









The neural vulnerabilities in reward processing in gambling disorder

AMY JING-WEN YIN¹ , ANISE M. S. WU^{2,3**} ,
YINGXIN XIONG^{2,3} , LIFFY KA HENG LEONG³,
CAREN MAN WAI LEI^{2,3}, JING ZHAI^{2,3} ,
DAVIS KA CHIO FONG^{3,4} , ZHEN YUAN^{3,5} ,
RUEY-SONG HUANG^{3,6}  and ROBIN CHARK^{3,4*} 

Journal of Behavioral Addictions

14 (2025) 2, 1010-1020

DOI:

10.1556/2006.2025.00049

© 2025 The Author(s)

¹ Department of Psychiatry, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524001, China

² Faculty of Social Sciences, University of Macau, Macau, PRC

³ Centre for Cognitive and Brain Sciences, University of Macau, Macau, PRC

⁴ Faculty of Business Administration, University of Macau, Macau, PRC

⁵ Faculty of Health Sciences, University of Macau, Macau, PRC

⁶ Faculty of Science and Technology, University of Macau, Macau, PRC

FULL-LENGTH REPORT



Received: October 31, 2024 • Revised manuscript received: February 4, 2025; April 21, 2025 • Accepted: May 19, 2025
Published online: June 23, 2025

ABSTRACT

Background and aims: Clinical diagnosis of gambling disorder (GD) remains challenging due to the heterogeneity in symptoms and a lack of consistency in the proposed neural mechanisms. Effective classification of GD may depend on neural representations of either risky decision-making or reward processing. *Methods:* To address these challenges, we recruited more than 100 individuals with GD and matched healthy controls, utilizing event-related fMRI during a novel risky decision-making task to elicit neural representations of risky decision-making and reward processing. *Results:* During the decision phase, there was no significant difference observed between the two groups even when a very liberal threshold was used. During reward processing, the GD group exhibited significantly increased activation in the right inferior frontal gyrus, right anterior insula, and bilateral posterior cingulate cortex in the risky reward condition compared with the healthy controls. A notable neural activation characteristic was the distinct response between risk-win and risk-loss conditions in reward processing, particularly in the right inferior frontal gyrus in the GD group. The classification for GD using the neural representation of reward yielded an area under the curve of 0.75 (± 0.11 SD). *Discussion and conclusion:* These findings integrate biological and behavioral perspectives to provide new insights into the reward processes underlying GD. These findings highlight specific neural representations associated with GD and suggest potential biomarkers for diagnostic evaluation in GD.

KEYWORDS

gambling disorder, behavioral addiction, risky decision making, reward processing, fMRI

INTRODUCTION

The diagnostic criteria and clinical perspectives of gambling disorder (GD) are controversial. It has been classified as pathological gambling in the ICD-10 and further as gambling disorder in the ICD-11. These classifications were based on recognition of several similarities between the behavioral and neurobiological presentations of GD and SUDs (C. Holden, 2001). The most prominent commonalities lie in the risky decision-making (Pineau et al., 2016; Raimo, Cropano, Trojano, & Santangelo, 2021) and reward system. While research on

* Corresponding author.

E-mail: robinchark@gmail.com

** Corresponding author.

E-mail: anisewu@um.edu.mo

brain structure and neurotransmitters provides compelling biological evidence supporting these parallels (Boileau et al., 2013; van Holst et al., 2018; Yip et al., 2017, 2018; Zois et al., 2017), it is still a challenge in the clinical estimation on GD due to the heterogeneous in behavioral symptoms and the lack of the identified biological representations.

It has long been a debate regarding the dominant role of risky decision-making (Pineau et al., 2016; Raimo et al., 2021) and reward processes in GD (Pineau et al., 2016; Raimo et al., 2021). The related neural dysfunction has been reported in several brain areas in decision and reward-related tasks, involving ventral striatum (VS) (Balodis et al., 2012; de Greck et al., 2010; Reuter et al., 2005; Romanczuk-Seiferth, Koehler, Dreesen, Wüstenberg, & Heinz, 2015; Sescousse, Barbalat, Domenech, & Dreher, 2013; Sescousse et al., 2016; Worhunsky, Malison, Rogers, & Potenza, 2014), ventromedial prefrontal cortex (vmPFC) (Jody Tanabe et al., 2007; Worhunsky et al., 2014), anterior insula (aInsula) (Balodis et al., 2012; Limbrick-Oldfield et al., 2017; Tsurumi et al., 2014), dorsolateral prefrontal cortex (dlPFC) (Crockford, Goodyear, Edwards, Quickfall, & El-Guebaly, 2005; Fujimoto et al., 2017; Gelskov, Madsen, Ramsøy, & Siebner, 2016), and anterior cingulate cortex (ACC) (Kober et al., 2016; Limbrick-Oldfield et al., 2017; Miedl, Fehr, Meyer, & Herrmann, 2010; Miedl, Peters, & Büchel, 2012), as well as extended clusters in the dorsal medial part of dorsolateral prefrontal cortex (dmPFC) (Limbrick-Oldfield et al., 2017), superior frontal gyrus (SFG) (M. N. Potenza, Leung, et al., 2003; Marc N Potenza, Steinberg, et al., 2003), middle frontal gyrus (MFG) (Romanczuk-Seiferth et al., 2015), inferior frontal gyrus (IFG) (Limbrick-Oldfield et al., 2017; Miedl et al., 2010) (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009) (Knoch et al., 2006; Romanczuk-Seiferth et al., 2015), and posterior cingulate cortex (dPCC) and temporoparietal junction (TPJ) (Strang & Park, 2017) (Strombach et al., 2015).

However, neurobiological studies describe a complex yet inconsistent pattern of activation in these processes. These inconsistencies may largely stem from the fMRI experimental designs. One contributing factor is the synchronous onset of the decision and reward stimulation, making it challenging to extract specific neural representations for decision-making or reward processing (Gelskov et al., 2016; Power, Goodyear, & Crockford, 2012; Jody Tanabe et al., 2007). Another factor may be the complexity of the tasks used, which involve multiple overlapping processes such as reward expectation/prediction, value evaluation and reinforcement learning during decision-making. For example, tasks like the monetary incentive delay task (MIDT) has been argued that the cues in the decision phase evoking the prediction and value evaluation (Anna E Goudriaan, De Ruiter, Van Den Brink, Oosterlaan, & Veltman, 2010). In addition, the tasks using gambling imagery or videos did not focus on the safe and risky trade-offs during decision-making, which are essential in gambling contexts (Crockford et al., 2005; A. E. Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005; Kober et al., 2016; Limbrick-Oldfield et al., 2017; Marc N Potenza, Steinberg, et al., 2003).

Electrophysiological studies on primates have revealed that unpredictable reward delivery is crucial for effectively triggering dopamine release (Fiorillo, Tobler, & Schultz, 2003), which may lead to impulsive risky decision-making. It was suggested that unpredictable rewards tied to risky decisions would be eligible for exploring the behavior and neural representations in GD (Gold, Badgaiyan, & Blum, 2015).

