of the PFC necessary for contextual processing and found activation in the lateral parts of the prefrontal cortex. Together, these results suggest that specific portions of the prefrontal cortex play a particularly important role in assessing the context for decision making.

Like the anterior to posterior functional gradient previously discussed, there is also a reported superior to inferior division of labor within the prefrontal cortex, where the ventral area is more involved in processing specific, object-related information, while the dorsal prefrontal cortex is involved in more general functions of monitoring strategic behavior. This puts the DLPFC in prime position to mediate contextual processing across a wide variety of situations. Indeed, research suggest that this region of the PFC is involved in maintaining representations of learning across various states, a.k.a. context in both humans and animals (Sakagami & Watanabe, 2007; Tanji et al., 2007). Moreover, if we are to assume hierarchical processing in the prefrontal cortex, as in Koechlin and Summerfield's (2007) cascade model, then simple S-R associations can be mediated by just premotor regions of the prefrontal cortex, whereas ambiguous/conflicting information, requiring additional processing, recruits more anterior regions of the frontal lobes. In ambiguous economic decisions, it can be argued that there is an increased search for contextual cues (probability of reward, in this case) to aid in making a final choice.

Given these functional divisions, activity in the DLPFC reported by both Bach et al. (2009) and Huettel et al. (2006) may represent an increased search for contextual cues

that requires greater cortical involvement than just sensorimotor cortex activation. Our results are consistent with Bach and colleagues' (2009) interpretation of DLPFC function in decision making tasks involving varying levels of uncertainty, which suggests that the DLPFC mediates a search for context when faced with uncertainty. Additionally, this view states that neural computational demands change as a function of the level of ambiguity, with greater activity being associated with situations involving intermediate ambiguity when compared to situations with no ambiguity (risk) or full ambiguity (ignorance). This is precisely what our parametrically weighted data suggest, as we observed that using a more "complex" function that places a greater demand on ambiguity processing for intermediate levels of ambiguity results in activity in more anterior regions of the prefrontal cortex along with the DLPFC. Similarly, our results using a more "simple" linear function also elicited activity in the DLPFC, suggesting that DLPFC function alone can resolve can resolve comparatively easy decisions without the need to recruit more anterior regions of the PFC. Thus, we can explain the increased activity in the DLPFC reported by both Huettel and colleagues (2006) and Hsu and colleagues (2005), as their tasks used a relatively simple "all or none" manipulation of ambiguity that did not require additional processing from regions of the prefrontal cortex associated with cognitive control.

Overall, our findings of ambiguity processing in the DLPFC make an important addition to the existing literature investigating uncertainty and decision making. Previous studies have provided differing accounts regarding ambiguity processing in the DLPFC. Whereas studies such as Huettel and colleagues (2006) and Hsu and colleagues (2005) have advanced the notion that activity in the DLPFC increases linearly as a function of

ambiguity, other studies such as Bach and colleagues (2009; 2001) propose that activity in the DLPFC is greatest when ambiguity is intermediate. Although we certainly observed lateral regions of the prefrontal cortex were implicated in uncertainty processing as discussed above, we also observed specific regions in the frontal cortex exhibit a greater response in situations of partial ambiguity that leads us to believe that areas of the lateral prefrontal cortex are involved in the search for meaningful information. Figure 10 sums up results across three different studies showing ambiguity-related processing in the brain compared to risk-related processing, and shows that when we discuss ambiguity processing in the prefrontal cortex, we are talking about the same specific region.

However, our results provide direct support for Bach and colleagues (2009) who argue that the functional pattern associated with an "inverted U" function reflects not just the search for information (context), but rather a search for *useful* information which is best represented in trials that contain only intermediate levels of ambiguity. For risky decisions (decisions with no ambiguity), it can be argued that one does not need to search for context, as all necessary information regarding possible outcomes is readily available. Conversely, it may be inefficient to search for context during fully ambiguous decisions given the complete lack of information regarding possible outcomes, which is nearly impossible. It is only during situations involving partial ambiguity where it is beneficial to try to maximize utility, which can be done by evaluating what Huettel and colleagues (2006) call the "multiplicity of all possible interpretations" for each option. This requires not only contextual control, as one integrates various decision variables from the current stimulus, but also episodic control, as one integrates outcomes for previous decisions.

Again, our results showing greater recruitment of anterior regions of the frontal cortex given an inverted-U function are consistent with this notion. Moreover, this interpretation of DLPFC function accounts for results in previous studies showing activity in the posterior inferior frontal gyrus during outcome prediction when contextual cues implied uncertainty in both economic (Li et al., 2006) and non-economic tasks (Huettel et al., 2005).

4.1.3. Ambiguity and the Insula

Previous neuroimaging studies have found that the anterior insula is recruited for decision making under conditions of uncertainty, including both risk and ambiguity (Huettel et al., 2005; Kuhnen & Knutson, 2005; Paulus et al., 2003; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). First, we considered the possibility that the insula is in fact associated with uncertainty processing in decision making. Our results show significantly elevated levels of insula activity for trials in which there was high levels of uncertainty. Specifically, our contrasts comparing risk versus ambiguity (*a100 > a0*, and *a100+a80 > a0 + a15*) show high levels of insula activity. Additionally, we observed bilateral insula activation when we collapsed trials across all levels of uncertainty and compared trials in which subjects chose to play the variable lottery versus the constant lottery. This pattern of results matches that found by Paulus and colleagues (2003) who also found increased activity in the anterior insula when subjects chose to place safe bets as opposed to risky ones. Finally, we found insula activity in our parametric analysis using a linear function.

Increased insula activation during risk-taking decision making is consistent with the function of the insula in linking cognitive and affective components (Sawamoto et al., 2000). Anatomical studies in rhesus monkeys show that the insula receives input from both dorsolateral prefrontal and posterior parietal cortex (Selemon & Goldman-Rakic, 1988), regions highly linked with decision making processes. In particular, the anterior part of the posterior parietal lobe, including the IPS, sends efferent projections to the insula (Cavada & Goldman-Rakic, 1989a). Moreover, tracing studies in animals show that the insula also receives projections from the amygdala (McDonald, Shammah-Lagnado, Shi, & Davis, 1999). Therefore, it is understandable that we observed activity in the insula as well as DLPFC associated with high levels of ambiguity.

However, there is also the possibility that the insula activity that we observed was not associated with uncertainty, but rather other cognitive processes linked to the processing of aversive situations. First, we noted more pronounced activation in the insula for trials associated with uncertainty; the insula was more active in trials in which subjects chose to play the uncertain lottery than in trials in which subjects chose to play the safe lottery. Second, we observed increased activity in the anterior insula in situations in which subjects lost money; however, the anterior insula was also active in trials where the win was unexpected. That is, we observed increased insular activity for trials in which subjects chose to play the uncertain lottery and won compared to trials in which subjects chose to play the certain lottery and, of course, received a reward. Finally, we observed robust insula activity when we compared trials in which it was advantageous to play the variable lottery against trials in which it was advantageous to play the safe lottery. These lines of evidence, as well as our previous observation that

activity in the anterior insula is present as uncertainty increases, seems to suggest that activity in the anterior insula may not reflect uncertainty processing or other similar decision making variable. Rather, insular activation is modulated by the potential of negative or adverse outcomes, such as not being able to predict whether a future outcome will be rewarding or punishing, as observed for unexpected wins, or being able to recognize bad decisions, as observed for variable lotteries with low EV.

Insula activation occurs in a wide variety of task conditions. There is, however, an emerging consensus that insula activation is frequently associated with reactions to aversive stimuli or situations. Previous neuroimaging studies have shown increased insula activation during the processing of stimuli associated with negative affective properties such as fear (Morris et al., 1998) or disgust (Phillips et al., 1998). Additionally, studies show increased insula activity when anticipating physical distress, via an electric shock (Chua, Krams, Toni, Passingham, & Dolan, 1999; Ploghaus et al., 2001; Sawamoto et al., 2000), as well emotional distress (Liotti et al., 2000). In fact, insula activation appears to be critical for linking cognitive and affective processing. For example, both aversive pavlovian conditioning (Buchel, Morris, Dolan, & Friston, 1998) and aversive trace conditioning (Buchel, Dolan, Armony, & Friston, 1999) were associated with increased insula activation. Moreover, insula activity was modulated by perceptual awareness of threat (Critchley, Mathias, & Dolan, 2002), penalty (Elliott, Friston, & Dolan, 2000), or error-related processes (Menon, Adleman, White, Glover, & Reiss, 2001). Finally, previous research links insula activation to adverse environmental stimuli (Becerra et al., 1999; Davis, 2000; Tracey et al., 2000).

4.1.4. Expected Value

Along with our behavioral data that show subjects were successfully able to distinguish good lotteries from bad ones based on our simple manipulation of EV, we found several regions across the brain that exhibited value-related activity. These regions included regions of both ventral medial prefrontal cortex (particularly the medial and lateral parts of the orbitofrontal cortex comprised of BAs 11 and 32) and dorsal medial prefrontal cortex (specifically BAs 8 and 24), striatum and posterior parietal cortex (BA 7) that were active when we compared brain activity on trials with high EV against trials with low EV. In other words, these regions were found to be more active when subjects were presented with a "good" lottery. Additionally, we found increased activity in the ventral striatum as a function of winning money, regardless of uncertainty. Together, these findings suggest that subjects were able to track the current rewards, but also predict rewarding outcomes. These results are compatible with findings from human and primate studies that find value-related regions throughout the brain, which we will discuss separately. One limitation that we faced was caused by the fact that exploring neural responses to changes in EV was a secondary aim of the study. As a result, the number and composition of trials were not ideal to investigate neural responses to EV as a function of increasing ambiguity. Separating trials so that we could look at both EV and ambiguity would have resulted in too few trials and not enough statistical power to tease apart more nuanced effects.

4.1.4a. Value-Related Signals in the Striatum

Most notably, we observed value-related activity in the ventral striatum when we divided trials according to outcome. As expected, we saw increased activity in the ventral striatum when subjects received a reward, as activity in this region has been shown to be crucial for reward-mediated learning. Additionally, we observed a robust response in the ventral striatum when we separated trials in which subjects won money depending on whether the win was unexpected (the outcome of playing a variable lottery) or fully expected (the result of playing a certain lottery). Together our results match results from both animals and humans showing the striatum's role in reward-guided learning.

