



ARTICLE

Neural and neurocognitive markers of vulnerability to gambling disorder: a study of unaffected siblings

Eve H. Limbrick-Oldfield^{1,2}, Inge Mick^{3,4}, Rachel E. Cocks^{2,3}, Remy S. A. Flechais³, Samuel Turton³, Anne Lingford-Hughes³, Henrietta Bowden-Jones⁵ and Luke Clark^{1,2}

Psychological and neurobiological markers in individuals with gambling disorder (GD) could reflect transdiagnostic vulnerability to addiction or neuroadaptive consequences of long-term gambling. Using an endophenotypic approach to identify vulnerability markers, we tested the biological relatives of cases with GD. Male participants seeking treatment for GD ($n = 20$) were compared with a male control group ($n = 18$). Biological siblings of cases with GD ($n = 17$, unrelated to the current GD group) were compared with a separate control group ($n = 19$) that overlapped partially with the GD control group. Participants completed a comprehensive assessment of clinical scales, neurocognitive functioning, and fMRI of unexpected financial reward. The GD group displayed elevated levels of self-report impulsivity and delay discounting, and increased risk-taking on the Cambridge Gamble Task. We did not observe impaired motor impulsivity on the stop-signal task. Siblings of GD showed some overlapping effects; namely, elevated impulsivity (negative urgency) and increased risk-taking on the Cambridge Gamble Task. We did not observe any differences in the neural response to win outcomes, either in the GD or sibling analysis compared with their control group. Within the GD group, activity in the thalamus and caudate correlated negatively with gambling severity. Increased impulsivity and risk-taking in GD are present in biological relatives of cases with GD, suggesting these markers may represent pre-existing vulnerability to GD.

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INTRODUCTION

Gambling disorder (GD) is a behavioural addiction characterized by a loss of control over gambling to a degree that causes functional impairment, particularly in the financial realm. Research findings in disordered gamblers are sometimes applied to illuminating the ‘chicken-and-egg’ problem in substance addictions, in which observed differences could reflect either pre-existing vulnerability to addiction or the neuroadaptive (or neurotoxic) consequences of chronic substance consumption [1, 2]. As a ‘drug-free addiction’, effects in disordered gamblers have been argued to indicate vulnerability uncontaminated by these consequences. Despite its intuitive appeal, this argument is weakened by evidence of neuroplasticity induced by behaviour alone, for example in longitudinal MRI investigations of motor skill learning [3]. The chronic cycle of wins and losses experienced by a problem gambler may cause similar reorganization of brain motivational circuitry.

One way to isolate vulnerability markers is by studying unaffected relatives, in an ‘endophenotype’ approach [4–6]. Previous studies in first-degree relatives of people with GD display elevated rates of disordered gambling and alcohol use disorders [7–9], but are yet to examine underlying neurocognitive mechanisms. As a high-risk group, biological relatives have both a genetic overlap with the affected individual and may also share environmental risk factors such as childhood adversity [10]. Twin

studies indicate that genetic factors contribute around 50% of the risk of GD [11, 12]. The current study examines biological siblings of patients with GD, who are expected to express neural and neurocognitive dispositional markers.

We focus on impulsivity, risky decision-making, and reward processing as domains that are central to the pathophysiology of GD. Individuals with GD have been shown to have higher self-reported impulsivity [13, 14], choice impulsivity (on delay discounting) [15], and impaired motor impulsivity [16]. Individuals with GD also show elevated risk-taking on decision-making tests including the Iowa Gambling Task [17] and Cambridge Gamble Task [18–21]. Similar cognitive alterations are observed in substance use disorders [1]; genetic variation in these traits overlaps with genetic risk for addictive disorders [22], and individual differences have further value in predicting treatment outcomes [23]. Several studies have examined the neural response to rewarding outcomes (i.e. monetary wins) in GD using functional MRI (fMRI), focussing on ventral striatum, medial and orbital prefrontal cortex, and insula. A recent meta-analysis [24] of these studies described reduced activity in this network in individuals with GD [25–27], although other studies have reported no alteration in win reactivity [28, 29] or even win-related hyperactivity in GD [30, 31].

This evidence for both hypo- and hyper-reactivity of reward circuitry appeals to distinct theoretical frameworks for addiction,

¹Centre for Gambling Research at UBC, Department of Psychology, University of British Columbia, Vancouver, Canada; ²Department of Psychology, University of Cambridge, Cambridge, UK; ³Centre for Psychiatry, Division of Brain Sciences, Imperial College London, London, UK; ⁴Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany and ⁵National Problem Gambling Clinic, CNWL NHS Foundation Trust, Imperial College London, London, UK
Correspondence: Eve H. Limbrick-Oldfield (eve@psych.ubc.ca) or Luke Clark (luke.clark@psych.ubc.ca)

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which are relevant to vulnerability. Evidence for reward hypo-activity is interpreted within the reward deficiency framework, which posits that risky, high stimulation behaviours like gambling compensate for a developmentally sluggish reward system [32, 33]. Conversely, evidence for reward hyper-activity may be interpreted within the incentive salience (or incentive sensitization) hypothesis, that the response to drug- (or gambling-) related stimuli becomes amplified with ongoing use [34, 35]. These two theories are not mutually exclusive: reward deficiency is a theory of addiction vulnerability, whereas incentive salience is a theory of addiction development. For our participants with GD, we hypothesized that impulsivity and risk-taking would be elevated relative to controls. We predicted dysregulation of reward circuitry using our neuroimaging probe, although we did not have a strong directional prediction given inconsistencies in past research [36] and the contrasting effects of reward deficiency and incentive salience. For our high-risk group of unaffected siblings, we predicted elevated impulsivity and risk-taking, and hypo-activity of brain reward circuitry, as neurocognitive and neural expressions specifically aligned with reward deficiency as a vulnerability process. Recent evidence points to such effects for substance use vulnerability, in a two year prospective study of mid-adolescents [37] (see also [38, 39]) as well as in unaffected siblings of stimulant users [5, 40], and the present study presents a comparable analysis for GD.

