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Aberrant neural signatures of decision-making: Pathological gamblers display cortico-striatal hypersensitivity to extreme gambles

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ABSTRACT

Pathological gambling is an addictive disorder characterized by an irresistible urge to gamble despite severe consequences. One of the hallmarks of pathological gambling is maladaptive and highly risky decision-making, which has been linked to dysregulation of reward-related brain regions such as the ventral striatum. However, previous studies have produced contradictory results regarding the implication of this network, revealing either hypo- or hypersensitivity to monetary gains and losses. One possible explanation is that the gambling brain might be misrepresenting the benefits and costs when weighting the potential outcomes, and not the gains and losses per se. To address this issue, we investigated whether pathological gambling is associated with abnormal brain activity during decisions that weight the utility of possible gains against possible losses. Pathological gamblers and healthy human subjects underwent functional magnetic resonance imaging while they accepted or rejected mixed gain/loss gambles with fifty–fifty chances of winning or losing. Contrary to healthy individuals, gamblers showed a U-shaped response profile reflecting hypersensitivity to the most appetitive and most aversive bets in an executive cortico-striatal network including the dorsolateral prefrontal cortex and caudate nucleus. This network is concerned with the evaluation of action–outcome contingencies, monitoring recent actions and anticipating their consequences. The dysregulation of this specific network, especially for extreme bets with large potentials consequences, offers a novel understanding of the neural basis of pathological gambling in terms of deficient associations between gambling actions and their financial impact.

Introduction

Pathological gambling is a mental disorder characterized by an irresistible urge to engage in monetary gambling despite harmful consequences. With a prevalence reaching 1–2% in many Western societies (Welte et al., 2008; Wardle et al., 2010), this disorder constitutes a severe public and personal health issue. Pathological gambling has recently been classified as a behavioral addiction and shares many core symptoms with drug addictions such as withdrawal, tolerance, and high preoccupation (Petry 2007; Leeman and Potenza 2012).

Risky decision-making is an important hallmark of pathological gambling. Indeed, gamblers have a high tolerance toward risk (Clark 2010; Brevers et al. 2013), and pathological gambling has been linked to alterations of dopaminergic regions linked to reward, risk, and motivation, such as the ventral striatum and the ventromedial prefrontal cortex (vmPFC) (van Holst et al. 2010; Limbrick-Oldfield et al. 2013; Potenza 2014). However, while some studies have found *hypo*activation of the mesolimbic reward pathway in response to the anticipation or outcome of rewards (Reuter et al. 2005; de Ruiter et al. 2009; Balodis et al. 2012), other studies have reported *hyper*activation of the same pathway to anticipated reward (van Holst et al. 2012; Worhunsky et al. 2014), anticipated losses (Romanczuk-Seiferth et al. 2015), or gambling cues (Crockford et al. 2005; Goudriaan et al. 2010). Interestingly, positron emission tomography (PET) studies revealed no general differences between gamblers and healthy controls in the magnitude of striatal dopamine release (Joutsa et al. 2012; Linnet et al. 2011) but showed a positive correlation between striatal dopamine release and gambling severity (Joutsa et al. 2012), and dopamine release and gambling excitement (Linnet et al. 2011). These discrepant response patterns are reflected in two main accounts of pathological gambling. On the one hand, the reward deficiency theory predicts a hyposensitive

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reward system due to a dysfunctional dopamine D2 receptor found in substance addicts (Blum et al. 1990; Noble et al. 1991) and gamblers (Comings et al. 1996; Comings et al. 2001). A lower dopaminergic tone in the brain would push gamblers to seek higher rewards, in order to reach the threshold at which a "reward cascade" is initiated in the brain. On the other hand, the sensitization theory predicts a strong motivational bias toward objects of addiction (Robinson and Berridge 1993, 2008) leading to hypersensitivity in dopaminergic regions. In gamblers, the motivation to gamble would be triggered by gambling cues in the environment, which would override the incentive value of alternative sources of reward (Goldstein and Volkow 2002; Goldstein et al. 2007).

