Evaluating Gambling Disorder in an American Indian Population Using a Probability Discounting Task during an fMRI Scan

By

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Abstract

Probability discounting has a rich history of investigating choice behavior, especially as it pertains to risky decision making. Gambling involves risky decision making through choice behavior, which makes it an ideal behavior to investigate using discounting tasks. With multiple comorbid features, in addition to environmental factors, the American Indian population have been a neglected population of study. Utilizing outcome measures from a pre-scan probability discounting task, the current study manipulated indifference points two equate task difficulty to evaluate behavioral and neurobiological differences in gamblers versus non-gamblers. Results showed differences in behavioral tasks (lower discounting rates) and neurobiological processes within those in the gambling group. Results of the current study identified both consistent and inconsistent findings with previous studies which may highlight new findings specific to the American Indian gamblers. Findings of the current study show a troubling combination of neurobiological and behavioral dysfunction that add to the hazard of ease of access to gambling and gambling environments.

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Table of Contents

List of Figures

Introduction

Gambling, and by extension problem gambling, has been around for thousands of years (Masukawa, 2016), yet, until 1980 it was not classified as an addictive disorder. Pathological gambling was first introduced in the Diagnostic and Statistical Manual (DSM) III and was characterized by persistent and recurrent maladaptive patterns of gambling behavior. It was classified under the category of "disorders of impulse control not elsewhere classified" (American Psychiatric Association, 1980). More recent editions of the DSM have added behavioral addictions to the already established diagnosis of substance-related and addictive disorders (American Psychiatric Association, 2013). Gambling disorder (GD) is currently defined as persistent and recurrent problematic gambling behaviors that lead to significant personal and/or social impairments (American Psychiatric Association, 2013). Although previous editions of the DSM only established criteria for a clinical diagnosis, the DSM-V added classifications for severity. According to the DSM-V, a person needs to identify with 4 of the 9 qualifying criteria to be diagnosed with a GD (Reilly & Smith, 2013). It further subdivides gambling behaviors into three severities based on the number of criteria met (mild (4-5 criteria), moderate (6-7 criteria), and severe (8-9 criteria; American Psychiatric Association, 2013)).

One key risk factor for GD is proximity to a casino. Specifically, those who reside within 10 miles of a casino are twice as likely to have issues with problem gambling than those living further away (Welte, Barnes, et al., 2004). Additionally, researchers have found that gambling convenience (ease of access to gambling activities) was also a significant predictor in addition to overall proximity (Patterson et al., 2015). These findings are important because they highlight an elevated risk for the American Indian (AI) population due to proximity to gambling establishments and ease of access to gambling. Of the more than 2.4 million self-identified AI's

in the United States, over 20% live on a reservation with a casino (Taylor & Kalt, 2005). Further, approximately half of AIs residing in the continental United States belong to tribes that operate casino-style gaming operations on tribal lands (Evans & Topoleski, 2002). In a study of 7th-12th grade AI students, approximately 75% had gambled in the past year (Okuda et al., 2016), compared to the national average of 45%-55% (Stinchfield, 2011; Winters & Anderson, 2000). Additionally, in a survey of public school students in Minnesota, 17.4% of the AI children reported daily/weekly gambling behavior, compared to 12.3% of the white students. (Stinchfield et al., 1997).

Widespread gambling availability has led to significant economic consequences. In 1982, only three states allowed legalized gambling (e.g., Nevada, New Jersey, and Montana) with the exception of state run lotteries (Fenich, 1996). That same year U.S. consumers lost an estimated $10.4 billion due to gambling. In 1988, the Indian Gaming Regulatory Act gave AI's the right to operate casinos and gaming institutions on their own land. As of 2002, The National Indian Gaming Commission estimated more than 240 of the 562 AI tribes offered some sort of gambling activities at more than 500 casinos (Ashton, 2002). By 1995, overall gambling losses had increased to more than $40 billion (Ghezzi et al., 2000). Currently, there are roughly 1000 casinos in the United States with over $100 billion dollars in annual reported losses by gamblers (Statista Research Department, 2018).

Along with gambling availability, gambling activities are constantly evolving. Frequent gamblers (those who gamble at least twice a month), however, still show a preference for traditional casino style gambling activities. Specifically, frequent gamblers prefer engaging in traditional casino games (22.5%), electronic gambling machines (18%), and numbers/lotto (5%; Binde et al., 2017).

Although there are economic benefits of operating casinos, they also potentiate unintended problems that put this population at risk. For instance, growing up on an AI reservation is associated with higher levels of post-traumatic stress disorder and intergenerational trauma (Ehlers et al., 2013), which are correlated with high rates of GD (Okuda et al., 2016; Patterson et al., 2006). Growing up on a reservation has also been correlated with risk factors, such as trauma, stress, impulsive behaviors, early exposure to gambling, and addiction - all of which are also associated with GD (Potenza, 2013).

Approximately 80% of adults in the United States engage in some form of gambling each year (Barnes et al., 2017). More specifically, 76.9% of white Americans and 80.1% of AIs engaged in some form of gambling in the past year (Barnes et al., 2017). Although past year engagement rates are similar, marked differences are noted across populations when comparing frequent gambling (2+ times a week) and those with GD (4 or more DSM criteria in the past year). Specifically, 9.3% of white Americans engaged in frequent gambling, with 1.8% reaching GD criteria. By contrast, 12.6% of AI's frequently gambled with 10.5% meeting GD criteria (Welte et al., 2001).

Gambling disorder is associated with a host of comorbid features (e.g., anxiety, bipolar, and alcohol use disorders). Of those diagnosed with GD, 35% have one comorbid disorder, 24.6% have two comorbid diagnosis, and almost 3% have three separate comorbid diagnosis (Ibanez et al., 2001). Comorbid diagnosis for psychological disorders include substance use disorder (57.5%; Lorains et al., 2011), anxiety (37.4%; Lorains et al., 2011), and mood disorders (37.9%; Lorains et al., 2011). Specific to alcohol, 23% of those with GDs have a concurrent alcohol use disorder (Ibanez et al., 2001; Kessler et al., 2008) with as many as 34.8% reaching alcohol use disorder/dependence classification within their lifetime (Ibanez et al., 2001).

Although AIs have a lower rate of past year alcohol use (47%) compared to white Americans (68%), they show higher rates of alcohol use disorder (5.5%) than their white counterparts (4.3%; Patterson et al., 2015). With increased proximity to casinos (Welte, Wieczorek, et al., 2004), higher levels of comorbid diagnosis (Dannon et al., 2006; Lorains et al., 2011), and past exposure to trauma (Ehlers et al., 2013), the AI population is at a significantly increased risk of GD.

Probability Discounting

Behavioral economics, specifically the assessment of probability discounting (PD), may be an ideal approach for investigating gambling. With its capacity to evaluate responding across levels of risk, PD tasks are a logical parallel for gambling involvement. Probability discounting evaluates the choice of a smaller, yet certain outcome, against a larger, probabilistic outcome. Likewise, gambling involves risking money that one already has (smaller/certain) to chance receiving a larger reward that is probabilistic in its outcome (larger/probabilistic). By using PD tasks to analogue gambling, it allows researchers to manipulate constraints of availability. Manipulating constraint allows for analysis of the systematic change in subjective value of a consequence as a function of the probability of receiving that outcome – with nonlinear regression being used to quantify patterns of responding.

Probability discounting tasks allow for within-subject manipulations to assess participant specific responding. For instance, during the initial round of PD tasks, participants are presented with a choice between a smaller, yet certain outcome (100% chance of $50), versus a larger, probabilistic outcome (probabilistic chance of $100). Using an amount titrating procedure, if the participant selects the certain outcome, then the amount of the probabilistic outcome is increased to make it subjectively more appealing. Conversely, if the participant selects the probabilistic

outcome, then the amount of the probabilistic outcome is decreased to make it subjectively less appealing. This is repeated across several choices within each probability to establish an indifference point at each probability. An indifference point is thought to be the point at which both the certain and probabilistic outcomes are subjectively equal to the participant (Mazur, 1987). The resulting indifference points (y-axis) are plotted at a range of odds against (x-axis) to plot the parametric function, which shows the subjective devaluation across probabilities.

Probability discounting curves are often fit using least-squares non-linear regression that employ variations on Mazur (1987)'s hyperbolic equation,

(1)

$$V = A/(1 + h\theta)$$

in which V is the subjective value of some amount (A) of reward with some odds against receiving the consequence as ($\theta = (1-p)/p$) (Rachlin et al., 1991), with the process modulated by the discounting rate (h). Myerson and Green (1995) updated this equation by adding a scaling parameter (s) to the entire denominator, reflected in Equation 2,

(2)

$$V = A/(1+ h\theta)^s.$$

The scaling parameter (s) incorporates Stevens (1957) power law that is based on psychophysical scaling parameters. Instead of raising the whole denominator to the power function (s), Rachlin (2006) added the scaling parameter to the independent variable (odds against parameter) only, making the new model,

(3)

$$V = A/(1+ h\theta^s).$$

To evaluate discounting rates, *h* values are interpreted as the rate an outcome decreases in value as a function of the probability of its receipt. In other words, *h* represents the rate of discounting. As the probability of an outcome decreases, or the odds against increase, the rational decision is to switch to the certain outcome. Shallower (i.e., smaller) *h* values in probabilistic outcomes are representative of risky behavior. In other words, smaller *h* values demonstrate a willingness to take risks, whereas larger values reflect aversiveness to risk (Peters & Buchel, 2009).

In research, PD tasks are used to evaluate patterns of responding across many types of goods and/or outcomes. Certain outcomes of interest, however, present unique problems that may prohibit manipulations in the context of a research study. Specifically, some commodities may be unethical or illegal to provide to participants (e.g., sex and/or drugs) without authorization and others may be impractical to manipulate (e.g., long-term medication side-effects). As such, PD studies have substituted hypothetical outcomes. Although real rewards may be preferred, studies have shown the consistency of choices made for both real and hypothetical outcomes (Hinvest & Anderson, 2010; Lawyer et al., 2011; Matusiewicz et al., 2013). Additionally, high test-retest reliability has been reported in studies evaluating PD rates over time using both real (Peters & Buchel, 2009) and hypothetical rewards (Ohmura et al., 2006).

Gambling involves risky behaviors. More specifically, gambling involves risking small amounts of money for the chance of acquiring a larger reward. This makes PD well suited for investigating the constraints under which gamblers' choices are influenced by their sensitivity to reward devaluation. More specifically, PD results have shown that those with GD are less sensitive to reward devaluation that risk entails. To investigate PD rates in gamblers compared to healthy controls, Madden et al. (2009) used a modified monetary choice questionnaire (Kirby &

Marakovic, 1996; Kirby et al., 1999) that utilizes monetary choices across a range of probabilistic outcomes. Potential outcomes were predetermined to allow for assessment across a wide range of discounting rates (Madden et al., 2009). Options were predetermined and the order in which the probabilities were presented were counterbalanced between subjects within both groups. Comparing treatment seeking men with a GD (n=19) to healthy controls (n=19), Madden et al. (2009) reported significantly less steep discounting by those with a GD than controls. Using questionnaires with predetermined probabilities and amounts for each question allows for comparison of responses across studies on exact outcomes. It does not, however, allow for within-subject individual titration. This means that individual indifference points may be constrained outside of their actual level and therefore may not fully represent responding in a naturalistic way. Although it may differentially impact task difficulty across participants, it does allow for evaluation of decision making at specific values and probabilities.

Using a computerized task with an amount titration procedure, Holt et al. (2003) administered a PD task to college students with a GD (n=19) and non-gambler controls (n=19). Each participant was administered two computerized PD tasks, in a counterbalanced method, with either a smaller magnitude reward ($1,000) or a larger magnitude reward ($50,000) offered across seven probabilities (95%, 90%, 75%, 55%, 30%, 10%, and 5%). Both groups reliably discounted large probabilistic rewards ($50,000) more steeply than small reward magnitudes ($1,000; Holt et al., 2003). Those with a GD diagnosis, however, discounted both outcomes less steeply than those without a GD. This shows a behavioral similarity across groups for overall discounting across magnitudes, but demonstrates those with a GD reliably discount probabilistic outcomes less steeply, independent of the reward magnitude (Holt et al., 2003).

Investigating PD, Shead et al. (2008) evaluated discounting rates of gains versus losses in a college sample of frequent gamblers. For discounting of losses, researchers used a smaller option that the participant was guaranteed to lose against a larger option with a probability of loss. By comparing responding for gains versus losses, researchers were able to evaluate decision-making involving positive and negative outcomes across six probabilities (95%, 90%, 75%, 50%, 25%, and 5%). A negative correlation of PD of gains versus losses was observed, where those who discount probabilistic gains more steeply tend to discount probabilistic losses relatively more shallowly (Shead et al., 2008). When scaled as odds against winning and odds against losing the discounting curves showed similar functions which reflects a strong negative correlation between discounting of gains and losses (Shead et al., 2008). These results support the idea of "risk attitudes," which states risk-averse individuals will discount probabilistic gains at higher rates while discounting probabilistic losses at a lower rate (Shead & Hodgins, 2009).

To further investigate PD of gains and losses for contingencies that maintain gambling engagement, Weatherly and Derenne (2012) evaluated a group of college students (n=149) comprised of mostly non-gambling females (85%). Participants completed a PD task involving both gains and losses of a smaller magnitude ($1,000) outcome and a larger magnitude ($100,000) outcome across five probabilities (99%, 90%, 50%, 10%, and 1%). To evaluate gambling contingencies, researchers used a Gambling Functional Assessment - Revised (GFA-R). The GFA-R is a 16-item, self-report measure that is used to isolate contingencies related to maintaining gambling behavior in individuals (Weatherly et al., 2011). Results from Weatherly and Derenne (2012) demonstrated a higher AUC measure for PD of losses than gains. Further, there was little difference in AUC measures when comparing smaller magnitude ($1,000) versus larger magnitude ($100,000) outcomes. Additionally, researchers reported that gambling

severity, measured by South Oaks Gambling Screener (SOGS), was more associated with negative reinforcement (escape-maintained behavior) than positive reinforcement (Weatherly & Derenne, 2012). Specifically, gambling as an escape (negative reinforcement) was a much stronger predictor of PD than positive reinforcement (monetary outcomes; Weatherly & Derenne, 2012). Although these findings were statistically significant, relations between gambling severity and PD rates were not completely reliable (Weatherly & Derenne, 2012), which is consistent with findings from (Shead et al., 2008). This means that escaping negative behaviors (withdrawal) may be more reinforcing than the monetary rewards (positive reinforcement) derived from gambling outcomes.