MATERIALS AND METHODS

Participants

Participants were considered for inclusion if they were aged 18 to 60, had good English comprehension, and no MRI contraindications. Participants were excluded if they suffered from other past or current DSM-IV Axis I psychiatric illnesses with the exception of past depression or anxiety disorders in the GD group, if they were currently taking any psychotropic medications, including over-the-counter opiates, or if they tested positive for illegal drug use using a urine screen or alcohol intoxication using a breath alcohol test, administered on test days (see Supplemental Information). Males with GD ($n = 20$) were recruited from the National Problem Gambling Clinic (NCPG), London, U.K. Diagnosis was confirmed using DSM-IV criteria and corroborated by scores ≥ 8 on the Problem Gambling Severity Index (PGSI) [41]. An independent group of participants who did not have current or past GD, but whose siblings had current GD ($n = 17$), were recruited through advertisements at the gambling clinic, local support groups for affected others, and local newspapers. A diagnosis of GD in the affected sibling was confirmed by a score ≥ 8 on the PGSI conducted by telephone with the affected individual. Given the unbalanced gender ratios in the GD (all male) and sibling (8 male, 9 female) groups, we recruited a total of 28 control participants (18 male) who were split into two partially-overlapping subgroups that were each demographically

comparable to the groups of interest. The control group matched to the GD group (conGD) consisted of 18 male participants. The control group matched to the sibling group (conSIB) consisted of nine of these male participants and ten female participants ($n = 19$). The UK National Research Ethics Service approved the protocol, and all volunteers provided written informed consent.

Procedure

Demographic and clinical characteristics. IQ was assessed using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence [42]. Participants completed the Beck Depression Inventory (BDI-II) [43], Beck Anxiety Inventory (BAI) [44], Alcohol Use Disorders Identification Test (AUDIT) [45], Drug Abuse Screening Test (DAST) [46], and the Fagerstrom Test for Nicotine Dependence (FTND) [47]. To control for childhood adversity as an environmental risk factor for GD [10, 48], we administered the Childhood Trauma Questionnaire (CTQ) [49]. Forms of gambling were assessed using a modified version of the South Oaks Gambling Screen (SOGS) [50].

Impulsivity and risky decision making. Self-report impulsivity was measured with the UPPS-P Impulsive Behaviour Scale [51]. Participants completed the Monetary Choice Questionnaire (MCQ) [52] as a 27-item measure of delay discounting that derives the hyperbolic discounting parameter, k , for three levels of reward magnitude. Participants completed two computerized neurocognitive tasks from the CANTAB assessment (Cambridge Cognition Ltd, Cambridge, UK): the Stop Signal Task [53] as a measure of motor impulsivity, and the Cambridge Gamble Task [54] as a measure of decision-making under risk. For full details on these measures, see Supplemental Information.

fMRI reward task. During their scan, participants completed a slot machine task [29, 55–57] (see Fig. 1). On each trial, the participant selected a play icon on the left reel, and then the right reel spun. If the two icons aligned on the payline, the participant won £0.50. Other outcomes won nothing. On a third of the trials participants were asked ‘How do you rate your chance of winning?’ after icon selection and ‘How much do you want to continue to play?’ after outcome. Each participant completed two EPI runs of 42 trials each on a 3T MRI scanner (see Supplemental Information).

Data analysis

The GD group and the sibling group were compared with their respective control groups in parallel sets of models. In cases where statistical assumptions were violated, we applied the same test in both sets of models. Behavioural analyses were run in R (R Core Team, Vienna); multilevel models were run in R using lme4. Analysis scripts are available online (<https://github.com/CGR-UBC/gambling-sibling-study>).

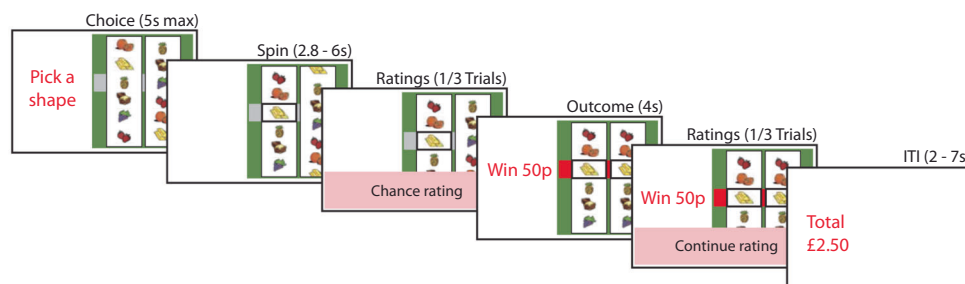


Fig. 1 A win trial on the slot machine task. On miss trials, the icons did not match on the pay line and the words “No win” were shown at outcome. On one third of the trials participants had to provide ratings on for the question “How do you rate your chance of winning?” before the spin, and a “How much do you want to continue to play?” rating after the outcome

Impulsivity and risky decision making. UPPS-P subscales were compared between groups using Welch's t-tests (two-tailed) which does not assume equal variances. For the MCQ and Cambridge Gamble Task, groups were compared using multilevel regression models (see Supplemental Information). On the Cambridge Gamble Task, two GD and one conGD did not complete the task. For the Stop Signal Task, groups were compared using Wilcoxon rank sum tests; two GD and one conGD did not complete the task, and the staircase algorithm failed to converge in two GD, one sibling, one conGD, and one conSIB.