Activity in the striatum has been linked to the anticipation of reward in studies in which the anticipatory phase and delivery of reward were carefully analyzed (McClure, Laibson, Loewenstein, & Cohen, 2004; J. P. O'Doherty, Deichmann, Critchley, & Dolan, 2002). This anticipatory signal in the striatum is modulated by various factors such as amount (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Delgado et al., 2003), probability (Hsu, Krajbich, Zhao, & Camerer, 2009) and expected value of the predicted outcome (Hsu et al., 2005; Luhmann, Chun, Yi, Lee, & Wang, 2008; Preuschoff et al., 2006; Tobler et al., 2007; Tom et al., 2007). More importantly, activity in the striatum has been shown to be correlated with behavioral preferences across different domains, similar to the activity of certain populations of orbitofrontal cortex (OFC) neurons thought to code for value or utility (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007; J. P. O'Doherty, Buchanan, Seymour, & Dolan, 2006; Small et al., 2003). Finally, it should be noted that although regions of the striatum can signal a predicted reward, other regions of the striatum are also able to respond to both immediate (McClure,

Laibson et al., 2004) as well as delayed rewards, implying that this region is necessary for temporal discounting of reward value (Kable & Glimcher, 2007; McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007).

4.1.4b. Valuation and the Medial Prefrontal Cortex

Like the striatum, we also observed increased activity in dorsal portions of the medial prefrontal cortex when subjects' choices resulted in wins. The dorsal medial prefrontal cortex is thought to have similar value-related functions similar to those observed in ventral regions of the striatum. Studies have shown that the dorsal medial prefrontal cortex can track both receipt of current reward as well as expected reward (Knutson, Fong et al., 2001; Knutson et al., 2003; Kuhnen & Knutson, 2005). Moreover, studies show that activity in regions of the dorsal medial prefrontal cortex is modulated by the level of EV of the expected reward (Knutson et al., 2005; Luk & Wallis, 2009). Activity in the dorsal medial prefrontal cortex is also correlated with behavioral preferences, reflecting each individual's valuation of different options (Hare et al., 2009; McClure, Li et al., 2004). Like the striatum, it should be noted that recent studies have also reported overlapping representations of both action and stimulus values in the dorsal medial prefrontal cortex (Chib, Rangel, Shimojo, & O'Doherty, 2009; Glascher, Hampton, & O'Doherty, 2009).

Further ventrally along the medial prefrontal cortex, one important finding was that although we observed increased activity in the orbitofrontal cortex as a result of receiving a reward, we did not observe any activity associated with valuation in the orbitofrontal cortex, as predicted, when we compared all trials with high EV against trials

with low EV. As discussed previously, the orbitofrontal cortex is one region of the brain whose function is highly linked to the valuation of stimuli in decision making contexts in both humans and primates (Paddoa-Schioppa & Assad, 2008; 2009). Neurons in the orbitofrontal cortex have been shown to reflect subjects' willingness to pay to consume presented goods (FitzGerald, Seymour, & Dolan, 2009; Plassman et al., 2007) as well as self-reported experiences of pleasantness (Plassman, 2008). Thus, we expected to find increased activity throughout the orbitofrontal cortex for trials in which subjects were presented with a variable lottery of high EV like we did in the striatum and MPFC.

Instead we found activation in the OFC when we separated trials not only according to EV, but also according to subjects' choice; trials were separated based on whether subjects chose to play the variable lottery (uncertain) versus the constant lottery (certain). First, we compared trials in which the variable lottery had a greater EV than the constant lottery and found increased OFC activity for trials in which subjects chose to play the variable lottery over the safe lottery. Additionally, we found OFC activity associated with playing the variable lottery even when its EV was lower than the constant lottery.

One factor to consider is that this task was not novel to subjects by the time they entered the scanner, unlike other studies looking at value and uncertainty in decision making tasks. It is possible that subjects previously developed general representations of what an advantageous lottery was versus a disadvantageous one based on value and preference, and only had to refine these representations once in the scanner. Further support for this claim comes from our observation of activity in regions of the parietal cortex that are also linked to value-based decision making, such as the posterior parietal

cortex and posterior cingulate gyrus. Thus, we argue here that activity in the orbitofrontal cortex was likely modulated by a process of valuation that is more likely to occur when under states of uncertainty, as subjects must constantly try to assign value with only partial information regarding reward. This explanation would account for why we did not observe orbitofrontal cortex activity associated with playing the safe lottery, as this option was always available to be previously valued.

4.1.4c. Valuation in the Parietal Cortex

One region we found to be active when we contrasted trials with high EV and Trials with low EV was the intraparietal sulcus (BA 7). Furthermore, we found evidence of valuation processes in the parietal cortex when trials were separated based on whether subjects chose to play the variable lottery (uncertain) versus the constant lottery (certain). As stated earlier, evidence suggests that the abstract value of goods is computed and/or represented in regions of the orbitofrontal cortex (J. P. O'Doherty, 2004; Padoa-Schioppa & Assad, 2006, 2008; Wallis & Miller, 2003) and that regions of the parietal cortex, specifically LIP in monkeys and intraparietal sulcus in humans, use value representations calculated in the orbitofrontal cortex to drive choice selection (Astafiev et al., 2003; Dorris & Glimcher, 2004; Heekeren et al., 2006; Platt & Glimcher, 1999).

Along with activity in the posterior regions of the lateral parietal lobe, we found increased activity in a region we did not predict to reflect value-related signals: the posterior cingulate (BAs 23 and 31). Evidence suggests that the posterior cingulate is crucial for linking value representations to events and actions to adaptively influence behavior. The posterior cingulate is interconnected with brain areas known to be

involved in learning and motivation or that are sensitive to reward and reinforcement such as the thalamus (Gabriel, Vogt, Kubota, Poremba, & Kang, 1991), caudate (Baleydier & Mauguiere, 1980; Yeterian & Van Hoesen, 1978) and orbitofrontal cortex (Baleydier & Mauguiere, 1980). Additionally, the posterior cingulate is connected to the anterior cingulate, which is thought to also play a role in reward-mediated learning (Ito, Stuphorn, Brown, & Schall, 2003; Niki & Watanabe, 1979; Shidara & Richmond, 2002). Finally, given its anatomical location, the posterior cingulate gyrus also receives input from areas involved in vision, action and attention from the parietal cortex (Andersen, Asanuma, Essick, & Siegel, 1990; Baleydier & Mauguiere, 1980; Blatt, Andersen, & Stoner, 1990; Cavada & Goldman-Rakic, 1989a, 1989b; Morecraft, Geula, & Mesulam, 1993; Pandya, Van Hoesen, & Mesulam, 1981; Vogt & Pandya, 1987), DLPFC (Barbas & Mesulam, 1985; Barbas & Pandya, 1989; Selemon & Goldman-Rakic, 1988), and frontal eye fields (Barbas & Mesulam, 1981; Vogt & Pandya, 1987). Indeed, studies show activity in the posterior cingulate is linked to both attention processes as well as motivational ones in decision making tasks, suggesting that the posterior cingulate carries information that could be used to link events and outcomes in a context-dependent fashion (Dean, Crowley, & Platt, 2004; McCoy, Crowley, Haghighian, Dean, & Platt, 2003).

4.1.4d. EV and Learning

Finally, our analysis of EV according to choice revealed increased activation across a series of regions sensitive to maximum choice probability such as the putamen and the caudate nucleus. First, this pattern of activation fits with studies showing that the

putamen and premotor cortex are activated specifically during action selection (Gerardin et al., 2004) and are involved in linking stimulus-action associations (Ashby, Turner, & Horvitz, 2010; Daniel & Pollmann, 2010; Seger, Peterson, Cincotta, Lopez-Paniagua, & Anderson, 2010). Studies in non-human primates have suggested that neurons in this area are intimately involved in linking reward and motor behavior (Ikeda & Hikosaka, 2003; Kawagoe, Takikawa, & Hikosaka, 1998; Kobayashi et al., 2007; Lauwereyns, Watanabe, Coe, & Hikosaka, 2002). Additionally, lines of evidence suggest that the anterior caudate nucleus is involved in acquiring and updating S-R associations that lead to reward (J. O'Doherty et al., 2004; Seger et al., 2010; Tricomi, Delgado, & Fiez, 2004) via interactions with cortical reward centers (Knutson et al., 2003; Kringelbach, 2004). Moreover, activity in regions of the posterior caudate has been linked with successful learning of probabilistic reward-outcome associations (Foerde, Knowlton, & Poldrack, 2006; Nomura et al., 2007; Seger & Cincotta, 2005, 2006).

This pattern of activation makes intuitive sense in terms of corticostriatal interaction: the anterior caudate nucleus is thought to be strongly connected to anterior regions of the prefrontal cortex while the putamen is thought to be linked to premotor regions of the prefrontal cortex, and function in the posterior caudate is connected to the temporal and occipital lobes(Alexander, Crutcher, & DeLong, 1990; Haber, Fudge, & McFarland, 2000; Haber, Kim, Mailly, & Calzavara, 2006; Lawrence, Sahakian, & Robbins, 1998; Seger, 2008). Our results suggest that while subjects were assigning value to various lotteries, they were also attempting to learn the most rewarding stimulus-response-outcome associations in a probabilistic learning environment. This is important

for understanding our pattern of results and potentially explains why we did not see striatal activity for trials associated with deterministic and certain choices.

4.2. Conclusions

Throughout our lives we make decisions ranging from seemingly simple to complex, such as which mode of transportation to take to work or deciding whether to pursue a career in academia or industry. A common problem we face in most decisions is uncertainty, which economic decision theory classifies as either "risky," in which outcomes are uncertain but their probabilities are known, or "ambiguous," in which the probabilities of uncertain outcomes are unknown. Understanding how the brain processes various neural representations of uncertainty, especially ambiguity, is one of the central motivating problems of the emerging discipline of neuroeconomics (Glimcher and Rustichini, 2004).

Defining what is meant by "ambiguity" has been, and remains, a challenge for economic theorists and neuroeconomists because no two individuals necessarily perceive the same ambiguity in a decision problem (Ghirardato et al., 2004). Whereas risk can be defined in terms of certainty equivalents and expected values, there is no analog in ambiguous choice. In previous studies attempting to dissociate risk from ambiguity, ambiguity was defined differently: in the ambiguous condition designed by Hsu et al. (2005) and Huettel et al. (2006) the probabilities were completely hidden and thus unknowable. More recently, Bach and colleagues introduced a task with three uncertainty conditions: risk, ambiguity, and ignorance, where the ignorance condition was directly comparable to the ambiguity manipulation used by Hsu et al. (2005) and

Huettel et al. (2006) and the ambiguity condition represented a form of uncertainty between risk and full ambiguity. Unfortunately, the Bach and colleagues (2009) study does not allow for the study of choice behavior, as it opted to use classical conditioning to train subjects.