Participant recruitment for gambling studies have seen a shift away from using DSM criteria for recruitment and severity classification to using the SOGS (Lesieur & Blume, 1987). The SOGS questionnaire is a 20-item screener based on DSM gambling criteria that offers a convenient means by which to screen clinical populations for gambling disorder (Lesieur & Blume, 1987). To evaluate reliability and validity of the SOGS, Stinchfield (2002) used large samples from a gambling treatment population (n=1589) and healthy community sample (n=803). Using a telephone survey, investigators administered the SOGS and DSM-IV gambling criteria screener to evaluate classification abilities of the SOGS compared to the DSM-IV. Researchers reported overall satisfactory reliability and validity outcomes for the SOGS in both screening for and classification of gamblers (Stinchfield, 2002). The classification accuracy of the SOGS screener was much more sensitive for those in the gambling treatment population (α=.99) compared to community samples (α=.67; Stinchfield, 2002). Although the control group showed a high false positive rate (50%), this was due to 4 subjects being identified as problem gamblers while only 2 of those satisfied the DSM -IV criteria as a problem gambler. Overall

sensitivity of both screeners was good, however, the SOGS typically identifies a higher rate of gambling prevalence due to the inclusion of subjective questions rather than purely behavioral questions (Stinchfield, 2002).

Using the SOGS as a screening tool has opened new avenues for understanding gambling disorder, specifically in PD studies. The first study to report a negative relation between PD and SOGS was Holt et al. (2003). In a small group of participants (n=38), researchers showed that college students with high SOGS scores (4+) had lower rates of PD than those with low SOGS scores (0-1; Holt et al., 2003). These findings are consistent with those of Madden et al. (2009) who used a PD task to investigate the relation between PD and SOGS scores. In a small group of participants (n=38), researchers found a negative correlation between SOGS scores and PD rates ($r = -.46$, $p < .01$). Additionally, Madden et al. (2009) reported significantly higher SOGS scores with pathological gamblers (7-20) compared to controls (0-4) with no overlap between groups. These results reflect an inverse relation between gambling severity and PD rates which reflects a propensity for more risky decision making as a function of SOGS scores.

Probability Discounting tasks are reliable and robust means by which to study gambling disorder. Sometimes, however, research studies are limited in their ability to answer complex questions. To understand the processes that underlie gambling behavior, interdisciplinary approaches need to incorporate complimentary techniques, such as behavioral economics paired with neuroimaging. Alone, PD has told one side of the story about devaluation of risky outcomes. Pairing PD tasks with functional Magnetic Resonance Imaging (fMRI) techniques has increased the range of experimental questions researchers are able to investigate. For example, differences in gamblers and non-gamblers can be evaluated with studies that concurrently investigate neural correlates while engaging in a PD task (Miedl et al., 2012; Peters & Buchel,

2009). This has helped to uncover a more complex interaction between neurobiological processes that accompany risky decision making of those with a gambling disorder.

fMRI research

Behavioral economic research has helped to identify core behavioral processes involved in gambling. Understanding the neurobiological processes that undergird these behavioral processes, however, may help us understand the broader framework involved in GD. One valuable resource has been the addition of fMRI to behavioral studies. Combining interdisciplinary approaches has given researchers the ability to correlate neurobiological activity with decision-making, highlighting patterns of brain activity associated with those decisions.

Functional MRI studies use blood oxygenation level dependence (BOLD) measures to evaluate changes in blood oxygenation levels during task involvement. Increased blood flow in a given area suggests greater activity in that region (Fox et al., 1986). Higher levels of neurobiological activity require more oxygen, and therefore, require increased blood flow to compensate for increased oxygen demand (Fox et al., 1986; Rees et al., 1997). Baseline measures are first taken during resting state scans (no task) and compared to scans in which the participant is responding to an experimental task. This allows for measures to be acquired across the whole brain during specific tasks. During analyses, differences in activity levels can highlight regions that show increased or decreased activity as a function of the task. Specifically, neurobiological activity is acquired while participants complete a behavioral and/or neuropsychological tasks, such as Stroop tasks (Potenza et al., 2003), simulated casino games (Miedl et al., 2010), or PD tasks (Miedl et al., 2012; Peters & Buchel, 2009). These measures are then compared to resting state scans to identify regions of interest (ROI's) that show differential activity.

Studies comparing neuro-correlates during PD task scans have provided additional insight into the neural activity associated with risky choice. In an exploratory study of neural activity during risky decision making, Peters and Buchel (2009) examined BOLD activity as participants completed a monetary incentive delay (MID) style PD task. Subjects (n=22) attended two pre-scan appointments in which they completed PD tasks at two separate time points (median time between behavioral sessions was 9 days) and then a scan session in which they completed a modified PD task (median 4 days after second behavioral session). The pre-scan appointments allowed subjects to become familiar with the task, allowed researchers to evaluate stability of discounting, and collected indifference points used during the scan task. Participants made decisions across seven probabilities (100%, 99%, 96%, 84%, 54%, 28%, and 17%; Rachlin et al., 1991) at pre-scan appointments and during an fMRI scan. Instead of presenting both the certain and probabilistic option on the screen, only the probabilistic outcome was shown during the scan task. Participants were shown the probabilistic option, then had to inhibit response during a 3-7 s (jitter) and then had 2 seconds in which to make their choice. For the scan appointment, pre-scan indifference points were used to equate tasks so participants would make approximately 50% of choices for both the smaller/certain and larger/uncertain outcomes. By arranging the experimental design to constrain participant responses, it effectively equated task complexity and effort. This means that observed differences were not due to task difficulty, as well as ensuring enough choices of smaller-certain and larger-uncertain to make group comparisons.

To assess stability of discounting rates, a subset of participants (n=13) were brought back for a long-term (79-120 days) follow-up to evaluate stability of PD rates. Stability of PD rates were assessed at both short-term follow-up (for all participants) and long-term follow-up (for 13

participants). Results showed overall faster reaction times in the high value trials, compared to lower and similar value trials. Additionally, researchers have reported good stability on PD rates from shortly before scan (median 4 days; $r = .74$, $p = .00008$) and at the longer time range (79-210 days; $r = .76$, $p = .0026$). Additionally, researchers analyzed neural correlates from concurrent PD task and fMRI scan. Imaging analysis evaluated brain regions in which activity was positively correlated with subjective values from the PD task (Peters & Buchel, 2009). The most pronounced differences were in the right parietal lobe, occipital gyrus, and the ventral striatum. Additionally, researchers reported activity differences in the VS and OFC during PD tasks which means these regions may implicate this network when determining subjective value of outcomes that are either delayed or probabilistic

In a similar study, Miedl et al. (2012) evaluated those with a GD (n=16) against healthy controls (n=16) using a MID style PD task. All participants completed a short adaptive PD task prior to their scan appointment to determine PD rates across 7 probabilities (100%, 99%, 96%, 84%, 54%, 28%, and 17%) that were duplicated from Rachlin et al. (1991). Procedures were similar to those used in Peters and Buchel (2009) with the exception of the time between study visits. The current study had, on average, one day between visits. The pre-scan PD indifference points were used to equate tasks so that each participants chose approximately 50% of the smaller/certain outcomes and 50% of the larger/probabilistic outcomes. During the scan task, participants were only shown the probabilistic outcome, while the certain outcome (which remained the same) was not presented.

Results reflected less steep PD rates (not statistically significant) for those with a GD compared to the healthy controls using a one-tailed t-test. A non-statistically significant trend toward a negative correlation between gambling severity and PD rates was identified, which

suggests some effect of diminished risk sensitivity with increasing gambling severity. Additionally, Miedl et al. (2012) reported a small negative correlation between gambling severity and neurobiological activity in the VS and OFC when subjects were making decisions about probabilistic rewards during risky (low probability) reward trials (Miedl et al., 2012). Further, the correlation between the BOLD signal and subjective interpretation of reward outcome in the VS was less pronounced in gamblers than in controls. This suggests a slight overall dysfunction in risk aversion (behavioral) instead of specific system dysfunction in the brain (neurobiological; Miedl et al., 2012). Additionally, all neural correlations in the PD tasks components were non-significant even at an uncorrected level. This means that although gamblers showed trends toward differential activity, these differences were not significant and, therefore, show little distinction from the healthy controls.

Although not specific to gambling disorder, Abidi et al. (2018) investigated the role of the reward system in healthy participants (n=14) using a modified PD task in conjunction with fMRI scan. The PD task was modified to account for two probabilistic outcomes – side effects (1%, 5%, 16%, 38%, 64%, 84%, 95%, 99.9%) and medication efficacy (1%, 5%, 16%, 38%, 64%, 84%, 95%, 99.9%) – across three levels of side effects (mild, moderate, and severe). Healthy participants made decisions about taking a medication as a function of both side effect risks and medication efficacy during an Echo-Planar Imaging scan. When making choices related to mild side effects, participants showed increased OFC and VS activity. In the severe side effect trials, however, activation was noted more widely in the frontal lobes, insula, amygdala and thalamus (Abidi et al., 2018). Additionally, they found a strong positive correlation between discounting rates quantified using area under the curve (AUC) and percent signal change in both the OFC and VS during mild side effect that became less pronounced in severe conditions.

Whereas a negative correlation between AUC and percent activation change was found in the insula and amygdala during severe conditions and became less pronounced in mild conditions.

Studies using PD tasks are time intensive, and therefore, are cost prohibitive during neuroimaging studies. As such, other approaches like simulated gambling tasks, have been used instead. Simulated slot machine tasks provide visual stimuli that are contextually similar to casino games and therefore more closely mimic real-world gambling engagement. While this approach allows for evaluation of gambling behavior with naturalistic cues, it may also obscure differences in behavioral processes due to respondent conditioning to gambling stimuli. Simulated slot machine tasks evaluate behavioral and neurobiological responses to gambling itself, whereas PD tasks evaluate behavioral processes specifically associated with decision-making across different risk levels. By adding in the additional contextual stimuli from simulated slot machine tasks, analyses of neurobiological differences may be reflecting Pavlovian responses developed from long histories of gambling involvement. By removing the unnecessary noise from additional stimuli, PD can investigate the operant influences of decision-making instead of the respondent influences of the environmental cues.

Neuroimaging study results have provided an additional level of understanding about underlying processes that may be inaccessible in behavioral studies alone. For instance, the near-miss effect has had mixed outcomes in behavioral studies. The near-miss effect is a phenomenon that is seen in gambling behavior, but more specifically, in slot machine gambling. The near miss is an “almost win” scenario where the first two reels on a slot machine show matching symbols, but the final symbol is incongruent with the others (Reid, 1986). In this outcome, the result is a loss, however, neurobiologically it has similar features to a winning outcome. Investigating the effects of near misses in behavioral studies has produced mixed results. Using simulated slot

machine tasks, some researchers have reported no effect for increased gambling behavior (Whitton & Weatherly, 2009; Worhunsky et al., 2014), whereas other studies have reported differences in gambling behavior (Dixon & Schreiber, 2004; Kassinove & Schare, 2001). Although behavioral results have been inconsistent in providing evidence of a near miss effect, neuroimaging studies have added support for neurological activity associated with near-miss effect. These results have demonstrated that even though the outcome is a loss, neurologically, the brain processes the outcome as similar to a win (Habib & Dixon, 2010; Sescousse et al., 2016).

Additional studies have found inconsistencies between behavioral processes and neurobiological activity. For example, Worhunsky et al. (2014) used a simulated slot machine task with three groups; pathological gamblers, cocaine users, and healthy controls. Researchers examined reaction times and neural activity during anticipation of a reinforcing outcome. No between-group differences were seen in behavioral reaction time. Those with a gambling disorder, however, showed increased activity in the ventral striatum, insula and medial prefrontal cortex (mPFC; Worhunsky et al., 2014) during reward anticipation, relative to both healthy controls and cocaine dependent participants. Neuroimaging, therefore, can add a level of sensitivity to behavioral studies that other tasks alone do not offer. It gives researchers the ability to identify differences, specifically neurobiological activity, that undergirds behavioral processes and decision making.

Monetary Incentive Delay tasks have also added to the understanding of altered neural functioning in those with a GD. Monetary Incentive Delay tasks were developed for concurrent use with imaging studies to evaluate striatal activity during anticipation of rewarding outcomes (Balodis & Potenza, 2015; Knutson et al., 2000). Once a trial begins, a cue is shown to

participants before a variable delay period begins - signaled by an anticipation target that alerts participants to a potential upcoming reward (Knutson et al., 2000). Once the target is displayed, participants respond as quickly as possible to the reward cue. This task was designed to evoke reaction of the dopaminergic system in the ventral tegmental area during reward anticipation, as well as behavioral response time across different reward magnitudes (Schultz et al., 1998). At the individual level, healthy controls completing this task showed activation in the caudate and mesial prefrontal cortex during rewarding trials and activation of the anterior cingulate cortex during punishing trials (Knutson et al., 2000). These same patterns of activation held significant differences at the overall group level, as well (Knutson et al., 2000).

Additional evidence of dysregulation in GD comes from studies using the Stroop task to evaluate response inhibition. This task focuses on the prefrontal cortex, which has been implicated in poor impulse control (Potenza et al., 2003). The Stroop task was developed to study inhibitory control, with more robust results when combined with imaging studies. The Stroop task presents frequent combinations of congruent color-word pairs, but occasionally presents incongruent color-word pairs which requires response inhibition (Leung et al., 2000). Using the Stroop task to evaluate reaction time and neural correlates during behavior, Potenza et al. (2003) compared pathological gamblers (n=13) against healthy controls (n=11). Both groups performed similarly on the Stroop task in terms of correct/incorrect responses, as well as reaction time to incongruent stimuli. Neural activity was similar across groups, such as decreased activity in the ventral anterior cingulate; however, gamblers showed decreased activity in the ventromedial prefrontal cortex (vmPFC) compared to healthy controls. The vmPFC has been implicated in both decision making (Bechara, 2001) and reward processing of monetary outcomes (Breiter et al., 2001). This may indicate prefrontal dysfunction, which is consistent

across behavioral studies evaluating executive function and decision-making in those with GD (Goudriaan et al., 2005; Goudriaan et al., 2006; Marazziti et al., 2008). Taken together, neuroimaging studies have produced results that stress the involvement of the brain's mesolimbic reward system and the prefrontal cortex in GD.