Functional MRI. Three participants (one GD, one sibling, one control) were fully excluded, and three participants (one GD, two controls) contributed only one run, due to excess in-scanner motion (see Supplemental Information). Two participants (one GD, one sibling) were excluded due to computer error during acquisition. Data are reported from 18 GD compared to 17 conGD, and 15 siblings (7 male) compared to 18 conSIB (8 male).

Brain imaging data were analyzed using the FMRIB Software Library (FSL). Statistical analyses were carried out in FEAT (FSL Expert Analysis Tool) using a general linear model approach (see Supplemental Information). Outcomes were modelled with four separate regressors; wins, near misses before the payline, near misses after the payline, and full misses [29, 55, 56]. Two first-level contrasts were constructed: the first compared win outcomes to all non-win outcomes, the second compared near-miss outcomes to full-miss outcomes. In addition to testing group differences, we tested correlations with gambling severity (PGSI) score within the GD group.

The voxel-wise group-level statistics were masked using the win minus non-win contrast from an independent dataset of 16 healthy participants who completed the same slot machine task with an identical analysis pipeline (Limbrick-Oldfield & Clark, unpublished; see Supplemental Information) (see Fig. 3a). Foci were family-wise error (FWE) corrected using cluster-based thresholding ($Z = 3.1$ $p < 0.05$). This functionally derived map of reward-related activity was also used to derive three a priori regions of interest proximal to ventral striatum, medial PFC, and anterior insula (see Fig. 3c), which were sensitive to win and near-miss outcomes in previous experiments with this task [29, 55, 56]. Featquery was used to extract the median percent signal change within each region. All statistical maps reported here are available online (<https://neurovault.org/collections/5527/>).

RESULTS

Within the GD group, the median PGSI score was 18 (range 10–25). All other participants scored zero on the PGSI, with the exception of a single sibling scoring one. All GD participants reported engaging in multiple forms of gambling. The GD and conGD groups did not significantly differ in age, WAIS-estimated IQ, childhood trauma (CTQ), or alcohol consumption (AUDIT) (see Table 1a). The GD group reported significantly higher depression (BDI) and anxiety (BAI) scores. The sibling group did not differ significantly from the conSIB group on any demographic or clinical scales, although they did show a non-significant increase in BDI ($r = 0.25$). The groups were also comparable for past 12 month reported smoking and illicit drug use, and within those that did smoke or report drug use, there were no differences in FTND or DAST severity. These group comparisons were repeated for the subsets of participants included in each reported analyses, and the results remained qualitatively unchanged.

Impulsivity and risky decision making

The GD group scored significantly higher than conGD on the Negative Urgency, Positive Urgency, and Lack of Planning subscales of the UPPS-P (Table 1b). The siblings scored significantly higher than conSIB on Negative Urgency.

On delay discounting (MCQ), the GD group showed steeper discounting rates (i.e. elevated impulsivity) than conGD (main effect of group, $b = -0.51$, 95% CI $[-1.00, -0.023]$, $p < 0.05$) (Table 1c). There was a significant main effect of reward magnitude ($b = -0.43$, 95% CI $[-0.54, -0.32]$, $p < 0.001$) that did not differ by group ($b = -0.048$, 95% CI $[-0.16, 0.063]$, $p = 0.40$). For the siblings comparison, we observed no overall group difference ($b = 0.14$, 95% CI $[-0.39, 0.67]$, $p = 0.59$), and the significant effect of magnitude ($b = -0.53$, 95% CI $[-0.68, -0.39]$, $p < 0.001$) did not differ between groups ($b = -0.11$, 95% CI $[-0.26, 0.032]$, $p = 0.13$).

For the Stop Signal Task, there were no significant group differences in SSRT, go reaction time, go discrimination errors, or the probability of a successful stop, (Table 1d).

For the Cambridge Gamble Task, we first analyzed decision quality in the GD and conGD groups (Fig. 2a). The addition of box ratio (i.e. the level of risk) significantly improved the model ($\chi^2(3) = 43.02$, $p < 0.001$) as did the addition of group ($\chi^2(1) = 6.30$, $p < 0.05$), but not the group by box ratio interaction ($\chi^2(1) = 0.54$, $p < 0.46$). Across all participants, as box ratio decreased, participants were less likely to choose the majority colour ($b = -0.77$, 95% CI $[-1.42, -0.22]$, $p < 0.01$). The GD group chose the majority colour less often than conGD ($b = -2.02$, 95% CI $[-3.88, -0.47]$, $p < 0.05$). For the siblings analysis (Fig. 2b), the addition of box ratio significantly improved the model ($\chi^2(3) = 24.56$, $p < 0.001$; box ratio across all participants $b = -1.42$, 95% CI $[-3.18, -0.10]$, $p < 0.05$), but the addition of group ($\chi^2(1) = 0.14$, $p = 0.71$) and the group by box ratio interaction did not ($\chi^2(1) = 3.65$, $p = 0.056$).

