Individual Differences in the Frontal-Striatal Reward Network: Decision-Making and Psychiatric Disease

by

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Abstract

The frontal-striatal reward network is involved in many reward-related behaviors, including decision-making and those related to psychiatric disease. One important class of decisions involves the conflict between immediate rewards and delayed gratification. Temporal discounting preferences reflect how a person makes decisions that involve tradeoffs over time. A fundamental question is how people vary and what accounts for this variation in temporal discounting preferences, both behaviorally and neurobiologically. In addition, psychiatric diseases, such as social anxiety, are associated with deficits in behaviors that involve social reward. Here I report two experiments that provide evidence for two major factors that contribute to differences in temporal discounting preferences: personality traits and the underlying frontal-striatal reward network, both during task and at rest. Finally, I report underlying differences in the organization of the frontal-striatal reward network in social anxiety disorder.

In the first study, I investigated the frontal-striatal reward network that underlies personality traits and the association of personality with temporal discounting preferences. Higher neuroticism was associated with a greater preference for immediate rewards and greater impulsivity, and higher conscientiousness with a greater preference for delayed rewards and less impulsivity. Executive-control and reward regions in the frontal-striatal reward network were more activated when higher conscientiousness participants selected a smaller-sooner reward and, conversely, when higher neuroticism participants selected a larger-later reward. Both cases involved choices that went against predispositions implied by personality. In the second study, I investigated how resting-state intrinsic functional brain organization (functional connectivity) of the frontal-striatal reward network varies with temporal discounting preferences. Increased patience and decreased impulsivity were associated with stronger functional connectivity between the nucleus accumbens and prefrontal executive control regions, including the dorsolateral prefrontal cortex. These findings reveal that the intrinsic strength of the frontal-striatal network is associated with differences in temporal discounting preferences. In the third study, I investigated the differences in the organization of the frontal-striatal reward

network in social anxiety disorder. There was decreased functional connectivity between the nucleus accumbens and other reward regions, including the ventromedial prefrontal cortex, and decreased functional connectivity between the ventromedial prefrontal cortex and executive control regions of the prefrontal cortex. Taken together, these results indicate that the frontal-striatal reward network is associated with individual differences in reward-related behavior.

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1. Introduction

A fundamental goal of neuroscience is to understand the function and organization of the human brain and how this leads to individual differences in human behavior in both healthy people and people with psychiatric disease. One important class of behaviors is those that involve making decisions that result in rewarding outcomes. Much variability exists across individuals with respect to decision-making processes involving reward, and the function and organization of the human brain is essential for understanding this variability.

People frequently must decide between the immediate consumption of goods and forgoing immediate consumption for the greater benefit of those goods in the future. People often struggle with this decision, given the common desire for immediate reward and gratification. When making these tradeoffs, people tend to discount future consumption relative to immediate consumption at different rates (Frederick et al., 2002). Impatient temporal discounters prefer sooner consumption to delayed consumption by discounting the future at a greater rate than shallow discounters. Not only do individuals exhibit differences in their level of patience in temporal discounting preferences, but these temporal discounting preferences also vary within people across time. At the extremes this can lead to inconsistent preferences at different time points, where people reverse their preferences for the same relative delay of rewards (see Frederick et al. 2002 for further review). For example, a person may prefer $10 now over $20 one week from now. They reverse preferences when the reward is moved one year into the future, preferring $20 in one year and a week to $10 in one year. An important question is: what

is the neurobiological basis for how individuals vary with their temporal discounting preferences?

Previous neuroimaging research has identified key brain regions involved in temporal discounting. Reward regions in the ventral striatum, including the nucleus accumbens (NAcc), are associated with immediate rewards and a person's personal subjective value of rewards (Knutson et al., 2001a; Knutson et al., 2001b). In addition, executive control regions in the prefrontal cortex are associated with delayed rewards and the subjective value of rewards (McClure et al., 2004; Kable & Glimcher, 2007). These two regions, the ventral striatum/NAcc and the prefrontal cortex, form the frontal-striatal reward network (Dehaene & Changeux, 2000). Within the frontal-striatal reward network there are sub-regions that are involved with specific roles in reward and behavior. The ventral striatum and the NAcc are involved with reward anticipation (Knutson et al., 2001a; Knutson et al., 2001b). The ventromedial prefrontal cortex (vmPFC) and regions in the medial orbitofrontal cortex (OFC) are involved in encoding the outcome of reward and translating reward into a unique representation of subjective value (Gläscher et al., 2009; Montegue & Berns, 2002). The strength of the structural connectivity between the ventral striatum, mPFC, lateral OFC, and dorsolateral prefrontal cortex (DLPFC) predicts rewarded behaviors (Cohen et al., 2009; Hollerman, Tremblay, & Schultz, 2000). In particular, the DLPFC is involved with top-down processing and executive control in reward-related decision-making (Barraclough, Conroy, & Lee, 2004; Bechara, 2005). Understanding the integration of the processes of these sub-regions will lead to a better understanding of the neurobiological basis for individual differences in decision-making and behavior.

The frontal-striatal reward network has also been associated with individual differences in psychiatric disease (Chau, Roth, & Green, 2004). Reduced activation in the NAcc was associated with affectively positive rewarding stimuli, and importantly this was also reflected in decreased functional connectivity between the NAcc and the lateral prefrontal cortex in people with depression (Heller et al., 2009). Deep brain stimulation of the NAcc resulted in decreased depression and lasting increased activation in the NAcc, mPFC, and DLPFC (Schlaepfer et al., 2008). In depression, reward and motivation is associated with the frontal-striatal reward network; other psychiatric disorders, such as social anxiety disorder, may also be related to differences in the frontal-striatal reward network. Social anxiety disorder (SAD) is associated with fear of negative social evaluation (Hofmann, 2007). Because SAD is typically thought of as a dysfunction in response to fear, much of the research has focused on differences in amygdala activation and its connectivity with the OFC (Bruel, et al., 2011; Liao et al., 2010). However, like depression, it is also likely that SAD is associated with differences in response to reward, and is therefore likely reflected in differences in the frontal-striatal reward network. Behavioral inhibition, a precursor to SAD, is associated with increased striatal activation for anticipation of reward (Guyer et al., 2006) and no differentiation between positive rewards and no rewards in vmPFC activation (Helfinstein et al., 2011). This indicates that an altered region involved with reward response (NAcc) (Knutson et al., 2001a; Knutson et al., 2001b) and an altered region involved with translating reward into a representation of value (vmPFC) (Gläscher et al., 2009; Montegue & Berns, 2002) may result in a dysfunction of the frontal-striatal reward network in SAD.

The subsequent chapters present evidence that individual differences in the frontal-striatal reward network are reflected in both differences in reward-related behavior and psychiatric disease. The first part of the thesis focuses on individual differences in temporal discounting. In Chapter 2, I relate differences in stable personality traits to individual differences in temporal discounting preferences. Behaviorally, higher conscientiousness was associated with lower short-term impatience and more consistent time preferences, whereas higher neuroticism was associated with higher short-term patience and less consistent time preferences. These differences were also reflected in differences in the task-based functional magnetic resonance imaging blood-oxygen-level dependent (fMRI BOLD) signal. Executive control regions and reward regions were simultaneously more activated when participants with higher conscientiousness chose smaller-sooner rewards, and conversely these same regions were more activated when participants with higher neuroticism chose larger-later rewards. This indicates that the frontal-striatal reward network integrates both executive control and reward regions when making decisions that are contrary to a person's temporal discounting preferences, as related to personality.

Given the strong relationship between individual temporal discounting preferences and the frontal-striatal activation during task, I next investigated whether differences in the temporal discounting preferences are reflected in the intrinsic functional organization of brain networks (functional connectivity) absent from task. In Chapter 3, I relate individual differences in temporal discounting preferences to functional connectivity networks of the NAcc in the brain at rest. Because the brain is at rest, these networks reflect the relationship between spontaneous activation in the BOLD signal and

individual differences in temporal discounting. Participants that had increased short-term patience and more consistent time preferences exhibited increased functional connectivity between the NAcc and regions in the prefrontal cortex, including the mPFC and DLPFC. This supports that a strongly integrated and functionally connected frontal-striatal reward network is associated with individual differences in temporal discounting.

In Chapter 4, I relate individual differences in the frontal-striatal reward network to SAD. Because people with SAD often behave differently in socially rewarding environments, the underlying organization of the frontal-striatal reward system is likely to be altered. SAD was associated with decreased resting-state functional connectivity between three key regions in the frontal-striatal reward network: the NAcc, vmPFC, and DLPFC. These regions are involved in reward anticipation, translating reward into value, and top-down executive control in reward-related decisions, respectively (Knutson et al., 2001a; Knutson et al., 2001b; Gläscher et al., 2009; Montegue & Berns, 2002). This decreased strength of the functional connectivity between these three regions reflects differences in the neurobiological basis of SAD.

2. Personality Influences Temporal Discounting Preferences: Behavioral and Brain Evidence

Personality traits are stable predictors of many life outcomes that are associated with important decisions that involve tradeoffs over time. Therefore, a fundamental question is how tradeoffs over time vary from person to person in relation to stable personality traits. We investigated the influence of personality, as measured by the Five-Factor Model, on time preferences and on neural activity engaged by intertemporal choice. During functional magnetic resonance imaging (fMRI), participants made choices between smaller-sooner and larger-later monetary rewards. For each participant, we estimated a constant-sensitivity discount function that dissociates impatience (devaluation of future consequences) from time sensitivity (consistency with rational, exponential discounting). Overall, higher neuroticism was associated with a relatively greater preference for immediate rewards and higher conscientiousness with a relatively greater preference for delayed rewards. Specifically, higher conscientiousness correlated positively with lower short-term impatience and more exponential time preferences, whereas higher neuroticism (lower emotional stability) correlated positively with higher short-term impatience and less exponential time preferences. Cognitive-control and reward brain regions were more activated when higher conscientiousness participants selected a smaller-sooner reward and, conversely, when higher neuroticism participants selected a larger-later reward. The greater activations that occurred when choosing rewards that contradicted personality predispositions may reflect the greater recruitment of mental resources needed to override those predispositions. These findings reveal that stable personality traits fundamentally influence how rewards are chosen over time.

2.1 Introduction

Many decisions involve a conflict between immediate rewards and delayed gratification - between, for example, receiving a smaller cash amount now and a larger cash amount next year. Formal temporal discounting models specify how subjective present value, which is the personal value (utility) of money or a particular good obtained at a specific date, decreases as that date moves further into the future (Frederick et al., 2002). A fundamental question is how such value varies from person to person in relation to stable personality traits. Further, is personality associated with the neurobiological competition between immediate and delayed rewards as decisions are made, or with integration among neural systems involved with both immediate and delayed rewards, dependent on the behavioral predisposition associated with personality type?

Both temporal discounting and the influence of personality traits on behavior have been studied extensively, but there is limited evidence about either how major personality factors, such as the Big Five Personality traits (Costa & McCrae, 1992), influence temporal discounting or how personality traits and temporal discounting are related with one another in terms of brain processes. Personality traits predict variation in goal-directed behaviors that involve tradeoffs between immediate and delayed consequences, including health and exercise (Conner & Abraham, 2001), academic performance (Chamorro-Premuzic & Furnham, 2003; Paunonen, 2003), years of education (Goldberg et al., 1998), and job performance (Barrick et al., 2001). Each of these endeavors requires sacrifice of current satisfactions in exchange for remote rewards, so it might be hypothesized that personality traits influence temporal discounting.

The most widely used and validated self-report of personality is the Big Five questionnaire (Costa & McCrae, 1992), which yields independent measures of conscientiousness, neuroticism, extraversion, openness to experience, and agreeableness. One study found that greater extraversion was associated with higher discounting rates, but only in people with lower cognitive scores, and that greater neuroticism was associated with higher discounting rates, but only in people with higher cognitive scores (Hirsch et al., 2008). Also, tryptophan depletion increases discounting rates in individuals with higher neuroticism (Demoto et al., 2012). Impulsiveness can also be measured as a trait by a questionnaire. Greater trait impulsivity correlated with preference for immediate rewards and increased discounting rates (Sripada et al., 2011) and also difficulty resisting immediate rewards (Diekhof et al., 2012). Thus, personality variables have been related to variation in discounting rates, but there has been no straightforward relation reported between the Big Five personality factors and variation in temporal discounting.

Personality has been linked to the consistency of intertemporal decisions, as revealed by impulsivity and procrastination. Individuals who score high on neuroticism report more impulsive behavior (Whiteside & Lynam, 2001) and more procrastination (Lee et al., 2006); conversely, conscientiousness is associated with less procrastination (Lee et al., 2006). We therefore hypothesized that greater conscientiousness would be associated with greater willingness to wait for reward, whereas greater neuroticism (or instability that can be associated with impulsiveness) would be associated with lesser willingness to wait for reward.

If personality traits alter temporal discounting preferences, there are two major alternative ways in which this could occur in the brain. Some neuroimaging studies have found that

different brain regions are associated with immediate versus delayed rewards (e.g., McClure et al., 2004). These findings raise the possibility that variation in personality may be understood in the framework of a dual-system competition model, in which a fast, visceral system responds to immediate rewards, and a slow deliberate system considers delayed rewards. Personality could tip the balance of this competition. Other neuroimaging studies have found that brain regions appear to integrate information about immediate versus delayed rewards (e.g., Kable & Glimcher, 2007). These findings raise the alternative possibility that variation in personality may be understood in a system integration model, in which personality does not influence one or another competing system, but rather multiple systems operating in concert.

Neuroimaging studies of temporal discounting have provided evidence for both competition and integration under varying experimental designs (reviewed in Peters & Büchel, 2011). Evidence for competition comes from functional neuroimaging that has associated brain responses to immediate rewards with subcortical reward systems, and brain responses to delayed rewards with prefrontal and other neocortical regions thought to support cognitive control (McClure et al., 2004). Regions in the reward system, including the ventral striatum, medial prefrontal cortex, and posterior cingulate cortex, exhibited higher levels of activation when people chose immediate rewards over delayed rewards (McClure et al., 2004). Conversely, regions associated with cognitive control, such as the dorsolateral prefrontal cortex, were associated with the value of the delayed rewards (McClure et al., 2004). The lateral prefrontal cortex also has a causal role in the self-control needed to select delayed rewards (Figner et al., 2010). Evidence for integration comes from the finding that activation in ventral striatum appears to track the

subjective value of rewards, calculated as a hyperbolic discount function, simultaneously with regions in prefrontal and posterior cingulate cortices (Kable & Glimcher, 2007). Regions including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, middle temporal gyrus, somatosensory cortex, primary motor cortex, and the striatum were also associated with the subjective value of rewards (Onoda et al., 2011).