Using PD tasks in combination with neuroimaging has added to the understanding of the neural networks that are activated during risky decision-making. Study outcomes have demonstrated that behavioral results are not always consistent with neural activity. This means that understanding the interaction of these separate systems will help build a more robust understanding of behavioral addictions. Additional research is needed to highlight the interaction of these systems and specifically their involvement with gambling. Research on GD has been ongoing for decades, but the AI community has largely been ignored in previous studies. American Indians have a higher risk for developing GD and gambling related comorbidities, along with closer average location to gambling environments. This study, therefore, should help add to the collective understanding of the differences this population faces when dealing with GD.

Methods

Participants

Participants between the ages of 18-65 were recruited from the AI population by the Center for American Indian Community Health (CAICH) to participate in the present study. Participants were 24 AIs of differing tribes (e.g., Kaw, Pawnee, Dakota) spanning the Midwest plains. Using DSM-V criteria 12 AIs with GD and 12 healthy controls were recruited with mean ages of 37 for gamblers (SD= 13.99) and 36 for controls (SD= 10.85). During recruitment, participant demographics were matched across groups. Participants were excluded from

participation if they reported any condition contraindicating magnetic resonance imaging (e.g., vascular clips, metallic objects in body, non-removeable medical equipment), current use of psychotropic medication (e.g., Alprazolam, Klonopin, Haloperidol), current or past abuse of illicit substances (e.g., methamphetamine, heroin, cocaine), diagnosis of severe neurological or psychiatric illness (e.g., Parkinson's disease, Multiple Sclerosis, Major Depressive Disorder), inability to read and speak English fluently, left-handedness, or pregnancy. All participants were compensated $115 for their time in the study and received a $20 gas card to help with transportation expenses.

Upon arrival at Hoglund Biomedical Imaging Center at Kansas University Medical Center, participants were greeted by a research assistant and escorted to a consultation room. The consultation room was 8' x 12' with a bank of windows along one wall. The other wall had a door and bookshelf. There was a round table with chairs in the middle of the room with a couch to the side. Research assistants described the study and allowed the participants to ask questions prior to obtaining written consent. After consent was obtained, all other paperwork was completed, including demographics, payment form, and the MR screener which was used for the MR technicians to verify the participants' ability to go into the scanner without issue.

Probability Discounting (pre-scan)

Next, participants completed a probability discounting practice task conducted on an encrypted laptop computer. Instructions were displayed on screen, as well as being read aloud to participants. For this task, participants were instructed

> *"Now, you'll be making decisions about some probability of receiving some amount of money. You'll see different probabilities of receiving amounts of money. Although you will not receive these amounts, pretend you will have the*

chance of receiving the amount and answer honestly. You can select between the two options by pressing the 1 and 2 buttons on this line of numbers. Press the 1 button for the option on the left and the 2-button for the option on the right."

Participants were then asked to complete four rounds of trials - one round at each of the probabilities (90%, 70%, 50% and 10%). Probabilities were presented in descending order and all trials were completed for each probability before moving on to the next probability. Within each probability, participants started on an option for a certain chance of $50 or a probability of $100. Using an amount titrating procedure, the dollar amount was then titrated by 50% for the next trial. If the smaller certain option was chosen, then the certain outcome was decreased to make it subjectively less appealing. Conversely, if the probabilistic outcome was chosen, then that amount was increased. Once the amount was titrated, participants where then presented with a new choice of a certain versus probabilistic outcome. Participants completed six trials per condition across each of the four probabilities. After completion of the task, the research assistant opened the E-Data file and retrieved the indifference points. These values were later entered into the computer in the scanner to equate the tasks for all participants.

fMRI Scan

After all questionnaires and tasks were completed, participants were escorted to the locker room area to change into scrubs. Participants were instructed to remove any metal from their body, including, hair ties, underwire bras, and piercings. Once changed, participants were taken to the scanner where the tech repeated the safety screener to ensure no loose metal in/on the participants. Additionally, the techs verified participants' surgical histories and further screened for any metal or electronic devices inside of the participant. Participants that wore

glasses were fitted with scanner compatible prescription goggles, and sight was checked by technician before the fMRI session.

The MR tech escorted participants into the scanning area and ensured each participant was correctly situated in the scanner in a comfortable position that they would be able to maintain for the duration of the scans (blankets were offered for extra warmth). The head coil was placed over the participants head once in the scanner. A screen just above the participant had the task projected onto it and participants were given a control pad that had two buttons, side-by-side, that correlated with the choices projected onto the screen. The MR tech made sure the screen was visible to the participant and any last-minute adjustments were made.

After participants were situated in the scanner, the MR tech returned to the holding room with the researcher to begin scans. Indifference points from the practice rounds were entered for each participant at each of the four probabilities (90%, 70%, 50%, and 10%). Using individual indifference points, tasks were equated for individual participants across the study (i.e., the monetary values presented were individualized based on the participants' pre-scan indifference points). The function of equating the tasks across participants was to prevent markedly different patterns of choice to investigate the processes that support choice, rather than the choices themselves. The same instructions from the practice round were orally delivered to participants in the scanner (instructions were not displayed on screen). Instructions were stated the same as during practice,

> *"Now, you'll be making decisions about some probability of receiving some amount of money. You'll see different probabilities of receiving amounts of money. Although you will not receive these amounts, pretend you will have the chance of receiving the amount and answer honestly. You can select between the*

two options by pressing the left button for the option on the left of the screen, and the right button for the option on the right side of the screen."

Once instructions were delivered, the program was loaded and automatically triggered by the start of the scanner. All stimuli (PD choices) were presented using E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA) for the scan portion of the task. The same adjusting amount PD procedure was used from the pre-scan testing, however, for the scan task, percentages were displayed in a pseudorandomized order. The screen above the participant showed the two options (the certain and probabilistic outcomes) the participant was to choose between. Options were presented in black text on a white background, with the certain outcome being randomized between the right and left side of the screen for each trial. Participants were presented with an initial choice between a smaller, yet certain outcome (100% chance of $X), versus a larger, probabilistic outcome (X% chance of $100). Participants made 32 choices per round (approximately 8 choices per probability), for three total rounds (total of 96 choices), to determine an indifference point at each probability. Between trials the instructions were repeated by the MR tech and each trial ended with a fixation cross that turned from black to gray to signify the end of the round.

Scanning was performed on a 3-Tesla full body Siemens Skyra scanner (Siemens, Erlangen, Germany) fitted with a 20-channel head and neck coil. Scans collected included an anatomical scan and 3 functional scans during the probability discounting task. T1-weighted 3D MPRAGE anatomic images were obtained (TR/TE 2300/2.95 ms, flip angle 9°, FOV = 256 mm, matrix = 240 x 256, slice thickness = 1.2 mm). These images provided slice localization for functional scans and co-registration with fMRI data. Gradient echo blood oxygen level dependent (BOLD) scans were acquired in 43 interleaved slices at a 40° angle to the AC/PC line

(TR/TE = 2500/25.0 ms, flip angle = 90, matrix = 80 x 80, slice thickness = 3 mm, in-plane resolution = 2.9 mm). The duration of each functional run varied based on individual participant reaction times.

Each round ended with a fixation cross that turned from black to gray. After completion of the scans, participants were escorted to the changing rooms to return to their street clothes. After changing, participants were escorted to a small office (4' x 7') in which the SOGS questionnaire was administered in addition to completing the timeline follow back for gambling behavior over the previous 90 days. Once all testing was complete, participants received their compensation and were thanked for their time.

Analysis

fMRI Pre-processing

All data was managed using RedCap electronic data capture tools hosted at University of Kansas Medical Center (Harris et al., 2019; Harris et al., 2009). Data preprocessing and statistical analyses were performed in AFNI (Cox, 1996). Preprocessing steps included motion correction, alignment, spatial smoothing, and normalization. The fMRI images were realigned to the minimum outlier in each run to correct for motion. The images were spatially smoothed to 4 mm FWHM Gaussian kernel. Anatomic images were aligned to functional images and spatially normalized to Montreal Neurological Institute space using non-linear warping implemented with AFNI's automated algorithm. Within each functional run were registered to the minimum outlier. Data points were censored if motion within a volume was greater than 0.3 mm. Statistical contrasts were conducted using multiple regression analysis with motion parameters included as nuisance regressors. Regressors representing the experimental conditions of interest (i.e., High, Mid, and Low Probability) were entered into the regression analysis using a duration modulated

basis function. Timing files were created in Microsoft Excel to identify the beginning and end of each individual trial. Trials were separated into three groups (High, Mid and Low Probability). High probability trials consisted of the 90% probabilities, Mid probability trials consisted of the 70% and 50% probabilities, and the Low probability trials were set for the 10% probabilities. The quality of the fMRI data was checked for processing errors, alignment, and motion issues.

Behavior Analysis

Inclusionary criteria for analyses of behavioral components was determined by using the criteria outlined by Johnson and Bickel (2008) to evaluate and remove non-systematic data. Although developed for use on Delay Discounting data, these criteria are well suited to evaluate PD data (Johnson & Bickel, 2008; Rasmussen et al., 2010) when evaluated in a descending order. Participants' data were removed if an increase of more than 20% of the undiscounted amount was noted from one condition to the next, starting with the second indifference point, or if the final condition indifference point was not less than the first by at least 10%. Applying these criteria to the participant pool, four gamblers and three controls were removed from analyses for the behavioral components.

Analyses and curve fitting (Equation 3) were performed in GraphPad Prism (version 8). Differences in PD rates were calculated using h rates (discounting rates) and AUC analysis. Importantly, AUC provides a direct measure of discounting (Abidi et al., 2018) and is not linked to any theoretical framework (Myerson et al., 2001). AUC is calculated using the trapezoid method that calculates the aggregate data (area) under the data path (curve; Myerson et al., 2001).

(4)

$$AUC = \Sigma(x_{i+1} - x_i)\frac{(y_i + y_{i+1})}{2}$$

fMRI Analysis

After preprocessing of individual scans was complete, exclusionary criteria was applied to finalized groups for analysis. Of the 24 participants, four subjects (2 gambler and 2 control) were removed due to not completing scans. Two additional gamblers were removed due to excessive motion in the scanner (greater than 50% of data were censored). The data analysis focused on a whole-brain voxel-wise analysis of variance (ANOVA) implemented by AFNI's 3dMVM (Chen et al., 2014) to determine brain activation (i.e., percent signal change from baseline) main effects and interactions [Probability (Low, Mid, Hight) x Group (Gambler, Control). AFNI's 3dClustSim was used to estimate the probability of false positives and correct for multiple comparisons at $p < 0.05$ and $\alpha < 0.05$.

Results

Behavioral Results

Group median indifference points from pre-scan PD tasks are shown in Figure 1 for both groups across each of the indifference points (90%, 70%, 50%, and 10%). Probability discounting curves were analyzed using Rachlin (2006)'s hyperboloid equation ($V = A/(1+h\theta^{s})$). This equation allows for two free parameters during analysis. To control for this, the scaling parameter was shared across all participants (s=0.8165). Figure 2 shows probability discounting curves for both groups. Analysis showed a good fit for both groups (R^2=0.9858), with gamblers fit (R^2=0.9955) showing a slightly better account of variance than controls (R^2=0.9703). When fitting Equation 3 to individual subjects' data the fit was fair for gamblers (mean R^2=.8642; SD=.16) and controls (mean R^2=.8926; SD=.09), with the mean log-transformed discounting rate (LN[*h*]) significantly differing between groups (t(17) = -3.795, p=.002)). As a confirmatory step, this analysis was also conducted using Area Under the Curve. Area Under the Curve measures of

indifference points were lower for Controls (M=.427, SD=.212) compared to Gamblers (M=.672, SD=.057). An unpaired t-test comparing AUC showed a statistically significant group difference (t(15) = -2983, p= .009).

SOGS scores (Figure 3a-3c) are presented for gamblers (range 4-16; M=9.375, SD=3.70) and controls (range 1-3; M=1.44, SD=0.73). Using an independent samples t-test with Welch's correction revealed a statistically significant group difference (t(15) = 6.318, p< .001). Group differences are shown in a bar graph (Figure 3a) and scatterplot graph (Figure 3b) with the line representing median SOGS score. Spearman correlational analyses were performed comparing SOGS scores to discounting rates (*h* value) in Figure 3c. Using a Spearman correlation analysis, results indicated a statistically significant negative correlation (r(15) = -.617, p= .006) between SOGS scores and discounting rates (*h* value).

Number of hours gambled in the last 90 days is shown in Figure 4. Because gamblers' self-report data for hours and days gambled was hypothesized to be higher than that of the controls, a one-tailed independent samples t-test with Welch's correction was used to evaluate differences. Results yielded a statistically significant difference in the number of hours gambled over the last 90 days (t(7) = 2.023, p = .041) between Gamblers (M=79.875, SD=108.24) and Controls (M=2.444, SD=2.79). Additionally, using the same analysis on number of days gambled (Figure 5) yielded a statistically significant difference (t(7) = 4.142, p =.002) between Gamblers (M=19.375, SD=12.14) and Controls (M=1.22, SD=1.30) in the last 90 days.

fMRI Results

Whole brain analysis found no significant Group x Condition interaction or main effect of Group. A main effect of probability condition was found in decision-making regions of the dorsal medial prefrontal cortex (dmPFC; x,y,z = -2, 44, 33, p<.05, corrected) and attention

regions of the precuneus (x,y,z = -5, -69, 58), $p<.05$, corrected) demonstrating greater activation in low compared to high probability conditions (Figure 6). Using a two-way ANOVA for analysis on the dmPFC (Figure 7) revealed a statistically significant effect by condition (Probability) = ($F(2, 2) = 316.7$, $p = .0031$). Using a two-way ANOVA on data from the precuneus (Figure 8) revealed a statistically significant effect by condition (Probability) = ($F(2, 2) = 61.59$, $p = .0160$).