To date, there remains a lack of identified neuropathology in GD and specific neural representation for the effective classification of GD. The specific neural characteristics and their relationship within risky decision-making and reward processing may be crucial for feature identification and classification in GD. To address these issues, we recruited participants diagnosed with GD and closely matched healthy controls (HC) to examine the neural representations using task-related functional magnetic resonance imaging (fMRI). A simple poker task was utilized to separate the neural response related to risky decision-making and unpredictable rewards. The neural presentations associated with decision-making and reward processing were analyzed separately in GD and HC groups. Considering the relatively small sample size in the extant work (21.88 ± 13.73 GD; 24.98 ± 19.16 HC) (Clark, Boileau, & Zack, 2019), we recruited more than 100 participants (including both people with GD and their healthy control) to significantly increase statistic power.

METHODS

Participants

Participants aged 18 to 55 were recruited through social media or non-governmental organizations. All participants went through a series of screening protocols. Initially, they were screened via telephone or online self-reporting DSM-5 items. Then the screened participants underwent a structured clinical interview (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004) and diagnosis conducted by an experienced psychiatrist following DSM-5 criteria (American Psychiatric Association & Association, 2013). Exclusion criteria included any physical disease, psychosis due to general medical conditions, other mental illnesses (e.g., major depression, bipolar disorder, manic episode, anxiety disorder), medical conditions (especially those requiring dopaminergic medications or involving substance abuse), and family history of psychosis. Symptom severity was measured using the Yale-Brown Obsessive Compulsive Scale Adapted for Pathological Gambling (GD-YBOCS) (Goodman et al., 1989), which assesses gambling symptom severity across thoughts/urges and behavior subscales. Intelligence Quotient (IQ) was assessed using proxy items from the Scholastic Aptitude Test (SAT) (Frey & Detterman, 2004). The Hamilton Anxiety Rating Scale (HAM-A) (M. Hamilton, 1959) and Hamilton Depression Rating Scale (HAM-D) (Max Hamilton, 1986) were used to evaluate the severity of anxiety and depression. Risk attitude was assessed using the Domain-

Specific Risk-Taking (DOSPERT) scale, which evaluates risk-taking tendencies across five content domains: financial decisions, health/safety, recreational choices, ethical considerations, and social decisions (Weber, Blais, & Betz, 2002; Wu & Cheung, 2014). Two participants were excluded due to the use of dopaminergic medications and a history of schizophrenia, respectively, while another two voluntarily withdrew. A matched healthy control (HC) group with comparable age and sex distributions was recruited. Healthy participants with gambling experience and without problematic gambling were classified into the HC group. All participants were right-handed. A total of 50 GD and 53 HC participants completed all experimental protocols.

The demographic and clinical characteristics of GD and HC are presented in Table S1 and the details are described in Results of Supplementary Materials.

Experimental design and paradigm

The experimental design and paradigm are illustrated in Fig. 1A and B. Participants engage in a simplified poker game (Reiley, Urbancic, & Walker, 2008) against a computer opponent, using a special deck containing only “King” and “Queen.” At the beginning of each trial, players ante \$1 by default. The participant’s card is then randomly revealed on the screen, prompting their decision to fold or bet. If the

participant chooses to fold, the current trial ends, and the computer wins the pot. If the participant decides to bet, an additional \$1 is automatically added to the pot, and the computer’s response (either call or fold) is randomly displayed on the screen. If the computer folds, the participant wins the pot, netting \$1. If the computer calls, another \$1 is added to the pot by default, and the participant either wins the pot with a “King” (netting \$2) or loses the pot with a “Queen” (losing \$2). Thereby, the task-induced three conditions depending on the response of participants in the decision-making stage: (1) risky decision (RD) when betting with a “Queen,” (2) safety decision (SD) when folding with a “Queen,” and (3) non-decision (ND) when betting with a “King.”

There are five conditions in the reward stage, depending on the participant’s response: (1) risky decision with high compensation (RDwin) when participants bet with a “Queen” and the computer folds, resulting in a net gain of \$2; (2) risky decision with high penalty (RDloss) when participants bet with a “Queen” and the computer calls, resulting in a loss of \$2; (3) safety decision making with a predictable low penalty (SDRloss) when participants fold with a “Queen,” resulting in a predictable loss of \$1; (4) non-decision-making with high compensation (NDdouble) when participants bet with a “King” and the computer calls, resulting in a net gain of \$2; and (5) non-decision-making