Individual differences in reward processing have been associated with individual differences in the magnitude of activation occurring in these neural systems. Increased impulsivity, measured by temporal discount functions, was associated with lower activation in the ventral striatum and nucleus accumbens while responding to delayed rewards (Ballard & Knutson, 2009; Ripke et al., 2012). However, the ventral striatum has also been shown to have higher activation for steeper, more impulsive temporal discounters while waiting for the receipt of a reward (Jimura et al., 2013). Cognitive control regions, including the dorsolateral prefrontal cortex, showed greater deactivation to the delay of reward in impulsive temporal discounters (Ballard & Knutson, 2009). Thus both reward and cognitive control systems have exhibited variation in activation that was associated with variation in temporal discounting preferences between immediate and delayed rewards.

We employed a single model of constant sensitivity function (Bleichrodt et al., 2009; Ebert and Prelec, 2007) to examine the relation of personality to both behavior and brain function. We chose this model, relative to other models of temporal discounting, because it offers two formal measures of time preference, one of impatience (pure discounting) and one of impulsivity. The impatience measure captures how much weight people give to future outcomes. The impulsivity measure captures whether time discounting promotes

inconsistent decisions about future outcomes, such that, for example, a person's 'morning preferences' might yield a decision to work rather than party in the evening, but his 'evening preferences' would yield the opposite. Using this model, with the separate impulsivity parameter, is especially appropriate because of the established relationship between impulsivity and neuroticism (Whiteside & Lynam, 2001). We examined whether each of these two temporal-discounting measures correlated with personality-related psychological variables and neural activity.

We therefore aimed to integrate economic, psychological, and neurobiological perspectives to understand how personality differences are associated with making economic choices over time. We characterized the personalities of healthy young adults who performed temporal discounting choices while undergoing functional magnetic resonance imaging (fMRI), and analyzed their time discounting functions. We also measured cognitive abilities because of evidence that such abilities can influence temporal discounting (Shamosh & Gray, 2008; Shamosh et al., 2008) and interact with the personality trait of extraversion (Hirsch et al., 2008). We hypothesized that conscientiousness would be associated with relatively more consistent time preferences and shallower discounting or preferences for relatively longer delays, and, conversely, that neuroticism would be associated with relatively less consistent time preferences and with deeper discounting or preferences for relatively shorter delays.

Functional neuroimaging analyses, analogous to the behavioral analyses, focused on the relation between personality traits and selection of shorter versus longer delays in the context of the amount of subjective value gained by a person's choice. With this type of fMRI analysis, we asked whether personality influences in relation to subjective value

would manifest in the brain as variation in competition between subcortical and cortical systems (with personality factors differentially associated with the two systems), or as an integration between subcortical and cortical systems (with personality factors similarly associated with the two systems).

2.2 Methods

2.2.1 Participants

Participants were 40 healthy young adults between ages 20 and 32 (right handed, mean age = 24.9 years, 22 females) screened for prior neurological disorder. Three participants were excluded from analysis due to invalid data: One had missing fMRI data; one switched hand response button boxes; one had excessive movement that required the removal of 253 outlier data points (threshold of $z = 3$ relative to the mean intensity and composite motion with threshold of 1 mm relative to previous time point). The study was approved by the Committee On the Use of Humans as Experimental Subjects at MIT in accordance with World Medical Association Declaration of Helsinki. All participants gave informed consent.

2.2.2 Participant Characterization

Participants completed the 60-item Neuroticism-Extroversion-Openness Five Factor Inventory (Costa & McCrae, 1992). Responses were scored for neuroticism, extroversion, openness to experience, conscientiousness, and agreeableness. Intelligence for each participant was assessed with the Full-Scale Intelligence Quotient (FSIQ) estimate from

the American National Adult Reading Test (Wechsler, 1981). Working memory ability was assessed with two tests: (1) the Letter-Number Sequencing test from the WAIS-R (Wecsler, 1981), and (2) a Multiple-category N-back task adapted from Salthouse, Atkinson, & Berish (2003).

2.2.3 Neuroimaging

Behavioral Assessment of Temporal Discounting During scanning, participants were presented with 108 trials consisting of two options: (1) a smaller monetary reward with a shorter delay and (2) a larger monetary reward with a longer delay. Participants were informed that one of their choices would be randomly selected as a true payoff. One option was presented initially for 2–8s (counterbalanced across shorter and longer delays), followed by both options presented until the participant made a choice or the trial timed out (after a total of 14s). A fixation cross was presented for the remaining time after the choice. Options were presented side-by-side, and the order and side of shorter and longer delays was fully counterbalanced across trials (Figure 2.1).

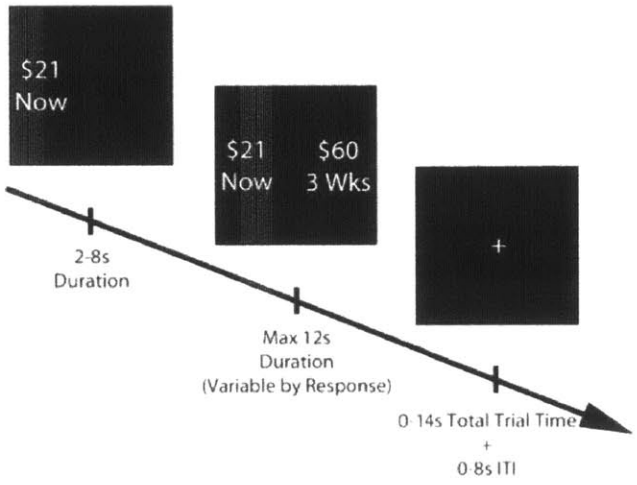

Figure 2.1. An example trial, showing timing and presentation of options. Each option consisted of a dollar amount paired with a delay. The first option was displayed (side of presentation counterbalanced) for 2-8s, followed by the appearance of a second option for 6-12s (14s – first option duration) or until a response was made. A fixation cross was presented for any remainder of the 14s trial period, and for a 0-8s inter-trial interval.

Sixty trials contained delays of 0 (immediate), 21, 60, 180, and 365 days, with rewards ranging from $30 to $150. These intervals were selected to approximate log(time) intervals. The remaining 48 of the 108 trials were adaptive. This adaptive method assured that some trials provided options that were close to equivalent in subjective value. Using the starting values from the practice session increased the likelihood that the in-scanner adaptive trials more rapidly converged toward each participant's indifference point. The model was fit to all trials in the scanner, both fixed and adaptive options. This design enhanced the accurate estimation of the discounting model by increasing the number of observations most sensitive to a participant's subjective value in decision making. One of the options was always an immediate reward and the other was a delayed reward of $60 or $150 at each of the four delays. The immediate alternatives for each reward/delay pair

were determined in an adaptive fashion using a staircase procedure. The starting value of the immediate alternative for each reward/delay pair was determined from the participant's behavior during a pre-scan session (described below). Depending upon the participant's responses to these trials, the next immediate reward was either raised or lowered, with the increments of change becoming successively smaller in log amounts. The minimum reward for adaptive trials varied across participants, dependent on the adaptive reward values from the staircase procedure. After scanning, participants received the reward from their choice on a randomly selected trial as a check. If there was a delay for the selected choice, a check was mailed to the participants at the scheduled date.

Prior to the fMRI session participants received 96 practice adaptive trials outside of the scanner with the same delays used in the MRI scanner. Starting values of $60 and $150 were paired with the delays and were adapted using the procedure above. The first staircase trial for each delayed reward was paired with an immediate reward alternative that was 1/2 of the log-delayed amount (rounded to the nearest dollar). Depending upon the participant's responses to these trials, the next immediate reward was either raised or lowered, with the increments of change becoming successively smaller in log amounts. The final values from this adaptive procedure were used as starting values for the adaptive trials during scanning.

2.2.4 Discounting Analysis

Data from the discounting task in the scanner were used to model each participant's subjective value using the constant sensitivity discounting function (Bleichrodt et al.,

2009; Ebert & Prelec, 2007), (Eq. 2.1), which allows formal separation of impatience levels and impulsivity and relate them to conscientiousness and neuroticism. In this model, β is a measure of pure exponential discounting or impatience. As β increases, people become more impatient. Time-sensitivity is measured by α. Rational compound discounting is equivalent to $\alpha = 1$. As α decreases, people become increasingly insensitive to differences between future time points. The limiting case $\alpha \sim 0$ yields dichotomous discounting, where an individual only distinguishes between 'now' and 'later,' treating all future dates as equivalent. This would promote extreme inconsistency in inter-temporal choices. In principle, inter-subject variation in α and β across people describes individual differences in temporal discounting. Maximum likelihood estimation, with the softmax activation function (Eq. 2.2) for the likelihood, was used to obtain the parameter estimates α and β from Eq. 2.1, and θ, the inverse temperature or slope parameter from the softmax function. θ reflects a random element in choice. $\theta = 0$ represents a person that chooses completely at random. As θ increases a person is more likely to choose the option with the highest subjective value. These parameters were estimated for each participant, and we related these discounting functions to each individual's personality measures. We calculated both Pearson correlations and Spearman rank correlations between each participant's estimated discounting parameters and personality measures. Because previous research has found a correlation between personality and both IQ and working memory (Shamosh & Gray, 2008; Shamosh et al., 2008), we also examined the Pearson correlations between personality and both IQ and working memory.

Equation 2.1.

$$f(t) = \exp\left(-(\beta t)^{\alpha}\right)$$

Equation 2.2.

$$p(Option\ Chosen_i) = \frac{e^{\theta \times f(t_i) * Reward\ Chosen}}{e^{\theta \times f(t_i) * Reward\ Chosen} + e^{\theta \times f(t_j) * Reward\ Rejected}}$$

2.2.5 fMRI Acquisition

Data were acquired using a 3-Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with a 12-channel phased array whole-head coil. 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) anatomical images (TR = 2530 ms, TE = 3.39 ms, flip angle = 7°, 1.33 mm slice thickness, 1.3 × 1 mm2 in plane resolution) and T2* - weighted EPI sequence functional images (TR = 2.0 s, TE = 30 ms, flip angle = 90°, 3 mm3 resolution, 300 timepoints per run with 3 runs, tilt = 22° upward from AC-PC line to minimize distortion and signal dropout, interleaved acquisition, using prospective acquisition correction) (Thesen et al., 2000) with full brain coverage were collected.

2.2.6 fMRI Analysis

The functional data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were preprocessed with realignment for motion correction, slice-time correction, artifact detection (threshold of z = 3 relative to the mean intensity and composite motion with threshold of 1mm

relative to previous time point), spatial smoothing (6mm full-width-half-maximum Gaussian kernel), and normalization and coregistration of the contrast images to each participant's anatomical scan using Freesurfer (Fischl et al., 2001; Fischl et al., 2002).

We used a general linear model (GLM) for the fMRI analysis that related personality variables to individually calculated subjective value for each participant. The GLM consisted of three vectors of onsets. The first corresponded to trials where participants chose the option with a shorter delay, and the second corresponded to trials where participants chose the option with a longer delay. Both onset vectors for choice consisted of unit values at the time of the presentation of the second option. A third vector corresponded to the presentation of the first option. Additional parametric regressors coincided with the onsets at presentation of the second option. Nuisance regressors were also included in the GLM; one for each artifactual time point, one for linear drift, and 7 motion parameters (3 rotation, 3 translation, and 1 composite). Three sessions were concatenated for the design matrix.

The parametric regressors represented the *utility surplus* of each decision; the difference in the subjective value between the option chosen and the option not chosen (all fMRI contrasts are with the parametric regressors). The utility surplus captures the subjective value of the entire option, which provides more information than other possible regressors (e.g., absolute monetary value or subjective value of a single option). This is also an important measure because we predicted a relationship between personality and the parameters of the constant sensitivity model, which determines each person's unique subjective value.

One parametric regressor corresponded to trials where the option with a shorter delay was chosen and the other regressor corresponded to trials where the option with a longer delay was chosen. For chosen shorter delays, the regressor was calculated as the subjective value of the option with the shorter delay minus the subjective value of the option with the longer delay (Utility Surplus Short). For chosen longer delays, the regressor was calculated as the subjective value of the option with the longer delay minus the subjective value of the option with the shorter delay (Utility Surplus Long). All subjective values were calculated by multiplying Eq. 2.1 by the monetary value of the options (assuming that utility was linear in money). When positive, this difference of the subjective value shows how much additional utility the participant gained by choosing the option with the larger modeled subjective value (based on their entire series of choices). When negative, this difference shows how much additional utility the participant could have received had they chosen the option with the larger modeled subjective value.

Because we were interested in the relationship between discounting, personality, and brain function, the subjective values associated with each trial were essential to evaluate these relationships, as opposed to other possible variables (e.g. actual values of the option chosen or the difference between the two monetary values). In addition we hypothesized a relationship between neuroticism and high impulsivity/high short-term impatience, and conscientiousness and low impulsivity/low short-term impatience. Therefore we separated these regressors dependent on whether a person chose the shorter delay or the longer delay in order to see how the preference for the length of delay related to different personality traits and brain function. Finally, we used the difference in subjective value or

utility surplus because this value represents both the difficulty of the choice and the actual utility gained or lost on each trial.

We used the personality scores of conscientiousness and neuroticism as second level covariates in separate second level group analyses. Two separate second level group analyses avoided collinearity between the personality dimensions. Conjunctions of thresholded (FDR < .05) correlation maps were performed (Nichols et al., 2005). All analyses applied a cluster level false discovery rate (FDR) threshold of $p < .05$.