Secondary analysis of correlations between AUC and percent activation change were run on specific regions of interest (e.g., ACC, mPFC, and visual cortex) as a function of condition. Using a Pearson correlational analysis , results indicated a statistically significant negative correlation between AUC and percent activation change at both the Low probability ($r(18) = -.629$, $p= .005$) and Mid probability ($r(18) = -.32$, $p = .03$) seen in figures 9 and 10, respectively. Results in the High probability condition showed a negative correlation; however, this correlation did not reach statistically significant levels. No other regions showed a statistically significant results with AUC and percent activation change.

Discussion

Results of the current study replicated and extended findings in both the behavioral and neurobiological literature on decision making in those with a GD. Specifically, gamblers showed higher indifference points across all probabilities which reflects a lower level of PD. This demonstrates a propensity to chance outcomes to a higher degree or to engage in more risky decision-making than controls. These results are consistent with previous research showing more shallow discounting by gamblers (Holt et al., 2003; Madden et al., 2009; Miedl et al., 2012) versus controls on PD tasks. In the current study, controls showed a sharp decline in preference for probabilistic outcomes once the probability dropped below 90%. This means that soon after

certainty is removed, controls forgo the risky outcome. Gamblers, however, show less willingness to forgo the probabilistic outcome for the certain one. Taken together, these findings suggest those dealing with GD are more likely to engage in sub-optimal decision-making, especially as risk increases.

Chance itself is not inherently bad. For example, gambling involves chancing a small amount of a resource for the opportunity to acquire a larger amount of that resource with little to no extra effort. Taking calculated chances is different, however, than risks which involve an element of underlying danger. Specifically, Shead and Hodgins (2009) showed a pattern of behavior that reflects those willing to engage in riskier behaviors tend to overvalue gains and undervalue losses (risk attitudes). With a stronger preference for the probabilistic option, gamblers continue to risk outcomes, even when the outcome is less than advantageous. Healthy controls show a quick and steep switch to the certain option at high probabilities which demonstrates a preference for certainty, or loss avoidance (Shead & Hodgins, 2009). As the proverb says, "A bird in the hand is worth two in the bush." Gamblers, however, overvalue the potential outcome (two in the bush) and undervalue the certain outcome (bird in the hand; Shead & Hodgins, 2009). Rather than attending to the risk, gamblers may focus more directly on the potential outcome rather than the probability of receiving it. For gamblers, the magnitude of the uncertain outcome may be more influential than the risk involved with that behavior. This is supported by the results of the current study that show those more likely to take a risk (gamblers) have higher rates of these same risky behaviors in their past (past gambling involvement). These behaviors are a pattern of risky decision making – or more likely a type of behavioral trait, as has been demonstrated in delay discounting (Odum, 2011). This is where newer techniques, such as

multilevel modeling could be helpful in parsing apart components (e.g., magnitude versus probability) of individual and group level preferences (Jarmolowicz et al., 2020; Young, 2017).

The current study used a novel analytic approach developed by Abidi et al. (2018) to evaluate correlations between percent activation changes in ROIs with AUC measures. One region in particular (mPFC) showed a negative correlation across conditions (probabilities). Using a Spearman correlational analysis to compare AUC and percent activation change in the mPFC showed significant negative correlations of -.65 and -.55 in the mid and low probability conditions, respectively. The high probability condition was not statistically significant; however, it was consistent with the riskier conditions (e.g., negative correlation). These correlations highlight a specific involvement of the mPFC during decision making regarding riskier outcomes. The mPFC has been shown to be involved in conflict monitoring (Botvinick et al., 2004) and decision making regarding risky and rewarding outcomes (Bechara & Damasio, 2005). The negative correlation highlights an interesting process by which those who discount more (healthy controls) showed more reliance on the mPFC, whereas those who discount less steeply (gamblers) rely less on this region when processing risky outcomes. The observed differences may have to do with the participants and study design. Specifically, the current study was investigating differences between gamblers and controls, whereas Abidi et al. (2018) was evaluating healthy controls alone. Additionally, it could be an artifact of the task used by Abidi et al. (2018), as it asked participants to make decisions about a medication that had differing levels of side effects (probability and severity) and efficacy for a disease they did not have. Specifically, all participants were healthy controls but made decisions about potential risks and benefits of a medication for Multiple Sclerosis.

Results of the current study are partially consistent with the GD literature. Specifically, Peters and Buchel (2009) reported activation differences in the VS and OFC from baseline levels. Those differences were not found in the current study. Instead, differences in the dmPFC and precuneus were found as a function of condition – but not group. Previous studies also highlighted differential activity in the OFC during PD tasks (Peters & Buchel, 2009), specifically during low risk conditions (Abidi et al., 2018). Of note, the OFC activation differences seen in previous studies (Abidi et al., 2018; Peters & Buchel, 2009) were found while evaluating healthy controls, whereas Miedl et al. (2012) and the current study did not report these same findings when comparing PD in gamblers versus healthy controls. Additionally, methods from Peters and Buchel (2009) restricted participant response time to 2 seconds, which possibly impacted decision-making and reward valuation. This restricted time in which to make decisions and report responses could have added complexity to the task which wasn't reflected in the current study design. In the current study, participants were not restricted in the time they had to make their decision. The differences in the OFC, therefore, could have more to do with the timing constraint impacting cognitive control, rather than overall group differences in decision making. The current study did replicate and extend results of Miedl et al. (2012) which reported only trends toward significance between groups due to low power and high variability. Of note, results from Miedl et al. (2012) reported trends toward significance in uncorrected analysis, whereas results of the current study were only reported for corrected analyses.

Findings of the current study highlight a difference in decision-making regions of the dmPFC across conditions (probability). Specifically, the current results reflect a systematic decrease of activity in the dmPFC as the odds against increase. The decreased activity in the dmPFC as a function of the increasing odds against reflects a decreased need for neural support

during riskier decision making. Although this finding is novel for studies evaluating PD in gamblers, it is consistent with studies of neural activity during other tasks involving risky decision making. The dmPFC has been implicated in risky decision making compared to ambiguous decisions (Eickhoff et al., 2016). Specifically, risk processing has been shown to activate the dmPFC (Wu et al., 2021), however, the degree of activation is negatively correlated with risk preference (Xue et al., 2009).

The correlational findings of the current study in the dmPFC are novel to both gamblers completing PD tasks and the AI population during PD tasks. These results show that gamblers rely on the dmPFC similarly to controls when making risky decisions. This interpretation is likely given the differences in dmPFC activity across conditions, but not group. In other words, there are no significant differences between gamblers and controls in dmPFC activation while making similarly risky decisions. Of note, Tanabe et al. (2007) found evidence that dmPFC activity was reduced in both gamblers and non-gambles with a history of substance use during the Iowa Gambling Task. Speculatively, this could point to the fact that comorbid diagnosis and other related maladies could be driving differences in the dmPFC instead of GD, specifically.

In addition to results of the dmPFC, a main effect of condition (probability) in the attention regions of the precuneus was also identified. Gamblers showed a slightly higher level of activation in the precuneus across probabilities; however, this difference was not statistically significant across groups. The role of the precuneus, specifically in behavior, is still being debated across research specialties. The precuneus has been shown to be involved in the role of self-processing (Kircher et al., 2002), integrating motor coordination associated with visuo-spatial (Wenderoth et al., 2005), and response inhibition (Swick & Turken, 2002). Although the specific role(s) of the precuneus is still debated, it is situated in a unique region of the brain with

projections to much of the surrounding areas. The precuneus, therefore, is thought to be involved in multiple roles across several regions. Specific to response inhibition, the results highlight that those with GD do not show differential levels of function during decision making. Instead, differences may be in gamblers attending less to the risk and more to the potential outcome. This is supported by group level differences in discounting curves which reflect difference in subjective valuation of the outcome.

Using fMRI techniques in combination with behavioral tasks has helped add to the literature by investigating the neural function underlying the behavioral processes involved in both decision making, broadly, and gambling, specifically. Additional study data has helped to grasp the complexity of neural correlates of behavioral processes; however, it may be difficult to interpret. Specifically, results may not be consistent across studies depending on number of participants, tasks used, and amount of data collected. Further, imaging results only report differences in levels of activity and correlations with behavior to begin identifying potential answers. Behavioral studies are designed to address individual differences, as well as larger group differences, that highlight dysfunction in behavioral processes of decision making. Although having more data helps to understand the problem broadly, the difficulty lies in applying these results across studies and populations. Specifically, neuroimaging studies are typically restricted to the healthiest and cleanest of participants to ensure better data. In other words, those with more severe problems or multiple comorbidities may be excluded from these studies. In comparison, behavioral studies can use those data to understand individual differences. In a larger context, neuroimaging studies rely on large groups with which to investigate problems, whereas behavioral studies are designed to be much more sensitive to individual differences.

With gambling studies shifting toward using SOGS as a screening tool instead of the DSM criteria, additional relations can be investigated between gambling severity and rates of discounting. Previous studies have highlighted a negative correlation between SOGS scores and discounting rate (Holt et al., 2003; Madden et al., 2009). Results of the current study are consistent with previous studies demonstrating a negative correlation between gambling severity (SOGS scores) and discounting rate (Holt et al., 2003; Madden et al., 2009). The current study results reflect a strong negative relation in the rate of PD as a function of the increasing severity of GD. Specifically, the more severe the GD, the more likely a person is to take risks at lower likelihoods of a positive outcome. This pattern of behavior means that those with severe GD are most at risk of engaging in risky decision making.

Rates of gambling involvement showed significant group differences. Although this finding was not surprising, implications are important for those dealing with GD. Group level differences were found for both number of hours gambled, and number of days gambled, in the last 90 days, on a timeline follow-back questionnaire. The average number of hours gambled per session had a more than three-fold difference across groups which reflects gamblers not only gamble more days, but also longer periods of time on those days. Gamblers showed a higher level of involvement with gambling in the previous 90 days, lower discounting rates and higher SOGS scores. Taken together these results indicate that those with severe GD may be in a uniquely vulnerable position for negative consequences. Specifically, more severe GD (SOGS) is correlated with higher rates of risky decision making along with engaging in higher rates of gambling activities (both hours and days). This is consistent with results from Weatherly and Derenne (2012), that note the behavior of those with severe GD being maintained by negative reinforcement (escape maintained behavior) rather than positive reinforcement. This behavioral

pattern is consistent with those seen in other addictive disorders where those with long-term addiction seek their substance of choice to alleviate negative feelings rather than to deliver reinforcing psychoactive effects (Blume, 2001; Koob, 2020).

Although these findings inform research on GD, broadly, they are exponentially more important to those in the AI population, collectively. In addition to risky behaviors correlated with GD, those in the AI community may also be contending with increased proximity to casinos (Welte, Barnes, et al., 2004), increased ease of access to gambling (Patterson et al., 2015), and increased levels of comorbid diagnosis (Lorains et al., 2011) and past exposure to trauma (Ehlers et al., 2013). Individually, these components increase the potential for negative outcomes; however, collectively these components reflect the drastic impact on an underserved community population.

In summary, results showed behavioral differences in decision making across groups, yet neural function showed no statistically significant regions between groups. Although group differences did not meet statistical significance, two regions (dmPFC and precuneus) both showed significance as an effect of condition. Gamblers showed less-steep discounting than controls, higher SOGS, and more hours/days gambling in the past 90 days. Overall, these results show that behaviorally the groups were significantly different but do not differentially tap regions of the brain when making decisions across increased riskiness. In other words, either gamblers do not show neural differences from controls when making risky decisions or the lack of differences could be due to the specific population. Specifically, increased access to and availability of gambling establishments, past history of trauma, and increased risk of comorbidities may affect AIs as a whole, rather than differentially across those with GD and those without.

There were limitations to the study that need to be addressed in future research. The first limitation is the small group sizes and large amounts of variability within and between groups that reduced statistical power necessary to identify some group level differences. Non-systematic data across participants played a part in this limitation. By administering the pre-scan PD task as a screener, participants with non-systematic data could have been eliminated which could have increased results through increased statistical power. Using methods similar to Peters and Buchel (2009) where participants completed multiple pretests on separate visits could help reduce variability and non-systematic data. Although this could be beneficial, there is evidence that running discounting tasks multiple times, or to stability, likely taps difference brain regions when making decisions about outcomes. Likely, an approach similar to the current methods would be beneficial, with the first round of PD being used for participant screening. This could help to eliminate participants with non-systematic data – both increasing the significance and preventing over-exposure to the same task.

The next limitation is that indifference points from the pre-scan task were used to equate the task. By equating the tasks, it could be preventing some differences from being identified, however, those differences are likely due to the contextual variables rather than the underlying behavioral processes. By functionally equating the tasks, it reduces differences from task difficulty and allows a more direct comparison between groups in both behavioral and neurobiological measures. Although this approach does have some limitations, it is also beneficial in that is allows for other variables to be held constant to restrict extraneous variables. Specifically, task difficulty and range of indifferences points may confound findings if not held constant. Although it may restrict individual indifference points outside of the natural behavior of the individual, the overall pattern of responding is more applicable to group level analyses.

Another limitation of the current study was the attempt to replicate methods of previous PD studies by Peters and Buchel (2009) and Miedl et al. (2012). Both studies used pre-scan indifference points to equate tasks, so participants responded with approximately 50% of choices above and below their original indifference points. Controlling for variance of indifference points and task difficulty associated with PD tasks, the current study used pre-scan task indifference points to equate PD tasks. The goal was to recreate this design, however, around 70% of presented choices were above pre-scan indifference points. This was consistent within and across groups. Although the task did not reach the intended 50/50 split, keeping the percentages consistent across groups still functionally equated the tasks. With the PD task being subjectively equal for all participants, the differences observed in behavioral and neurobiological outcomes highlight differences in processes activated during decision-making. By holding all other variables constant, the outcomes can be attributed to processes, rather than task specific differences.