In the GD comparisons of bet size (Fig. 2c, e), the addition of box ratio improved the model for both ascending ($\chi^2(3) = 521.80$ $p < 0.0001$) and descending ($\chi^2(3) = 429.43$ $p < 0.0001$) bet conditions. As box ratio decreased, the percentage bet decreased (ascending $b = -13.90$, 95% CI $[-16.37, -11.42]$, $p < 0.0001$, descending $b = -12.12$, 95% CI $[-15.49, -9.08]$, $p < 0.0001$). In the ascending condition, the addition of group significantly improved the model ($\chi^2(1) = 5.51$, $p < 0.05$) such that GD placed higher bets than conGD across all box ratios ($b = -12.39$, 95% CI $[-16.37, -11.42]$, $p < 0.05$); the group and box ratio interaction did not improve the model ($\chi^2(1) = 0.51$, $p = 0.47$). In the descending condition, group ($\chi^2(1) = 0.45$, $p = 0.50$) and the group by box ratio interaction ($\chi^2(1) = 0.15$, $p = 0.70$) did not improve the model.

In the siblings comparisons of betting (Fig. 2d, f), we again observed effects of box ratio (ascending: $\chi^2(3) = 676.05$, $p < 0.0001$, $b = -11.74$, 95% CI $[-13.82, -9.65]$, $p < 0.0001$; descending: $\chi^2(3) = 440.27$, $p < 0.0001$, $b = -11.90$, 95% CI $[-14.05, -9.72]$, $p < 0.01$). In the ascending condition, the addition of group significantly improved the model ($\chi^2(1) = 10.68$, $p < 0.01$) such that siblings placed higher bets than conSIB ($b = -17.86$, 95% CI $[-28.06, -7.66]$, $p < 0.01$), but the group by box ratio interaction did not improve the model ($\chi^2(1) = 0.029$, $p = 0.87$). In the descending condition, neither group ($\chi^2(1) = 1.10$, $p = 0.29$) nor the group by box ratio interaction ($\chi^2(1) = 0.24$, $p = 0.62$) significantly improved the model.

fMRI reward task

The contrast of win > non-win outcomes revealed significant clusters of activity in all groups (Fig. 3b), including cingulate cortex and frontal pole (see Supplemental Table 2). All groups, with the exception of the sibling group, showed active clusters covering the ventral striatum and orbitofrontal cortex. With cluster-based thresholding, there were no significant differences in activity in either the GD versus conGD comparison, or the sibling versus conSIB comparison. Reward-related circuitry was interrogated further using three ROIs—bilateral caudate, paracingulate cortex, and bilateral orbito-frontal cortex—from the independent win mask (Fig. 3a). Both the GD and sibling groups displayed significant win-related signal increases in each of the three ROIs

Table 1. a: Demographic and clinical characteristics; b: Mean and standard errors for subscales of the UPPS-P Impulsivity Scale; c: Median and range for k-values at the three levels of reward magnitude for the Kirby Monetary Choice Questionnaire; d: Median and range for the variables of interest in the Stop-Signal Task

	GD	conGD	Siblings	conSIB	
a. Demographic and clinical characteristics (median and range)					
Age	30 (21–52)	30 (20–58)	35 (21–51)	33 (20–58)	$W = 157.5, p = 0.91, r = 0.02$
IQ	113 (83–134)	120.5 (78–131)	117 (90–137)	111 (87–129)	$W = 120, p = 0.19, r = 0.22$
BDI	14.5 (1–46)	2.5 (0–10)	2 (0–23)	0 (0–7)	$W = 116, p = 0.14, r = 0.25$
BAI	8 (0–33)	2 (0–17)	2 (0–25)	2 (0–9)	$W = 150.5, p = 0.73, r = 0.06$
CTQ (Emotional abuse)	6 (5–11)	6.5 (5–16)	8 (5–24)	7 (5–15)	$W = 127, p = 0.27, r = 0.19$
CTQ (Physical abuse)	5.5 (5–10)	5 (5–11)	5 (5–16)	5 (5–12)	$W = 137.5, p = 0.40, r = 0.14$
CTQ (Sexual abuse)	5 (5–7)	5 (5–11)	5 (5–15)	5 (5–13)	$W = 138, p = 0.32, r = 0.17$
AUDIT	5.5 (1–8)	5 (0–9)	5 (1–8)	4 (1–8)	$W = 160, p = 0.97, r = 0.01$
Used drugs in last 12 months	7	6	4	4	–
DAST	1 (1–2)	1 (1–5)	1 (1–1)	1 (1–5)	$W = 10, p = 0.45, r = 0.27$
N Smokers	7	7	4	4	–
FTND	3 (0–6)	3 (1–7)	1.5 (0–6)	3.5 (1–7)	$W = 11, p = 0.47, r = 0.26$
b. UPPS-P (mean and SE)					
Positive urgency	29.60 (9.73)	22.5 (7.08)	23.88 (7.11)	20.26 (7.27)	$t_{(33.72)} = -1.51, 95\% \text{ CI } [-8.49, 1.26], p = 0.14, r = 0.25$
Negative urgency	31.20 (7.04)	22.83 (5.48)	25.88 (5.63)	21.26 (6.41)	$t_{(33.99)} = -2.30, 95\% \text{ CI } [-8.70, -0.54], p < 0.05, r = 0.37$
(lack of) Perseverance	21.7 (4.34)	19.56 (3.76)	20.06 (5.21)	18.58 (4.57)	$t_{(32.10)} = -0.90, 95\% \text{ CI } [-4.83, 1.87], p = 0.37, r = 0.16$
(lack of) Planning	25.30 (6.21)	21.11 (4.52)	21.53 (4.85)	21.63 (4.98)	$t_{(33.74)} = -0.06, 95\% \text{ CI } [-3.23, 3.44], p = 0.95, r = 0.01$
Sensation seeking	35.95 (6.92)	34.50 (7.29)	32.59 (9.49)	32.00 (8.91)	$t_{(32.96)} = -0.19, 95\% \text{ CI } [-6.85, 5.67], p = 0.85, r = 0.03$
c. Kirby Monetary Choice Questionnaire (median and range)					
k (large)	–4.63 (–6.44––1.84)	–5.55 (–8.76––2.73)	–4.63 (–8.29––1.39)	–5.55 (–7.37––3.66)	–
k (medium)	–3.68 (–6.44––1.39)	–4.63 (–7.37––1.95)	–4.63 (–8.30––1.389)	–4.63 (–7.37––1.39)	–
k (small)	–3.67 (–6.45––1.40)	–4.634 (–8.29––1.84)	–4.64 (–7.37––1.84)	–3.69 (–6.45––1.84)	–
d. Stop-signal task (median and range)					
Go (correct) reaction time (ms)	401.5 (331–570)	375 (347–580)	439 (297–807.5)	415 (315–600)	$W = 101.5, p = 0.23, r = 0.21$
Go discrimination errors (N)	3 (0–44)	3 (1–21)	3 (0–16)	3.50 (1–9)	$W = 165, p = 0.28, r = 0.19$
p (Successful stop)	0.463 (0.403–0.538)	0.463 (0.400–0.600)	0.488 (0.413–0.750)	0.469 (0.400–0.563)	$W = 117.5, p = 0.54, r = 0.11$
SSRT (ms)	139.54 (96–237.50)	154.63 (105.50–259.51)	174.81 (128.25–245.00)	159.13 (83.50–270.25)	$W = 107, p = 0.32, r = 0.17$