2.3 Results

2.3.1 Behavioral Results

We used an intertemporal choice task in which participants chose between two options: (1) a smaller monetary reward with a shorter delay, and (2) a larger monetary reward with a longer delay (Figure 2.1). Each participant's data was fit to the two-parameter constant sensitivity function (Bleichrodt et al., 2009 & Ebert; Prelec, 2007). One parameter, α (where $0 \leq \alpha \leq 1$) measures time-sensitivity and impulsivity. Smaller α reflects greater impulsivity (less rational) and more short-term impatience, while $\alpha = 1$ reflects a rational discounter. The second parameter, β (where $0 \leq \beta$,) measures exponential discounting or pure impatience. Larger β reflects greater overall impatience. The distribution of the time-sensitivity/impulsivity parameter (α) was approximately Gaussian except for being truncated at 1, but the distribution of the pure-discounting parameter β was truncated at zero and skewed to the right, resembling an exponential distribution. Therefore, we took

the log transform of β to make the data more Gaussian. We assessed each participant's personality traits with the 60-item Neuroticism-Extraversion-Openness Five Factor Inventory (Costa and McCrae, 1992). The influence of personality factors on temporal discounting was analyzed by calculating Pearson correlations between personality factors and the discounting parameters α and $\log(\beta)$. Based on our hypotheses, we examined correlations of neuroticism and conscientiousness on an *a priori* basis, but also performed an exploratory analysis of extraversion, agreeableness, and openness.

As hypothesized, conscientiousness was positively correlated with α ($r = .47$, $p = .002$). Neuroticism was negatively correlated with α ($r = -.41$, $p = .008$) (Figure 2.2). The other three personality factors did not correlate with α ($p > .13$). However, our hypotheses regarding β were not supported, as there were no correlations between personality and $\log(\beta)$ ($p > .33$). The correlation with α indicates that personality was related to impulsivity differences and deviations from exponential discounting toward hyperbolic discounting. The lack of correlation between personality and $\log(\beta)$ indicates that personality was not related to exponential discounting when separating impulsivity from the exponential parameter. In addition, conscientiousness was negatively correlated with neuroticism in these participants ($r = -.33$, $p = .037$). There were no significant correlations between α and $\log(\beta)$, or between either α or $\log(\beta)$ and variation in cognitive abilities as measured by an IQ estimate or two measures of working memory capacity.

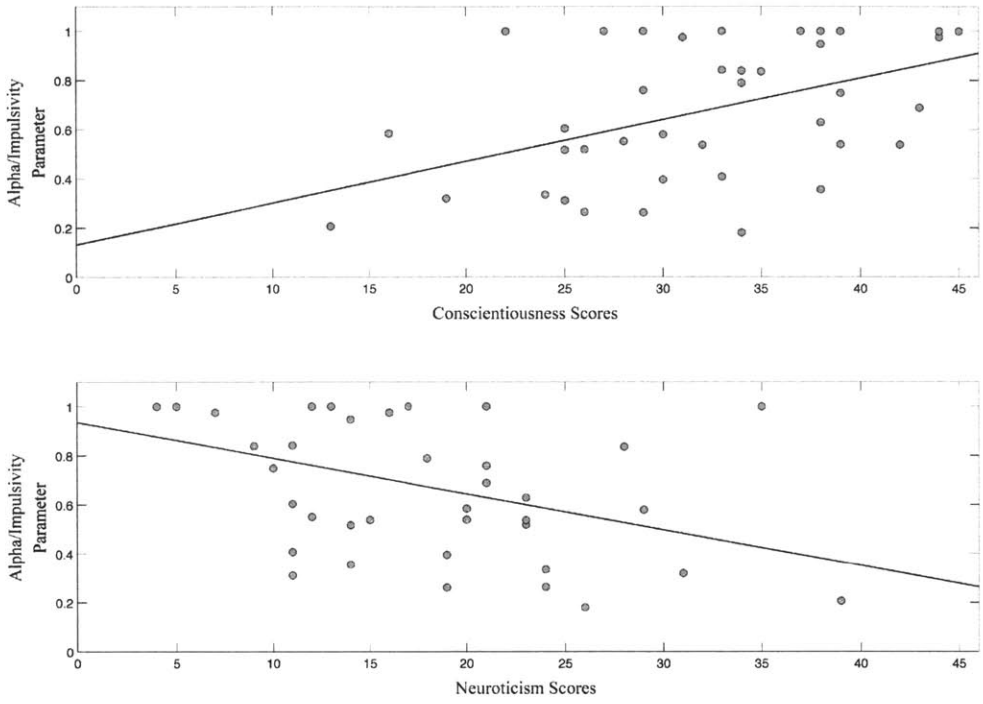

Figure 2.2. Scatter plot for each individual's conscientiousness score and α (top), and for each individual's neuroticism score and α (bottom).

Because α is constrained at 1, it is difficult to assess the normality of α. Therefore, we also calculated the Spearman rank correlations between personality factors and discounting parameters α and $\log(\beta)$. The results were highly similar to the Pearson correlations. Conscientiousness was positively correlated with α ($r = .44$, $p = .005$) and neuroticism was negatively correlated with α ($r = -.40$, $p = .005$). As with the Pearson correlation there were no significant correlations between $\log(\beta)$ and personality traits. There were also no correlations between either α or $\log(\beta)$ and variation in cognitive abilities as measured by an IQ estimate or two measures of working memory capacity. However, α and $\log(\beta)$ were negatively correlated using the Spearman rank correlation ($r = -.79$, $p < .001$).

We did not find the correlation between α and log(β) using the Pearson correlation that we did with the Spearman correlation, which is likely due to the lack of normality. However, the significant negative Spearman rank correlation between these two parameters is consistent with the expected direction of the relationship. Increasing α is associated with greater shot-term patience and decreasing log(β) is associated with greater patience overall. Therefore, the negative correlation supports the expected relationship between the two parameters. All correlations were calculated in separate models. We also assessed the goodness-of-fit of the constant sensitivity model. The model was fit separately to the 40 participants. The model was a good fit for 85% of the participants using a χ^2 threshold of .05.

We also asked participants to report annual income in eight income brackets from $0 to over $250,000. Greater income was marginally correlated with lower α ($r = -.33$, $p = .055$). Many participants were young adults in college or graduate school, so there may have been an atypical relation between present and anticipated future earnings.

2.3.2 fMRI Results

Subjective Value In Relation to Choosing Shorter vs. Longer Delays

We examined the relations of neuroticism and conscientiousness to intertemporal choice in the brain because only these personality factors correlated behaviorally with such choices. Because neuroticism and conscientiousness were negatively correlated, two

separate second level group analyses were conducted to avoid collinearity between the two personality dimensions. We estimated each participant's utility surplus, the difference in the subjective value between the option chosen and the option not chosen, on each trial. The first contrast examined the utility surplus, relative to each participant's subjective value (SV) of the two options presented, between trials where a shorter delay was chosen versus those where a longer delay was chosen (Utility Surplus Short vs. Utility Surplus Long). There were no significant activations correlated with neuroticism. However, greater conscientiousness correlated positively with increased activation in the ventral and dorsal striata, bilateral dorsolateral prefrontal cortex (DLPFC), left orbitofrontal cortex (OFC), precuneus, and bilateral superior parietal lobe (Figure 2.3 and Supplementary Table 2).

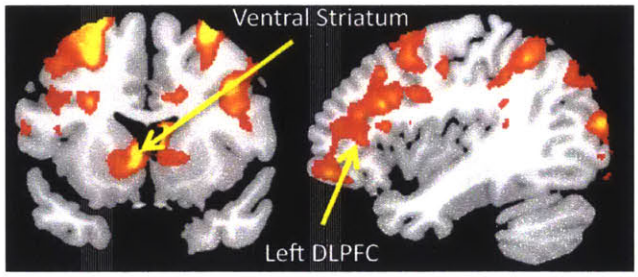

Figure 2.3. Contrast images for Utility Surplus Short vs. Utility Surplus Long with conscientiousness as the covariate. Peak voxel of the ventral striatum: t = 3.77, MNI coordinates: (-6, 15, 3). Peak voxel of the left middle frontal gyrus: t = 3.12, MNI coordinates: (-41, 24, 25) (clusterwise $p_{FDR} < .05$).

The second contrast examined utility surplus, relative to each participant's SV of the two options presented, between selecting a longer delay versus a shorter delay (Utility Surplus Long vs. Utility Surplus Short). There were no significant activations correlated with conscientiousness, but greater neuroticism correlated positively with greater

activations in the ventral striatum, bilateral DLPFC, bilateral insula, anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), and bilateral OFC (Figure 2.4). Next we examined the variation in the left and right ventral striatum activations that associated personality and intertemporal choice (Figure 2.5). Individual parameter values were extracted from the overlap between the anatomically defined head of the caudate, which includes surrounding tissue of the ventral striatum (WFU_PickAtlas, Maldjian et al., 2003), and the larger clusters of correlation between the two personality factors and intertemporal choices that were found in each second-level analyses (i.e., conscientiousness in Figure 2.3 and neuroticism in Figure 2.4). Contrast values were then extracted from each individual's first-level contrast images. The Utility Surplus Short vs. Utility Surplus Long contrast correlated with conscientiousness and the Utility Surplus Long vs. Utility Surplus Short contrast correlated with neuroticism. Increasing contrast values from the first level contrast map were positively associated with personality scores.

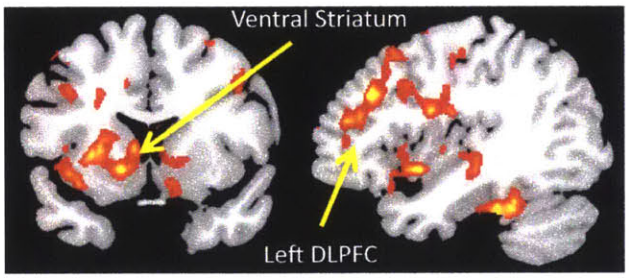

Figure 2.4. Contrast images for Utility Surplus Long vs. Utility Surplus Short with neuroticism as the covariate. Peak voxel of the ventral striatum: t = 3.36, MNI coordinates: (-14, 10, -6). Peak voxel of the left middle frontal gyrus: t = 4.08, MNI coordinates: (-37, 29, 30) (clusterwise $p_{FDR} < .05$).

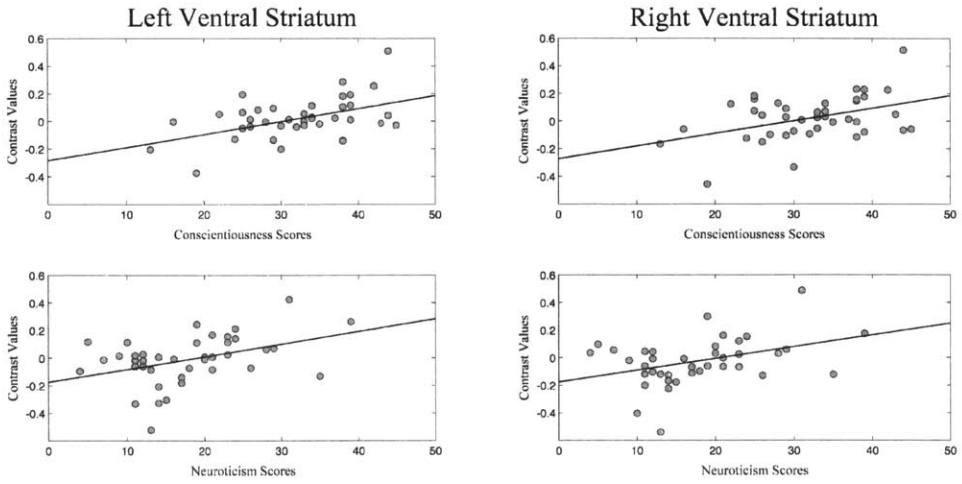

Figure 2.5. Scatter plots for each individual's conscientiousness score vs. fMRI contrast parameter values for the left ventral striatum and right ventral striatum for the contrast Utility Surplus Short > Utility Surplus Long, and for each individual's neuroticism score vs. left ventral striatum and right ventral striatum for the contrast Utility Surplus Long > Utility Surplus Short. Contrast values were extracted from each individual's first level contrast map.

There were apparent similarities in activations associated with both personality dimensions of conscientiousness and neuroticism, and these apparent co-localizations were statistically examined in a conjunction analysis (Nichols et al., 2005) (FDR corrected threshold of $p < .05$). There was indeed substantial overlap in the brain regions associated with conscientiousness or neuroticism (Figure 2.6). Selecting the option that was behaviorally opposed to a person's discounting tendency (i.e., selecting the shorter delay for a person with high conscientiousness or selecting the longer delay for a person with high neuroticism) was associated with widespread activation of areas associated with reward (ventral striatum) and with cognitive control (DLPFC).

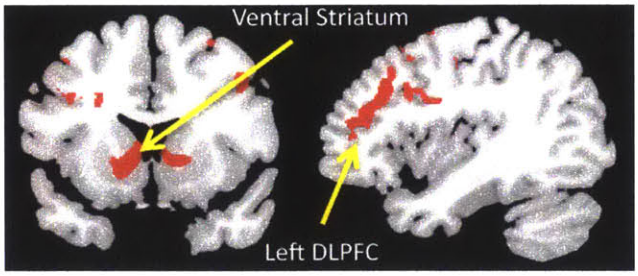

Figure 2.6. Overlap between the two contrast images: (1) Utility Surplus Short vs. Utility Surplus Long with conscientiousness as the covariate and (2) Contrast images for Utility Surplus Long vs. Utility Surplus Short with neuroticism as the covariate.

To be certain that these fMRI results were not due to working harder or taking longer when choosing the option that was behaviorally opposed to a person's discounting tendency, we analyzed the correlations between neuroticism and response time when the longer delay was chosen and between conscientiousness and response time when the shorter delay was chosen. There were no significant correlations in either case (ps > .21). High neuroticism scores were not associated with taking longer when choosing the longer delay, nor were high conscientiousness scores associated with taking longer when choosing the shorter delay.

2.4 Discussion

Economists and psychologists have described many differences in people's discounting preferences and behaviors (Frederick et al., 2002), and here we describe a convergence of behavioral economics, personality, and brain function that appears to contribute to such individuality. With respect to personality, higher conscientiousness correlated positively with lower short-term impatience and more exponential time preferences, while higher

neuroticism correlated positively with higher short-term impatience and less exponential time preferences. Thus, the estimated discount functions of people with high neuroticism implies strong impatience for short delays, but relatively less impatience when the same trade-off between delay and monetary amount is moved into the future. This discounting profile would promote temporally inconsistent behavior, where a decision made in the morning might be reversed in the evening. In contrast, the discount functions of people with high conscientiousness exhibit both lower impatience with respect to short term delays, as well as more time consistency.