An additional limitation of the current study is the evaluation of PD across a limited number of probabilities. The majority of studies (Holt et al., 2003; Miedl et al., 2012; Peters & Buchel, 2009) used seven probabilities that were pulled from Rachlin et al. (1991) of 100%, 99%, 96%, 84%, 54%, 28%, and 17%. Utilizing this range of options allows for comparison across a wide range of probabilities while also evaluating subtle yet important differences at similar rates at both high (100%, 99%, and 96%) and low percentage (28% and 17%). Additionally, studies have used a range of potential probabilities, such as six (Shead et al., 2008) or five (Weatherly & Derenne, 2012) probabilities to evaluate discounting rates. Using only four probabilities may have impacted the ability to identify subtle differences. Previous research, however, by Matusiewicz et al. (2013) has demonstrated good reliability when evaluating four

probabilities - consistent with Yi et al. (2010). With statistically significant group differences in the PD task, this was likely not a limitation in the current study.

Finally, contextual variables related to gambling behavior are a much more complicated component to address within the scope of limitations. By removing extraneous variables found in the gambling environment, specific behavioral and neurological processes can be identified and evaluated. This allows for evaluation of the fundamental processes underlying gambling behavior that are consistent across gamblers, apart from environmental influence. Gambling stimuli may complicate the findings by concurrently tapping multiple processes, whereas the current study was able to hold other components steady to evaluate processes underlying decision-making. By removing these variables, however, the impact of classically conditioned stimuli, and how they influence gambling behavior, are not able to be studied. Specifically, auditory and visual stimuli need to be investigated to understand the impact on neural activity underlying behavioral processes. For future studies, investigating the connections between contextual variables within a casino and the impact on both behavioral and neurobiological processes could highlight notable differences. Additionally, behaviors specific to the gambling environment, such as betting, collecting winnings, and paying losses could highlight some subtleties that are lost due to the setting of the study. Although this could be considered a limitation, the fact that statistically significant differences are consistently found in the absence of these variables demonstrates the strength of these differences.

In summary, this study replicated some previous findings of GD using PD tasks in an fMRI study, but also highlighted new findings that need to be further investigated. These differences need to be evaluated in a larger cohort to increase statistical power to evaluate the subtleties noted in activation differences that did not pass statistical significance. Further

research is needed to replicate and extend these findings to treatments that may target the mediation of the risky outcome with the reward drive. Additional treatments for increasing PD rates in gamblers may be of significant interest until more information is gained on the neural processes tapped by gamblers during decision-making.

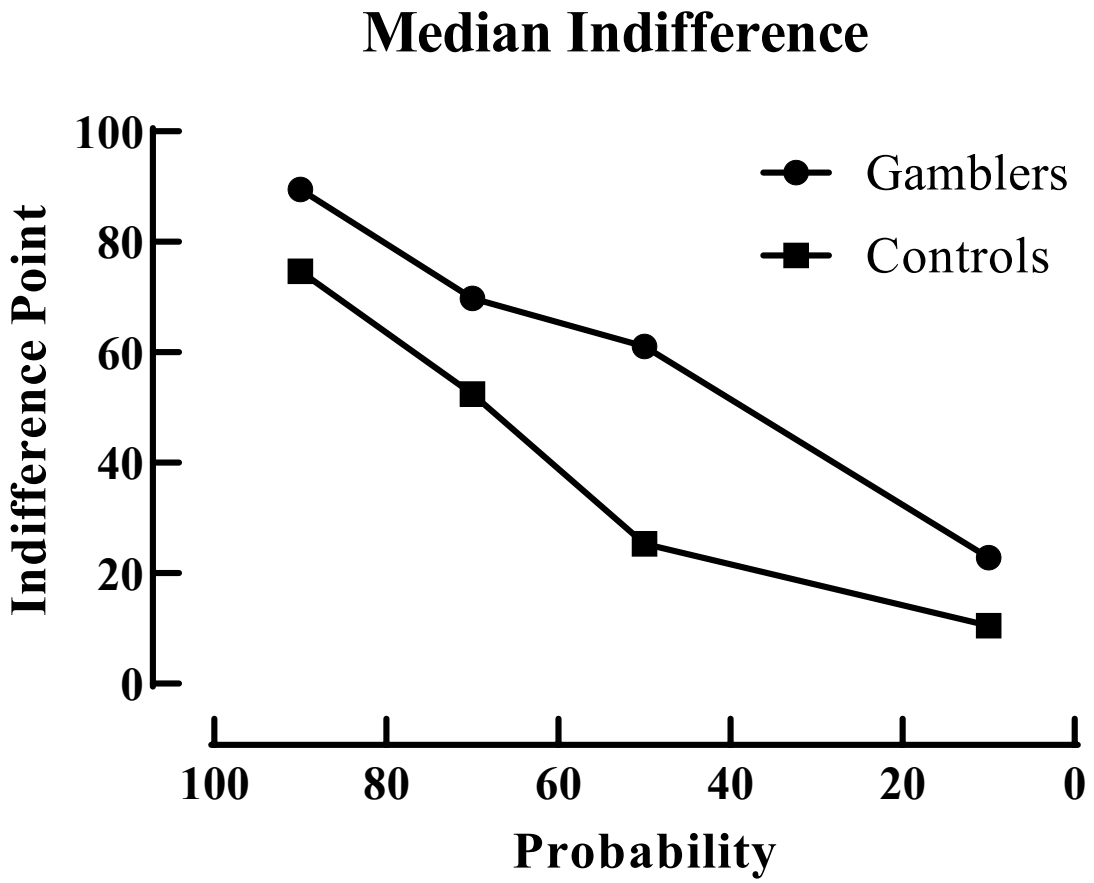

Figure 1: Group Median Indifference Points. Indifference points on pre-scan task of probability discounting across all probabilities (90%, 70%, 50%, and 10%). Squares denote controls and circles denote gamblers.

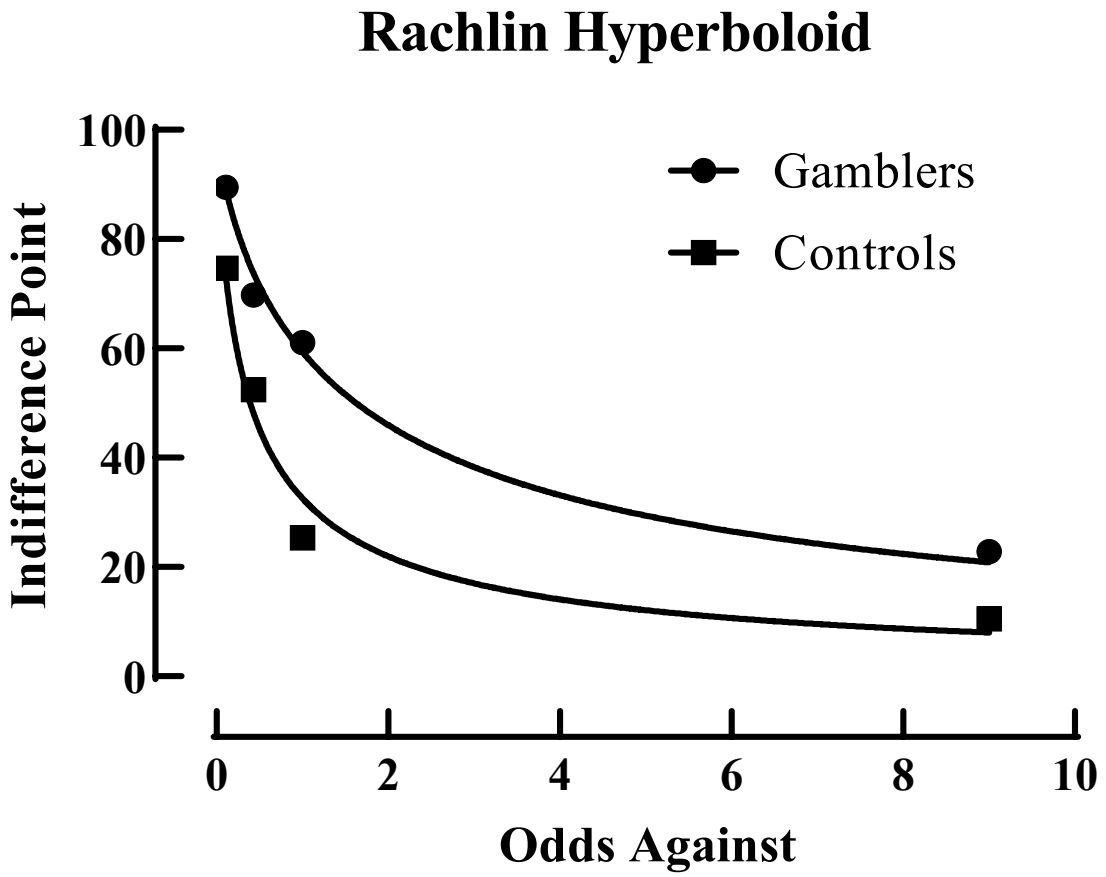

Figure 2: Probability Discounting Curves. Discounting curves using Rachlin's Hyperboloid equation with gamblers denoted as circles and controls with squares. Overall fit showed an r^2=0.9858 with Gamblers (r^2=0.9955) and Controls (r^2=0.9703) each showing good fits. Gamblers showed a much more-shallow discounting rate (h =0.6038) compared to controls (h =2.134).

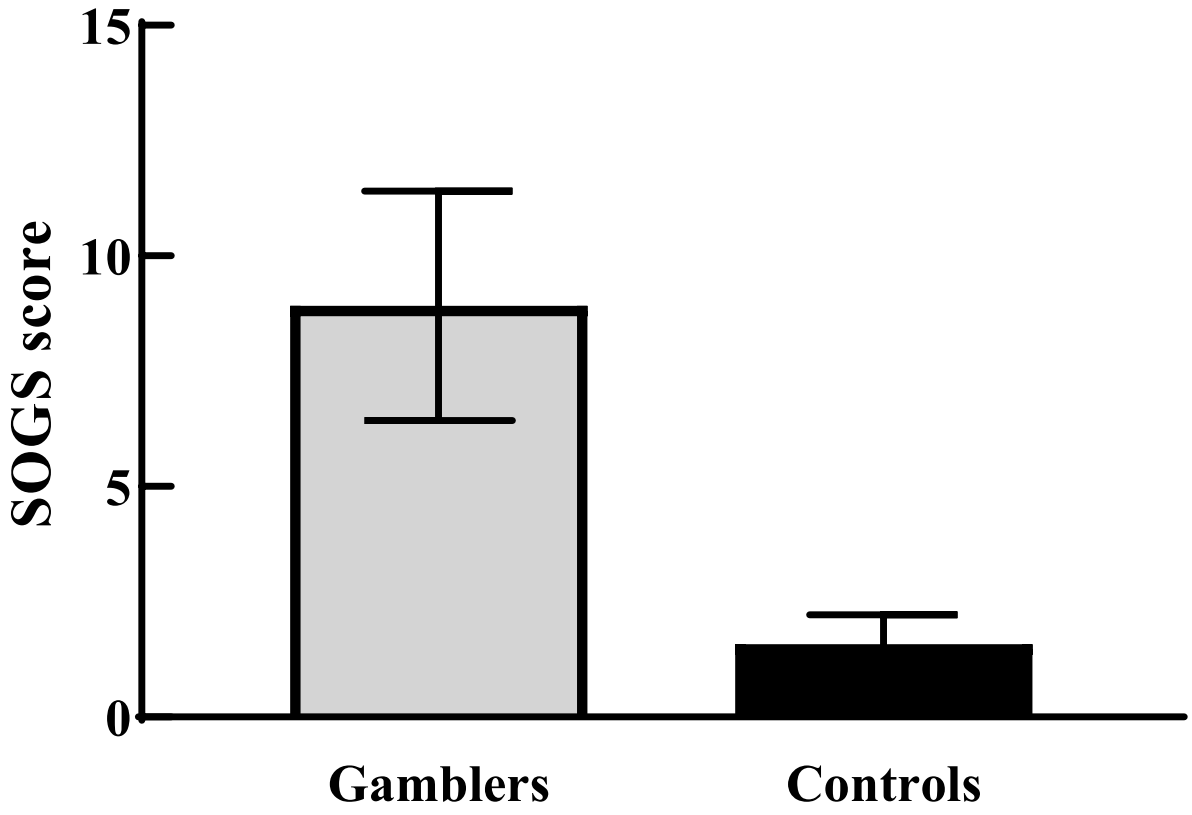

Figure 3: Group Mean South Oaks Gambling Screener Scores. Group means on South Oaks Gambling Screener with 95% confidence interval for gamblers (M=9.375, SD = 3.70) and controls (M=1.44, SD = 0.73). Results of an independent samples t-test with Welch's correction revealed a statistically significant group difference ($t(15) = 6.318$, $p < .001$).