The present study provided a novel paradigm designed to address how decisions are made under varying states of uncertainty, ranging from risk to ambiguity. More important, the present study was designed to address limitations of previous studies looking at decision making under uncertainty: explore neural regions sensitive to hidden but searchable information by parametrically controlling the amount of information hidden from the subject by using different levels of ambiguity manipulations instead of just the one, as used in previous studies (Bach et al., 2009; Hsu et al., 2005; Huettel et al, 2006), and allowed subjects to freely choose the best option. Although our results do not support the existence of a distinct cognitive process for ambiguity, we cannot make a positive and definitive statement about what processes together constitute decision making under ambiguity. Here, we show that both risk and ambiguity share a common network devoted to uncertainty processing in general. Moreover, we found support for the hypothesis that regions of the DLPFC might subserve contextual analysis when search of hidden information is both necessary and meaningful in order to optimize behavior in a decision making task; activation in the DLPFC peaked when the degraded information could be resolved by additional cognitive processing.

Our results help to underscore the importance of studying varying degrees of uncertainty, as we found evidence for different neural responses for intermediate and high levels of ambiguity that are easy to ignore depending on how ambiguity is defined.

Additionally, our results help reconcile two seemingly incompatible accounts of brain activity during ambiguous decision making, one suggesting that uncertainty increases linearly and another suggesting ambiguity processing is greater at intermediate levels. The graded coding of uncertainty we reported may reflect a unified neural treatment of risk and ambiguity as limiting cases of a general system evaluating uncertainty mediated by the DLPFC which then recruits different regions of the prefrontal cortex as well as other valuation and learning systems according to the inherent difficulty of a decision.

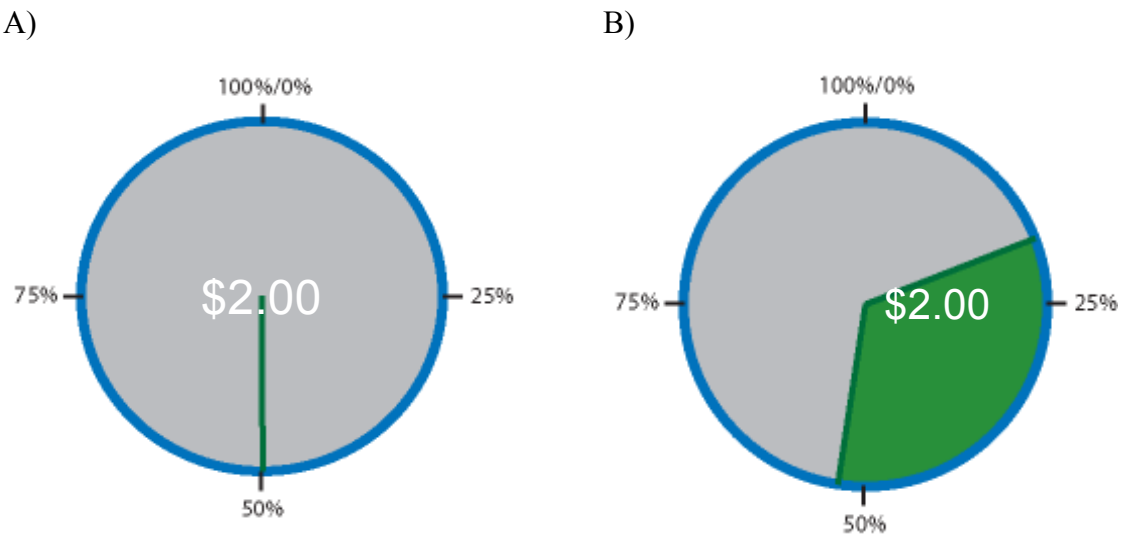

Figure 1. Examples of the stimuli presented to subjects. A) Risky lottery (a0) showing a dial pointing to a specific probability of obtaining the sum of money in the center of the circle, and should be interpreted as 50% chance of winning $2.00. B) Here, we show a partially ambiguous lottery (a33). Subjects are told that the dial is hidden within the green field, suggesting a range of outcome probabilities.

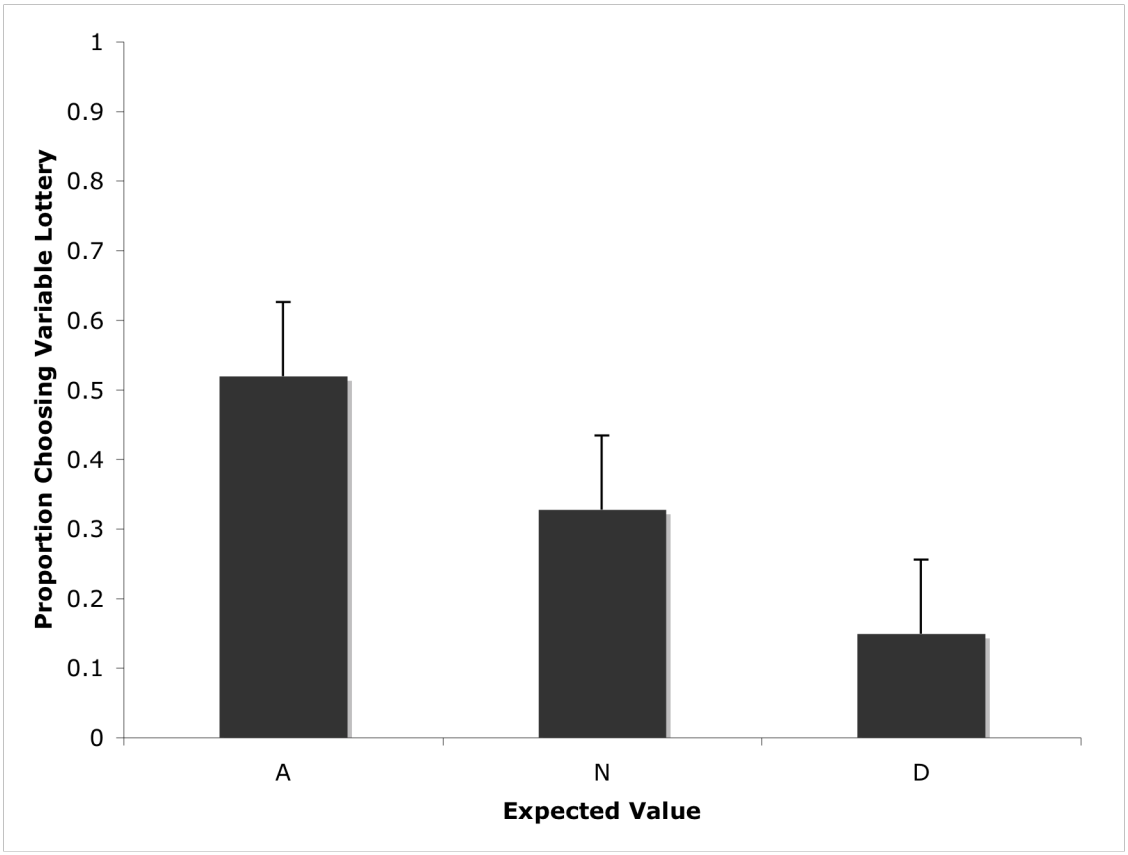

Figure 2. Behavioral data showing the proportion of ambiguous lotteries chosen according to expected value (EV). Our data suggests that subjects successfully learned to distinguish "good" from "bad" lotteries using EV for choice evaluation. Subjects played the variable lottery significantly more when its EV was higher than the constant lottery. Conversely, subjects chose to play the constant lottery significantly more when the variable lottery was associated with low EV.

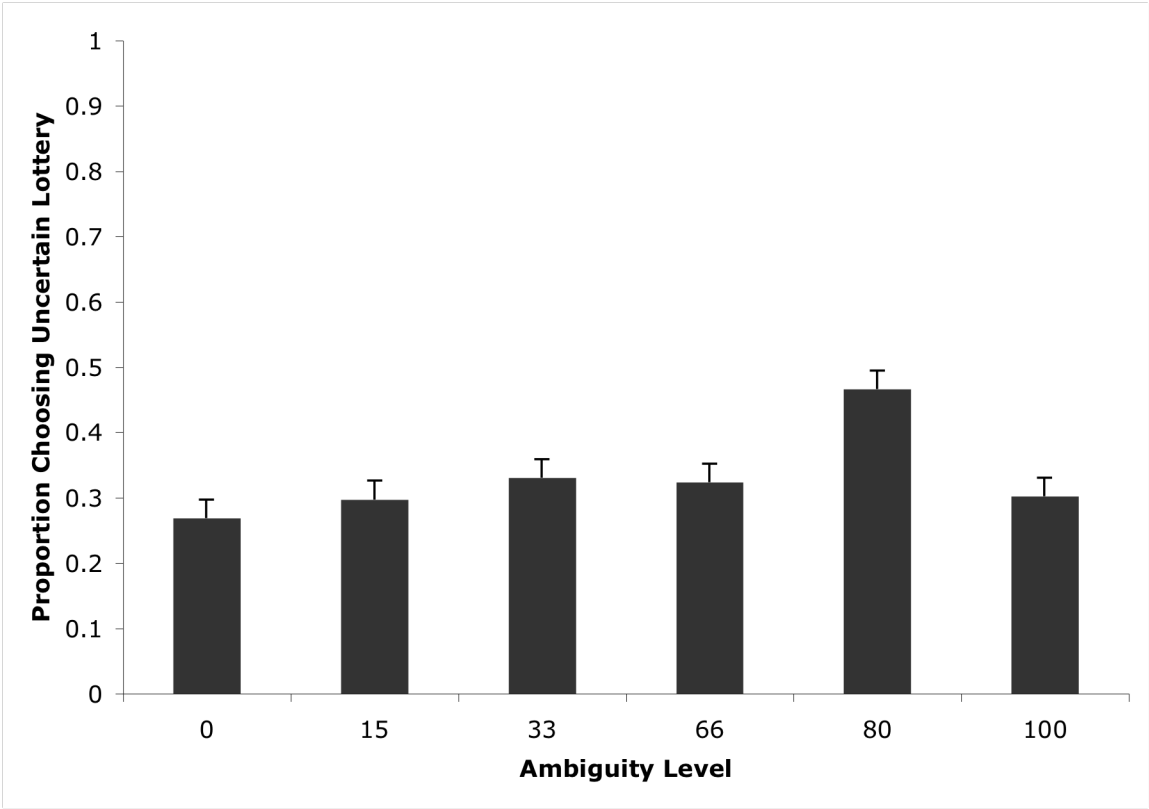

Figure 3. Subjects' behavioral preferences of playing the variable lottery across different levels of ambiguity. Although we found no statistical differences in ambiguity aversion across our various manipulations of ambiguity, a one-sample *t*-test against chance (.5) reveals that subjects significantly preferred constant lotteries when compared to uncertain ones.