The relation between personality and temporal discounting can be illustrated with examples of differences in subjective values for immediate versus delayed rewards for the participant who had the highest neuroticism score versus the participant who had the highest conscientiousness score. Assume that both are offered the option of $8 now or $10 in five days. Using their implied discount model, for the highly neurotic person, the subjective value of $10 in five days was $4.87, which was lower than the subjective value of $8 now. For the highly conscientious person the subjective value of $10 in five days was $9.93, which was higher than the subjective value of $8 now. Therefore, the highly neurotic person will choose the $8 now while the highly conscientious person will choose the $10 in five days.

We did not observe significant relations between cognitive measures of a verbal IQ estimate or two complex working memory tasks conceptualized as indexing executive functions. This differs from prior findings that related higher scores on measures of intelligence and working memory capacity with lower temporal discounting (Shamosh & Gray, 2008; Shamosh et al., 2008) and the interaction of extraversion and emotional

stability/reversed neuroticism with cognitive ability and temporal discounting (Hirsch et al., 2008). The lack of convergence with our data may reflect a restricted high range of cognitive abilities in the present study (Mean IQ = 120). In any case, the absence of a relation between cognitive measures and temporal discounting in the present study indicates that influence of personality on temporal discounting preference was not secondary to variation in cognitive ability.

With respect to brain function, the regions activated have been observed in prior studies of temporal discounting, such as those associated with reward (e.g., striatum) and cognitive control (e.g., prefrontal cortex) (Kable & Glimcher, 2007; McClure et al., 2004), but the activations showed a novel pattern in relation to personality. Greater activations in the brain regions occurred as options were chosen that were contradictory to personality preferences, i.e., when more conscientious people chose the shorter delay or more neurotic people chose the longer delay. Many of these contradictory choices were rational, but it appears that making a choice that contradicts a disposition may require more mental resources that are reflected in greater activations. This is analogous to evidence of greater brain activation when people perform tasks that are inconsistent versus consistent with cultural preferences (Hedden et al., 2008). The present findings may be contrasted with other conditions of temporal discounting in which reward regions respond selectively to immediate rewards whereas regions associated with cognitive control respond similarly to immediate and delayed rewards (McClure et al., 2004). Here, brain regions supporting reward and cognitive control appeared to operate in an integrated fashion for an economic decision that was contradictory to personality preferences.

Prior studies have related individual differences in impulsivity to variation in temporal discounting and in brain function. One study found a relation between individual differences in trait impulsivity, measured by a questionnaire, and activation in MPFC (Sripada et al., 2011). Another study dissociated the subjective valuation stage from the choice stage in such decisions and found that greater impulsivity, measured by preferences in intertemporal choices, was associated with reduced activations in lateral prefrontal regions at the choice stage (Liu et al., 2012). Other similar cognitive control regions, including the DLPFC, showed a greater decrease in activation for delayed reward in impulsive discounters (Ballard & Knutson, 2009). Impulsive discounters also showed decreased activation in the ventral striatum while responding to delayed rewards (Ballard & Knutson, 2009; Ripke et al., 2012), but showed increased activation in the ventral striatum while anticipating the outcome of a delayed reward (Jimura et al., 2013). People with high trait impulsivity showed decreased activation in the nucleus accumbens/ventral striatum when successfully resisting choosing suboptimal immediate rewards (Diekhof et al., 2012). Although the NEO-FFI does not provide a direct measure of impulsivity, neuroticism scores have been associated with high impulsivity (Whiteside & Lynam, 2001). The present study is thus in accord with these prior neuroimaging studies in identifying the ventral striatum, MPFC, and DLPFC regions as being related to personality-related variation in intertemporal choice.

The present findings occurred in the context of a specific model of temporal discounting, constant sensitivity, and a specific experimental measure of temporal discounting. The constant sensitivity model allowed for separation of pure discounting or impatience, represented by β, which was not associated with personality variation, from impulsivity/short-term impatience and preference consistency, represented by α, which was associated with variation in both conscientiousness and neuroticism. Other discounting models, such as the simple hyperbolic model, do not separate discounting from impulsivity (both are captured in a single parameter). Another feature of our experimental measure that may be beneficial for estimating discount rates was the adaptive procedure used in some of the trials. The adaptive procedure ensured that participants were presented with difficult trials with options near their indifference point, which is important for estimating the model more accurately for each individual.

The present study documented individual differences in economic decision-making and brain function in relation to two fundamental dimensions of human personality, conscientiousness or neuroticism. These personality factors have wide-ranging relations to important human behaviors and outcomes. These two personality factors are predictive of job performance (Hurtz & Donovan, 2000), and in longitudinal studies higher conscientiousness is a predictor of longevity (Friedman et al., 1993) and lower risk for Alzheimer's disease (Wilson et al., 2007). The present study suggests that these personality factors are associated with quite different valuations of the short-term and the long-term, but that both factors are associated with predispositions that require similar integrated neural resources of reward and cognitive control regions when a specific choice violates that predisposition. Thus, the mental and neural characteristics associated

with stable personality traits wield considerable power over the choice between immediate and delayed gratification.

3. The Frontal-Striatal Network is Associated with Increased Patience and Decreased Impulsivity in Temporal Discounting

Temporal discounting preferences reflect how a person makes decisions that involve tradeoffs over time, and people vary widely in their temporal discounting preferences. These economic decisions involve brain regions associated with reward and executive control. A fundamental question is what neurobiological networks underlie these differences in preferences. We investigated how resting-state intrinsic functional brain organization (functional connectivity) with the nucleus accumbens, a region associated with reward, varies with differences in temporal discounting preferences. Functional connectivity of the reward system was analyzed by calculating whole-brain temporal correlations with bilateral nucleus accumbens. This functional connectivity was related to each participant's constant-sensitivity discount function that dissociates impatience (devaluation of future consequences) from time sensitivity (consistency with rational, exponential discounting). Increased patience and decreased impulsivity were associated with significantly stronger functional connectivity between the nucleus accumbens and prefrontal executive control regions, including the dorsolateral prefrontal cortex. These findings reveal that the strength of the underlying functional frontal-striatal network is associated with differences in temporal discounting preferences.

3.1 Introduction

People often face decisions involving the tradeoff between immediate and delayed gratification. These decisions reflect preferences that vary across individuals (Shamosh et al., 2008). Psychological factors, including differences in intelligence, working memory (Shamosh et al., 2008) and personality (Hirsh, Morisano, & Peterson, 2008; Manning et al., 2014) have been related to differences in intertemporal choice or temporal discounting. Here, we asked whether variation in the intrinsic functional organization of the brain, in particular reward-related regions, is associated with differences in temporal discounting preferences. We examined the relation between individual differences in temporal discounting and individual differences in the intrinsic functional organization (functional connectivity) of the brain as measured from resting-state fMRI, which identifies neural networks as defined by regions exhibiting correlated, low-frequency fMRI signals in the absence of external stimuli (Biswal et al, 1995; Fox et al, 2005).

Individual differences in intertemporal choice can be modeled with temporal discounting models that reflect an individual's subjective present value (utility) of money or goods obtained at a specific point in time. This subjective value decreases as the receipt of money or a good is moved further into the future (Fredrick et al., 2002). We investigated how the magnitude of discounting parameters from the constant sensitivity discounting model, specifically patience and impulsivity, (Eq. 3.1; Ebert & Prelec, 2007; Bleichrodt et al., 2009), are associated with patterns of resting-state functional connectivity networks. The constant sensitivity model has an advantage over other models because it consists of two parameters that separately measure two components of discounting. One parameter measures impatience (pure discounting), which reflects how much weight

people place on future outcomes. The other parameter measures impulsivity, which reflects inconsistent discounting preferences. For example, a person's preferences in the beginning of the week might be to decide to exercise rather than relax during the upcoming week, but his preferences later in the week would be the opposite.

Neuroimaging studies have shown that activation in reward and executive control regions are associated with decision making involving temporal discounting. A key region in the reward system, the ventral striatum, which includes the nucleus accumbens (NAcc), exhibited higher levels of activation when people chose immediate rewards over delayed rewards, whereas regions associated with executive control, such as the dorsolateral prefrontal cortex (DLPFC), were associated with the value of the delayed rewards (McClure et al., 2004). In addition, lateral prefrontal cortex has a causal role in the executive control needed to select delayed rewards (Figner et al., 2010). The subjective value of rewards, calculated as a hyperbolic discount function, was associated with activation in both the ventral striatum and prefrontal cortex (Kable & Glimcher, 2007). The functional connectivity strength between the ventromedial prefrontal cortex (vmPFC), another region associated with a person's subjective value (Bartra et al., 2013), and the DLPFC predicted hyperbolic discount rates during a temporal discounting task (Hare et al., 2014). When choosing rewards with longer delays compared to rewards with shorter delays there was greater functional connectivity between the DLPFC and the striatum during a temporal discounting task (van den Bos et al., 2014). Thus, interactions between ventral striatal reward regions and DLPFC appear to subserve decision making for immediate versus delayed rewards.

Two studies have shown a relation between transient functional connectivity and intertemporal choice on a decision-by-decision basis (Hare et al., 2014; van den Bos et al., 2014), but little is known about sustained or trait-like functional connectivity that would be associated with stable individual differences for such decisions. Such sustained functional connectivity can be measured during rest in the absence of task performance. One study showed that the strength of the functional connectivity between a network of brain regions, using a region of interest (ROI) analysis, that were associated with the magnitude of reward (money) were positively correlated with hyperbolic discount rates (increased impulsivity), whereas the strength of the functional connectivity between the network of regions associated with delay were negatively correlated with hyperbolic discount rates (decreased impulsivity) (Li et al., 2013).

Here, we focused specifically on the ventral striatal region most associated with reward anticipation, the nucleus accumbens (NAcc) (Knutson et al., 2001a; Knutson et al., 2001b), and how variation in its intrinsic functional connectivity relates to variation in temporal discounting. We related variation in resting-state functional connectivity of the NAcc to variation in levels of impatience levels and impulsivity (Ebert & Prelec, 2007; Bleichrodt et al., 2009), (Eq. 3.1). We hypothesized that increased functional connectivity between the reward-sensitive NAcc and executive control regions (DLPFC) would be associated with increased patience and decreased impulsivity, as measured by the parameters of the constant sensitivity discount function.

3.2 Methods

3.2.1 Participants

Participants were 35 healthy young adults (right handed, mean age 25.1 years, 19 females). All participants were right handed and screened for prior neurological disorders. One participant was excluded from the analysis due to excessive movement. All participants gave informed consent.

3.2.2 Procedure

All participants completed a standard temporal discounting task. Participants were presented with 108 trials consisting of two options: (1) a smaller monetary reward with a shorter delay and (2) a larger monetary reward up to $150 with a longer delay. Participants were informed that one of their choices would be randomly selected as a true payoff. Options were presented side-by-side, and the order and side of shorter and longer delays was fully counterbalanced across trials (Figure 2.1). Sixty trials contained delays of 0 (immediate), 21, 60, 180, and 365 days, with rewards ranging from $30 to $150. These intervals were selected to approximate log(time) intervals. The remaining 48 of the 108 trials were adaptive. This adaptive method assured that some trials provided options that were close to equivalent in subjective value. The model was fit to all trials, both fixed and adaptive options. This design enhanced the accurate estimation of the discounting model by increasing the number of observations most sensitive to a participant's subjective value in decision making. For the adaptive trials one of the options was always an immediate reward and the other was a delayed reward of $60 and

$150 at each of the four delays. The immediate alternatives for each reward/delay pair were determined in an adaptive fashion using a staircase procedure. The starting value of the immediate alternative for each reward/delay pair was determined from the participant's behavior during a practice session (described below). Using the starting values from the practice session increased the likelihood that the adaptive trials in the experimental/non-practice session would more rapidly converged toward each participant's indifference point. Depending upon the participant's responses to these trials, the next immediate reward was either raised or lowered, with the increments of change becoming successively smaller in log amounts. The minimum reward for adaptive trials varied across participants dependent on the adaptive reward values from the staircase procedure. Participants received the reward from their choice on a randomly selected trial as a check. If there was a delay for the selected choice, a check was mailed to the participants at the scheduled date.

Figure 3.1. Example trial: Each option consisted of a dollar amount paired with a delay. The side of the shorter and longer delays were counterbalanced across trials.

Prior to the experimental session participants received 96 practice adaptive trials with the same delays used in the practice session. Starting values of $60 and $150 were paired with the delays and were adapted using the procedure above. The first staircase trial for each delayed reward was paired with an immediate reward alternative that was 1/2 of the log-delayed amount (rounded to the nearest dollar). Depending upon the participant's responses to these trials, the next immediate reward was either raised or lowered, with the increments of change becoming successively smaller in log amounts. The final values from this adaptive procedure were used as starting values for the adaptive trials during experimental session.

3.2.3 Discounting Analysis

Data from the discounting task in the experimental session were used to model each participant's subjective value using the constant sensitivity discounting function (Ebert & Prelec, 2007; Bleichrodt et al., 2009), (Eq. 3.1), which allows formal separation of impatience levels and impulsivity. In this model, α represents impulsivity and β is a measure of pure exponential discounting or impatience. Time-sensitivity is measured by α. Rational compound discounting is equivalent to $\alpha = 1$. As α decreases, people become increasingly insensitive to differences between future time points. The limiting case $\alpha \sim 0$ yields dichotomous discounting, where an individual only distinguishes between 'now' and 'later,' treating all future dates as equivalent. This would promote extreme inconsistency in inter-temporal choices. Pure exponential discounting or impatience is measured by β. As β increases, people become more impatient, but does not affect the consistency of time preferences. In principle, inter-subject variation in α and β across people describes individual differences in temporal discounting. Maximum likelihood

estimation, with the softmax activation function (Eq. 3.2) for the likelihood, was used to obtain the parameter estimates α and β from equation 1, and θ, the inverse temperature or slope parameter from the softmax function. θ reflects a random element in choice. θ =0 represents a person that choses completely at random. As θ increases a person is more likely to choose the option with the highest subjective value.