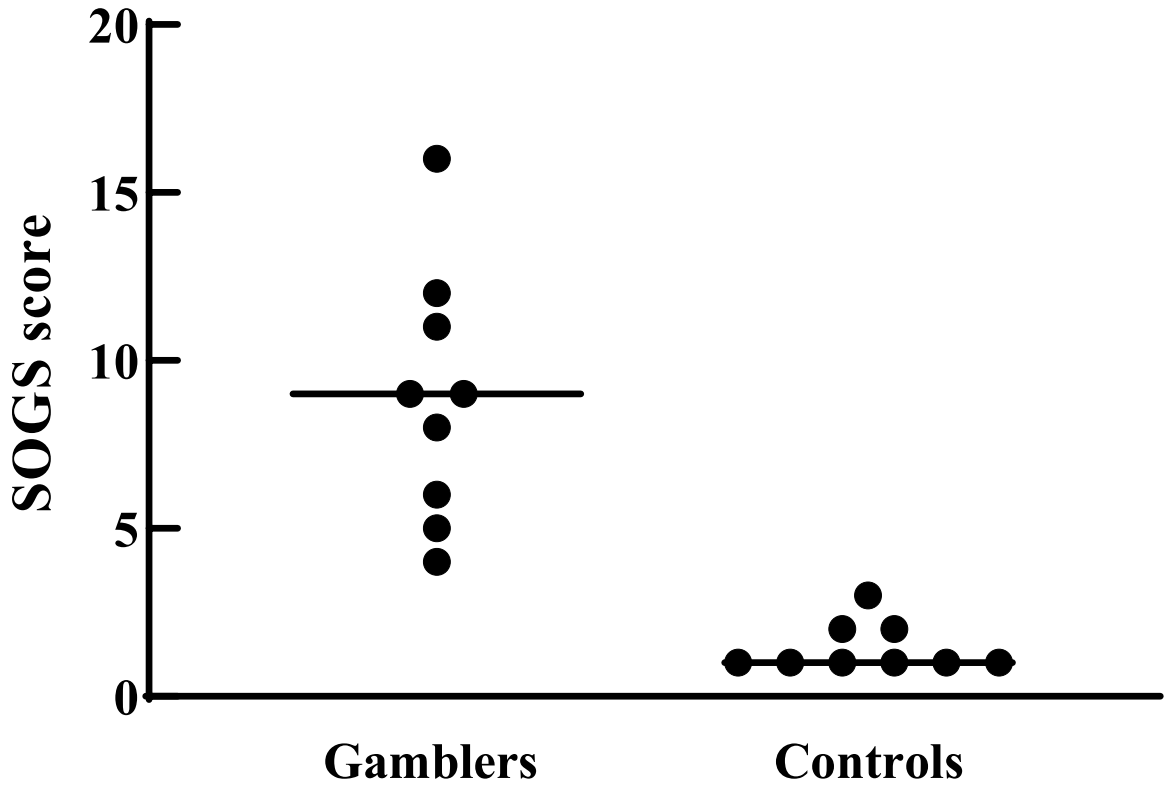

Figure 4: Scatterplot of Group South Oaks Gambling Screener scores. Group South Oaks Gambling Screener scores with line representing group median.

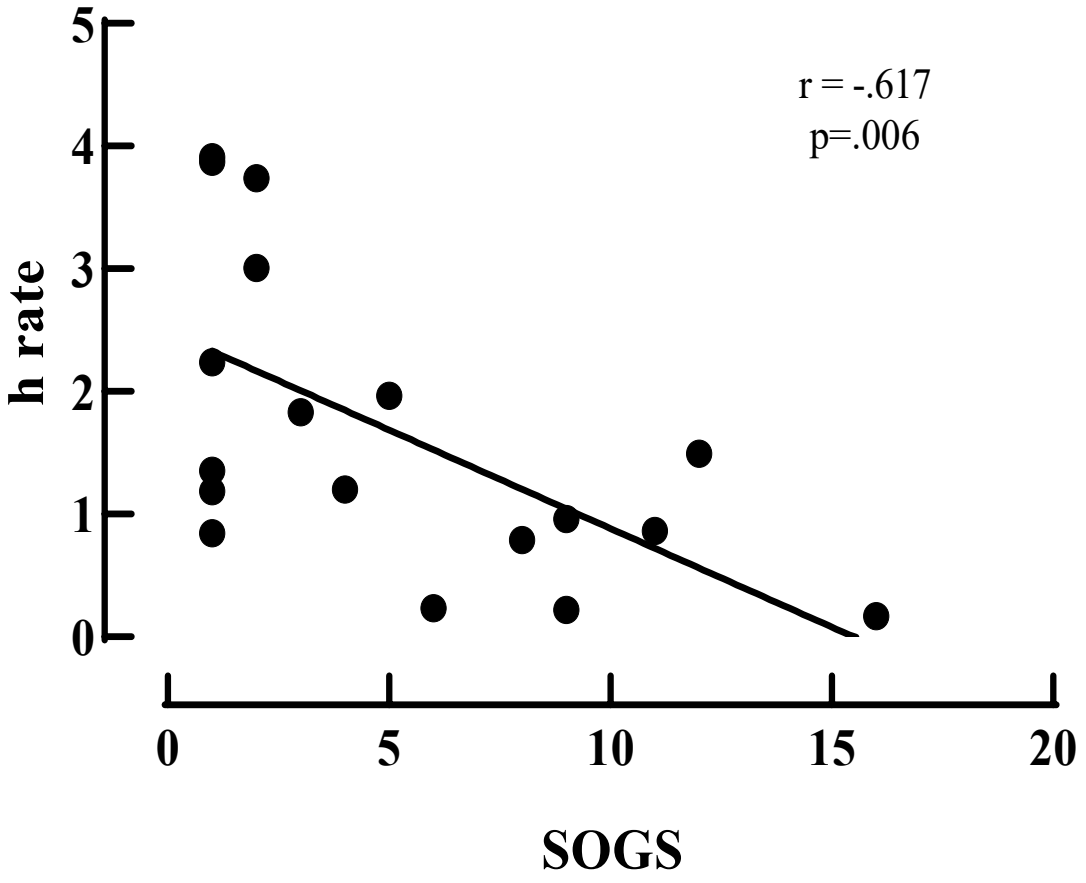

Figure 5: Correlation of Discounting Rate and South Oaks Gambling Screener Scores. Spearman correlation analysis of discounting rate (h rate) and SOGS scores. Results show a statistically significant correlation of -.617 with a p=.006.

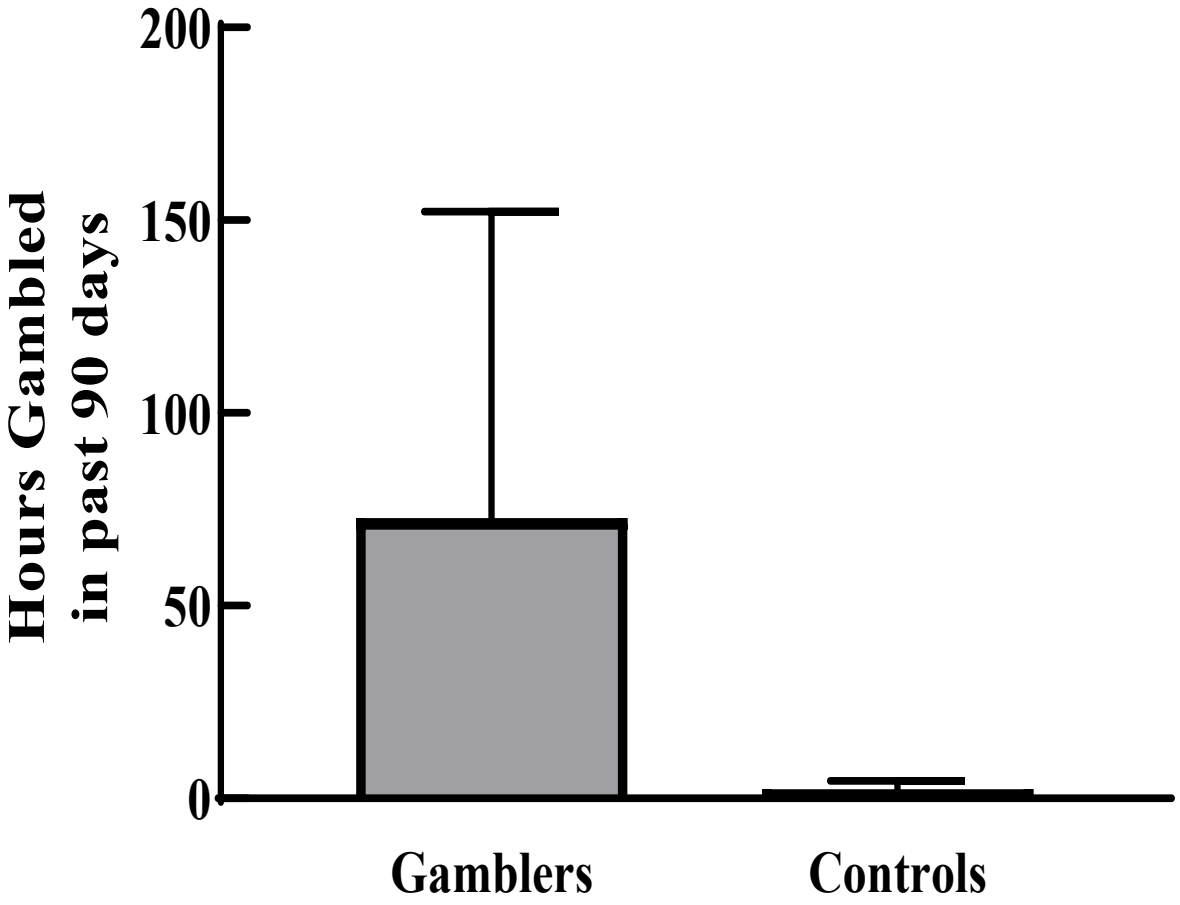

Figure 6: Group Mean Hours Gambled. Hours gambled in past 90 days with 95% confidence interval. Using a one-tailed independent samples t-test with Welch's correction shows a statistically significant group difference t(7) = 2.023, p=.041 between Gamblers (M=79.875, SD=108.24) and Controls (M=2.444, SD=2.79).

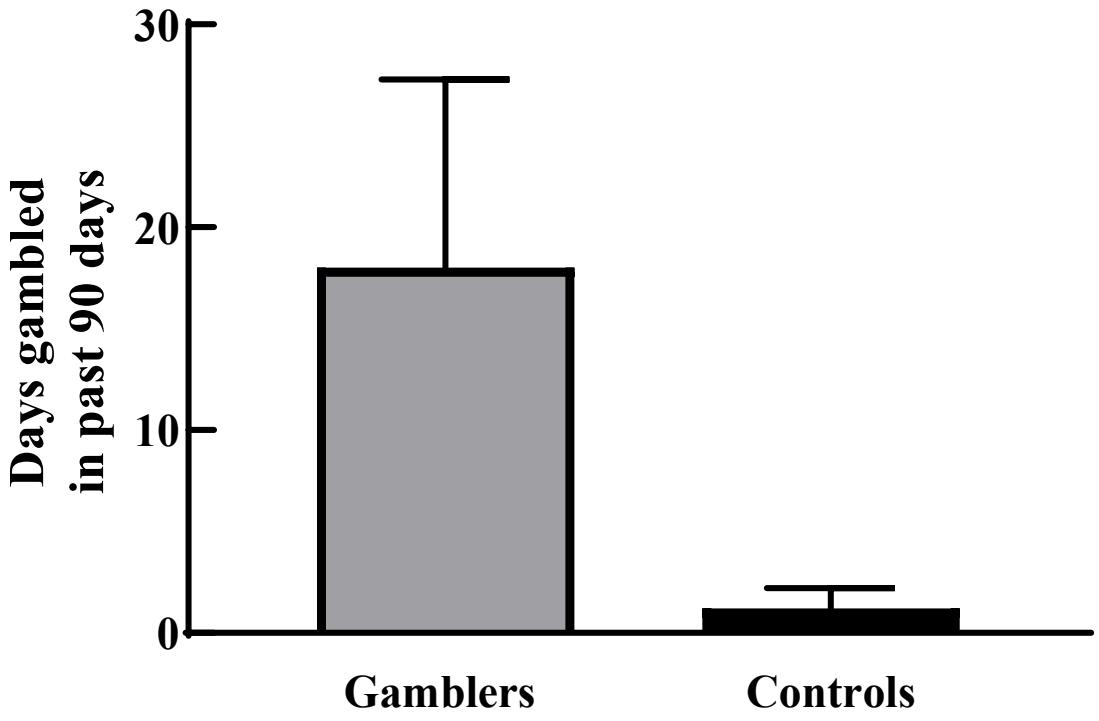

Figure 7: Group Mean Days Gambled. Days gambled in the past 90 days with 95% confidence interval. One-tailed independent samples t-test with Welch's correction t(7) = 4.142, p=.002 between gamblers (M=19.375, SD=12.14) and Controls (M=1.22, SD=1.30) in the last 90 days.

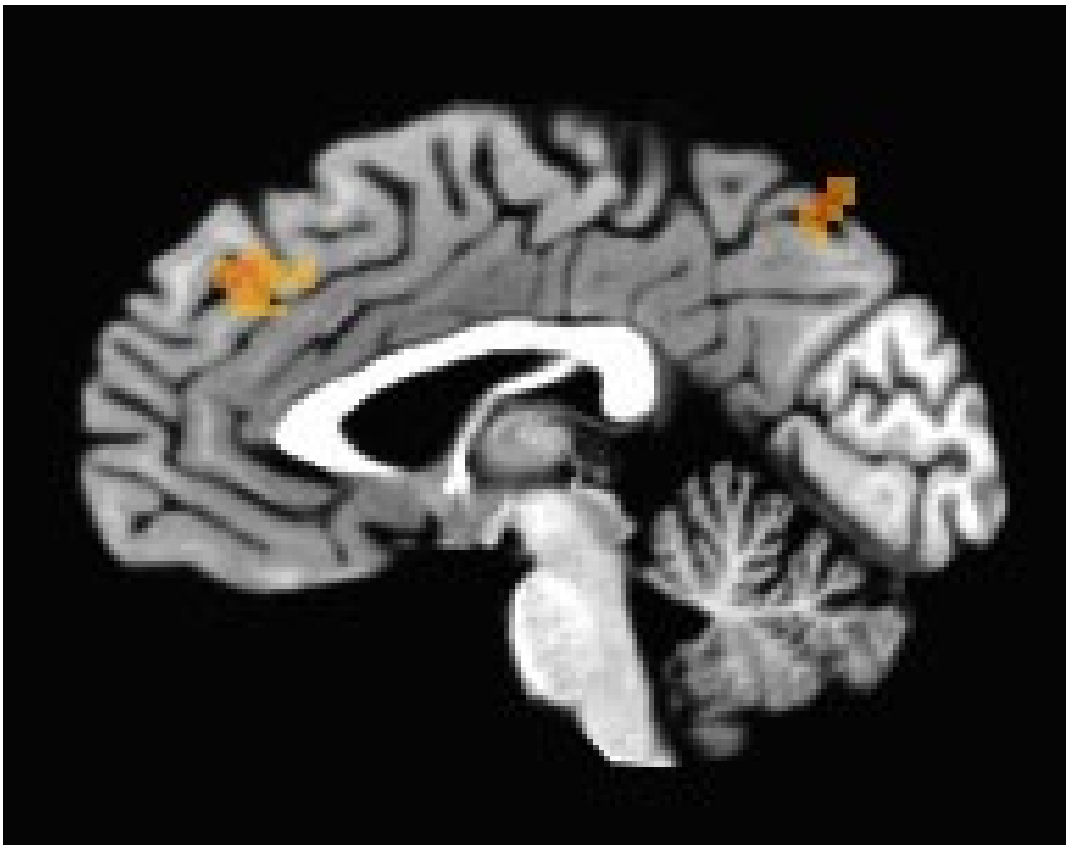

Figure 8: Activation in dmPFC and Precuneus. Brain slice representing activation differences in the precuneus and dmPFC with $p<.05$ and $\alpha< .05$