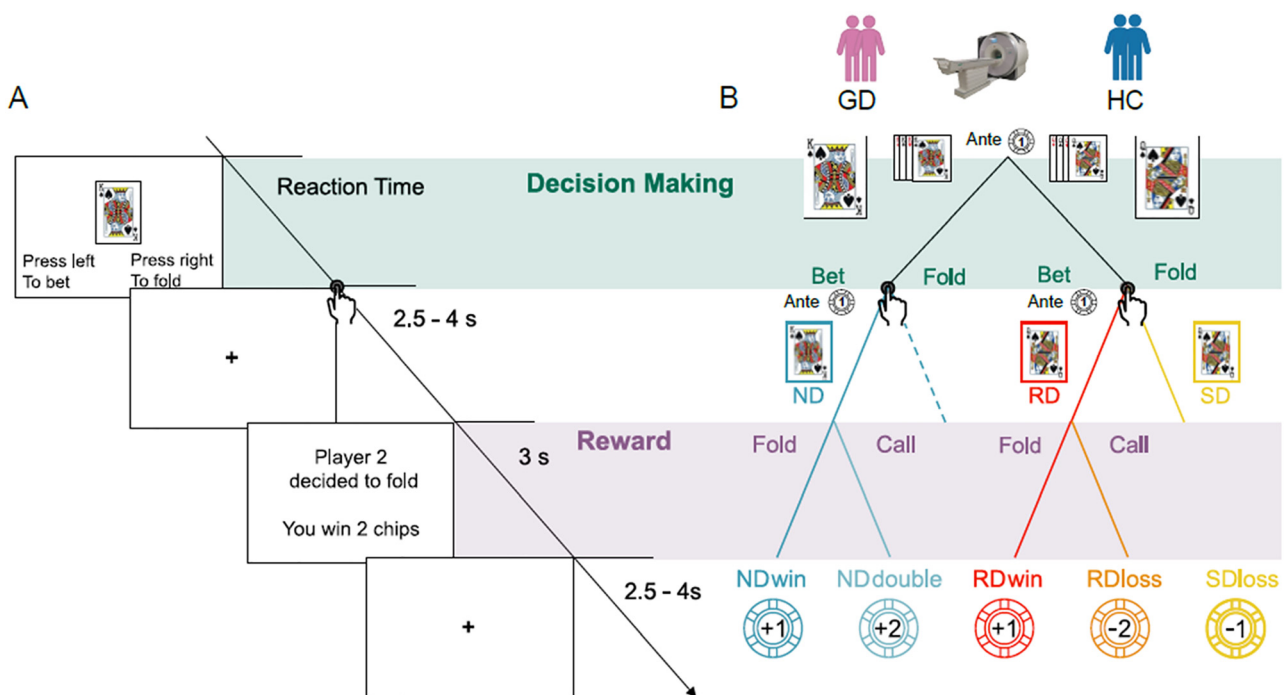


Fig. 1. The experimental design and paradigm

(A) The task design and paradigm. (B) The conditions in the task. The participants include GD and HC groups, and the decision stages include three conditions depending on participants’ responses. There are risky decisions when they bet with a “Queen” (RD), safety decisions as they fold with a “Queen” (SD), and non-decision-making as they bet with a “King” (ND). There are five conditions with the following reward stages: (1) risky bet with a “Queen,” and a win of \$2 (RDwin) – the colors were used to represent the corresponding conditions in the illustrations; (2) risky bet with a “Queen” with a loss of \$2 (RDloss); (3) safety fold with a “Queen” with a loss of \$1 (SDRloss); (4) non-decision when betting with a “King” with double gain of \$2 (NDdouble); and (5) non-decision when betting with a “King” with a net gain of \$1 (NDwin)

with low compensation (NDwin) when participants bet with a “King” and the computer folds, resulting in a net gain of \$1.

The event-related block design experiment consisted of four runs, each comprising 40 trials of poker tasks. There are equal chances of drawing a “Queen” or a “King,” and of seeing a “call” or a “fold” when the participant chooses to bet. Three practice trials were performed before the formal experiment. In order to make the risky decision (RD) incentive-compatible, bonuses were paid to participants based on the chips they held in a trial randomly drawn at the end of the experiment. Since each chip represents MOP 100 (approximately USD 12), the bonus that participants receive could be MOP 0, 100, 300, or 400. The task was designed and presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, USA).

The behavioral performance characteristics in fMRI experiments were illustrated in Fig. S1 A–C and details were described in the Results of Supplementary Materials and Table S2.

MRI data acquisition and statistical analysis

The MRI data acquisition and statistical analysis were described in Methods of Supplementary Materials.

Ethics

The ethics approval for conducting this project was obtained from the panel on research ethics of the affiliated university of the corresponding authors (ref.: BSERE20-APP014-ICI). The study was conducted in accordance with the Declaration of Helsinki and according to requirements of all applicable local and international standards. All participants gave written informed consent.

RESULTS

The specific neural activation in GD was found in the IFG

Our aim is to examine the main effect of diagnostics on the blood-oxygen-level-dependent (BOLD) response. During the decision phase, there was no significant difference observed between GD and HC groups even when a very liberal threshold was used ($p < 0.05$, uncorrected, Table S3, Fig. S3 A). During the reward processing, we observed significant diagnostic main effects involving several brain regions: IFG ($F = 23.40$, $p = 2.49E-02$, family-wise error (FWE) corrected), the right aInsula ($F = 30.52$, $p = 1.21E-03$, FWE corrected), aPCC ($F = 29.91$, $p = 1.57E-03$, FWE corrected), and left SFG ($F = 24.80$, $p = 1.38E-02$). Additionally, two clusters exhibited deactivation in the left lateral intraparietal sulcus (LIP) (Cluster 1, $F = 38.98$, $p = 3.35E-05$, Cluster 2, $F = 23.57$, $p = 2.33E-02$). The coordinates of peak voxel and corresponding statistical values are listed in Table S3 and illustrated in Fig. 2A and B. In the post-hoc analysis, the source of these differences primarily stemmed

from group comparisons (GD vs. HC) in the RDwin and RDloss conditions within the right aInsula, right IFG, and left aPCC, as well as in the NDdouble condition within the right SFG (detailed in Fig. 2C). The neural activation pattern and post-hoc analysis for main effect of task in decision and reward phases were illustrated in the Figs S2 and S3, the details were described in Results and Table S2 in Supplementary Materials.

The distinct neural activation between RDwin and RDloss conditions in GD

The diagnostic main effect of ROIs activation suggests a potentially distinguishing reward-related neural response between the GD and HC groups. The distinct neural activation observed in the RDwin and RDloss conditions might have the potential to differentiate the GD cohort from the HC cohort. To evaluate the classification efficiency, the four significant clusters in the main effect of diagnosis in reward processing were extracted. An SVMs classifier was applied to decode the neural signals in RDwin and RDloss conditions at the single-trial level. The classification accuracies were calculated based on the single-trial beta weights of RDwin and RDloss conditions. Significantly higher accuracies above chance level were observed in the ROIs in the RDloss condition of the GD group, involving the right aInsula, right IFG, left SFG, and aPCC (detailed data shown in Table S4). The highest accuracy was observed in the right IFG, with a mean accuracy of 71% ($t = 4.29$, $p = 2.33E-4$, Cohen's $d = 0.84$, 95% CI: 10.93–31.08), as shown in Fig. 2C. No significant above-chance accuracies were observed in the HC group (Table S4).

A comparison was made within the RDloss reward conditions between the GD and HC groups. The most significant difference was observed in the right IFG ($t = 2.89$, $p = 0.022$, Bonferroni correction, Cohen's $d = 0.75$, 95% CI: 7.33–40.45). Significant differences were also observed in the left SFG, right aInsula, and right aPCC, but they did not persist after Bonferroni correction (refer to the details in Table S4). These results suggest that the RDloss condition is particularly sensitive for classifying GD from the HC cohort, with effective classification regions located in the right IFG.

The dynamic diagnostic classification during reward of RD

To achieve more precise classification at the single-trial level, the dynamic classification of GD and HC groups was tracked using the timeseries of BOLD signals. Initially, the percentage change in BOLD signals within ROIs during reward conditions was extracted over 10 TRs (20s), as shown in Fig. 3. A trend of distinct BOLD responses of the RDwin and RDloss conditions was observed in the GD group, but not in the HC group. This trend was evident in the diagnostic main-effect-activated ROIs, particularly in the right IFG ($p < 0.05$), while no significant differences were observed in the right SFG, right aInsula, and left aPCC ($p > 0.05$) (shown in Fig. 3, columns A, B). Additionally,