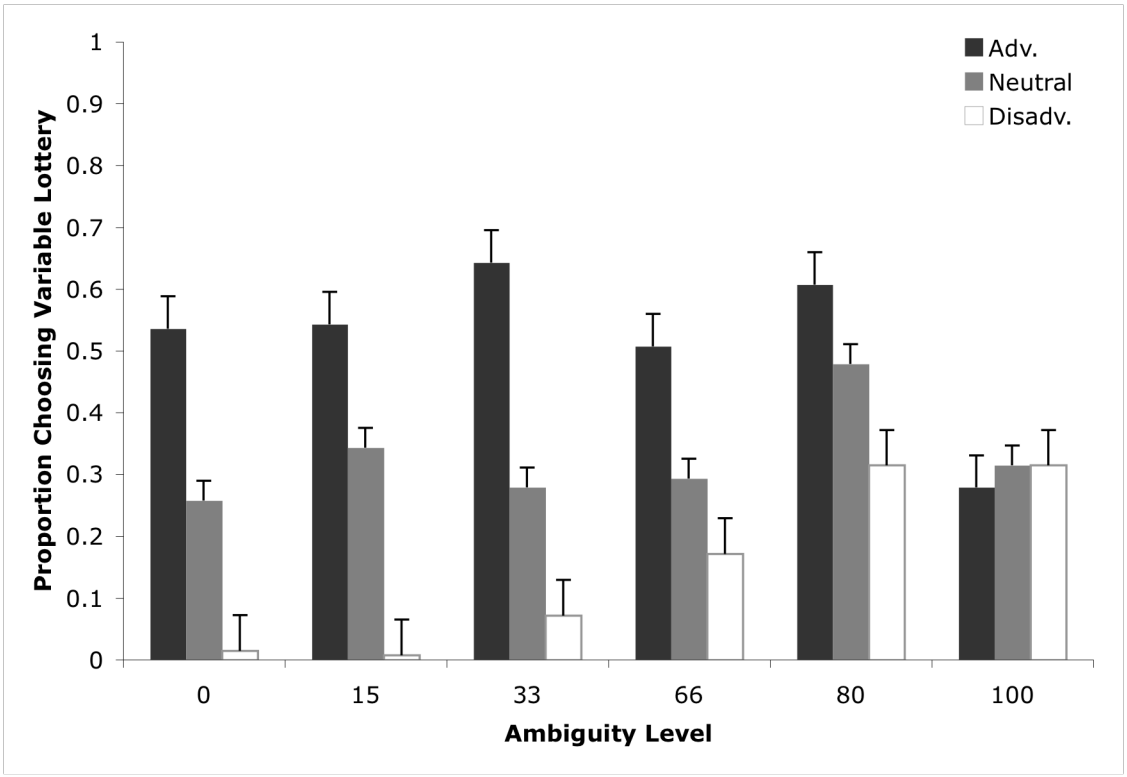

Figure 4. For trials in which it was advantageous to play the variable lottery, subjects demonstrated ambiguity aversion as ambiguity increases. For trials in which it was disadvantageous to play the variable lottery, subjects showed an increase in ambiguity preference likely caused by the difficulty of distinguishing "good" from "bad" lotteries. For neutral trials, subjects showed ambiguity aversion for the risky option throughout the length of the task.

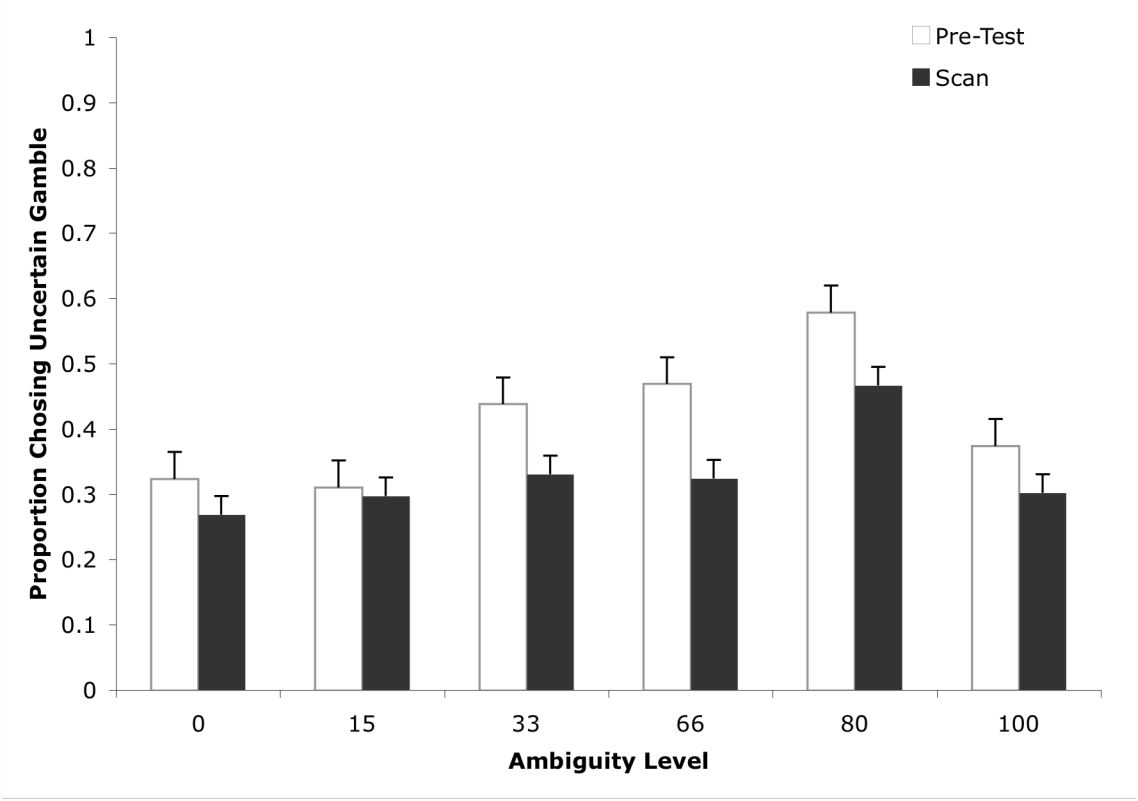

Figure 5. Behavioral preferences of playing the variable lottery with different levels of ambiguity across two sessions. Subjects demonstrated significant aversion to uncertainty during the scanning session for all manipulations of ambiguity.

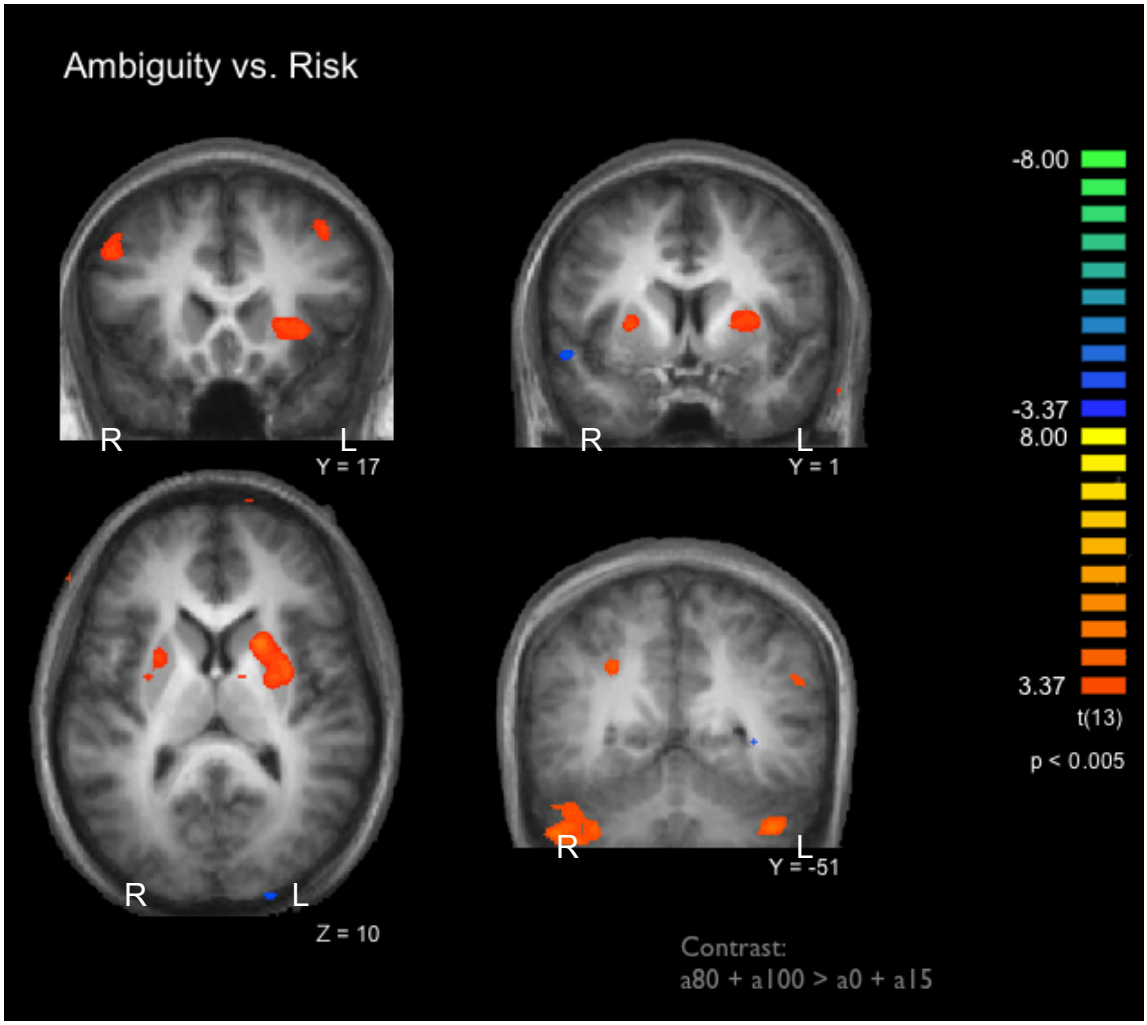

Figure 6. Comparison of BOLD responses associated with ambiguous decisions compared to risky decisions. Functional maps are overlaid on a T1-weighted average of all 14 participants' anatomicals. Cluster size threshold based on uncorrected voxelwise $p < 0.005$ and cluster size alpha < 0.05 as indicated in the methods section. Upper left panel shows bilateral activation of the DLPFC and insula. Both top right and bottom left panels show bilateral putamen activation. Finally, bottom right panel shows bilateral activation of the parietal lobe, including right intraparietal sulcus.