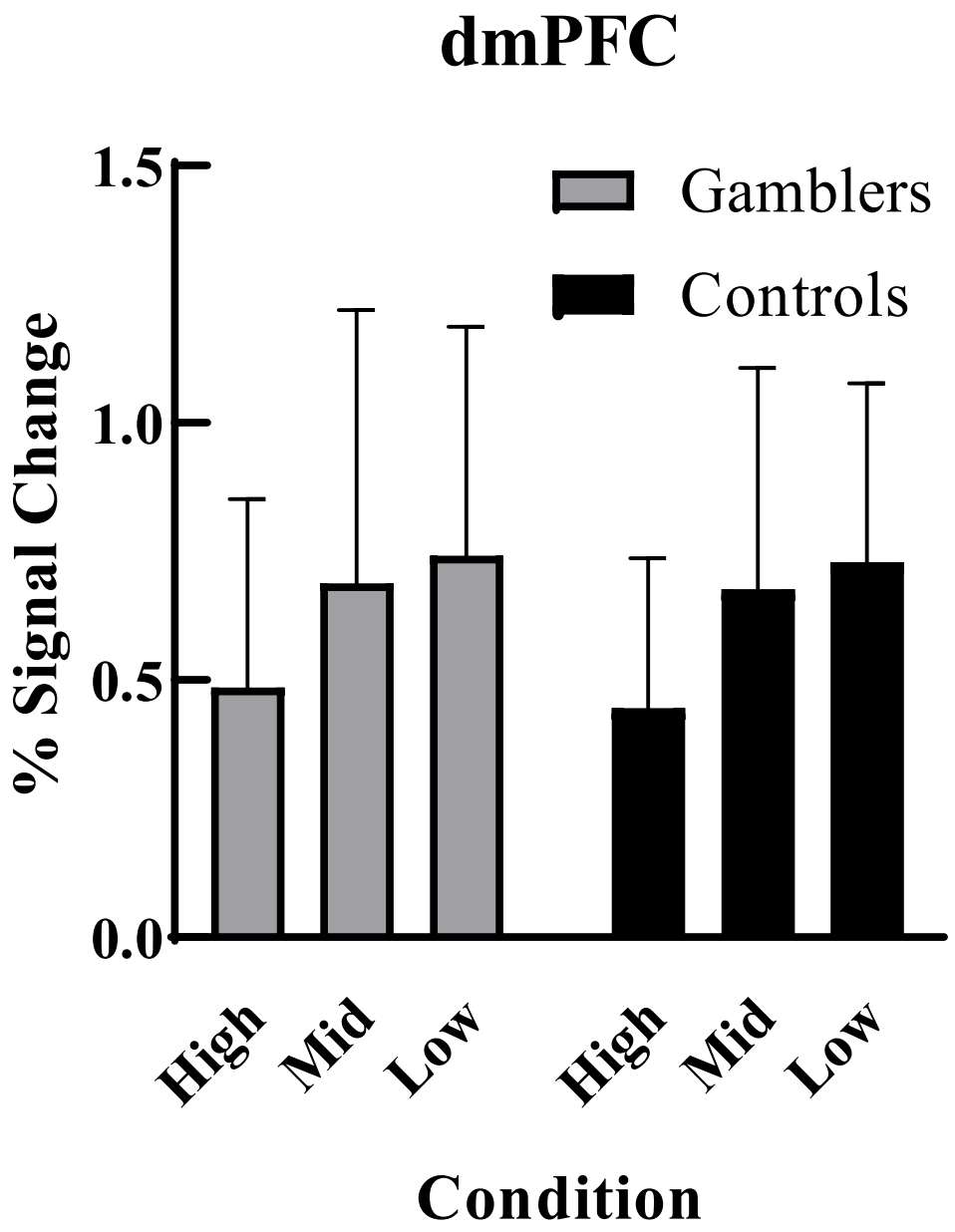

Figure 9: Condition Differences in Activation of dmPFC. Two-way ANOVA with significant effect of condition (High, Mid, and Low probability) = (F (2, 2) = 316.7, p = .0031) in the dmPFC

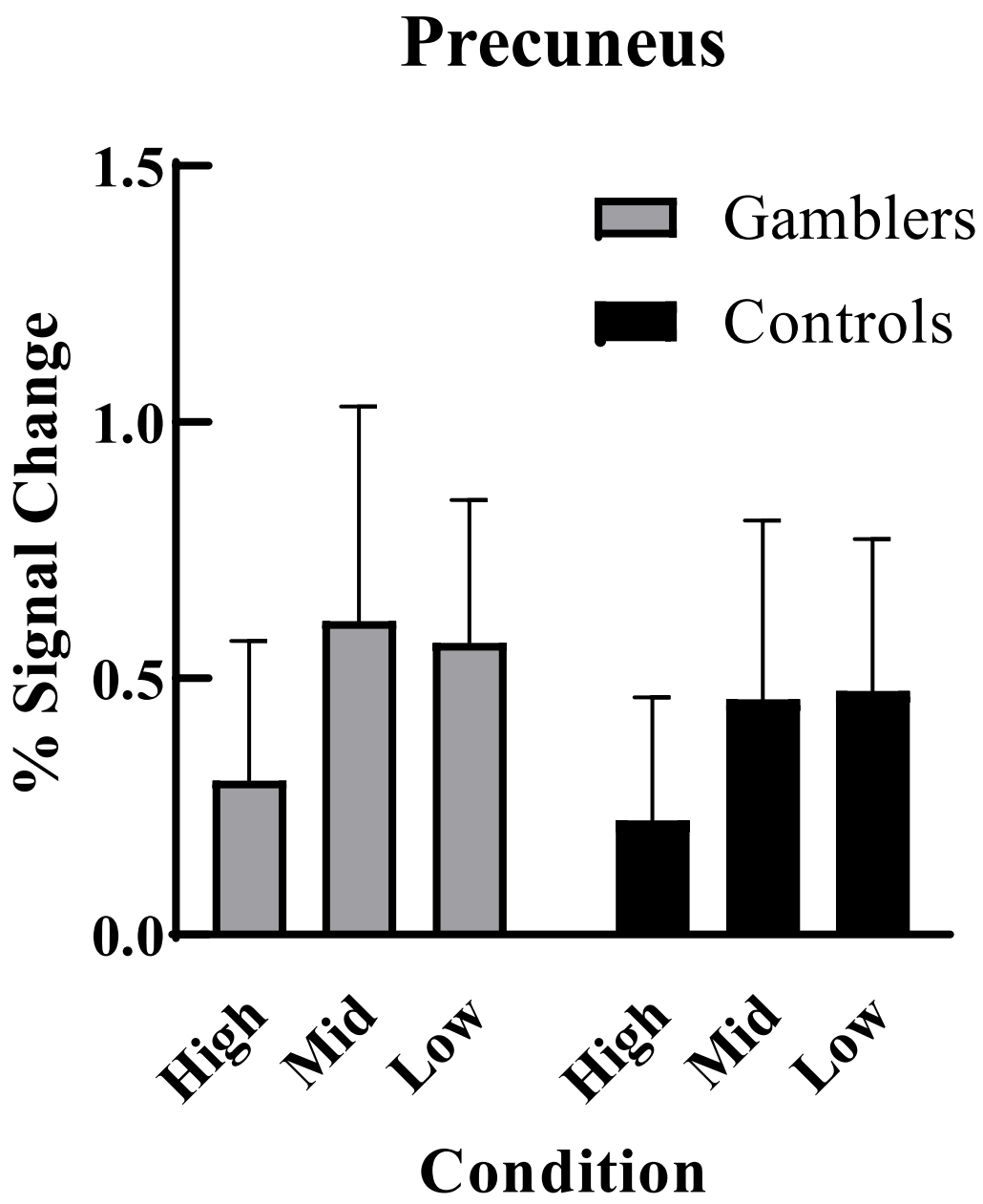

Figure 10: Condition Differences in Activation of Precuneus. Two-way ANOVA with significant effect of condition (High, Mid, and Low probability). = (F (2, 2) = 61.59, p = .0160) in the precuneus

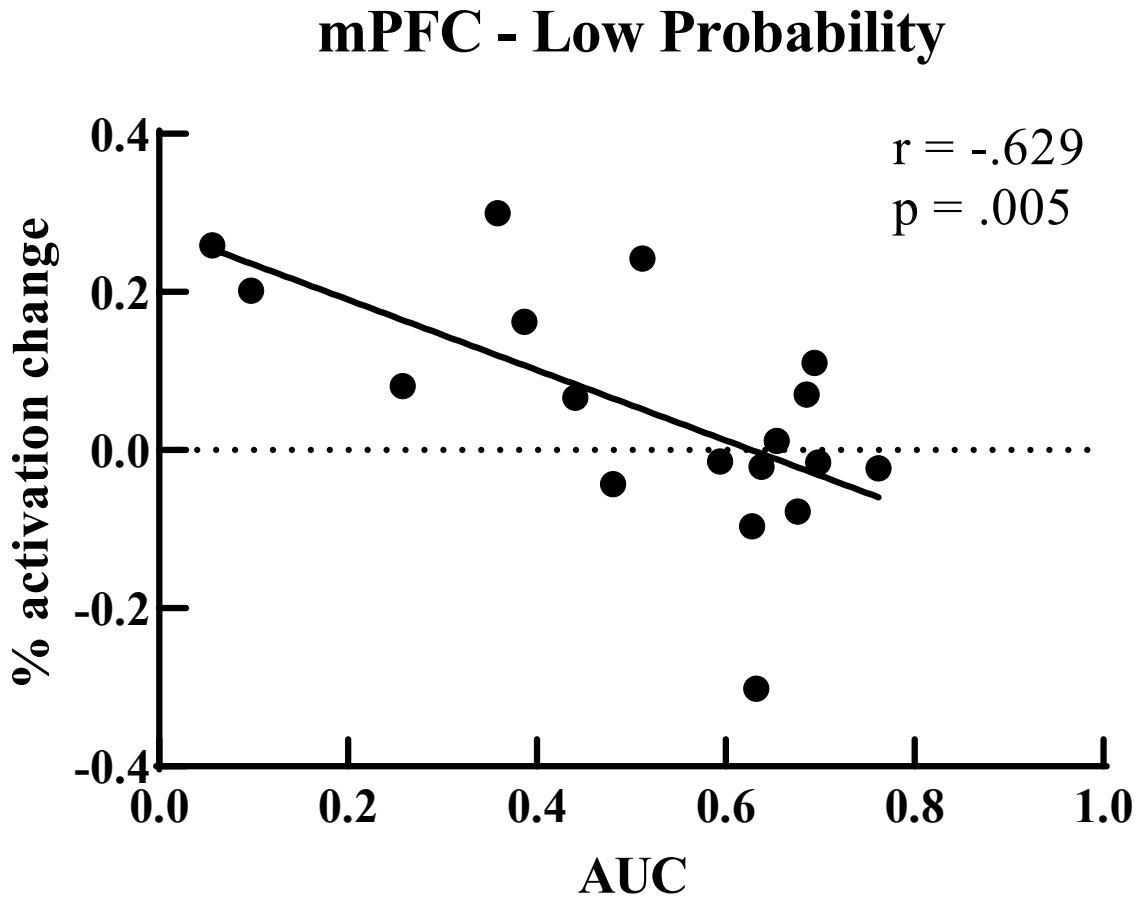

Figure 11: Correlation of AUC and Percent Activation Change – Low Probability. Pearson correlational analysis of the Low probability condition with results showing a statistically significant negative correlation (r(18) = -.629, p= .005) between AUC and percent activation change in the mPFC

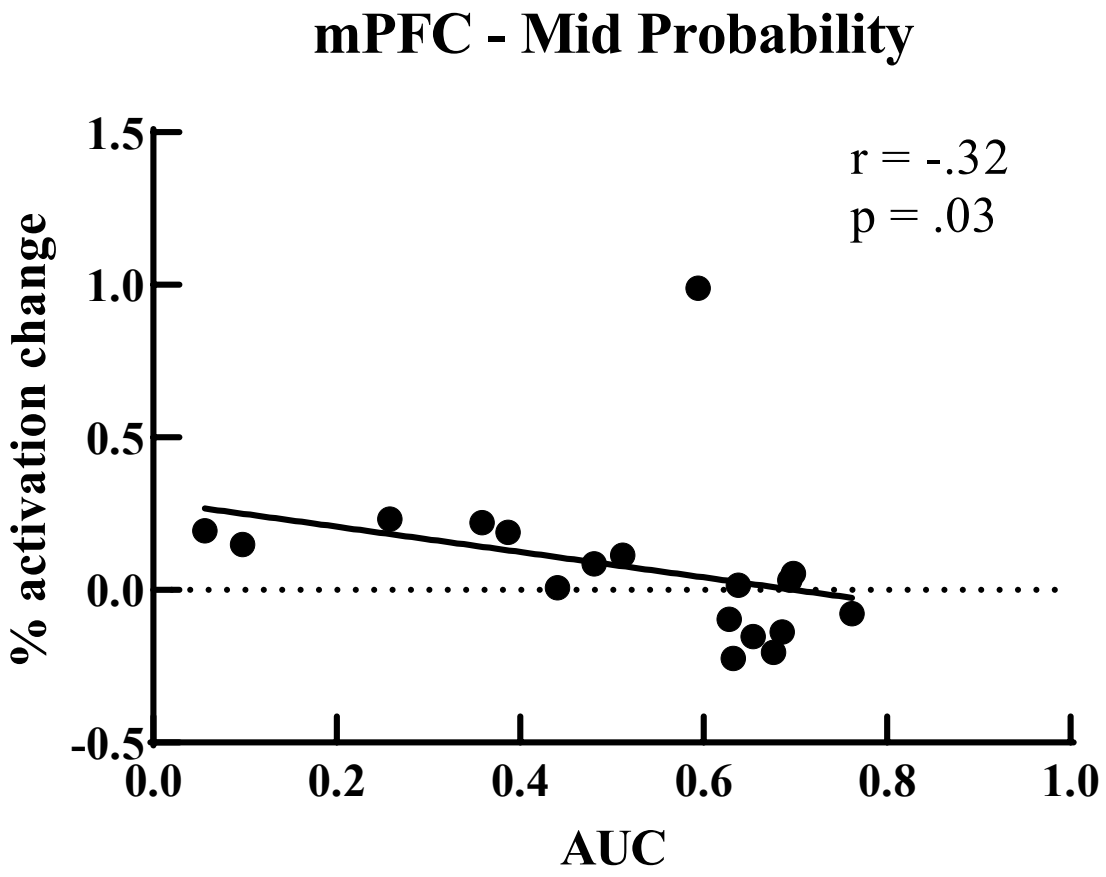

Figure 12: Correlation of AUC and Percent Activation Change – Mid Probability. Pearson correlational analysis in the Mid probability condition with results showing a statistically significant negative correlation (r(18) = -.32, p = .03) between AUC and percent activation change in the mPFC.