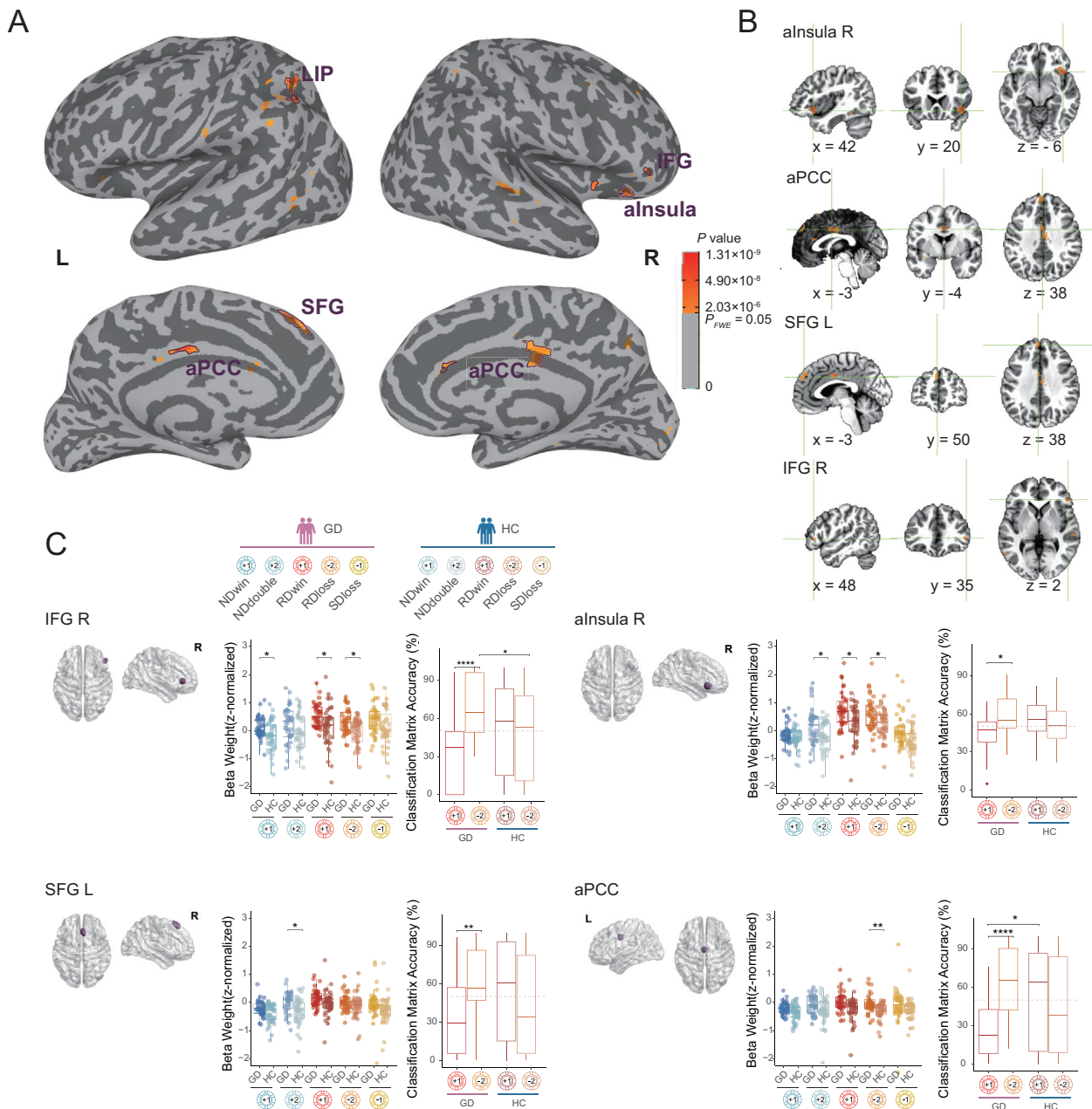


Fig. 2. The neural activation representation of the comparison between individuals with GD and HC in reward processing (A) The surface localization of neural activation for the diagnostic main effect during reward processes with 38 GD and 40 HC participants. $p < 0.05$, FWE corrected. Significant diagnosis main effects were observed in reward processing involving several brain regions: the right anterior insula (aInsula) ($F = 30.52$, $p = 1.21E-03$, FWE corrected), anterior posterior cingulate cortex (aPCC) ($F = 29.91$, $p = 1.57E-03$, FWE corrected), left SFG ($F = 24.80$, $p = 1.38E-02$), right inferior frontal gyrus (IFG) ($F = 23.40$, $p = 2.49E-02$, FWE corrected), and two clusters in the parietal region including the left lateral intraparietal sulcus (LIP) cluster1 ($F = 38.98$, $p = 3.35E-05$) and left LIP cluster2 ($F = 23.57$, $p = 2.33E-02$). (B) The activation clusters and the peak values in voxel-based coordination. (C) The post-hoc analysis for the activation regions, with the boxplots representing the median and interquartile range of the beta weights in the GLM analysis, and the scatters representing the beta weights for individuals. The second boxplot set represents the classification's accuracy matrix of the risk-win and risk-RDloss conditions in the GD and HC groups. The groups are illustrated with different color labels, as shown above the boxplot. All comparisons were Bonferroni corrected. The significance levels are represented by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.00001$

in the reward main-effect-activated ROIs, significant differences were evident in the right IFG/MFG ($p < 0.05$), right TPJ ($p < 0.05$), left VS ($p < 0.05$), right dlPFC ($p < 0.05$), and right VS ($p < 0.05$), while no significant differences were

found in the ACC, right SFG, right and left aInsula, or right PCC (shown in Fig. S3). This timeseries trend is consistent with the classification results obtained in our previous analysis using standardized beta weights. It is attributed to