Equation 3.1.

$$f(t) = \exp\left(-(\beta t)^{\alpha}\right)$$

Equation 3.2.

$$p(Option\ Chosen_i) = \frac{e^{\theta \times f(t_i) * Reward\ Chosen}}{e^{\theta \times f(t_i) * Reward\ Chosen} + e^{\theta \times f(t_j) * Reward\ Rejected}}$$

3.2.4 fMRI Acquisition

Data were acquired using a 3-Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with a 12-channel phased array whole-head coil. 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) anatomical images (TR = 2530ms, TE = 2.98ms, flip angle = 9°, 1 mm slice thickness, 1x1 mm^2 in plane resolution) and one 5 minute resting state scan was collected while participants fixated on a cross (T2* weighted gradient echo TR/TE/Flip = 2000ms/30ms/90°, 74 contiguous interleaved oblique slices, voxel size: 3 X 3 X 3). The sequence included prospective acquisition correction (PACE) for head motion (Thesen et al, 2000).

3.2.5 fMRI Analysis

The functional data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were preprocessed with realignment for motion correction, artifact detection (threshold of z = 3 relative to the mean intensity), and spatial smoothing (6mm full-width-half-maximum Gaussian kernel). To address any spurious correlations in resting-state networks caused by head motion, we used the Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect) to identify problematic time points during the scan. Specifically, an image was defined as an artifactual time point if the head displacement in x, y, or z direction was greater than .5 mm from the previous frame, or if the global mean intensity in the image was greater than 3 standard deviations from the mean image intensity for the entire resting scan. CompCor was used to estimate physiological and other sources of noise (Behzadi et al, 2007). Global signal regression was not used because it has been shown to bias and produce spurious negative correlations (Murphy et al, 2009; Saad et al, 2012). Anatomical volumes were segmented into grey matter, white matter, and cerebrospinal fluid (CSF) areas and the resulting masks were eroded (one voxel erosion) to minimize partial volume effects. The temporal time series characterizing the estimated subject motion (3 rotation and 3 translation parameters, plus another 6 parameters representing their first-order temporal derivatives) and artifactual covariates (one covariate per artifactual time point consisting of 0's everywhere and a "1" for the artifactual time point), as well as the blood oxygen level-dependent (BOLD) time series within the subject-specific white matter mask (3 PCA parameters) and CSF mask (3 PCA parameters), were used as temporal covariates and

removed from the BOLD functional data using linear regression, and the resulting residual BOLD time series were band-pass filtered ($0.009Hz < f < 0.08Hz$).

Left and right NAcc were *a priori* regions of interest (ROI) to be used as seeds in the functional connectivity analysis. The seeds were selected independently from reward activation studies in the literature. Two 5mm ROIs, one on the left and one on the right, from the center of activation in the NAcc regions (MNI: (-8,12,1), (11,11.,1); Figure 3.2) were selected from areas that showed increased activation to reward anticipation from Knutson et al. (2001b).

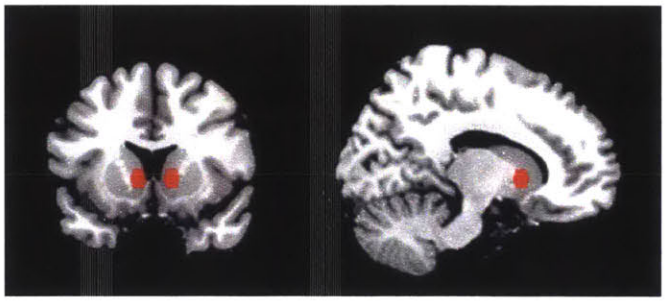

Figure 3.2. Nucleus Accumbens Seed. Bilateral nucleus accumbens seed used in resting-state functional connectivity analysis. MNI coordinates: (-8,12,1), (11,11,1).

First-level correlation maps were produced by extracting the residual BOLD time course from each seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed z-scores using the Fisher transformation to allow for second-level General Linear Model analysis. One sample t-tests with the discounting parameters α and β as second level covariates were performed on the Fisher transformed r-maps to examine the relationship between discounting and resting-state functional connectivity networks. All results were reported using a cluster-wise false discovery rate (Cluster-wise FDR)

threshold of .05 for multiple comparisons. All analyses were performed in the volume and the results were projected to an inflated cortical surface for visualization.

3.3 Results

We examined the whole-brain correlations between the bilateral NAcc and the discount parameter, β, and the impulsivity parameter, α, from the constant sensitivity function. A large β is associated with preferences for relatively shorter delays and a small β is associated with preferences for relatively longer delays. As hypothesized, there was increased functional connectivity between the NAcc and executive control regions as β from the constant sensitivity model (Eq. 3.1) decreased and people were more patient (Table 3.1). The cluster of regions that showed increased functional connectivity with the bilateral NAcc (FDR corrected, $p < .05$) and were also negatively correlated with β include the left DLPFC/BA9/BA46, left anterior PFC/BA10, left dorsal PFC/BA8, vmPFC, left premotor cortex, and dorsal anterior cingulate cortex (dACC) (Figure 3.3; peak voxel – MNI: -36, 38, 24). We then created one ROI that included all of these regions and extracted the regression coefficients for β for each voxel. The mean coefficient of β for this ROI was significantly less than zero (mean = -1.37, $p < .001$, two-tailed; Table 3.1). There were no regions with significant positive correlations with β.

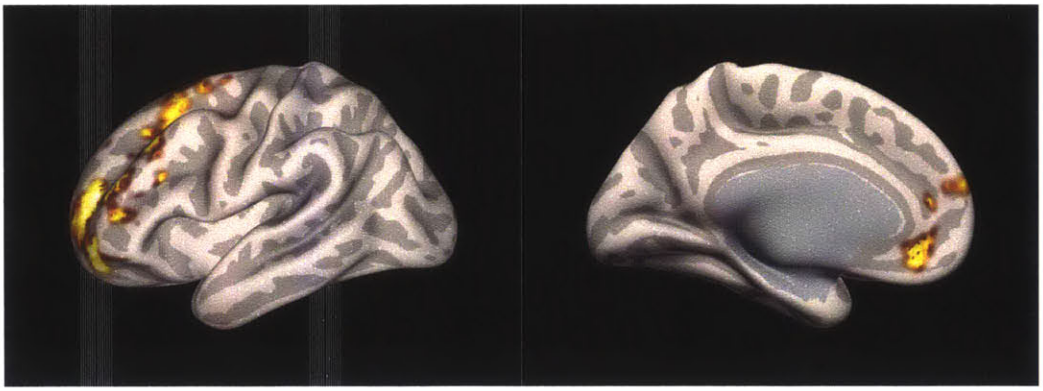

Figure 3.3. Resting-state functional connectivity with bilateral nucleus accumbens for regions that are negatively correlated with constant sensitivity discount parameter β (Cluster-wise FDR corrected, p = .05). Negative correlations with β represent greater overall patience.

As hypothesized, there was increased functional connectivity between the NAcc and executive control regions as α from the constant sensitivity model (Eq. 3.1) increased and people had increased short-term patience and more consistent time preferences (Table 3.1). The cluster of regions that showed increased functional connectivity with the bilateral NAcc (FDR corrected, $p < .05$) and were also positively correlated with α include left DLPFC/BA9/BA46, left dorsal PFC/BA8, left premotor cortex and left insula (Cluster 1; peak voxel – MNI: -42, -14, 20), ventral and dorsal posterior cingulate cortex (PCC), retrosplenial cortex/BA29/BA30, and anterior and posterior entorhinal cortex (Cluster 2; peak voxel – MNI: 10, -54, -34), and left posterior parietal cortex, left angular gyrus, left inferior, middle and superior temporal gyrus, left associative visual cortex/BA19, and left supramarginal gyrus (Cluster 3; peak voxel – MNI: -56, -2, -3) (Figure 3.4. We then created one ROI that included all of these regions and extracted the regression coefficients for α for each voxel. The mean coefficient of α for this ROI are significantly greater than zero (mean = .1669, $p < .001$, two-tailed; Table 3.1). There

were no significant negative correlations with α or decreased patience, as we also found with β.

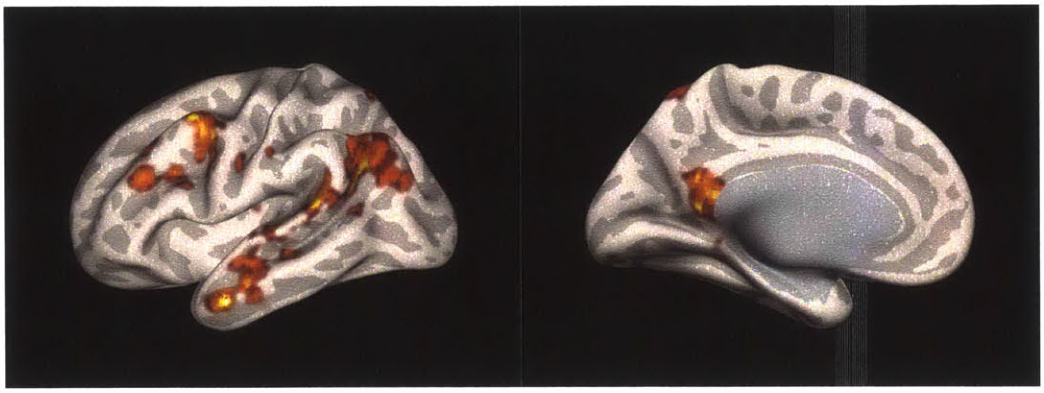

Figure 3.4. Resting-state functional connectivity with the bilateral nucleus accumbens for regions that are positively correlated with constant sensitivity discount parameter α (Cluster-wise FDR corrected, p = .05). Positive correlations with α represent increased rational/consistent time preferences and lower impulsivity.

Mean Regression Coefficients for Constant Sensitivity Parameters

Seed	Parameter	Mean Coefficient	p
NAcc	β	-1.370	< .0001
	α	0.1669	< .0001

Table 1. Mean regression coefficients for second level functional connectivity analysis. Mean coefficient for β is calculated from all significant voxels in Figure 3.3. Mean coefficient for α is calculated from all significant voxels in Figure 3.4.

3.4 Discussion

Temporal discounting preferences were associated with the strength of the intrinsic functional brain organization of the frontal-striatal network. Positive temporal

correlations between the reward-sensitive NAcc and executive control regions of the prefrontal cortex were associated with both increased patience and decreased impulsivity, as measured by the constant sensitivity discount function. The increased functional connectivity between the NAcc and regions in the prefrontal cortex, including the DLPFC, vmPFC, anterior PFC, and dorsal PFC, was associated with shallower exponential discounting, reflected in smaller β from the constant sensitivity discount function. Similarly, increased functional connectivity between the NAcc and regions in the prefrontal cortex, including the DLPFC and dorsal PFC, was associated with lower impulsivity and increased short-term patience, reflected in larger α. In addition, the PCC and lateral cortical regions in the temporal lobe and posterior parietal lobe were also associated with larger α, which have previously been found to be associated with subjective value in temporal discounting tasks (Kable & Glimcher, 2010). There were no regions that showed increased functional connectivity with the NAcc with either decreased patience or increased impulsivity.

Variation in functional connectivity of the NAcc that was associated with variation in temporal discounting was strongly left lateralized. Previous research has shown that as the delay increases in, activation in the left DLPFC, but not right DLPFC, decreases (Ballard & Knutson, 2009). Increasing the delay of a reward decreases its subjective value, which may lead to lower recruitment of executive control regions such as the DLPFC. A subsequent study established a causal relationship between the deactivation, using transcranial magnetic stimulation, of the left DLPFC and preference for immediate rewards (Figner et al., 2011). Our results are consistent with these studies and show increased patience and decreased impulsivity is associated with greater functional

connectivity between the reward region of the NAcc and the left DLPFC, but not the right.

Temporal discounting preferences vary widely across individuals (Shamosh et al., 2008; Hirsh, Morisano, & Peterson, 2008; Manning et al., 2014). While many factors may be associated with these differences, one important factor may be the underlying neurobiological network associated with discounting. Two major networks involved with discounting are the reward and executive control networks (McClure et al., 2004). However, there is debate about the nature of reward and executive control networks and their relation to impatience and impulsivity. One possible function of the reward network is to respond to immediate rewards, whereas a possible function of the executive control network is to respond to delayed reward (McClure et al., 2004). Another possibility is that reward networks and the prefrontal cortex respond to both immediate and delayed rewards (Kable & Glimcher, 2010).

In the present study, functional connectivity between the reward and cognitive control networks in the resting-state brain was associated with individual differences in temporal discounting. People who were more patient and less impulsive had significantly greater functional connectivity between the reward and prefrontal executive control networks. This supports our hypothesis that increased patience and decreased impulsivity is reflected in the strength of the functional connectivity between the NAcc and the PFC.

4. Altered Resting-State Functional Connectivity of the Frontal-Striatal Reward System in Social Anxiety Disorder

We investigated differences in the intrinsic functional brain organization (functional connectivity) of the human reward system between healthy control participants and patients with social anxiety disorder. Functional connectivity was measured in the resting-state via functional magnetic resonance imaging (fMRI). 53 patients with social anxiety disorder and 33 healthy control participants underwent a 6-minute resting-state fMRI scan. Functional connectivity of the reward system was analyzed by calculating whole-brain temporal correlations with a bilateral nucleus accumbens seed and a ventromedial prefrontal cortex seed. Patients with social anxiety disorder, relative to the control group, had (1) decreased functional connectivity between the nucleus accumbens seed and other regions associated with reward, including ventromedial prefrontal cortex; (2) decreased functional connectivity between the ventromedial prefrontal cortex seed and lateral prefrontal regions, including the anterior and dorsolateral prefrontal cortices; and (3) increased functional connectivity between both the nucleus accumbens seed and the ventromedial prefrontal cortex seed with more posterior brain regions, including anterior cingulate cortex. Social anxiety disorder appears to be associated with widespread differences in the functional connectivity of the reward system, including markedly decreased functional connectivity between reward regions and between reward regions and lateral prefrontal cortices, and markedly increased functional connectivity between reward regions and posterior brain regions.

4.1 Introduction

A fundamental goal of neuroscience is to understand the functional organization of brain networks that underlie neuropsychiatric disease. One prevalent disease is social anxiety disorder (SAD) (Kessler et al., 2005), a chronic psychiatric disorder characterized by fear of negative evaluation by others, which in turn leads to high levels of anxiety and avoidance of social situations (Hofmann et al, 2007). Multiple neuroimaging studies have focused on an increased amygdala response that is associated with social anxiety (Freitas-Ferrari et al., 2010). Here we asked whether there are also differences in SAD of the intrinsic functional organization of the reward system of the brain, i.e. brain regions that are activated by the anticipation or receipt of reward (Knutson et al., 2001a; Knutson et al., 2001b). We measured intrinsic functional organization from resting-state fMRI that identifies neural networks as defined by regions exhibiting correlated, low-frequency fMRI signals in the absence of external stimuli Biswal et al., 1995; Fox et al., 2005).