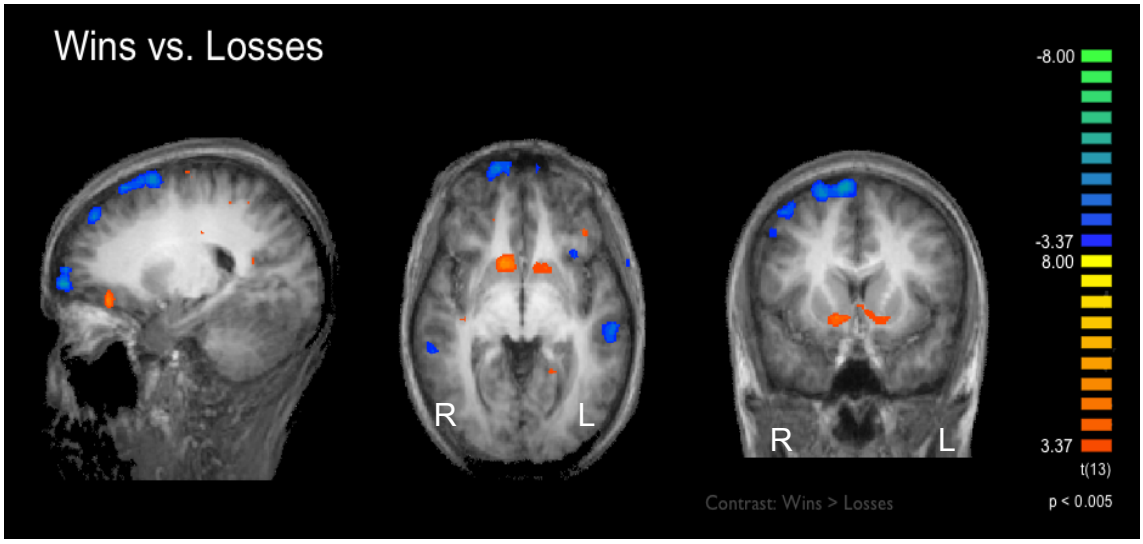

Figure 7. Neural responses associated with winning money compared to losing money. Again, functional maps are overlaid on a T1-weighted average of all 14 participants' anatomicals. Cluster size threshold based on uncorrected voxelwise $p < 0.005$ and cluster size alpha < 0.05 as indicated in the methods section. Left panel shows reward-related activity in the orbitofrontal cortex while middle and right panels show increased activity in the ventral striatum associated with winning money.

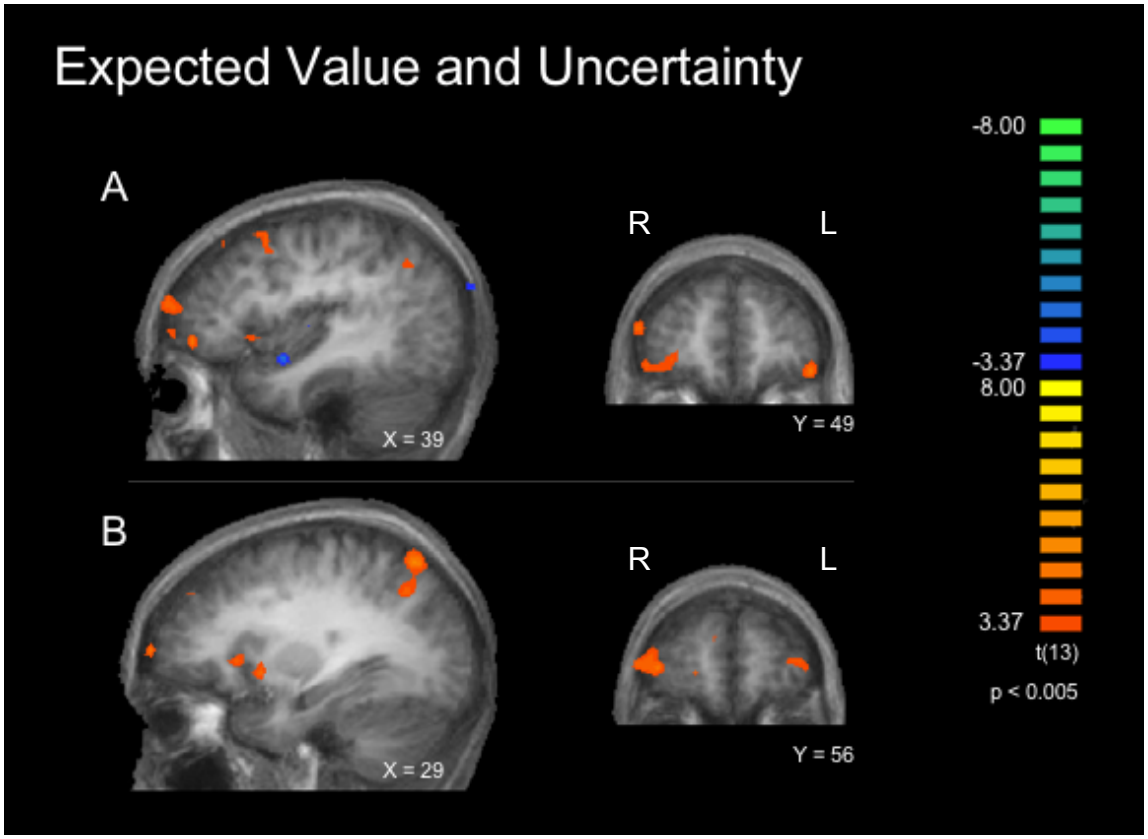

Figure 8. BOLD responses showing interaction of expected value and uncertainty. A) Neural activity associated with subject's choice of the uncertain lottery over the certain lottery in situations where the uncertain lottery was *greater* in EV than the certain lottery based on a *Uncertain Adv* > *Certain Adv* contrast. Top panels show activity in the orbitofrontal cortex, DLPFC and parietal cortex. B) Neural activity associated with subject's choice of the uncertain lottery over the certain lottery in situations where the uncertain lottery was *lower* in EV than the certain lottery based on a *Uncertain Disadv* > *Certain Disadv* contrast. Bottom panels show bilateral activation of the orbitofrontal cortex and parietal cortex. Both contrasts illustrate how uncertainty continuously modulates activity in regions previously implicated in only the initial valuation of stimuli/options.

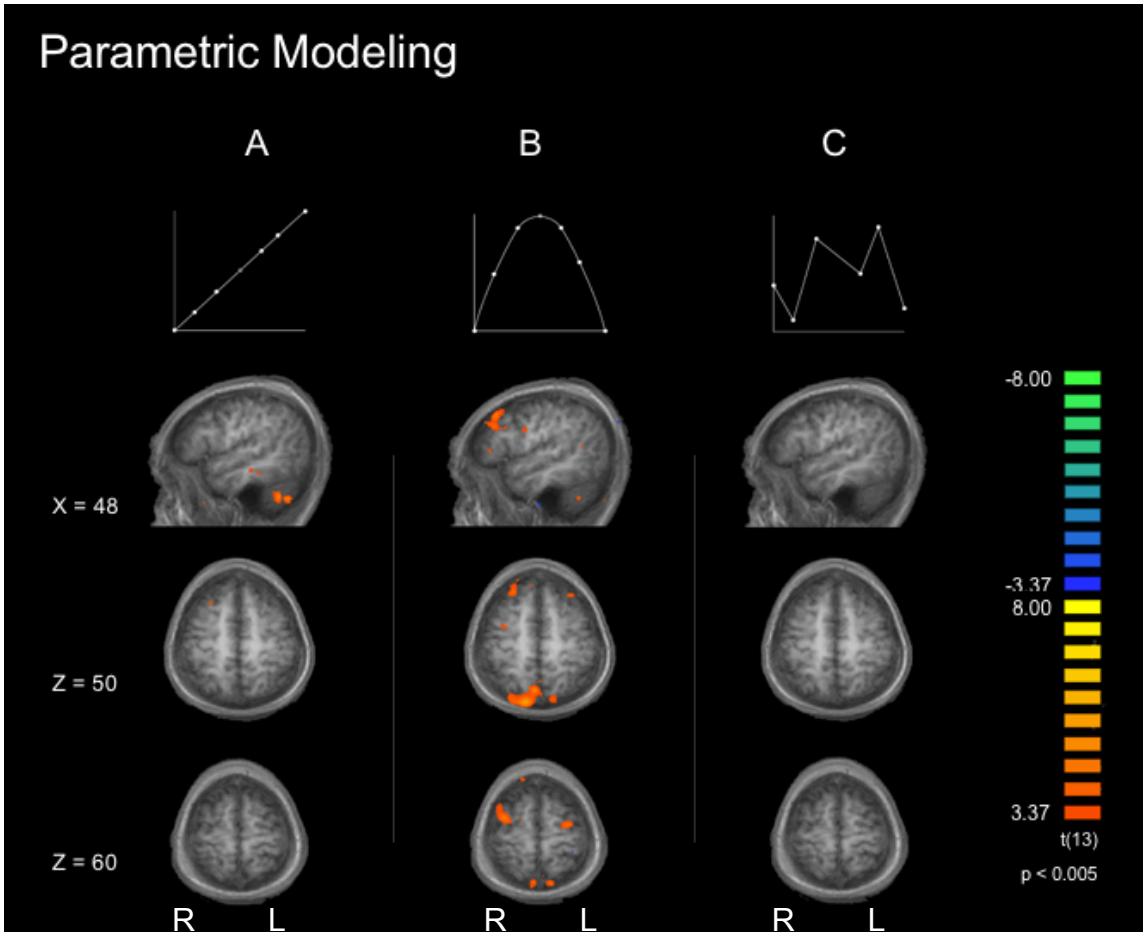

Figure 9. BOLD activity associated with various parametric models. Left column (A) shows areas of activity associated with parametric regressors emphasizing trials with high levels of ambiguity over trials with low ambiguity. Middle column (B) shows areas of activity associated with an "inverted U" function in which parametric weights emphasize trials with intermediate levels of ambiguity. Right column (C) shows regions of activity associated with random assignment of parametric weights. Although we see activity in the DLPFC associated with both the linear and parabolic models, the inverted U model recruits more anterior regions of the frontal cortex as well as posterior parietal cortex, suggesting that decisions associated with intermediate levels of ambiguity require more cognitive processing throughout the frontoparietal decision making network.