Data violated the assumption of normality, so Wilcoxon rank-sum tests were used to test for group differences. Significant ($p < 0.05$) group differences are highlighted in bold. Groups were compared using Welch's t -test. Significant group differences are shown in bold. See results text for the multilevel models. Wilcoxon rank-sum tests were used to compare groups.

SSRT Stop Signal Reaction Time, AUDIT alcohol use disorders identification test, BAI Beck Anxiety Inventory, BDI-II Beck Depression Inventory, CTQ Childhood Trauma Questionnaire, DAST Drug Abuse Screening Test, FTND Fagerstrom test for nicotine dependence, IQ intelligence quotient, SE standard error

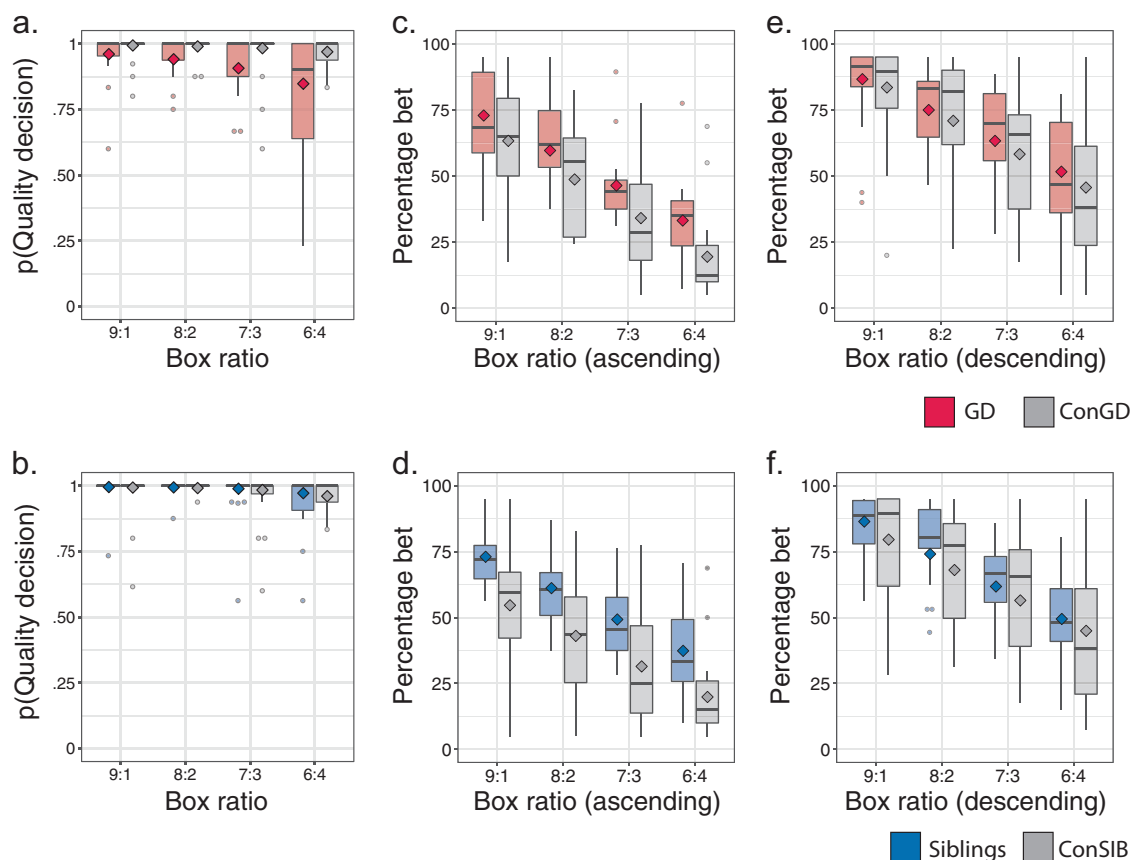


Fig. 2 Decision quality and the bet proportion during the Cambridge Gamble Task. Diamonds represent model prediction, observed data shown using Tukey Boxplots. **a, b** Decision quality as a function of box ratio and group, **c, d** Bet proportion in the ascending condition, **e, f** Bet proportion in the descending condition. Red = Gambling Disorder (GD). Blue = siblings

(Fig. 3c), which did not differ against controls in either set of comparisons.