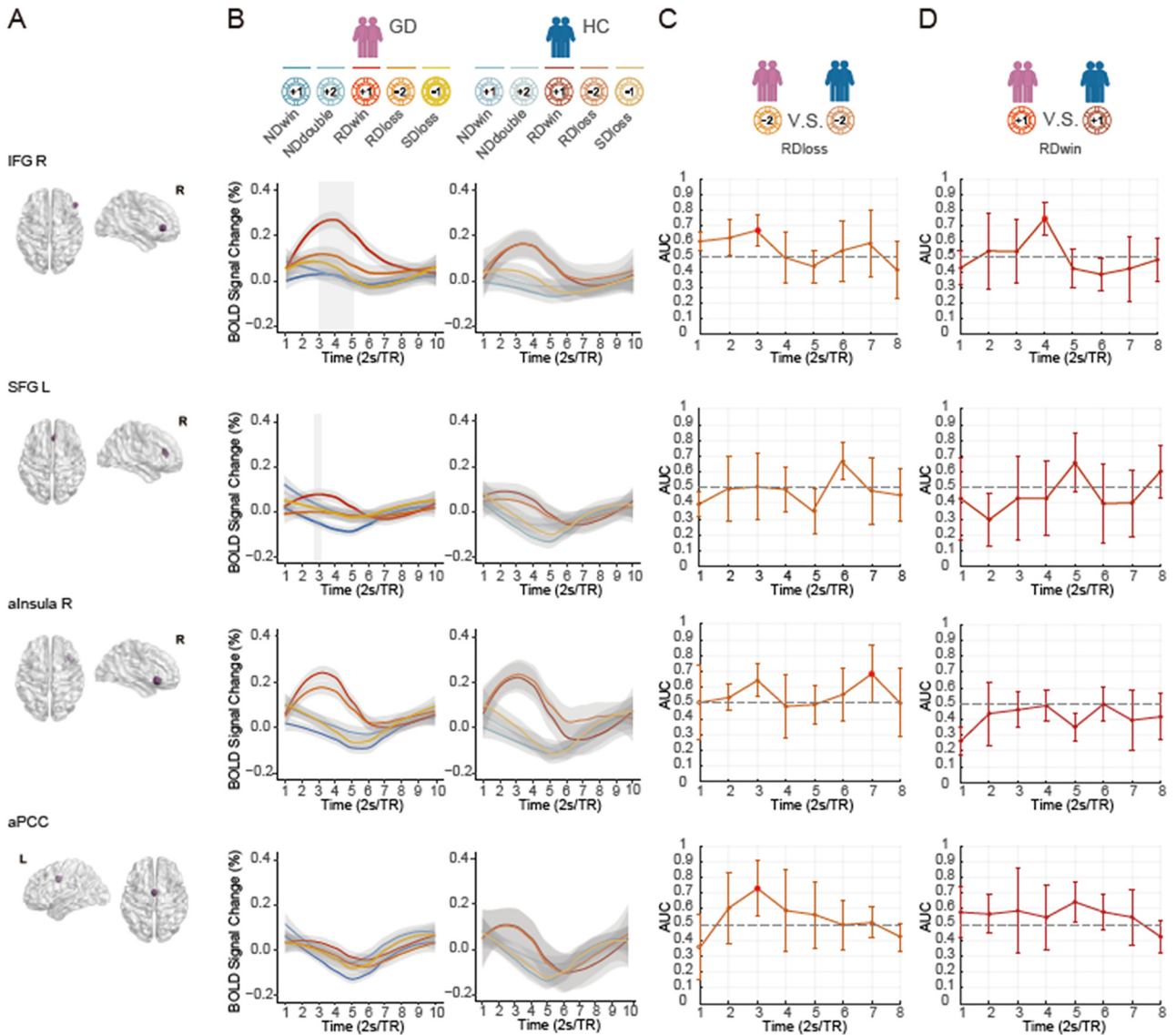


Fig. 3. The timeseries and dynamic classification for neural activation in the diagnostic main effect during the reward processes (A) Illustration of the brain region of the significant activation in the diagnostic main effect during the reward processes. (B) The averaged timeseries of the reward conditions for the GD and HC groups – in the color representations shown above the plots, the gray areas represent the distributions of each timeseries for each condition. The gray background indicates a significant difference in the timeseries at the corresponding time points between the RDloss and RDwin conditions, $p < 0.05$. (C) The classification for the timeseries in the risk-RDloss (RDloss) condition across time points within the 10 TRs following reward onset. The asterisk (*) sign represents the significance in Wilcoxon tests in comparison to the chance level of 50%. The significant threshold was $p < 0.05$. (D) The classification for the timeseries in the risk-RDloss (RDwin) condition across time points within the 10 TRs following reward onset. The star sign represents the significance in Wilcoxon tests in comparison to the chance level of 50%. The significant threshold was $p < 0.05$

the GD group exhibiting a lower BOLD signal response to the RDloss conditions, whereas the HC group did not show such differentiation between RDloss and RDwin conditions (all $p > 0.05$).

Then we investigated whether the binary classification performance could vary dynamically over time in the BOLD signal response to RD rewards. To achieve specific and effective classification, the total 3,024 single-trial percentage changes of BOLD signals were labeled separately as “GD” (1,440 trials) or “HC” (1,584 trials). The SVM classifier was

employed to track the classification performance at each time point from the reward onset up to 8 TRs (16s) for the RDwin and RDloss conditions separately. The area under the receiver operating characteristic curve (AUC) values were used to reflect the diagnostic classification performance. Significant AUC values ($AUC > 0.5$, $p < 0.05$) were detected at 3 s from reward onset in the ROI of the right IFG for the RDloss condition (0.66 ± 0.10 , $p = 0.027$), and at 4 s for the RDwin condition (0.75 ± 0.11 , $p = 0.003$), as illustrated in Fig. 3, columns C, D and Table S5. These

results demonstrate dynamic diagnostic classification and identify the optimal time point for classifying GD based on the BOLD signal response to the rewards of RD.

Discussion and conclusion

To identify the neuropathological vulnerability in GD and develop effective diagnostic classifiers, this study aims to use a task involving risk decision-making with unpredictable rewards in an fMRI experiment. The GD group exhibited significantly increased activation in the right IFG, right aInsula, and bilateral aPCC for risk-reward processing (both risk-win and risk-RDloss) compared to the HC group. A notable neural activation characteristic was the discrete response between risk-win and risk-RDloss conditions in the reward processing, particularly in the right IFG in the GD group — a pattern not observed in the HC group. Timeseries analysis of the risk-win and risk-RDloss conditions in the IFG showed effective classification with AUC values of 0.75 (± 0.11 SD) for the risk-RDloss condition. These findings highlight a specific neural vulnerability associated with risk-reward in the GD group. The effective classification based on the timeseries of right IFG activity supports the feasibility of using neural activation patterns for clinical evaluation in GD.

A useful lesson we learned is that the major differences in neural mechanisms were observed in reward processing but not the decision process. This current study introduced a novel task, tried to minimize the impact of the reward and cognitive on the decision process, and separate the neural activation to the decision and reward phases. We did not find any neural activation differences in the decision-making phase between GD and HC in this scenario of simple binary decision followed with an unpredictable reward. These results supported the argument on dominant reward deficiency in GD rather than decision-making, from the evidence of neural representations.

The significantly increased activation was shown in the right IFG, right aInsula, and bilateral aPCC during reward processing in the GD group compared with the HC group. To clarify the origins of these differences, post-hoc analysis was conducted using general beta weights, which represent the task-induced mean response. Overall, the GD group exhibited increased neural activation across the five conditions during reward processing. Significant differences in the right IFG and right aInsula were found in RDwin, RDloss, and NDwin/NDdouble conditions, suggesting these regions play fundamental roles in general reward processing, such as the executive control as the report in previous studies (Iversen & Mishkin, 1970) (Mazzola, Mauguère, & Isnard, 2017, 2019; Rachidi et al., 2021). A significant but weak activation in the aPCC was derived from the RDloss condition, indicating its potential role in processing risky rewards. The significant difference in the SFG was derived from the NDdouble condition. As reported in previous studies, the SFG has been associated with affective judgments and reward processing (J. Tanabe et al., 2007), with increased SFG activation observed during “win-rewards” in individuals with GD compared to control groups (Miedl et al., 2010). Our findings are consistent with these

results, further identifying this region as being specifically involved in heightened sensitivity to bounce-win rewards in the GD group.