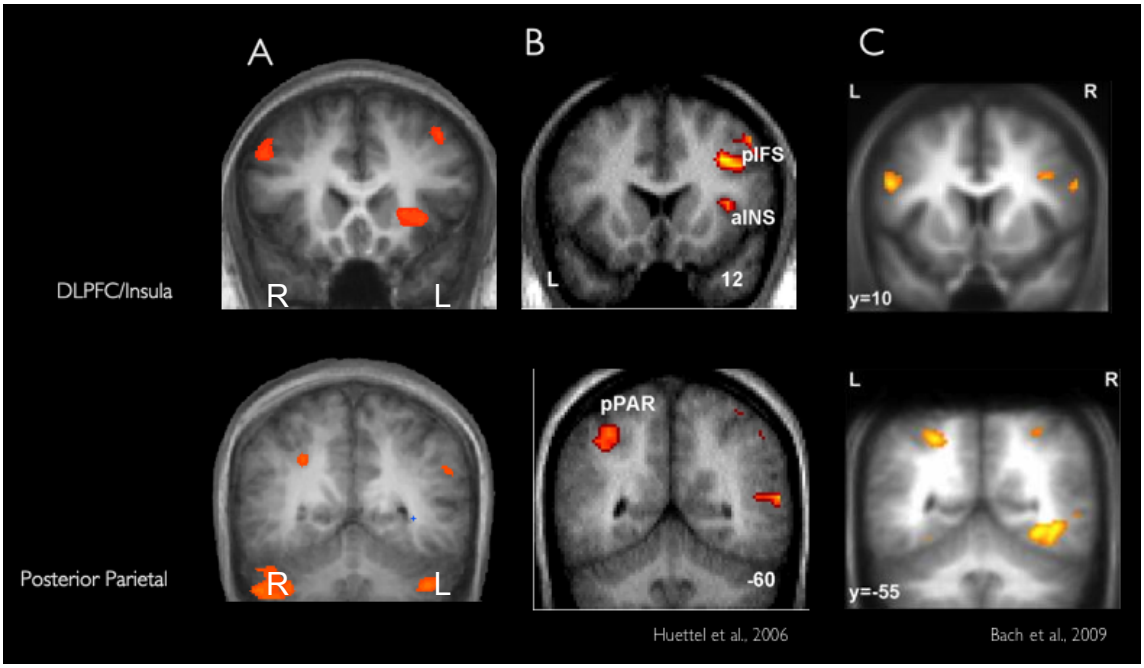

Figure 10. Comparison of results from three different studies investigating ambiguous decision making. A) Left column shows results from the current study. B) Middle column shows functional maps from Huettel and colleagues (2006). C) Right column shows functional maps from Bach and colleagues (2009). Our results match those of both Huettel et at. (2006) and Bach et al. (2009) when looking at categorical definitions of ambiguous decisions compared against risky decisions. All three studies find increased activity in the same region of the DLPFC and posterior parietal cortex, including the intraparietal sulcus, associated with choices under ambiguity.

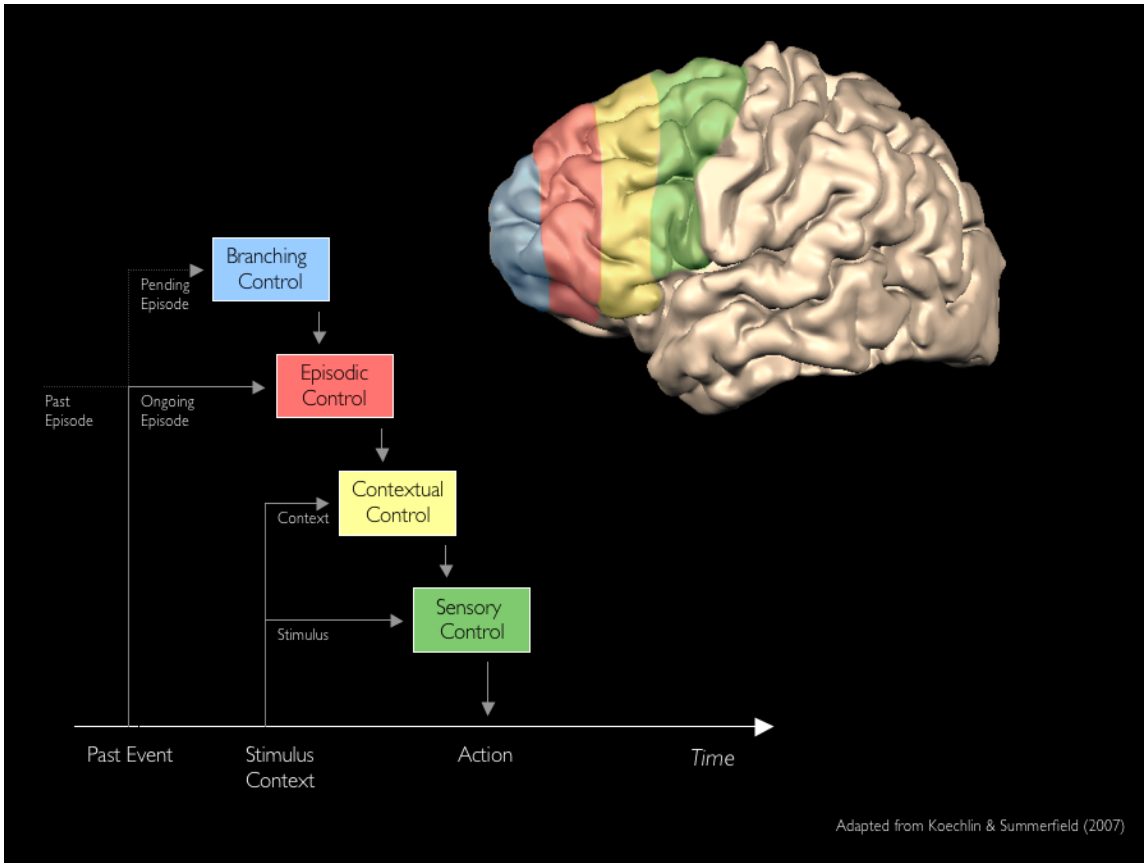

Figure 11. Simplified overview of Koechlin and Summerfield's model of cognitive control. Cognitive control is composed of various levels of control processes: sensory, contextual, episodic and branching, which are implemented from posterior to polar prefrontal regions. Sensory control is generally linked to activity in the premotor cortex and is associated with processing bottom-up information conveyed by the stimulus. Contextual control is linked with activity in posterior regions of the DLPFC and is associated with processing bottom-up and top-down information conveyed by the context in which a stimulus occurs. Episodic control is associated with the processing of information conveyed by a past event in the anterior DLPFC, whereas branching control is associated with processing information conveyed by events preceding the current trial and maintained in a pending state until completion of the ongoing episode in the most anterior regions of the prefrontal cortex. This model suggests that simple S-R associations only require sensory control and are mediated by the premotor cortex, while more complex associations requiring more cognitive control recruit more anterior regions of the prefrontal cortex.

Table 1. Areas of activation associated with choice selection in studies of decision making

Region of Activation	*Task*	*Method*	*Reference*
Caudate	Saccade	Primate Electrophysiology	Lau & Glimcher, 2008
Caudate	Lever Press	Primate Electrophysiology	Samejima et al., 2005
MPFC	Probabilistic Learning	Human fMRI	Knutson et al., 2003
MPFC	Choice Preference	Human fMRI	Kable & Glimcher, 2007
MPFC	Gambling	Human fMRI	Tom et al., 2007
OFC	Choice Preference	Human fMRI	Anderson et al., 2003
OFC	Choice Preference	Human fMRI	Gottfried et al., 2003
OFC	Choice Preference	Human fMRI	Hare et al., 2008; 2009
OFC	Choice Preference	Human fMRI	Kim et al., 2006
OFC	Choice Preference	Human fMRI	O'Doherty et al., 2001
OFC	Choice Preference	Human fMRI	O'Doherty et al., 2003
OFC	Choice Preference	Human fMRI	Plassman et al., 2007
OFC	Choice Preference	Human fMRI	Valentin et al., 2007
OFC	Gambling	Human fMRI	Knutson et al., 2005
OFC	IGT	Human Lesion	Bechara et al., 1996
OFC	Ultimatum Game	Human Lesion	Koenigs & Tranel, 2007
OFC	IGT	Human Lesion	Manes et al, 2002
OFC	IGT	Human Lesion	Rahman et al., 1999
OFC	Choice Preference	Human PET	Arana et al., 2003
OFC	Probabilistic Learning	Human PET	Rogers et al., 1999
OFC	Choice Preference	Human PET	Small et al., 2001
OFC	Choice Preference	Primate Electrophysiology	Padoa-Schioppa & Assad, 2006
OFC	Choice Preference	Primate Electrophysiology	Padoa-Schioppa & Assad, 2008
OFC	Saccade	Primate Electrophysiology	Roesch & Olson, 2005
OFC	Saccade	Primate Electrophysiology	Rolls et al, 1989
OFC	Saccade	Primate Electrophysiology	Thorpe et al., 1983
OFC	Saccade	Primate Electrophysiology	Tremblay & Schultz, 1999
OFC	Gambling	Primate Electrophysiology	Noonan et al., 2010
OFC	Stimulus Devaluation	Primate Lesion	izquierdo, Suda & Murray, 2004
OFC	Stimulus Devaluation	Primate Lesion	izquierdo, Suda & Murray, 2005
OFC		Primate Lesion	Raleigh & Steklis, 1981
OFC, DLPFC	Saccade	Primate Electrophysiology	Wallis & Miller, 2003
SNr	Probabilistic Learning	Human Electrophysiology	Zaghloul et al., 2009
Ventral Striatum	Probabilistic Learning	Human fMRI	Breiter et al., 2001
Ventral Striatum	Probabilistic Learning	Human fMRI	Knutson et al., 2001a
Ventral Striatum	Probabilistic Learning	Human fMRI	Knutson et al., 2001b
Ventral Striatum	Probabilistic Learning	Human fMRI	McClure et al., 2003
Ventral Striatum	Probabilistic Learning	Human fMRI	O'Doherty et al., 2003
Ventral Striatum	Probabilistic Learning	Human fMRI	Pessiglione et al, 2009
Ventral Striatum	Probabilistic Learning	Human Pharmacology	Frank et al., 2004
Ventral Striatum	Saccade	Primate Electrophysiology	Bayer & Glimcher, 2005
Ventral Striatum	Saccade	Primate Electrophysiology	Fiorillo et al., 2003
Ventral Striatum	Saccade	Primate Electrophysiology	Fiorillo et al., 2008
Ventral Striatum	Saccade	Primate Electrophysiology	Kobayashi & Schultz, 2008
Ventral Striatum	Saccade	Primate Electrophysiology	Roesch et al., 2007
Ventral Striatum	Saccade	Primate Electrophysiology	Schultz et al., 1997
Ventral Striatum	Saccade	Primate Electrophysiology	Tobler et al., 2003
Ventral Striatum	Saccade	Primate Electrophysiology	Tobler et al., 2005
Ventral Striatum	Saccade	Primate Electrophysiology	Waelti et al., 2001
VMPFC	Decision Making	Human fMRI	Kahnt et al., 2010
VMPFC	Decision Making	Human fMRI	Hare et al., 2010
VMPFC	Gambling	Human fMRI	Levy et al., 2010
VMPFC	Choice Preference	Human fMRI	Paulus & Frank, 2003
VMPFC	IGT	Human Lesion	Bechara et al., 1994
VMPFC	IGT	Human Lesion	Bechara et al., 1998
VMPFC	IGT	Human Lesion	Bechara et al., 1999
VMPFC	IGT	Human Lesion	Bechara et al., 2000
VMPFC	Choice Preference	Human Lesion	Fellows, 2006
VMPFC	Choice Preference	Human Lesion	Fellows & Farah, 2007
VMPFC	Saccade	Primate Electrophysiology	Watanabe, et al., 1996
VTA	Probabilistic Learning	Human fMRI	D'Ardenne et al., 2008