Within the GD group, win-related activity (win > non-win contrast) was negatively correlated with gambling severity (PGSI) in a single cluster extending from lateral thalamus to bilateral caudate, ($Z_{\max} = 3.86$, $MNI = [-16, -2, 14]$, 475 voxels) (Fig. 4). We did not observe any group differences in near-miss related activity (see Supplemental Information), or on the ratings of 'chances of winning' or post-outcome 'continue to play' (see Supplemental Information).

DISCUSSION

We show a profile of increased self-reported impulsivity (UPPS-P) and delay discounting (MCQ) in men with GD, in line with previous findings [13–15]. We found strong evidence for elevated negative urgency, with weaker evidence for increases in positive urgency and (lack of) planning subscales, and delay discounting. We found strong evidence of impaired decision making on the Cambridge Gamble Task in individuals with GD, placing both higher bets (a direct marker of risky choice) and also choosing the advantageous box colour less often than controls. From our psychological assessment, there was no evidence of differences on the UPPS-P sensation-seeking subscale (see also [14]), or stop-signal response inhibition, which in prior work can be disrupted in more severe GD cases [14, 16]. Some of the differences we observed were also detected in biological siblings of GD. The siblings showed increased scores on negative urgency (UPPS-P), although this was a weaker relationship than observed in our GD analysis. The siblings placed significantly higher bets on the Cambridge

Gamble Task, indicative of risk-taking. The difference we observed was greater in the sibling group, compared to the GD analysis (a difference from controls of ~17% compared to ~12%). The relative strength of the evidence we observed suggests the group differences we observed on the CGT may hold the most practical relevance as a marker for vulnerability to GD. On other GD-sensitive measures, no significant differences were observed in the siblings, including UPPS-P positive urgency and (lack of) planning subscales, delay discounting, and Cambridge Gamble Task decision quality.

Neuroimaging markers of reward processing were utilized to test reward deficiency as a biomarker of addiction vulnerability. Our hypothesis of reward hypo-activation in the siblings was not supported; indeed, we did not find evidence for any neuroimaging markers of GD vulnerability. As strengths of our analysis, we paid careful attention to in-scanner movement, which can be increased in GD [58], and our analysis focused on the win-related network identified using the same slot machine task in an independent healthy group. Our analysis corroborated win-related activity in the GD and siblings groups, in established reward-sensitive subcortical (striatum) and cortical (medial PFC) regions, consistent with earlier studies using this task [29, 55, 56, 59]. There was no evidence for between-group differences in reward signalling in either comparison, although we did observe a negative correlation between win-related activity in striatum and GD severity. Individual differences within GD groups are, in fact, often reported and may reflect the combination of individual differences in vulnerability loading and experience-dependent neuroadaptations [60]. A negative correlation with GD severity can be reconciled more readily with reward deficiency (a greater level of vulnerability associated with reward hypo-activation) than with