Animal and human research have converged to identify several brain regions that are consistently activated by reward, including the striatum, nucleus accumbens (NAcc), and ventromedial prefrontal cortical (vmPFC)/medial orbitofrontal (mOFC). The ventral striatum and NAcc are associated with reward anticipation (Knutson et al., 2001a; Knutson et al, 2001b), whereas the vmPFC is associated with receipt of reward (Knutson et al., 2001b). The vmPFC has also been shown to encode the value of reward outcomes in decision-making that requires action (Gläscher, Hampton, & O'Doherty, 2009). The vmPFC/mOFC likely plays a role in translating rewards to a representation of value (Montague & Berns, 2002). We were guided by this literature to select seeds (brain

locations) in the NAcc and vmPFC regions, and compare their intrinsic functional connectivity between the SAD and control groups.

Neuroimaging studies examining task-driven activations have indicated that the reward system is affected in SAD. People with SAD showed increased activation in the amygdala but decreased activation in OFC and vmPFC when anticipating negative emotional stimuli (Bruehl et al., 2011). SAD patients also showed increased temporal correlations between the amygdala and vmPFC/mOFC compared to healthy participants in resting-state functional connectivity (Liao et al, 2010). Striatal dysfunction also occurs in people with behavioral inhibition, a temperamental trait that is characterized by withdrawal from unfamiliar social situations and that might be a precursor of adult SAD (Bar-Haim et al, 2009). Behaviorally inhibited adolescents have shown altered striatal activation, including in the caudate and NAcc, to anticipated rewards and altered vmPFC activation for reward outcomes (Guyer et al, 2006; Helfinstein et al., 2011). Deep-brain stimulation of the NAcc was shown to decrease generalized anxiety, showing a causal role for the NAcc in anxiety (Bewernick et al., 2010). These results point to differences in the reward system between people who are socially anxious or behaviorally inhibited and those who are not.

Conceptually, it is plausible that SAD is associated with an altered reward circuitry. People typically find social interactions to be rewarding, but SAD patients often find such interactions to be aversive and anxiety provoking. Intrinsic functional connectivity may reflect chronic interactions among brain regions that mold large-scale functional networks. Reduced experience of social reward in SAD may be reflected by altered functional connectivity between the two major components of the reward system, which

are also associated with social reward, the NAcc and the vmPFC (Bartra, McGuire, & Kable, 2013). Translation of reward into reward value may involve interactions between NAcc and vmPFC, and decreased NAcc-vmPFC connectivity may reflect weakened translation of reward into reward value. We hypothesized that people with SAD would show decreased functional connectivity between the NAcc and the vmPFC.

4.2 Methods

4.2.1 Participants

Patients were recruited from the Center for Anxiety and Related Disorders at Boston University and the Center for Anxiety and Traumatic Stress Related Disorders at Massachusetts General Hospital. Control participants were recruited via advertisements from the community. Brain scans were performed at the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research at MIT. All participants gave written informed consent to all procedures. The procedures were approved by the Committee on the Use of Humans as Experimental Subjects at MIT, the Institutional Review Board at Boston University, and the Partners Human Research Committee at Massachusetts General Hospital.

Participants were 53 outpatients with SAD (generalized subtype; years with SAD: M = 16.8 years; age of onset: M = 13.4 years; age: M = 29.9 years; 44 right handed; 17 women) and 33 healthy Control participants (age: M = 29.4 years; 29 right handed; 14 women). The two groups did not differ significantly for mean age (Control: M = 29.4, *SD*

= 6.22; SAD: $M = 29.9$, $SD = 8.25$; $t(84) = .31$, $p = .76$), the proportions of men and women, ($\chi^2(1, N = 86) = .94$, $p = .33$), or the proportions of right-handed and left-handed individuals ($\chi^2(1, N = 86) = .37$, $p = .54$). Patient and Control groups did not differ significantly on IQ as estimated with the American National Adult Reading Test Full Scale Intelligence Quotient (Wechsler, 1981) (Control: $M = 118.6$, $SD = 7.22$; SAD: $M = 117.3$, $SD = 6.63$, $t(84) = 87$, $p = .39$).

Patients were off concurrent psychotropic medication for at least two weeks prior to the scanning session. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV or the Anxiety Interview Schedule for DSM-IV (APA, 1994). The diagnosis and diagnostic subtype specifier was assessed with the Anxiety Disorders Interview Schedule IV Revised (ADIS-IV-R) by experienced clinicians. The severity of social anxiety was measured using the clinician-administered version of the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) with a minimum LSAS score of 60 as an additional inclusion criterion ($M = 81.85$; range: 60-121).

Exclusion from the study occurred in the case of a lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders or obsessive-compulsive disorder; an eating disorder in the past 6 months; a history of substance or alcohol abuse or dependence (other than nicotine) in the last 6 months and posttraumatic stress disorder within the past 6 months. Entry of patients with other mood or anxiety disorders was permitted if SAD was judged to be the predominant disorder. In addition to the primary diagnosis of SAD, 18 participants also met diagnostic criteria for comorbid major depression disorder and 16 participants for comorbid anxiety disorders (generalized anxiety disorder: n = 12; post traumatic stress disorder: n = 1; specific phobia: n = 7;

panic disorder: 3). Both SAD and Control participants were excluded in the case of neurological disorders or serious medical illness.

No clinically relevant conditions in the Control group were permitted and the absence of these was confirmed prior to study inclusion using the Structured Clinical Interview for DSM-IV (APA, 1994). Patients scored significantly worse on both the Social Phobia and Anxiety Inventory (SPAI) (Turner et al., 1989) (Control: $M = 36.7$, $SD = 23.76$); SAD: $M = 112.6$, $SD = 22.27$), $t(84) = 14.99$, $p < .0001$, two-tailed) and the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) (Control: $M = 30.0$, $SD = 7.01$; SAD: $M = 54.8$, $SD = 10.51$, $t(83) = 11.97$, $p < .0001$, two-tailed). One SAD patient was missing the STAI score and was not included in this t-test.

4.2.2 fMRI Acquisition

Data were acquired using a 3-Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with a 32-channel phased array whole-head coil. 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) anatomical images (TR = 2530 ms, TE = 3.39 ms, flip angle = 9°, 1 mm slice thickness, 1 mm^2 in plane resolution) and one 6-minute resting state scan were collected while participants fixated on a cross (T2* weighted gradient echo TR/TE/Flip = 6000ms/30ms/90°, 67 contiguous interleaved oblique slices, voxel size: 2 X 2 X 2). The sequence included prospective acquisition correction (PACE) for head motion (Thesen et al., 2000).

4.2.3 fMRI Analysis

The functional data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/softwar/spm8/). Functional images were preprocessed with realignment for motion correction, slice-time correction, artifact detection and spatial smoothing (8mm full-width-half-maximum Gaussian kernel). To address any spurious correlations in resting-state networks caused by head motion, we used the Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect) to identify problematic time points during the scan. Specifically, an image was defined as an artifactual time point if the head displacement in X, Y, or Z direction was greater than .5 mm from the previous frame, or if the global mean intensity in the image was greater than 3 standard deviations from the mean image intensity for the entire resting scan. A two-sample t-test was performed using the number of artifactual time points to compare the difference in motion between the Control group and the SAD group.

CompCor was used to estimate physiological and other sources of noise (Behzadi, et al., 2007). Global signal regression was not used because it has been shown to bias and produce spurious negative correlations (Murphy et al., 2009; Saad et al., 2012). Anatomical volumes were segmented into grey matter, white matter, and cerebrospinal fluid (CSF) areas and the resulting masks were eroded (one voxel erosion) to minimize partial volume effects. The temporal time series characterizing the estimated subject motion (3 rotation and 3 translation parameters, plus another 6 parameters representing their first-order temporal derivatives) and artifactual covariates (one covariate per artifactual time point consisting of 0's everywhere and a "1" for the artifactual time point), as well as the blood oxygen level-dependent (BOLD) time series within the

subject-specific white matter mask (3 first principal components) and CSF mask (3 first principal components), were used as temporal covariates and removed from the BOLD functional data using linear regression, and the resulting residual BOLD time series were band-pass filtered ($0.008\text{Hz} < f < 0.083\text{Hz}$).

NAcc and vmPFC were *a priori* regions of interest (ROI) to be used as seeds in the functional connectivity analysis. The seeds were selected from prior reward activation studies (and thus independent of group differences in the present study). In order to minimize the number of statistical comparison, the NAcc (left and right NAcc) and vmPFC seeds (three locations) respectively, were combined into two analyses. Two 5mm-radius ROIs, one on the left and one on the right, from the center of activation in the NAcc regions (MNI: (-8,12,1), (11,11,1); Figure 4.1) were selected from areas that showed increased activation to reward anticipation from Knutson *et al.* (2001b). Three 10mm-radius ROIs from the center of activation in the vmPFC (MNI: (-6,24,-21), (6,30,-9), (9,27,-12)) were selected from areas that showed increased activation to reward value from Gläscher *et al.* (2009). The NAcc seeds were smaller in volume because the NAcc is considerably smaller in volume than the vmPFC.

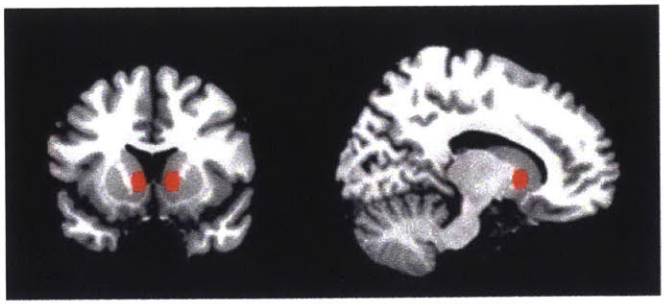

Figure 4.1. Nucleus Accumbens Seed. Bilateral nucleus accumbens seed used in resting-state functional connectivity analysis. MNI coordinates: (-8,12,1), (11,11,1).

The left and right NAcc ROIs both showed increased activation to reward anticipation simultaneously in the same study (Knutson et al., 2001b) and therefore were combined to create one NAcc seed. Similarly, the three vmPFC ROIs showed activation to reward value simultaneously in the same study (Gläscher, Hampton, & O'Doherty; 2009) and therefore were combined to create one vmPFC seed. Consistent with activation literature, both the individual NAcc locations and the individual vmPFC locations exhibited similar patterns of functional connectivity and similar alterations in the SAD group, which supported the validity of combining the individual locations into two seeds.

First-level correlation maps were produced by extracting the mean BOLD time course from each seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed Z-scores using the Fisher transformation to allow for second-level General Linear Model analysis. Two sample t-tests were performed on the Fisher transformed r-maps to examine the differences in resting state functional connectivity between Control and Patient groups. One set of t-tests examined differences for the bilateral NAcc seeds combined into a single network, and the other set of t-tests examined differences for the three vmPFC seeds combined into a single network. All results were reported using a cluster-wise false discovery rate (Cluster-wise FDR corrected) threshold of .05 for multiple comparisons. All analyses were performed in the volume and the results were projected to an inflated cortical surface for visualization.

4.3 Results

To ensure that results were not due to motion artifacts, we compared the number of artifactual time points in the SAD and Control groups. There was no significant difference between groups in the number of artifactual time points ($p = .35$).

4.3.1 Nucleus Accumbens Seed

Contrast: Control group > SAD group

The SAD group exhibited significant and widespread decreases in functional correlations (connectivity), compared to the Control group, between the NAcc seed (Figure 4.1) and multiple regions associated with reward, value, and decision-making, including vmPFC/BA11, bilateral medial anterior prefrontal cortex/BA10, bilateral inferior frontal gyrus, anterior regions of the dorsal anterior cingulate cortex (dACC), subgenual ACC, left temporal pole, left hippocampus, and bilateral putamen (Figures 4.2 & 4.3; Table 4.1). The region of maximal difference was a cluster that included the vmPFC, and in this cluster the Control group exhibited a significantly positive correlation, but the SAD group did not exhibit any significant correlation (Figures 4.2, 4.3, & 4.4).

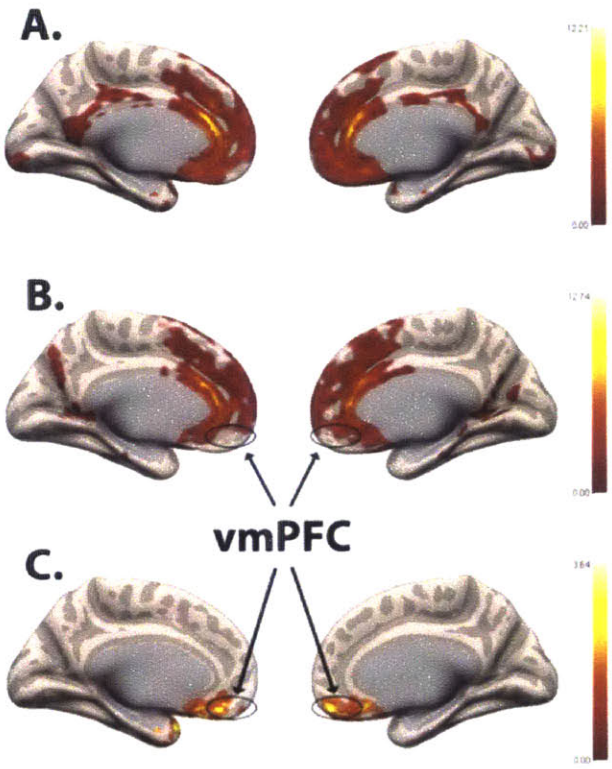

Figure 4.2. Nucleus Accumbens Seed Functional Connectivity Network of Control > SAD. Resting-state connectivity for **(A)** Control group, **(B)** SAD group, and **(C)** Control group > SAD group with bilateral nucleus accumbens seed from Figure 4.1 (Cluster-wise FDR corrected, $p < .05$; Peak voxel: (MNI Coordinates) (30, 12, -6; $p = .001$). (vmPFC = ventromedial prefrontal cortex)