Table 2. Areas of activation associated with choice selection in studies of decision making

Region of Activation	Task	Method	Reference
DLPFC	Perceptual Decision Making	Human fMRI	Forstmann et al., 2008
DLPFC	Perceptual Decision Making	Human fMRI	Donemech & Dreher, 2010
DLPFC	Gambling	Human fMRI	Mullette-Gillman, 2011
DLPFC	Choice Preference	Human fMRI	Camus et al., 2009
DLPFC	Perceptual Decision Making	Human fMRI	Kahnt et al., 2010
DLPFC	Perceptual Decision Making	Primate Electrophysiology	Kim et al., 2008
DLPFC	Perceptual Decision Making	Primate Electrophysiology	Leon & Shandlen, 1999; 2003
DLPFC	Perceptual Decision Making	Primate Electrophysiology	Hanes & Schall, 1996
DLPFC	Perceptual Decision Making	Primate Electrophysiology	Kim & Shandlen, 1999
Frontal Eye Fields	Saccade	Primate Electrophysiology	Gold & Shandlen, 2000
Frontal Eye Fields	Saccade	Primate Electrophysiology	Kim & Shandlen, 1999
IPS	Perceptual Decision Making	Human EEG	Philastides et al., 2007
IPS	Perceptual Decision Making	Human fMRI	Tosoni et al., 2008
IPS	Perceptual Decision Making	Human fMRI	Stark & Zohary, 2008
IPS	Perceptual Decision Making	Human fMRI	Astafiev et al., 2003
IPS	Perceptual Decision Making	Human fMRI	Sereno et al., 2001
IPS	Perceptual Decision Making	Human fMRI	Ploran et al., 2007
IPS	Perceptual Decision Making	Human fMRI	Ploran et al., 2011
IPS	Perceptual Decision Making	Human fMRI	Heekeren et al., 2006
IPS	Perceptual Decision Making	Human fMRI	Ho et al., 2009
IPS	Perceptual Decision Making	Human fMRI	James & Gauthier, 2006
IPS	Perceptual Decision Making	Human fMRI	Noppeney et al., 2010
IPS	Perceptual Decision Making	Human fMRI	Wheeler et al., 2008
IPS, DLPFC	Perceptual Decision Making	Human fMRI	Heekeren et al., 2004
IPS, DLPFC	Perceptual Decision Making	Human fMRI	Ivanoff et al., 2008
IPS, DLPFC	Perceptual Decision Making	Human fMRI	van Veen et al., 2008
IPS, DLPFC	Perceptual Decision Making	Human fMRI	Kayser et al, 2009
LIP	Saccade	Primate Electrophysiology	Churchland et al., 2008
LIP	Foraging	Primate Electrophysiology	Dorris & Glimcher, 2004
LIP	Saccade	Primate Electrophysiology	Dorris & Munoz, 1998
LIP	Saccade	Primate Electrophysiology	Glimcher & Sparks, 1992
LIP	Perceptual Decision Making	Primate Electrophysiology	Janssen & Shandlen, 2005
LIP	Saccade	Primate Electrophysiology	Kiani et al., 2008
LIP	Saccade	Primate Electrophysiology	Roitman & Shandlen, 2002
LIP	Saccade	Primate Electrophysiology	Shandlen & Newsome, 2001
LIP	Saccade	Primate Electrophysiology	Shandlen et al., 1996
LIP	Perceptual Decision Making	Primate Electrophysiology	Yang & Shandlen, 2007
LIP	Perceptual Decision Making	Primate Electrophysiology	Newsome et al., 1989
LIP	Saccade	Primate Electrophysiology	Colby et al., 1996
LIP	Saccade	Primate Electrophysiology	Deaner et al., 2005
LIP	Saccade	Primate Electrophysiology	Gnadt & Andersen, 1988
LIP	Saccade	Primate Electrophysiology	Gold & Shandlen, 2001
LIP	Saccade	Primate Electrophysiology	Goldberg et al., 1990
LIP	Saccade	Primate Electrophysiology	Hayden et al., 2007
LIP	Saccade	Primate Electrophysiology	Klein et al., 2008
LIP	Saccade	Primate Electrophysiology	Platt & Glimcher, 1997
LIP	Saccade	Primate Electrophysiology	Platt & Glimcher, 1999
LIP	Foraging	Primate Electrophysiology	Surgue et al., 2004
Superior Colliculus	Saccade	Primate Electrophysiology	Basso & Wurtz, 1997

Table 3. Areas of activation associated with various levels of uncertainty

Contrast	*Region of Activation*	*# of Voxels*	*BA*	*x*	*y*	*z*
Uncertain > Certain	**Cuneus-L**	345	17	-9	-61	15
	DLPFC-R	96	46	39	20	37
	DMPFC-Bi	2256	8	2	19	50
	Frontal Eye Fields-R	1027	6	39	7	48
	Frontal Pole-R	132	10	33	61	11
	Inferior Occipital Cortex-R	58	19	46	-73	-24
	Insula-L	65	13	-32	21	4
	Insula-R	1312	13	34	20	5
	Middle Temporal Gyrus-L	91	21	-60	-32	-6
	Middle Temporal Gyrus-R	484	21	61	-31	-3
	Occipital Cortex-L	625	18	-14	-87	-19
	Occipital Cortex-R	156	18	14	-96	1
	Occipitotemporal Junction-R	67	37	51	-49	9
	Posterior Cingulate-L	391	33	4	-29	25
	Putamen-L	56	-	-27	2	-4
	Superior Parietal Cortex-L	2195	7	-46	-57	44
	Superior Parietal Cortex-R	4417	7	33	-66	48
	Superior Temporal Gyrus-R	52	38	47	9	-9
	Supramarginal Gyrus-R	271	39	47	-53	33
	Ventral Striatum-Bi	380	-	-1	11	2
	VMPFC-L	190	32	-3	42	-4
Low > High Uncertainty	**DLPFC-L**	196	46	-46	17	35
(a0+a15 > a33+a66+a80+a100)	**DLPFC-R**	270	46	44	42	15
	DLPFC-R	207	9,46	39	36	32
	DLPFC-R	199	8	27	22	51
	Frontal Pole-R	208	10	21	60	11
	Fusiform Gyrus-R	150	20	28	-44	-20
	Inferior Temporal Gyrus-R	162	21,37	64	-39	-13
	Insula/Putamen	2325	13	-26	0	10
	Insula/Putamen-R	4789	13	24	6	9
	Intraparietal Sulcus-L	203	39	-37	-55	36
	Intraparietal Sulcus-R	251	39,40	28	-46	34
	Motor Cortex-L	273	4	-25	-8	57
	Motor Cortex-L	180	4	-33	-7	39
	Putamen-R	599	-	27	-17	6
	Superior Parietal Cortex-L	352	7	-27	-70	34
	Superior Parietal Cortex-R	517	7	14	-71	40
	Supramarginal Sulcus-L	647	39	-47	-46	30
	Supramarginal Sulcus-R	385	39	38	-42	28
High > Low Uncertainty	**Hippocampus-L**	2068	-	-26	-26	-11
(a80+a100 > a0+a15+a33+a66)	**Hippocampus-R**	358	-	24	-34	-8
	Hippocampus-R	368	-	24	-14	-15
	Middle Temporal Gyrus-L	280	21	-52	1	-5
	Occipital Lobe_r	302	18	32	-85	20
	Posterior Cingulate Gyurs-L	210	23	-10	-24	35
	Putamen/Anterior Caudate	678	-	21	10	7
	Superior Parietal Cortex-R	295	1,3	44	-33	59

BA = Broadmans areas. x,y,z, = Talairach coordinates (Talairach & Tournoux, 1988) of central voxel in activated cluster.**Bold**= negative *t*-values. Cluster size threshold based on uncorr
voxelwise p < 0.005 and cluster size alpha < 0.05