To obtain more details for task-induced neural activation, the timeseries analysis provides insights into the underlying dynamics of neural activation over time. Notably, in GD group, the discrete neural responses were observed between risk-win and risk-RDloss conditions across all reward-related regions, involving the VS, vmPFC, aInsula, dlPFC, ACC, dmPFC, SFG, MFG, IFG, and dPCC. However, this discrete pattern did not show in HC group. A similar phenomenon was reported in Miedl et al.’s study, which examined differences between low-risk and high-risk conditions in problem gamblers (Miedl et al., 2010). This evidence indicated that the discrete neural response pattern could be the specific characteristics in GD. The most pronounced difference was observed in the right IFG, a region consistently implicated in cognitive inhibition in various neuroimaging studies (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Garavan, Ross, Murphy, Roche, & Stein, 2002; Garavan, Ross, & Stein, 1999; Konishi et al., 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Rubia, Smith, Brammer, & Taylor, 2003). In scenarios requiring a trade-off between safety and risk, the right IFG is associated with risk aversion or risk inhibition, with its activity positively correlated with risk aversion (Christopoulos et al., 2009). Conversely, low activation in this region has been linked to increased risk-taking behavior (Knoch et al., 2006). In our study, the GD group exhibited reduced activation in the right IFG during risk-RDloss condition, suggesting a possible deficiency in risk inhibition among individuals with GD. Classification analyses based on single-trial beta weights and timeseries further supported these findings, demonstrating the accuracy with which individuals could be identified as having GD automatically. In summary, our study identifies a potential biomarker for GD through neural representation patterns, highlighting the utility of neural activation profiles in evaluating GD and offering promising avenues for future research and clinical applications.

In addition to the IFG regions, the neural circuitry involved in reward processing encompasses several cortical and subcortical areas, including the VS, dACC, dmPFC, PCC, SFG, MFG, and TPJ (Liu, Hairston, Schrier, & Fan, 2011). The VS, a critical component of the brain’s mesolimbic dopamine circuit, serves as a central hub in reward-motivated neural pathways across species. Dopamine pathways originating from the VS project to regions such as the ventromedial prefrontal cortex (vmPFC), dACC, and SFG/dlPFC (Haber & Knutson, 2010; Kim, Shimojo, & O’Doherty, 2011; McNamee, Liljeholm, Zika, & O’Doherty, 2015), while reciprocal projections extend back to the prefrontal cortex via the ventral pallidum (VP) and ventral tegmental area/substantia nigra (VTA/SN). Our study observed increased activation in these regions during risk-reward processing, consistent with previous research (Kober et al., 2016). Furthermore, bilateral activation of the aInsula, ACC, PCC, and orbitofrontal cortex (OFC) was noted,

indicating their involvement in the cognitive control network associated with reward processing (Liu et al., 2011). Previous studies have reported increased activation during gambling-related tasks in the left aInsula/frontal operculum and left ACC/dmPFC/SFG, as well as the right IFG, in individuals with GD (Limbrick-Oldfield et al., 2017). In our study, the activation of dmPFC and dACC merged into a single cluster due to anatomical considerations, although they represent distinct regions. This anatomical proximity often leads to overlapping activation patterns in neuroimaging studies (Clairis & Lopez-Persem, 2023). The dmPFC/dACC region is associated with cognitive processes such as conflict resolution, uncertainty monitoring, and error processing (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Clairis & Lopez-Persem, 2023; Shenhav, Botvinick, & Cohen, 2013), particularly in the context of reward-based decision making over time (Klein-Flügge, Bongioanni, & Rushworth, 2022). Additionally, the combined cluster of MFG and IFG activation has been linked to successful loss avoidance and a heightened sense of security (Romanczuk-Seiferth et al., 2015), and the TPJ has been implicated in social and economic decision-making (Strang & Park, 2017) (Strombach et al., 2015).

Limitations may exist in this study. Notably, the poker task may lead to polarized decision-making performance in some subjects. The factor of individual decision-making preferences should be accounted for in further analysis. In addition, the HC group included subclinical gamblers and participants without gambling experience. Furthermore, although we recruited an eligible sample size for the task-related experiment, considering the heterogeneity of mental illnesses, a larger sample with GD is still recommended to validate the classification in future studies. Finally, the temporal resolution is limited by the 2-second TR in the dynamic classification. Higher temporal resolution, which can be achieved by using a more minimal TR, would improve dynamic timeseries classification.

In conclusion, our study has uncovered specific neural representations of GD, especially in response to risk-related rewards. Notably, the discrete neural responses to risk-win and risk-RDloss observed in the right IFG. The classification of GD based on fMRI data underscores the potential utility of neural activation patterns in clinical evaluating of GD. For more precise classification, future studies should consider enrolling cohorts with similar neuropathological features, such as subclinical GD and Internet Gaming Disorder, to refine and enhance the specificity of the findings.

Funding sources: This project was funded by the University of Macau (grant no.: MYRG-GRG2023-00123-FBA, MYRG2022-00130-FSS, CRG-2020-00001-ICI, and MYRG-CRG2022-00003-FSS-ICI). The funding source had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Authors' contribution: AJWY: conceptualization, investigation, methodology, data analysis, writing-original draft &

editing, visualization. AMSW: conceptualization, funding acquisition, methodology, supervision, writing-review & editing. AYZ: investigation. LKHL: investigation. CMWL: investigation. JZ: investigation. DKCF: writing-review & editing. ZY: writing-review & editing. RH: methodology, writing-review & editing. RC: conceptualization, methodology, finding interpretation, supervision, writing-original draft & editing.

Conflict of interest: All authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at <https://doi.org/10.1556/2006.2025.00049>.

REFERENCES

- American Psychiatric Association, D., & Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). Washington, DC: American psychiatric association.
- Balodis, I. M., Kober, H., Worhunsky, P. D., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2012). Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. *Biological Psychiatry*, 71(8), 749–757. <https://doi.org/10.1016/j.biopsych.2012.01.006>
- Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P. M., ... Zack, M. (2013). The D2/3 dopamine receptor in pathological gambling: A positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C] raclopride. *Addiction*, 108(5), 953–963. <https://doi.org/10.1111/add.12066>
- Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature*, 402(6758), 179–181. <https://doi.org/10.1038/46035>
- Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron*, 33(2), 301–311. [https://doi.org/10.1016/s0896-6273\(01\)00583-9](https://doi.org/10.1016/s0896-6273(01)00583-9)
- Christopoulos, G. I., Tobler, P. N., Bossaerts, P., Dolan, R. J., & Schultz, W. (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *The Journal of Neuroscience*, 29(40), 12574–12583. <https://doi.org/10.1523/jneurosci.2614-09.2009>
- Clairis, N., & Lopez-Persem, A. (2023). Debates on the dorsomedial prefrontal/dorsal anterior cingulate cortex: Insights for future research. *Brain*, 146(12), 4826–4844. <https://doi.org/10.1093/brain/awad263>
- Clark, L., Boileau, I., & Zack, M. (2019). Neuroimaging of reward mechanisms in Gambling disorder: An integrative review. *Molecular Psychiatry*, 24(5), 674–693. <https://doi.org/10.1038/s41380-018-0230-2>