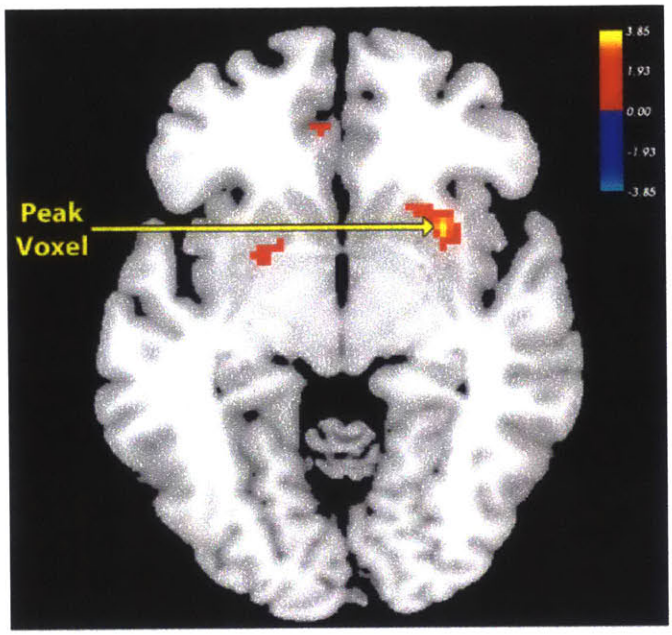

Figure 4.3. Peak Voxel Axial View for Nucleus Accumbens Seed Functional Connectivity Network of Control > SAD. Resting-state connectivity for Control group > SAD group with bilateral nucleus accumbens seed from Figure 4.1 (Cluster-wise FDR corrected, $p < .05$; Peak voxel: (MNI Coordinates) (30, 12, -6; $p = .001$). (vmPFC = ventromedial prefrontal cortex)

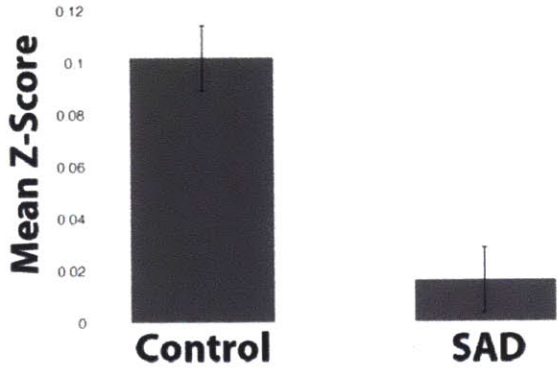

Figure 4.4. Nucleus Accumbens Seed Functional Connectivity Network Z-Scores of Control > SAD. Mean Fisher transformed correlation values for resting-state connectivity for ventromedial prefrontal cortex cluster from Figure 4.2C showing significant difference for Control group > SAD group with bilateral nucleus accumbens seed from Figure 4.1. Peak voxel (MNI coordinates): (30, 12, -6). Bars represent mean connectivity for each group for the ventromedial prefrontal cluster from Figure 4.2C. One-sample t-test relative to 0: Control: $p < .0001$; SAD: $p = .22$. Error bars represent standard errors.

Regions for Resting State-Connectivity Clusters

Seed	Contrast	MNI (X, Y, Z) Coordinates			Region	KE	p
NAcc	Control > SAD	30	12	-6	R. Putamen	1154	.001
	SAD > Control	0	-34	64	BA6	950	.006
vmPFC	Control > SAD: Cluster 1	-12	20	-20	BA25	1988	< .001
	SAD > Control: Cluster 1	6	-42	60	BA5	1273	.001
	SAD > Control: Cluster 2	20	-50	6	BA30	1056	.002
	SAD > Control: Cluster 3	-50	-56	-4	BA37	869	.006

Table 4.1. Regions of Significant Differences in Functional Connectivity Between SAD and Control Groups. MNI coordinates of peak voxels and statistical results of two-sample t-tests for functional connectivity contrasts.

To ensure that group differences were not the result of lower signal to noise ratio (SNR) in the vmPFC/mOFC cortex in the SAD group, we calculated the temporal SNR separately for the vmPFC cluster for each group. The SAD group had a higher temporal SNR in the vmPFC cluster (Control: $M = 141.95$, $SD = 32.85$; SAD: $M = 160.81$, $SD = 46.73$; $p < .046$, two-tailed). Therefore, increased functional connectivity in the Control group compared to the SAD group was not due to loss of signal in the SAD group.

Contrast: SAD group > Control group

The SAD group exhibited significant increases in connectivity, compared to the Control group, between the NAcc seed and more posterior regions including bilateral somatosensory association cortex, bilateral premotor cortex, bilateral primary motor cortex, and posterior ventral ACC (vACC) (Figure 4.5A; Table 4.1). The group differences reflected a pattern of negative correlations (anticorrelations) between the

NAcc seed and these posterior regions in the Control group versus a pattern of positive correlations between the NAcc seed and these regions in the SAD group (Figure 4.5B).

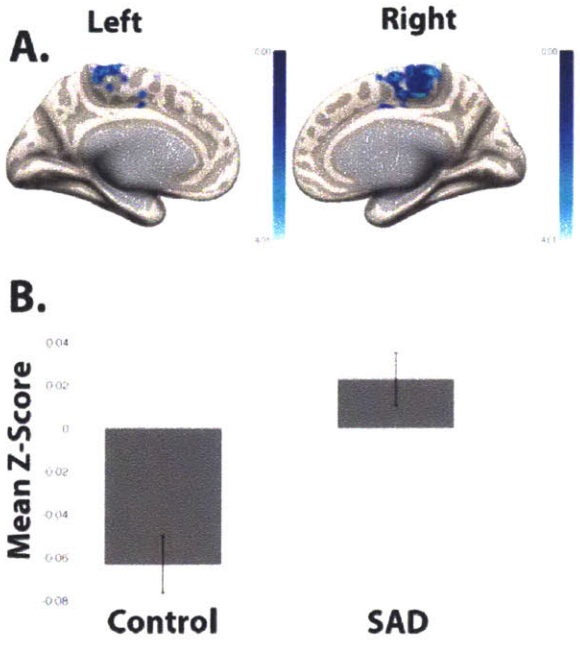

Figure 4.5. Nucleus Accumbens Seed Functional Connectivity Network of SAD > Control and Z-Scores. (A) Resting-state connectivity for SAD group > Control group with bilateral nucleus accumbens seed from Figure 4.1 (Cluster-wise FDR corrected, $p < .05$; Peak voxel: (MNI Coordinates) (0, -34, 64; $p = .006$). **(B)** Mean Fisher transformed correlation values for resting-state connectivity for cluster from Figure 4.5A showing significant difference for SAD group > Control group with bilateral nucleus accumbens seed from Figure 4.1. Peak voxel (MNI coordinates): (0, -34, 64). Bars represent the mean connectivity among for each group for the ventromedial prefrontal cluster from Figure 4.5A. One-sample t-test relative to 0: Control: $p < .0001$; SAD: $p = .07$. Error bars represent standard errors.

4.3.2 Ventromedial Prefrontal Cortex Seed

Contrast: Control group > SAD group

The SAD group also exhibited significant and widespread decreases in connectivity, compared to the Control group, between the vmPFC seed (Figure 4.6A) and regions associated with reward, decision-making, and planning, including bilateral NAcc, bilateral medial anterior PFC/BA10, bilateral DLPFC, bilateral inferior PFC, vACC, subgenual ACC, and dACC (Figures 6B & 7; Table 1). Both groups exhibited positive correlations between the vmPFC seed and the other regions, but the correlations were significantly greater in the Control group. The region of maximal difference included the NAcc and regions associated with cognitive control, the lateral PFC. In this cluster, both the Control and SAD groups exhibited significantly positive correlations (Figure 4.6B, 4.7, & 4.8).

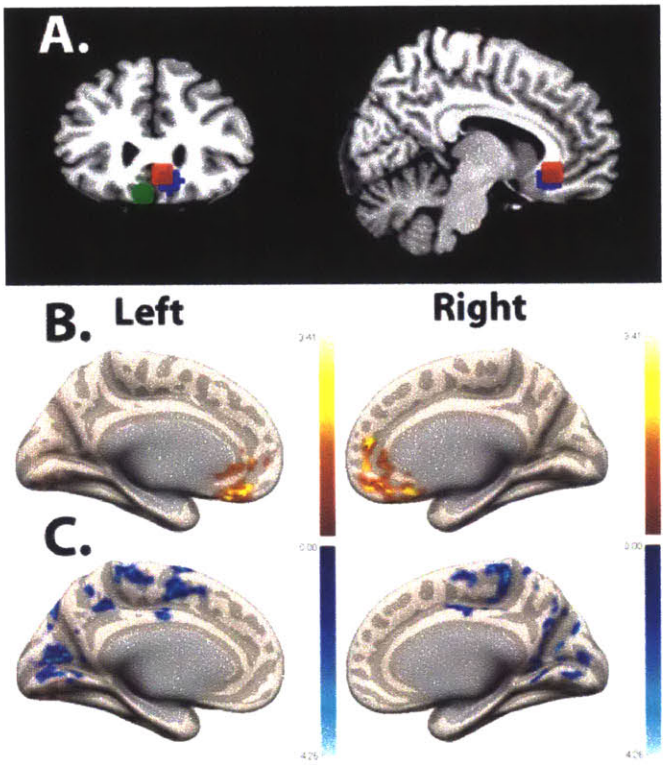

Figure 4.6. Ventromedial Prefrontal Cortex Seed Functional Connectivity Network. **(A)** Ventromedial prefrontal cortex seed used in resting-state functional connectivity analysis. MNI coordinates: (-6, 24, -21), (6, 30, -9), (9, 27, -12). **(B)** Resting-state connectivity for Control group > SAD group with ventromedial prefrontal cortex seed from Figure 4.6A (Cluster-wise FDR corrected, $p < .05$). Peak voxel (MNI coordinates): (-12, 20, -20; $p < .001$). **(C)** Resting-state connectivity for SAD group > Control group with ventromedial prefrontal cortex seed from Figure 4.6A (Cluster-wise FDR corrected, $p < .05$). Peak voxel cluster 1 (MNI coordinates): (6, -42, 60; $p = .001$). Peak voxel cluster 2 (MNI coordinates: (20, -50, 6; $p = .002$). Peak voxel cluster 3 (MNI coordinates): (-50, -56, -4; $p = .006$).

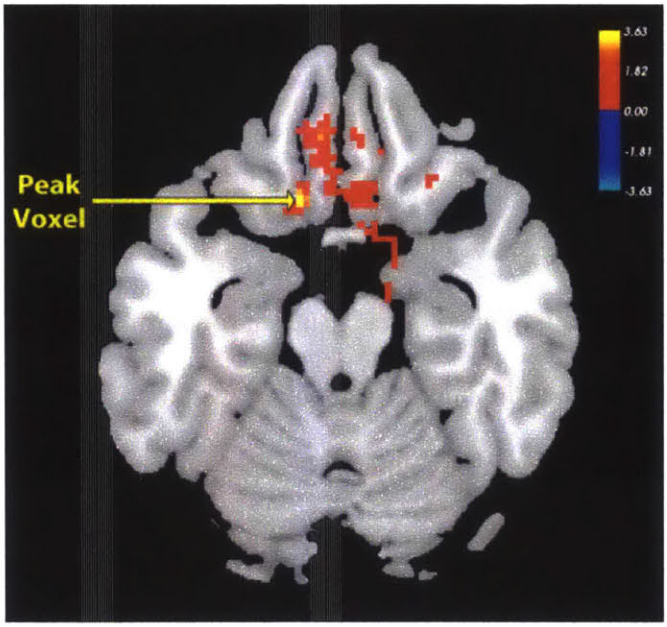

Figure 4.7. Peak Voxel Axial View for Ventromedial Prefrontal Cortex Seed Functional Connectivity Network of Control > SAD. Resting-state connectivity for Control group > SAD group with ventromedial prefrontal cortex seed from Figure 4.6A (Cluster-wise FDR corrected, $p < .05$). Peak voxel (MNI coordinates): (-12, 20, -20); $p < .001$).

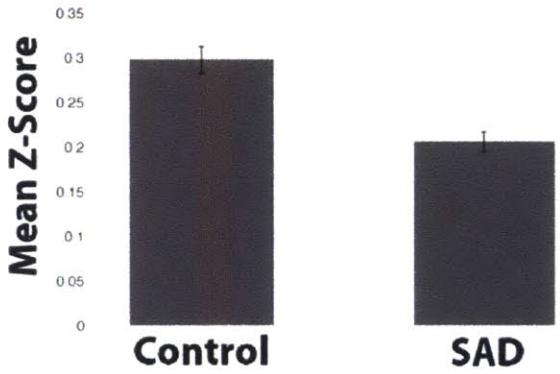

Figure 4.8. Ventromedial Prefrontal Cortex Seed Functional Connectivity Network Z-Scores of Control > SAD. Mean Fisher transformed correlation values for resting-state connectivity for clusters from Figure 4.5B showing significant difference for Control group > SAD group with ventromedial prefrontal cortex seed from Figure 4.6A. Bars represent the mean connectivity for each group for the medial prefrontal cluster from Figure 4.6B. Peak voxel Cluster 1 (MNI coordinates): (-12, 20, -20). One-sample t-test relative to 0: Control: $p < .0001$. SAD $p < .0001$. Error bars represent standard errors.

Contrast: SAD group > Control group

The SAD group exhibited significant increases in connectivity, compared to the Control group, between the vmPFC seed and multiple brain regions, including bilateral premotor, bilateral primary motor cortex, posterior vACC, dorsal PCC (dPCC), and bilateral somatosensory association cortex (cluster 1); bilateral somatosensory association cortex, dPCC, bilateral secondary visual cortex/BA18, and bilateral associative visual cortex/BA19 (cluster 2); and also left fusiform gyrus, left superior temporal gyrus, left middle temporal gyrus, left supramarginal gyrus, and left associative visual cortex (cluster 3) (Figure 4.6C; Table 1). The group differences reflected a pattern of negative correlations (anticorrelations) between the vmPFC seeds and these regions (all three clusters) in the Control group versus a pattern of either positive correlation in the SAD group (cluster 1 and 2, including posterior vACC; Figure 4.9A & 4.9B) or the absence of significant correlation in the SAD group (cluster 3; Figure 4.9C). There were no significant correlations within the SAD group between functional connectivity measures and clinical measures (LSAS, SPAI, and STAI).