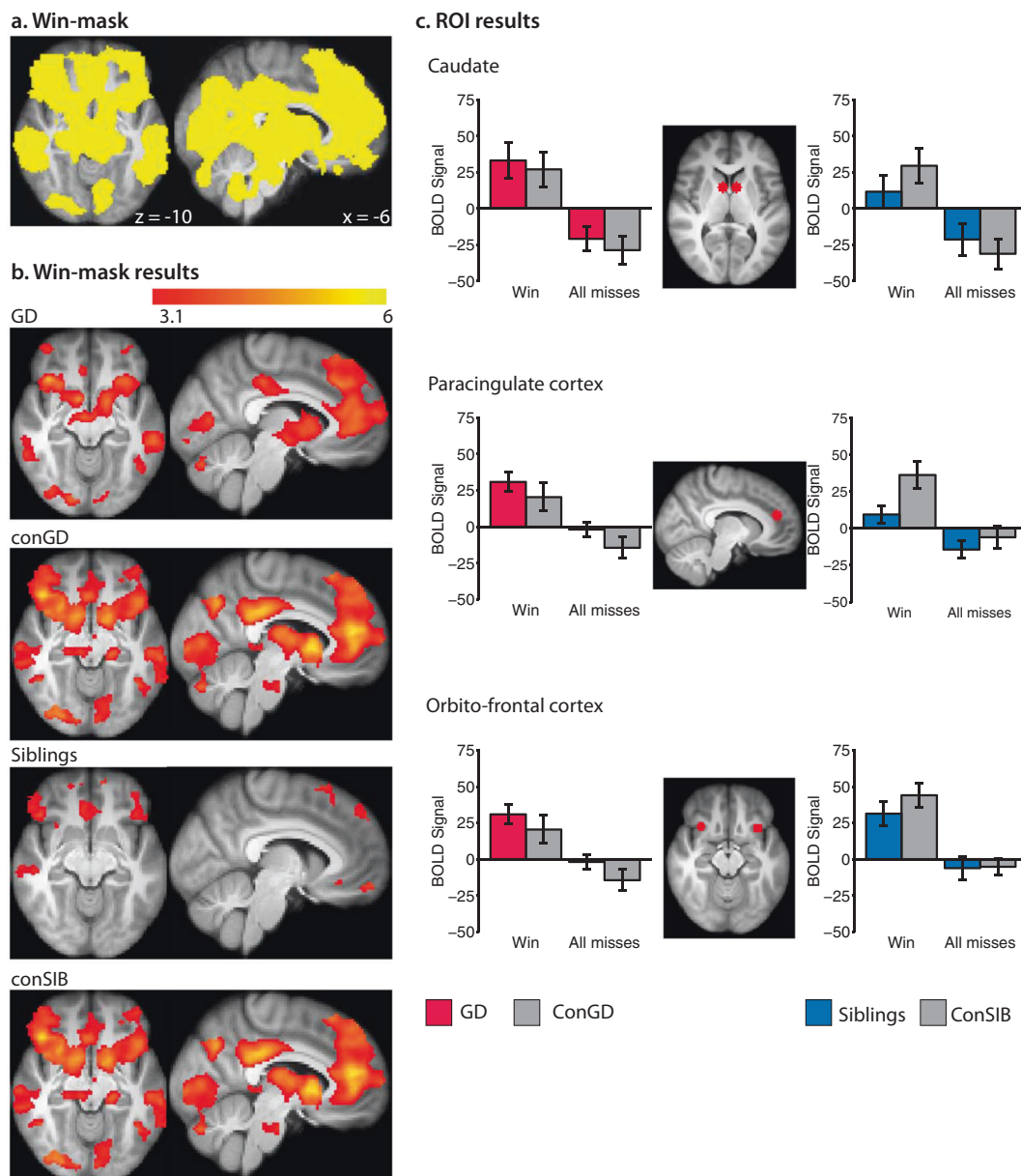


Fig. 3 Win related fMRI activity derived from the win > non-win contrast in the slot machine task. **a** Win-mask derived from an independent group of participants. **b** Significant clusters of activity revealed from our win-mask analysis. See Supplementary table S2 for a list of the peak coordinates of the significant clusters. All images cluster corrected, $Z > 3.1$, $p < 0.05$ and presented using radiological convention. **c** Region-of-interest analysis of win-related activity in the slot machine tasks. Center panel indicates location of region-of-interest on the group average brain, left panel shows GD (red) and conGD (grey) data, right panel shows sibling (blue) and conSIB (grey) data. The bilateral caudate ROI: The GD group showed a significant difference between win and all miss outcomes ($\chi^2(1) = 31.58$, $p < 0.0001$) but this difference was not modulated by group ($\chi^2(1) = 0.0026$, $p = 0.96$). Siblings also showed a significant difference between win and all miss outcomes ($\chi^2(1) = 18.12$, $p < .0001$), but this difference was not modulated by group ($\chi^2(1) = 2.01$, $p = 0.16$). The paracingulate cortex ROI: The GD group showed a significant difference between win and all miss outcomes ($\chi^2(1) = 41.06$, $p < .001$) but this difference was not modulated by group ($\chi^2(1) = 0.00$, $p = .99$). Siblings also showed a significant difference between win and all miss outcomes ($\chi^2(1) = 27.56$, $p < 0.0001$), and this difference was modulated by group ($\chi^2(1) = 4.05$, $p < 0.05$), with siblings showing reduced activity compared to the conSIBs group. The bilateral orbito-frontal cortex ROI: The GD group showed a significant difference between win and all miss outcomes ($\chi^2(1) = 32.17$, $p < 0.0001$) but this difference was not modulated by group ($\chi^2(1) = 1.02$, $p = 0.33$). Siblings also showed a significant difference between win and all miss outcomes ($\chi^2(1) = 29.22$, $p < 0.0001$), but this difference was not modulated by group ($\chi^2(1) = 1.22$, $p = 0.27$). GD gambling disorder, ROI region of interest

incentive salience (if GD severity should amplify gambling-related associations).

However, by using a cue-laden task based on slot machine gambling, our design may have been biased to detect incentive salience [61], and this may explain why we did not observe a between group difference that supported the reward deficiency

hypothesis in our GD analysis. In addition, the lack of evidence for fMRI effects in the GD siblings tempers a vulnerability interpretation of our severity correlation. Similar negative correlations between gambling severity and striatal reward activation have been reported in the context of overall hypo-activation in GD [25, 27]. Other studies have observed negative associations either