- Crockford, D. N., Goodyear, B., Edwards, J., Quickfall, J., & El-Guebaly, N. (2005). Cue-induced brain activity in pathological gamblers. *Biological Psychiatry*, 58(10), 787–795.
- de Greck, M., Enzi, B., Prösch, U., Gantman, A., Tempelmann, C., & Northoff, G. (2010). Decreased neuronal activity in reward circuitry of pathological gamblers during processing of personal relevant stimuli. *Human Brain Mapping*, 31(11), 1802–1812.
- Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*, 299(5614), 1898–1902. <https://doi.org/10.1126/science.1077349>
- Frey, M. C., & Detterman, D. K. (2004). Scholastic Assessment or g? The relationship between the Scholastic Assessment Test and general cognitive ability. *Psychological Science*, 15(6), 373–378. <https://doi.org/10.1111/j.0956-7976.2004.00687.x>
- Fujimoto, A., Tsurumi, K., Kawada, R., Murao, T., Takeuchi, H., Murai, T., & Takahashi, H. (2017). Deficit of state-dependent risk attitude modulation in gambling disorder. *Translational Psychiatry*, 7(4), e1085–e1085.
- Garavan, H., Ross, T. J., Murphy, K., Roche, R. A., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: Inhibition, error detection, and correction. *Neuroimage*, 17(4), 1820–1829. <https://doi.org/10.1006/nimg.2002.1326>
- Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America*, 96(14), 8301–8306. <https://doi.org/10.1073/pnas.96.14.8301>
- Gelskov, S. V., Madsen, K. H., Ramsøy, T. Z., & Siebner, H. R. (2016). Aberrant neural signatures of decision-making: Pathological gamblers display cortico-striatal hypersensitivity to extreme gambles. *Neuroimage*, 128, 342–352.
- Gold, M. S., Badgaiyan, R. D., & Blum, K. (2015). A shared molecular and genetic basis for food and drug addiction: Overcoming hypodopaminergic Trait/State by incorporating dopamine agonistic therapy in psychiatry. *The Psychiatric Clinics of North America*, 38(3), 419–462. <https://doi.org/10.1016/j.psc.2015.05.011>
- Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., ... Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, 46(11), 1006–1011. <https://doi.org/10.1001/archpsyc.1989.01810110048007>
- Goudriaan, A. E., De Ruiter, M. B., Van Den Brink, W., Oosterlaan, J., & Veltman, D. J. (2010). Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: An fMRI study. *Addiction Biology*, 15(4), 491–503.
- Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & van den Brink, W. (2005). Decision making in pathological gambling: A comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Brain Research. Cognitive Brain Research*, 23(1), 137–151. <https://doi.org/10.1016/j.cogbrainres.2005.01.017>
- Grant, J. E., Steinberg, M. A., Kim, S. W., Rounsaville, B. J., & Potenza, M. N. (2004). Preliminary validity and reliability testing of a structured clinical interview for pathological gambling. *Psychiatry Research*, 128(1), 79–88. <https://doi.org/10.1016/j.psychres.2004.05.006>
- Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, 35(1), 4–26. <https://doi.org/10.1038/npp.2009.129>
- Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, 32(1), 50–55. <https://doi.org/10.1111/j.2044-8341.1959.tb00467.x>
- Hamilton, M. (1986). The Hamilton rating scale for depression. In *Assessment of depression* (pp. 143–152). Springer.
- Holden, C. (2001). 'Behavioral' addictions: Do they exist? *Science*, 294(5544), 980–982. <https://doi.org/10.1126/science.294.5544.980>
- Iversen, S. D., & Mishkin, M. (1970). Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research*, 11(4), 376–386. <https://doi.org/10.1007/bf00237911>
- Kim, H., Shimojo, S., & O'Doherty, J. P. (2011). Overlapping responses for the expectation of juice and money rewards in human ventromedial prefrontal cortex. *Cerebral Cortex*, 21(4), 769–776. <https://doi.org/10.1093/cercor/bhq145>
- Klein-Flügge, M. C., Bongioanni, A., & Rushworth, M. F. S. (2022). Medial and orbital frontal cortex in decision-making and flexible behavior. *Neuron*, 110(17), 2743–2770. <https://doi.org/10.1016/j.neuron.2022.05.022>
- Knoch, D., Gianotti, L. R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. *The Journal of Neuroscience*, 26(24), 6469–6472. <https://doi.org/10.1523/jneurosci.0804-06.2006>
- Kober, H., Lacadie, C. M., Wexler, B. E., Malison, R. T., Sinha, R., & Potenza, M. N. (2016). Brain activity during cocaine craving and gambling urges: An fMRI study. *Neuropsychopharmacology*, 41(2), 628–637. <https://doi.org/10.1038/npp.2015.193>
- Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*, 122(Pt 5), 981–991. <https://doi.org/10.1093/brain/122.5.981>
- Konishi, S., Nakajima, K., Uchida, I., Sekihara, K., & Miyashita, Y. (1998). No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *The European Journal of Neuroscience*, 10(3), 1209–1213. <https://doi.org/10.1046/j.1460-9568.1998.00167.x>
- Limbrick-Oldfield, E. H., Mick, I., Cocks, R. E., McGonigle, J., Sharman, S. P., Goldstone, A. P., ... Bowden-Jones, H. (2017). Neural substrates of cue reactivity and craving in gambling disorder. *Translational Psychiatry*, 7(1), e992–e992. <https://doi.org/10.1038/tp.2016.256>
- Liu, X., Hairston, J., Schrier, M., & Fan, J. (2011). Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, 35(5), 1219–1236. <https://doi.org/10.1016/j.neubiorev.2010.12.012>
- Mazzola, L., Mauguière, F., & Isnard, J. (2017). Electrical stimulations of the human insula: Their contribution to the ictal semiology of