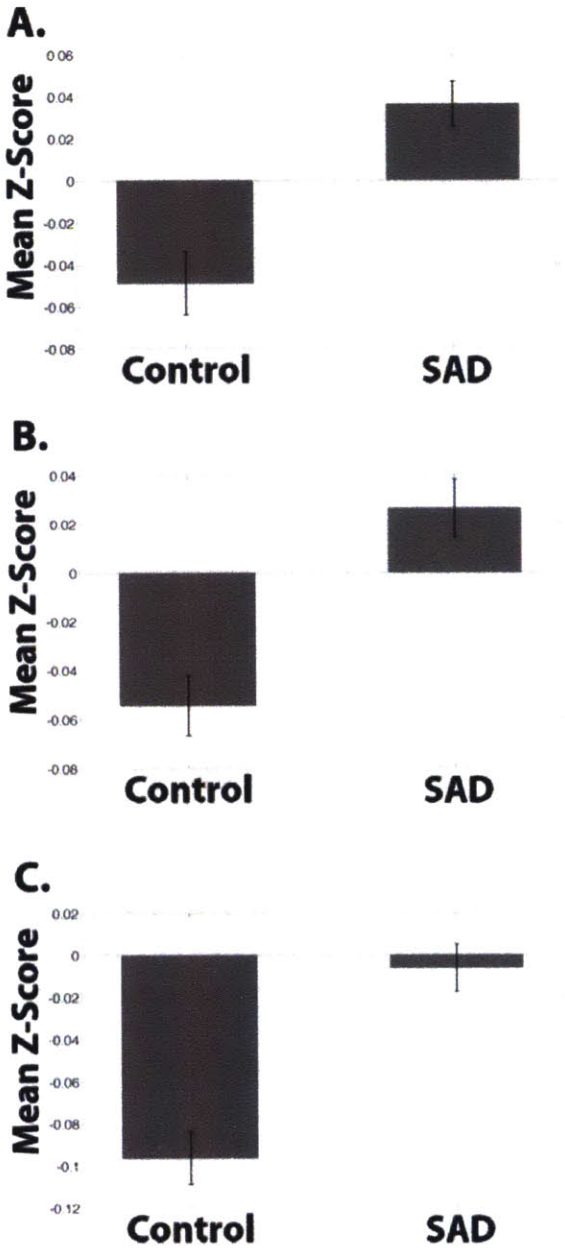

Figure 4.9. Ventromedial Prefrontal Cortex Seed Functional Connectivity Network Z-Scores of SAD > Control. Mean Fisher transformed correlation values for resting-state connectivity for clusters from Figure 4.6C showing significant difference for SAD group > Control group with ventromedial prefrontal cortex seed from Figure 4.6A. Bars represent the mean connectivity for each group for the clusters from Figure 4.6C. **(A)** Peak voxel Cluster 1 (MNI coordinates): (6, -42, 60). One-sample t-test relative to 0: Control: $p = .003$; SAD: $p = .001$. **(B)** Peak voxel Cluster 2 (MNI coordinates): (20, -50, 6). One-sample t-test relative to 0: Control: $p < .0001$; SAD: p .031. **(C)** Peak voxel Cluster 3 (MNI coordinates): (-50, -56, -4). One-sample t-test relative to 0: Control: $p < .0001$; SAD: $p = .58$. Error bars represent standard errors.

4.4 Discussion

People with SAD exhibited widespread alterations of the intrinsic functional brain organization of the reward system. Positive temporal correlations between two major components of the reward system, the NAcc and the ventral region of the vmPFC, were significantly reduced in the SAD group. Functional connectivity between both the NAcc and the vmPFC seed regions with multiple other anterior brain regions were significantly reduced in SAD, including prefrontal and anterior cingulate regions associated with decision-making. Conversely, the SAD group showed significantly increased functional connectivity between both the NAcc and the vmPFC seed regions with multiple posterior brain regions, including posterior ACC and posterior parietal association cortex. In these posterior regions, the Control group exhibited significant negative correlations (anticorrelations) with NAcc and vmPFC, whereas the SAD group exhibited either a reversal with a positive correlation or the absence of a correlation. Thus, the SAD group exhibited markedly decreased functional connectivity both between reward regions and also between reward regions and lateral prefrontal cortex, and markedly increased functional connectivity between reward regions and more posterior brain regions.

The SAD group showed greatly reduced functional connectivity within major components of the reward system, namely the NAcc and the vmPFC. The NAcc is associated with reward anticipation (Knutson et al., 2001a; Knutson et al., 2001b) and the vmPFC is associated with encoding the value of reward (Gläscher, Hampton, & O'Doherty, 2009). If social interaction is typically a source of substantial reward, then the absence of such reward due to chronic fear and anxiety about social interaction in SAD may diminish the frequency of interactions among these components of the reward

system. Alternatively, this reduced functional connectivity among these components of the reward system may result in people with SAD seeking less social interaction. The core reward system was also significantly less correlated in the SAD group with other brain regions implicated in decision-making and cognitive control that often interact with reward regions. These regions included bilateral DLPFC, bilateral lateral anterior prefrontal cortex/BA10, bilateral inferior frontal gyrus, and anterior regions of the dorsal anterior cingulate cortex (dACC), and subgenual ACC.

Whereas functional connectivity was decreased within the reward system and between the reward system and anterior brain regions, functional connectivity was increased in the SAD group between the reward regions and multiple posterior brain regions. There were also contrasting patterns in the group differences in anterior and posterior regions. In anterior regions, the SAD group exhibited positive correlations between reward regions, but these correlations were significantly less than in the Control group. In posterior regions, the Control group exhibited negative correlations with reward regions, whereas the SAD group exhibited either a positive correlation or the absence of a correlation; in both cases the SAD group exhibited significantly greater correlations relative to the Control group.

More specifically, the SAD group exhibited a positive correlation (and not the negative correlation of the Control group), between both the NAcc and the vmPFC and posterior regions including the posterior regions of the ACC and posterior parietal cortex. The findings in the Control group were consistent with a previous report of anticorrelated networks between the posterior ACC and both the striatum and vmPFC (Margulies et al.,, 2007). Posterior ACC has been shown to be involved in reward-related decisions,

becoming more activated as punishment increased (Fujiwara et al., 2009) or during decisions that involve minimizing punishment (Blair et al., 2006). The hyperconnectivity and lack of anticorrelations between reward regions and posterior ACC may reflect changes in the network due to the experience of avoiding social punishment and evaluation. Again, an alternative is that this hyperconnectivity may result in seeking less social interaction to avoid social punishment and evaluation. This, together with the decreased connectivity between the NAcc and vmPFC, may reflect an altered reward network in which reward prediction regions are less correlated with value encoding regions, and both of these reward regions are more correlated with regions that involve punishment. This may help explain how altered brain networks contribute to socially avoidant behavior in people with SAD.

Previous neuroimaging studies in SAD have found reduced structural connectivity (white-matter organization) and resting-state functional connectivity between subcortical regions and orbitofrontal cortex (Baur et al., 2013; Phan et al., 2009; Hahn et al., 2011). The reduced relations between prefrontal and subcortical regions, such as the amygdala, could reflect decreased prefrontal regulation of subcortical regions (Sladky et al., 2012). The present findings of reduced functional connectivity between prefrontal and subcortical reward-related regions also suggest reduced regulation of social reward.

There are both psychological and technical limitations of the present study. For the SAD group, the social interactions with researchers involved in performing the imaging may have influenced the nature of thought processes reflected in the connectivity measures. Also, there were no significant correlations between measures of SAD severity (LSAS, SPAI, STAI) and functional connectivity measures. Future research could explore the

relation of reduced functional connectivity between the NAcc and vmPFC in SAD patients with tasks that involve social reward. A technical limitation of the study is that we acquired data with a relatively long time of repetition (TR = 6 seconds). We used the 6 second TR in order to achieve high spatial resolution with whole-brain coverage because previous research has demonstrated that array coils provide the biggest increases in temporal SNR at high spatial resolutions (Triantafyllou, Polimeni, & Wald, 2011). Although this TR is unusually long, there is evidence that there are no significant differences in the correlation strengths between the resting state networks when comparing TRs of 2.5 s and 5 s (Van Dijk et al., 2010). Furthermore, the correlations observed in the Control group were similar to prior studies using more conventional shorter TRs (Cauda et al., 2011; Di Martino et al., 2008).

We investigated the intrinsic functional connectivity of the human reward system in people with social anxiety disorder. People with SAD had decreased functional connectivity between the NAcc seed, which encodes reward anticipation, and the vmPFC, which encodes reward value. People with SAD also had decreased functional connectivity between the vmPFC seed and the lateral anterior prefrontal cortex and the DLPFC, which are associated with decision making. The SAD group also did not have the typical anticorrelations between both the NAcc seed and the vmPFC seed with the posterior ACC, a region that is associated with punishment (Blair et al., 2006). The observation that independent analyses of NAcc and vmPFC seeds yielded similar differences in connectivity between the SAD and Control groups suggests that there is a widespread difference in reward-network functional connectivity in SAD, spanning regions involved in both reward anticipation and reward receipt and valuation.

5. Conclusion

This thesis presented three studies demonstrating that individual differences in behavior and psychiatric disease are reflected in the organization of the frontal-striatal reward network. This network consists of subcortical reward regions and top-down executive control regions in the prefrontal cortex. Three important sub-regions of this network are the NAcc that responds to reward anticipation (Knutson et al., 2001a; Knutson et al., 2001b), the vmPFC that translates reward into a representation of subjective value (Gläscher et al., 2009; Montague & Berns, 2002), and DLPFC that is involved in top-down executive control in decision-making (Barraclough, Conroy, & Lee, 2004; Bechara, 2005). The integration of these three processes is essential for reward-related decisions.

In Chapters 2 and 3, I showed that differences in the frontal-striatal reward network were associated with temporal discounting preferences. The task-based study in Chapter 2 related individual personality traits to temporal discounting preferences. Personality traits are stable characteristics of a person that predict many behaviors that involve delay of gratification. High neuroticism is associated with more impulsive behavior and increased procrastination (Whiteside & Lynam, 2001), whereas high conscientiousness is associated with decreased impulsive behavior and increased procrastination (Lee et al., 2006). These behaviors are both related to delay of gratification. I have extended this field of research by moving from pure behavioral correlates to relating personality to formal temporal discounting preferences represented by the constant sensitivity discount model (Ebert & Prelec, 2007; Bleichrodt et al., 2009). This model formally separates impatience from impulsivity, which reflects inconsistent temporal discounting

preferences. An important finding was that only impulsivity and the consistency of temporal discounting preferences were correlated with personality, and not impatience, which is reflected in exponential discounting. Neuroticism was correlated with increased impulsivity and less consistent time preferences. Conscientiousness was correlated with decreased impulsivity and more consistent time preferences. This pattern of correlations can explain many typical behaviors from impulsive spending to procrastination with health decisions. These correlations with temporal discounting preferences were also reflected in activations in the frontal-striatal reward network. Previous imaging studies have found conflicting evidence supporting two alternative views of the frontal-striatal reward network. One view is that the fast visceral system of the ventral striatum responds to immediate rewards, and competes with the top-down executive control system of the DLPFC, which responds to delayed rewards (McClure et al., 2004). The alternative view is that these systems integrate to respond to both immediate and delayed rewards (Kable & Glimcher, 2007). The results from Chapter 2 support the integration of reward and executive control, with a novel pattern in relation to personality. Greater activation in the frontal-striatal reward network occurred when options were chosen that were contradictory to personality preferences, but not when they were consistent with personality preferences. Specifically, greater activation in this network, in both the ventral striatum and the DLPFC, occurred when people who were more conscientious chose the shorter delay and people who were more neurotic chose the longer delay. This greater activation for choices that contradict a personality-related disposition may reflect the need for greater neurobiological resources to act against the predisposition. These results showed that individual differences in personality do influence temporal

discounting preferences, and these differences in personality and preferences are reflected in specific patters of activation in the frontal-striatal reward network.

In Chapter 3, I investigated if individual differences in temporal discounting preferences were reflected in spontaneous activation in the brain at rest. Temporal discounting preferences, as modeled by the constant sensitivity function, were associated with the strength of the temporal correlations (functional-connectivity) between the regions in the frontal-striatal reward network. Shallower exponential discounting or greater overall patience was associated with increased functional connectivity between the NAcc and regions in the prefrontal cortex, including the vmPFC and the DLPFC. Similarly, decreased impulsivity and more consistent temporal discounting preferences were associated with increased functional connectivity between the NAcc and regions in the prefrontal cortex, including the DLPFC. This reflects a pattern of integration of regions that are associated with specific processing in reward-related decisions, including both regions that respond to reward and those that are associated with executive control. These results are consistent with the results from Chapter 2, showing a pattern of integration of both reward and executive control regions. Importantly, this integration of these regions is associated with people that are more patient and less impulsive. Investigating the relation between resting-state functional connectivity networks and temporal discounting yielded two additional findings to the results from Chapter 2. First, these results showed that individual differences in temporal discounting preferences are reflected in the organization of brain networks in the absence of external stimuli are decision-making tasks. Second, these results show that both impatience and impulsivity, modeled separately, are associated with differences in brain function.

Finally in Chapter 4, I asked if social anxiety disorder (SAD) was associated with differences in the frontal-striatal reward network. SAD is associated with fear of negative social evaluation, and therefore much of the research has focused on brain regions associated with fear, such as the amygdala (Bruel et al., 2011; Liao et al., 2010). An alternative view is that dysfunction in the frontal-striatal reward system may reflect differences in response to social reward in SAD. Positive temporal correlations between the NAcc and the vmPFC were significantly reduced in people with SAD compared to healthy control participants. Functional connectivity between the vmPFC and executive control regions, including the anterior PFC and the DLPFC, were significantly reduced in people with SAD. These widespread differences in the functional connectivity of the frontal-striatal reward network involve regions associated with reward anticipation, receipt, and valuation. This decreased functional-connectivity between major components of the frontal-striatal reward system may reflect less reward from social interactions or it may result in less exposure to social interactions.

Reward-related behavior depends on responding to rewards and translating these rewards into value, while simultaneously integrating top-down executive control processes to guide action. These specific processes are associated with key components of the frontal-striatal reward network. Differences in the domains of decision-making and psychiatric disease are reflected in differences in the brain regions associated with both reward and executive control. These results take a step forward in understanding how individual differences in decision-making, personality, and psychiatric disease are related to differences in the same frontal-striatal reward network.

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