Table 4. Areas of activation associated with ambiguity

Contrast	***Region of Activation***	*# of Voxels*	*BA*	*x*	*y*	*z*
a100 > a0	DLPFC-L	100	46	-45	20	37
	Inferior Temporal Gyrus-L	395	20,21	-57	-29	-16
	Lingual/Fusiform Gyrus-L	2242	19,37	-41	-53	-17
	Middle Temporal Gyrus-L	176	21	-50	-25	-9
	Occipital Cortex-L	1318	17,18,19	-26	-77	-14
	Occipital Cortex-R	956	17,18	25	-68	-5
	Post-Central Gyrus-R	1127	2,40	44	-19	23
	Premotor Cortex-Bi	444	6	0	-3	50
	Putamen/Caudate-R	495	-	21	14	5
	Putamen-R	389	-	28	3	12
	Superior Parietal Cortex-L	256	7	-18	-33	59
a100 + a80 > a0 + a15	Anterior Cingulate Gyrus-R	27	24	9	23	35
	DLPFC-L	317	46	-45	17	37
	DLPFC-R	495	9,46	34	21	47
	Frontal Pole-L	34	10	-26	51	24
	Frontal Pole-R	531	10	41	48	14
	Hippocampus-L	692	-	-26	-30	-10
	Hippocampus-R	98	-	27	-33	-4
	Inferior Temporal Gyrus-R	743	20,21	53	-25	-12
	Middle Temporal Gyrus-L	211	21	-52	1	-5
	OFC	107	11	18	61	-2
	Parietal Cortex-L	92	39	-51	-50	27
	Parietal Cortex-R	294	39	27	-50	33
	Posterior Parietal Cortex-L	333	7	-13	-77	36
	Premotor Cortex-R	78	6	51	9	26
	Putamen/Caudate/Insula-L	1026	13	-26	2	8
	Putamen/Caudate/Insula-R	3021	13	24	7	8
	Superior Parietal Lobe--R	334	7	2	-80	35

BA = Broadmans areas. x,y,z, = Talairach coordinates (Talairach & Tournoux, 1988) of central voxel in activated cluster.**Bold**= negative *t*-values. Cluster size threshold based on uncorr
voxelwise $p < 0.005$ and cluster size alpha < 0.05

Table 5. Areas of activation associated with winning money

Contrast	*Region of Activation*	*# of Voxels*	*BA*	*x*	*y*	*z*
Wins > Losses	Angular Gyrus-R	562	40	49	-33	25
	Cuneus-R	166	19	10	-88	30
	DLPFC-L	1921	46	-26	23	36
	DMPFC-R	682	8	4	35	38
	Frontal Eye Fields-R	769	8	4	20	55
	Frontal Pole-L	354	10	-8	59	21
	Frontal Pole-R	6227	10	30	61	12
	Fusiform Gyrus-L	1343	37	-30	-48	-16
	Hippocampus-R	1930	-	32	-11	-14
	Inferior Frontal Gyrus-R	568	45	42	19	7
	Insula-L	334	13	-39	-8	6
	Middle Temporal Gyrus-R	417	21	58	-31	-2
	Occipital Cortes-L	118	17	-26	-81	10
	Occipital Cortex-L	359	18	-6	-70	-7
	Occipital Cortex-R	3965	17,18,19	19	-56	-3
	Occipital Cortex-R	104	17	5	-88	3
	Occipitoparietal Junction-R	1453	22,39	44	-68	10
	OFC-L	217	11	-28	38	-1
	Parahippocampal Gyrus-L	263	-	-23	-15	-7
	Parahippocampal Gyrus-R	281	-	30	-29	-15
	Post-Central Gyrus-R	168	1,2	62	-26	26
	Posterior Caudate-R	1558	-	22	-20	31
	Posterior Cingulate Gyrus-R	1386	23,31	11	-37	47
	Posterior Cingulate/Precuneus-L	5643	23,30,31	-15	-58	14
	Pre-Central Gyrus-R	259	4	55	2	11
	Superior Parietal Cortex-L	8150	2,7,40	-23	-36	51
	Superior Parietal Cortex-R	2977	7,40	49	-62	42
	Superior Parietal Cortex-R	402	7	16	-35	62
	Superior Temporal Gyrus-L	3315	40,42	-56	-25	16
	Superior Temporal Gyrus-R	540	41,42	51	-18	9
	Supplementary Motor Area-R	146	6	38	7	54
	Ventral Striatum-Bi	1126	-	0	12	-1
	VMPFC-L	182	32	-11	48	9
Unexpected Wins > Expected Wins	DLPFC-L	968	9,46	-39	45	28
	DLPFC-R	476	9	26	33	53
	Frontal Eye Fields-R	1367	8	14	15	65
	Frontal Pole-R	1508	10	34	54	28
	OFC-L	881	11	-34	47	4
	Posterior Caudate-L	2572	-	-19	-18	21
	Posterior Cingulate Gyrus-Bi	4131	23,31	-1	-29	28
	Premotor Cortex/DLPFC-R	4667	6,46	40	8	41
	Premotor Cortex-L	731	6	-47	6	52
	Putamen/Insula-L	850	13	-28	-3	-3
	Putamen/Insula-R	3032	13	30	14	4
	Superior Colliculi-Bi	340	-	0	-33	-2
	Superior Parietal Cortex-Bi	8985	7,40	8	-64	44
	VMPFC-L	812	32	-4	30	-1

BA = Broadmans areas. x,y,z, = Talairach coordinates (Talairach & Tournoux, 1988) of central voxel in activated cluster.**Bold**= negative *t*-values. Cluster size threshold based on uncorr
voxelwise $p < 0.005$ and cluster size alpha < 0.05

Table 6. Areas of activation associated with EV

Contrast	*Region of Activation*	*# of Voxels*	*BA*	*x*	*y*	*z*
Adv. Trials > Disadv. Trials	DLPFC-L	215	45	-47	16	17
	Fusiform Gyrus-L	849	20	-31	-21	-22
	Inferor Temporal Gyrus-L	171	21	-46	-67	-11
	Insula-L	305	13	-36	20	6
	Insula-R	768	13	37	21	4
	Middle Temporal Gyrus-L	1772	21	-56	-42	3
	OccipitoParietal Fissure-L	218	31	-18	-59	22
	Superior Parietal Cortex-L	2759	7	-34	-63	55
	Superior Parietal Cortex-R	2350	7	36	-63	49
	Supplementary Motor Area-L	371	6	-52	5	48
	Supplementary Motoro Area-R	658	6	43	9	50
	VMPFC-L	935	32	-13	31	10
Disadv. Uncertain > Disadv. Certain	Frontal Pole-L	262	10	-32	57	11
	Frontal Pole-R	2561	10	41	54	14
	Frontal Pole-R	512	10	14	66	10
	Insula-L	272	13	-27	21	-4
	Insula-L	711	13	-42	14	6
	Insula-R	2704	13	32	19	2
	Occipital Cortex-L	322	19	-38	-74	-14
	SMA-R	484	6	15	13	62
	SMA-R	372	6	4	3	67
	Superior Parietal-L	257	7	-30	-58	41
	Superior Parietal-L	253	7	-34	-62	53
	Superior Parietal-R	2336	7,40	26	-67	51
Adv. Uncertain > Adv. Certain	DLPFC-R	302	9	40	12	50
	DLPFC-R	525	9	24	18	59
	DLPFC-R	228	9	23	34	56
	DMPFC-R	501	8	3	35	42
	Frontal Pole-L	181	10	-26	68	2
	Frontal Pole-R	2521	10	34	59	21
	Hippocampus-R	327	-	31	-10	-15
	Middle Temporal Gyrus-L	211	21	-58	-29	-5
	Occipital Lobe-R	220	18	25	-89	-13
	Occipital-Parietal Junction-R	783	39	45	-59	32
	OFC-L	386	11	-38	47	-2
	OFC-R	1185	11	39	51	4
	OFC-R	806	11	18	67	6
	Parahippocampal Gyrus-L	236	36	-29	-34	-18
	Posterior Cingulate-Bi	1700	23	1	-28	32
	Pre-Central Gyrus-L	422	4	-61	-24	26
	Pre-Central Gyrus-R	399	4	54	-10	22
	Superior Parietal-L	607	2	-50	-31	53
	Tail of Caudate-L	232	-	-19	-23	26

BA = Broadmans areas. x,y,z, = Talairach coordinates (Talairach & Tournoux, 1988) of central voxel in activated cluster.**Bold**= negative *t*-values. Cluster size threshold based on uncorrecte voxelwise $p < 0.005$ and cluster size alpha < 0.05

Table 7. Areas of activation resulting from parametric manipulation

Model	***Region of Activation***	*# of Voxels*	*BA*	*x*	*y*	*z*
Linear	DLPFC-L	246	46	-46	19	37
	DLPFC-R	283	9,46	33	21	47
	Inferior Temporal Gyrus-L	776	20,21	-58	-28	-16
	Insula-L	230	13	-31	12	6
	OFC-L	33	11	-2	36	-10
	Parahippocampal Gyrus-L	216	36	-26	-31	-11
	Parietal Cortex-L	179	7	-13	-77	37
	Precuneus-L	257	17,18,31	-25	-70	26
	Putamen/Insula-R	2271	13	24	11	11
	Superior Parietal Cortex-L	174	40	-26	-53	44
Inverted U	**Anterior Cingulate Gyrus-L**	204	24	-5	33	21
	Body/Tail of Caudate-R	2588	-	17	-14	20
	DLPFC-R	1744	9,46	46	24	34
	DLPFC-R	1486	9	30	41	43
	Frontal Pole-R	164	10	9	60	3
	Middle Temporal Gyrus-R	209	37	58	-56	-6
	MPFC-L	467	24,32	-8	37	12
	Parietal Cortex-L	1194	39	-41	-45	33
	Parietal Cortex-R	9419	7,39,40	19	-64	36
	Pre-Central Gyrus-L	1119	4	-27	-7	64
	Pre-Central Gyrus-R	4440	4,6	29	0	54
	Pre-Central Gyrus-R	183	4	15	-3	57
	Premotor Cortex-L	491	6	-32	1	33
	Putamen-L	643	-	-23	-1	17
	Putamen-L	315	-	-28	-4	2
	Putamen-R	1882	-	27	-8	2
	Superior Parietal Cortex-L	1398	7	-17	-71	55
	VLPFC-R	256	45	40	30	8
Random	**Hippocampus-R**	206	-	27	-31	-4
	Middle Temporal Gyrus-L	235	22	-53	2	-5
	Parietal Cortex-R	261	7	2	-82	35
	Pre-Central Gyrus-R	437	4	27	-18	69
	Putamen-L	1096	-	-26	4	8
	Putamen-R	1785	-	24	7	9

BA = Broadmans areas. x,y,z, = Talairach coordinates (Talairach & Tournoux, 1988) of central voxel in activated cluster.**Bold**= negative *t*-values. Cluster size threshold based on uncorr
voxelwise $p < 0.005$ and cluster size alpha < 0.05

CHAPTER 5 - REFERENCES

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