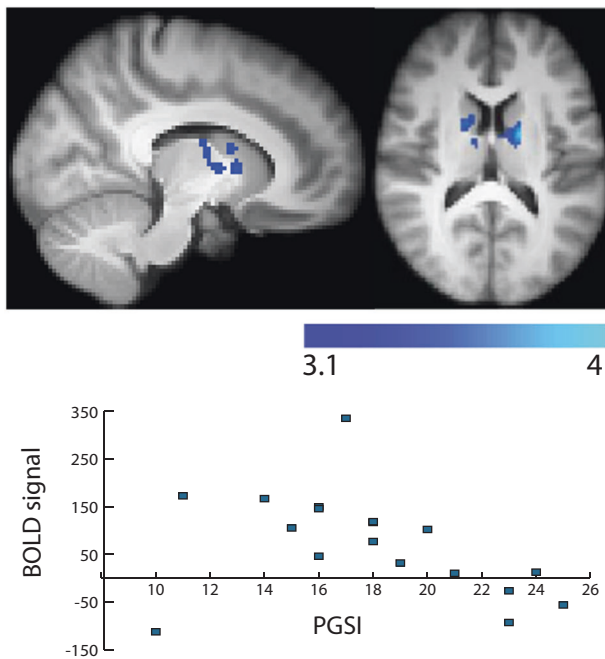


Fig. 4 Win > all miss activity negatively correlates with PGSI score in the participants with Gambling Disorder. **a** A single cluster of activity peaks in white matter [$-16, -2, 14$], but extends to the caudate nuclei. **b** BOLD signal from this cluster extracted at the individual level. All images cluster corrected, $Z > 3.1$, $p < 0.05$ and presented using radiological convention. BOLD blood oxygen level dependent, PGSI problem gambling severity index

in the absence of an overall case-control difference (e.g. [62]), as seen here, or even in the context of group hyper-activation [31, 63].

With respect to our findings in the sibling group, it is those effects that are strongly and reliably associated with GD that we observed in the siblings. Increases in risky choice and mood-related impulsivity (urgency) are consistently associated with GD [14, 18–21, 64, 65]. Our findings that these signals overlap with the profile in GD mitigates against the possibility that differences in biological relatives could reflect *resiliency* against the disorder rather than risk [66]; this concern is arguably greater in adult samples who have passed the average age of onset [48]. However, caution is warranted against asserting genetic mediation of these findings, as biological siblings share both genes and environmental upbringing. Moreover, any vulnerability markers in first-degree relatives are expected to be attenuated relative to the signal in actual cases, as genetics are only partially shared. Nevertheless, as a putative endophenotype, risky decision-making does meet criteria of heritability [67]. Specific gene variants affecting dopamine and serotonin have been implicated in GD [68–70] and variation in the cannabinoid receptor gene (CNR1) in a healthy sample affected Cambridge Gamble Task bet size [71].

It is notable that our evidence for endophenotypic signals in the GD siblings was observed on psychological measures, and our data do not support any changes on reward neuroimaging. It is often assumed that neuroimaging is the more sensitive procedure, although in other research looking at adolescent (age 14) markers of alcohol consumption, reward-related personality traits and genetic markers showed stronger signals than neuroimaging measures [39, 72]. In a subset of the IMAGEN prospective study, a blunted ventral striatum response to reward anticipation at age 14 predicted drinking and smoking frequency at age 16 [37, 38]. Cambridge Gamble Task risk-taking was available in the IMAGEN assessment, but was not a significant predictor of drug use. However, using a wheel of fortune task that isolates risky choice,

Morales et al. [73] saw that increased ventral striatal signal on high-risk decisions predicted earlier initiation of binge-drinking, as did a behavioural index of risky choice. The event-related structure may be critical here as both healthy adolescence and substance use disorders have been associated with reduced anticipatory signalling but enhanced activity to reward delivery [24, 74, 75]. These prior analyses, as well as the reward deficiency hypothesis of addiction vulnerability, centre on striatal signalling [76, 77]. By contrast, risk-taking and mood-related impulsivity may indicate a relatively greater role of orbital and lateral prefrontal pathophysiology [65, 78]. Functional disruption in this circuitry is widely supported in GD [25, 30] but few studies speak directly to its role in vulnerability. Our findings are compatible with a recent structural MRI mega-analysis in GD showing a distinct profile of orbitofrontal morphology that is neurodevelopmental in origin [79].

We found no evidence of group differences in near-miss related activity, and the ‘continue to play’ ratings (delivered intermittently on 1/3 trials) did not support any subjective effects of these outcomes. A previous study had reported increased striatal activation to near-misses in a GD group compared to healthy controls, with no corresponding difference in win-related activity [29]. This study used a shorter version of the slot machine task than prior research, which afforded reduced power to examine the near-miss outcomes, and drew from a treatment-seeking population, rather than through community advertisement.

As limitations, our sample of GD siblings was small due to challenges with recruitment, which is unsurprising for an illness that causes much strain within families [80]. A specific issue with the siblings approach in the present study was the unbalanced demographics, especially with respect to gender: the GD group were entirely male, whereas our siblings included both men and women. This in turn necessitated parallel comparisons using two subsets of a larger control group, with 9 overlapping male controls. The heritability of GD has been ascertained largely in male samples, with limited data in females [81]. There is also some evidence that the non-genetic environmental contribution to GD is mostly derived from non-shared (i.e. unique) environment [82] that may not be expressed in siblings. Although the siblings were screened carefully for mental illness, we have limited data on family history and so our study cannot ascertain the specificity of these markers to GD. Sensitivity analyses for assessing the impact of clinical variables (e.g. BDI depression) were limited by collinearity with gambling severity scores, and small sample size. We note that BDI score in individuals with GD has been shown to modulate the neural response to reward [62], and impaired decision-making has been observed in first-degree relatives of suicide completers [83] and obsessive compulsive disorder [84], which are conditions that share pathophysiological overlap with GD [79].

In conclusion, our investigation of unaffected siblings of people with GD identified impulsivity and risky choice as candidate endophenotypic markers of GD vulnerability. The observed sensitivity of self-reported and cognitive markers over reward neuroimaging helps to arbitrate between neuroscientific hypotheses of addiction vulnerability. Ongoing characterization of vulnerability markers may inform algorithms for ascertaining gambling risk and pave the way for targeted prevention strategies.

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ADDITIONAL INFORMATION

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