- Insular seizures. *Journal of Clinical Neurophysiology*, 34(4), 307–314. <https://doi.org/10.1097/wnp.0000000000000382>
- Mazzola, L., Mauguière, F., & Isnard, J. (2019). Functional mapping of the human insula: Data from electrical stimulations. *Revue Neurologique*, 175(3), 150–156. <https://doi.org/10.1016/j.neurol.2018.12.003>
- McNamee, D., Liljeholm, M., Zika, O., & O'Doherty, J. P. (2015). Characterizing the associative content of brain structures involved in habitual and goal-directed actions in humans: A multivariate fMRI study. *The Journal of Neuroscience*, 35(9), 3764–3771. <https://doi.org/10.1523/jneurosci.4677-14.2015>
- Miedl, S. F., Fehr, T., Meyer, G., & Herrmann, M. (2010). Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. *Psychiatry Research: Neuroimaging*, 181(3), 165–173.
- Miedl, S. F., Peters, J., & Büchel, C. (2012). Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Archives of General Psychiatry*, 69(2), 177–186.
- Pineau, F., Roze, E., Lacomblez, L., Bonnet, A. M., Vidailhet, M., Czernecki, V., & Corvol, J. C. (2016). Executive functioning and risk-taking behavior in Parkinson's disease patients with impulse control disorders. *Journal of Neural Transmission (Vienna)*, 123(6), 573–581. <https://doi.org/10.1007/s00702-016-1549-y>
- Potenza, M. N., Leung, H. C., Blumberg, H. P., Peterson, B. S., Fulbright, R. K., Lacadie, C. M., ... Gore, J. C. (2003). An fMRI stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *The American Journal of Psychiatry*, 160(11), 1990–1994. <https://doi.org/10.1176/appi.ajp.160.11.1990>
- Potenza, M. N., Steinberg, M. A., Skudlarski, P., Fulbright, R. K., Lacadie, C. M., Wilber, M. K., ... Wexler, B. E. (2003). Gambling urges in pathological gambling: A functional magnetic resonance imaging study. *Archives of General Psychiatry*, 60(8), 828–836.
- Power, Y., Goodyear, B., & Crockford, D. (2012). Neural correlates of pathological gamblers preference for immediate rewards during the iowa gambling task: An fMRI study. *Journal of Gambling Studies*, 28(4), 623–636. <https://doi.org/10.1007/s10899-011-9278-5>
- Rachidi, I., Minotti, L., Martin, G., Hoffmann, D., Bastin, J., David, O., & Kahane, P. (2021). The insula: A stimulating island of the brain. *Brain Science*, 11(11). <https://doi.org/10.3390/brainsci11111533>
- Raimo, S., Cropano, M., Trojano, L., & Santangelo, G. (2021). The neural basis of gambling disorder: An activation likelihood estimation meta-analysis. *Neuroscience and Biobehavioral Reviews*, 120, 279–302. <https://doi.org/10.1016/j.neubiorev.2020.11.027>
- Reiley, D. H., Urbancic, M. B., & Walker, M. (2008). Stripped-down poker: A classroom game with signaling and bluffing. *The Journal of Economic Education*, 39(4), 323–341.
- Reuter, J., Raedler, T., Rose, M., Hand, I., Gläscher, J., & Büchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience*, 8(2), 147–148. <https://doi.org/10.1038/nn1378>
- Romanczuk-Seiferth, N., Koehler, S., Dreesen, C., Wüstenberg, T., & Heinz, A. (2015). Pathological gambling and alcohol dependence: Neural disturbances in reward and loss avoidance processing. *Addiction Biology*, 20(3), 557–569. <https://doi.org/10.1111/adb.12144>
- Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*, 20(1), 351–358. [https://doi.org/10.1016/s1053-8119\(03\)00275-1](https://doi.org/10.1016/s1053-8119(03)00275-1)
- Sescousse, G., Barbalat, G., Domenech, P., & Dreher, J.-C. (2013). Imbalance in the sensitivity to different types of rewards in pathological gambling. *Brain*, 136(8), 2527–2538.
- Sescousse, G., Janssen, L. K., Hashemi, M. M., Timmer, M. H., Geurts, D. E., Ter Huurne, N. P., ... Cools, R. (2016). Amplified striatal responses to near-miss outcomes in pathological gamblers. *Neuropsychopharmacology*, 41(10), 2614–2623.
- Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The expected value of control: An integrative theory of anterior cingulate cortex function. *Neuron*, 79(2), 217–240. <https://doi.org/10.1016/j.neuron.2013.07.007>
- Strang, S., & Park, S. Q. (2017). Human cooperation and its underlying mechanisms. *Current Topics in Behavioral Neurosciences*, 30, 223–239. https://doi.org/10.1007/7854_2016_445
- Strombach, T., Weber, B., Hangebrauk, Z., Kenning, P., Karipidis, I. I., Tobler, P. N., & Kalenscher, T. (2015). Social discounting involves modulation of neural value signals by temporoparietal junction. *Proceedings of the National Academy of Sciences of the United States of America*, 112(5), 1619–1624. <https://doi.org/10.1073/pnas.1414715112>
- Tanabe, J., Thompson, L., Claus, E., Dalwani, M., Hutchison, K., & Banich, M. T. (2007). Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. *Human Brain Mapping*, 28(12), 1276–1286.
- Tsurumi, K., Kawada, R., Yokoyama, N., Sugihara, G., Sawamoto, N., Aso, T., ... Takahashi, H. (2014). Insular activation during reward anticipation reflects duration of illness in abstinent pathological gamblers. *Frontiers in Psychology*, 5, 102896.
- van Holst, R. J., Sescousse, G., Janssen, L. K., Janssen, M., Berry, A. S., Jagust, W. J., & Cools, R. (2018). Increased striatal dopamine synthesis capacity in gambling addiction. *Biological Psychiatry*, 83(12), 1036–1043. <https://doi.org/10.1016/j.biopsych.2017.06.010>
- Weber, E. U., Blais, A. R., & Betz, N. E. (2002). A domain-specific risk-attitude scale: Measuring risk perceptions and risk behaviors. *Journal of Behavioral Decision Making*, 15(4), 263–290.
- Worhunsky, P. D., Malison, R. T., Rogers, R. D., & Potenza, M. N. (2014). Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence. *Drug and Alcohol Dependence*, 145, 77–86.
- Wu, J., & Cheung, H. Y. (2014). Confirmatory factor analysis of DOSPERT scale with Chinese university students. *Psychological Reports*, 114(1), 185–197. <https://doi.org/10.2466/09.03.PR0.114k15w2>
- Yip, S. W., Morie, K. P., Xu, J., Constable, R. T., Malison, R. T., Carroll, K. M., & Potenza, M. N. (2017). Shared microstructural features of behavioral and substance addictions revealed in areas of crossing fibers. *Biol Psychiatry Cogn Neurosci Neuroimaging*, 2(2), 188–195. <https://doi.org/10.1016/j.bpsc.2016.03.001>

Yip, S. W., Worhunsky, P. D., Xu, J., Morie, K. P., Constable, R. T., Malison, R. T., ... Potenza, M. N. (2018). Gray-matter relationships to diagnostic and transdiagnostic features of drug and behavioral addictions. *Addiction Biology*, 23(1), 394–402. <https://doi.org/10.1111/adb.12492>

Zois, E., Kiefer, F., Lemenager, T., Vollstädt-Klein, S., Mann, K., & Fauth-Bühler, M. (2017). Frontal cortex gray matter volume alterations in pathological gambling occur independently from substance use disorder. *Addiction Biology*, 22(3), 864–872. <https://doi.org/10.1111/adb.12368>