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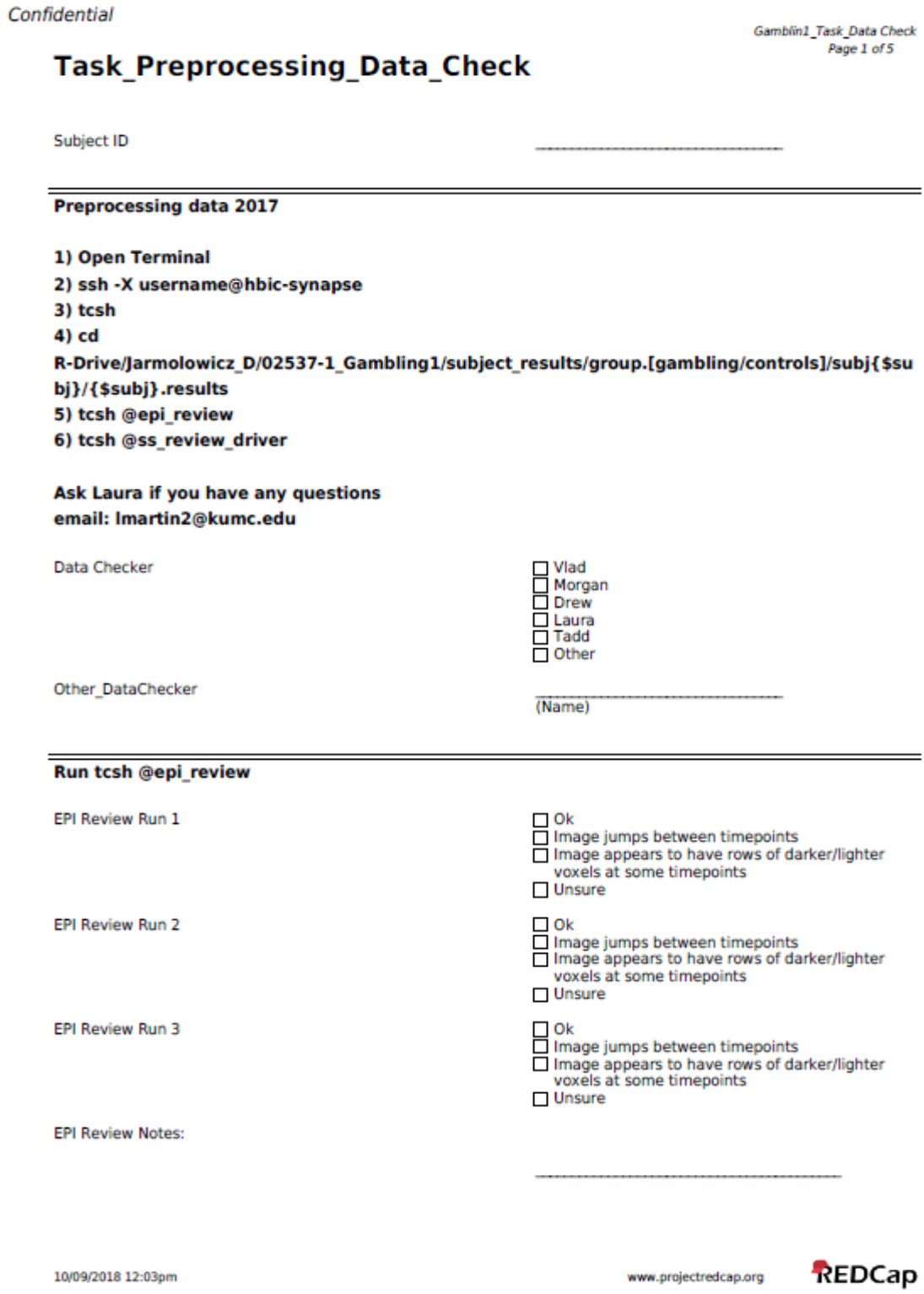
Supplemental Materials:

Task Preprocessing Checklist (RedCap)



Confidential

Gamblin1_Task_Data Check
Page 1 of 5

Task_Preprocessing_Data_Check

Subject ID _____

Preprocessing data 2017

1) Open Terminal
2) ssh -X username@hbic-synapse
3) tcsh
4) cd
R-Drive/Jarmolowicz_D/02537-1_Gambling1/subject_results/group.[gambling/controls]/subj{$subj}/{$subj}.results
5) tcsh @epi_review
6) tcsh @ss_review_driver

Ask Laura if you have any questions
email: lmartin2@kumc.edu

Data Checker
- ☐ Vlad
- ☐ Morgan
- ☐ Drew
- ☐ Laura
- ☐ Tadd
- ☐ Other

Other_DataChecker _____ (Name)

Run tcsh @epi_review

EPI Review Run 1
- ☐ Ok
- ☐ Image jumps between timepoints
- ☐ Image appears to have rows of darker/lighter voxels at some timepoints
- ☐ Unsure

EPI Review Run 2
- ☐ Ok
- ☐ Image jumps between timepoints
- ☐ Image appears to have rows of darker/lighter voxels at some timepoints
- ☐ Unsure

EPI Review Run 3
- ☐ Ok
- ☐ Image jumps between timepoints
- ☐ Image appears to have rows of darker/lighter voxels at some timepoints
- ☐ Unsure

EPI Review Notes:

_____

10/09/2018 12:03pm www.projectredcap.org REDCap

For this next section, review the various outputs from the @ss_review_driver command

Step 1: type 'tcsh @ss_review_driver' to begin

Final Voxel Resolution = 2.5 x 2.5 x 2.5	◯ Yes ◯ No
Average Motion per TR	◯ < 0.3 mm ◯ 0.31 - 1 mm ◯ 1 - 3 mm ◯ > 3 mm
Max Motion Displacement	◯ < 3 mm ◯ 3-6 mm ◯ > 6 mm
Max Censored Displacement = Max Motion Displacement	◯ Yes ◯ No
Max Censor Displacement Value	_____ (What is the max censor displacement?)
Num of Runs = 3	◯ Yes ◯ No
Fraction Censored in Run 1	◯ < 5% ◯ 5-10% ◯ 10-15% ◯ 15-20% ◯ > 20%
Fraction Censored in Run 2	◯ < 5% ◯ 5-10% ◯ 10-15% ◯ 15-20% ◯ > 20%
Fraction Censored in Run 3	◯ < 5% ◯ 5-10% ◯ 10-15% ◯ 15-20% ◯ > 20%
Censor Fraction	◯ < 5% ◯ 5-10% ◯ 10-15% ◯ 15-20% ◯ > 20%
Number of Regs of Interest = 3	◯ Yes ◯ No
Does any stimulus have more than 20% for the "fraction of TRs censored per stim"?	◯ Yes ◯ No
Blur estimates = 4 to 6	◯ Yes ◯ No

Notes for @ss_review_basic

(List and describe any notes from the SS Review Basic)

Step 2: Review Censor Plots

Do the plots look bad?

- ☐ OK
- ☐ lots of time points censored as outliers (e.g. lots of green lines in red plot)?
- ☐ lots of time points censored for motion (e.g. lots of green lines in black plot)?
- ☐ overall plot shows lots of censoring (e.g. lots of green lines on plot in second window)?
- ☐ Some censoring but not too bad?
- ☐ Unsure

Notes on censor plots

Step 3: Alignment Check

Alignment of anatomy to functional scans

- ○ good
- ○ ok
- ○ bad
- ○ unsure

Notes on Alignment

Step 4: Regression Warnings

Regression warnings

- ☐ Full F
- ☐ Catch
- ☐ Risk
- ☐ Safe
- ☐ Risk-Catch
- ☐ Safe-Catch
- ☐ Risk-Safe
- ☐ RS-C

Notes on Regression Warnings: Cut and paste warnings from Terminal

Step 5: Review Matrix Plots

Matrix plots look ok?

- ◯ Yes
- ◯ No
- ◯ Unsure

Notes on Matrix Plots

_____

Step 6: Review Stats

Where is the max F-stat?

- ◯ Occipital Lobe
- ◯ Parietal Lobe
- ◯ Frontal Lobe
- ◯ Temporal Lobe
- ◯ SubCortical
- ◯ Other

Are there 21 sub-briks?

- ◯ Yes
- ◯ No

(click on OLay button on right side of the screen)

Notes on stats

_____

Step 7: Review Normalized Brain

Can review from the stats pop-up in @ss_review_driver, but may need to open up other versions of the anatomical if there are questions

Review Normalized Brain

- ☐ Ok
- ☐ Lots of non-brain left after skull strip?
- ☐ Lots of cortex cut off with skull strip?
- ☐ Brain appears warped or stretched?
- ☐ Unsure

Notes on Normalized Brain

_____

Step 8: Recommendation

Include in group analysis?

- ◯ Yes
- ◯ No
- ◯ Unsure

Notes on decision to include/exclude in group analysis

_____

Final Review

Final Reviewer

- ☐ Vlad
- ☐ Morgan
- ☐ Drew
- ☐ Laura
- ☐ Tadd
- ☐ Other

Other Reviewer

_____
(Name)

Final Decision: Include in group analysis?

- ○ Yes
- ○ No

Final Review Notes

_____

Hoglund Brain Imaging Center

Magnetic Resonance Imaging (MRI Environment Screening Form

The MR system has a very strong magnetic field that may be hazardous to individuals entering the MR environment or MR system room if they have certain metallic, electronic, magnetic, or mechanical implants, devices, or objects. Therefore, all individuals are required to fill out this form BEFORE entering the MR environment or MR system room. ***Be advised, the MR system magnet is ALWAYS on.***

Personal Health History

Please answer the following:

☐Yes ☐No Cardiac Pacemaker	☐Yes ☐No Previous MRI	☐Yes ☐No Harrington Rods
☐Yes ☐No Gastric Pacemaker	☐Yes ☐No Able to Lie Flat	☐Yes ☐No Eyelid Spring/Wire
☐Yes ☐No Cardiac Defibrillator	☐Yes ☐No Claustrophobic	☐Yes ☐No Prosthetic Device
☐Yes ☐No Heart Valve Replacement	☐Yes ☐No BB, Foreign Body, GSW	☐Yes ☐No Dentures/Partials
☐Yes ☐No Aneurysm/Vascular Clips	☐Yes ☐No Neurostimulation Device	☐Yes ☐No History of Seizures
☐Yes ☐No Stents, Filters or Coils	☐Yes ☐No Hearing Aide	☐Yes ☐No Motion Disorder
☐Yes ☐No Kidney/Liver Transplant	☐Yes ☐No Cochlear Implant	☐Yes ☐No Body Piercing(s)
☐Yes ☐No Kidney Disease or Diabetes	☐Yes ☐No History of Metal in Eyes	☐Yes ☐No Permanent Eyeliner
If yes, type of dialysis _____	☐Yes ☐No Medication Skin Patch	☐Yes ☐No Bladder Stimulator
☐Yes ☐No Liver Cirrhosis/Cancer	☐Yes ☐No Vascular IV Access	☐Yes ☐No Insulin Pump
If yes, Creatinine _____ *GFR* _____	☐Yes ☐No Hydrocephalus/Spinal Shunt	☐Yes ☐No Implantable Device

Surgeries

Have you ever had surgery? ☐*Yes* ☐*No If yes, Please indicate below.*

Year	Type	Year	Type
Year	Type	Year	Type

Current Medications

Have you taken any medications today (e.g., pain, sedative, medications)? ☐*Yes* ☐*No If yes, Please indicate below.*

Drug Name	Dosage	Time of Last Dose	Drug Name	Dosage	Time of last dose

Female Patients

If applicable, please answer the following questions:

☐Yes ☐No I.U.D. Device ☐Yes ☐No Pregnant (or suspect) ☐Yes ☐No Breastfeeding ☐Yes ☐No Late Menstrual Cycle

I attest that the above information is correct to the best of my knowledge. I have read and understand the entire contents of this form and have had the opportunity to ask questions regarding the information on this form.

_____ *Patient Name (Please Print)*

___/___/___ *Date of Birth*

_____ *Weight*

_____ *Medical Record Number*

_____ *Patient Signature*

___/___/___ *Date*

_____ *Height*

Form completed by (if not patient): ☐*Spouse* ☐*Relative* ☐*Legal Guardian* ☐*Nurse* ☐*Technologist* ☐*Other*

_____ *Print Name*

_____ *Signature*

IMPORTANT INSTRUCTIONS

Before entering the MR environment or MR system room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercings, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnet strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners & clothing with metallic threads. ***Lockers are provided.***