These discrepancies underscore that the neural basis of pathological gambling remains unsettled. While studies contrasting monetary punishments and rewards can address how decision-values are computed in the brain, they do not address how gains and losses are integrated during gambling. Recently, we developed a gambling task that probes both the magnitudes of gain and loss values separately, as well as how gains and losses are balanced against each other in "mixed" (gain/loss) gambles (Gelskov et al. 2015). When balancing gains and losses, people tend to be more sensitive to potential losses than to equivalent gains, a decision-bias known as loss aversion (Kahneman and Tversky 1979). In practice, people typically reject 50/50 gambles unless they can win around twice as much as they can lose. Previous studies using mixed gambles with healthy participants found that the separate valuation of gains and losses involve reward-related dopaminergic target regions, specifically the ventral striatum and the vmPFC (Tom et al. 2007). However, when the entire gain/loss gamble is taken into account (i.e., potential gain, potential loss, and the consequences of winning or losing), other studies have found an important role for the amygdala in loss aversion (De Martino et al. 2010; Gelskov et al. 2015). In the present study, we used this task in a population suffering from gambling addiction as a means to gain insight into aberrant value-based decision-making.

Recently, a behavioral study found that problem gamblers are less loss averse than control subjects (Brevers et al. 2012, but see also Giorgetta et al. 2014). Here, we ask whether pathological gambling might reflect deficient balancing of possible gains against losses during decision-making. In a recent study, we found that activity of the amygdala and ventral striatum reflected the degree of loss aversion in healthy participants when they decided to accept or reject extreme gain–loss gambles (Gelskov et al. 2015). Here, we used individual gambling behavior to investigate how the decision-making process is tuned by inter-individual variation in loss aversion (i.e. being more or less loss averse), and whether loss aversion is also reflected in mesolimbic reward-related areas in gamblers. To address these issues, we used fMRI and a gambling task in which participants had to accept or reject mixed gambles on the basis of the ratio between the absolute gain and loss value. Our study design allowed us to address whether pathological gamblers balance positive and negative values differently from healthy controls and whether the integration of gain–loss ratios in gambling decisions is associated with abnormal activity in brain regions involved in value-based decision-making.

Material and methods

Participants

Fourteen male, un-medicated pathological gamblers (mean age in years: 29.43; SD: 6.05; range: 20–40) and 15 healthy control subjects (all male; mean age in years: 29.87; SD: 6.06; range: 21–38) were recruited specifically for this study. Two additional gamblers were initially scanned but excluded before inclusion in the analysis because they misunderstood the task: One participant only responded when accepting a bet, while another participant thought that all gambles would be paid out at the end of the session. Gamblers were recruited through a Danish treatment center for pathological gambling. No participant had additional mental health issues apart from pathological gambling based on the structural clinical interview for DSM-IV, Axis I (SCID-I, Research version, patient and nonpatient versions; First et al. 2002), including disorders such as drug use or dependency. The presence of pathological gambling was confirmed by structural interview based on the SCID module for pathological gambling. All gamblers had a South Oaks Gambling Screen (SOGS) score above 5 (Table 1; Lesieur and Blume 1987; Danish versions of SOGS and SCID modules were translated by J. Linnet). Participants were screened for MR compatibility, history of neurological disorders, and signed informed consent forms. The study was approved under the ethical protocol KF 01–131/03, issued by the local ethics committee.

Participants were tested on two separate days 1–2 weeks apart. During the first test session, participants underwent neuropsychological testing, questionnaires, and interviews (see Table 1). Participants were also endowed with 200 Danish Kroner (i.e., the Danish monetary currency, DKK, 1 DKK ≈ 0.16 US dollar), which they were told to bring back the following week for the fMRI test session as a gambling stake.

Gambling task and stimuli

During the fMRI session, participants performed a gambling task, which required them to accept or reject mixed gain–loss gambles with equal probability of winning or losing (Fig. 1A). On each trial, subjects were presented with a pie chart with either a potential gain amount or a potential loss amount, according to main condition (i.e. "loss first"

Table 1
Demographic and neuropsychological characteristics of participants.

Variables, group means (SD of means)	Pathological gamblers ($n = 14$)	Control subjects ($n = 15$)	Test statistics (2-sample, 2-tailed *t*-tests and chi-square tests)
Demographic data			
Age (years)	29.43 (6.05)	29.87 (6.06)	$t(27) = 0.2, P = 0.85$
Educational level[a,b]	3.15 (1.68)	4.6 (1.12)	$t(26) = 2.72, P = 0.01$
Clinical data			
Gambling score (SOGS)	11.36 (3.97)	0.33 (0.9)	$t(27) = 10.48, P < 0.001$
Smokers[b]	4	0	$\chi^2 = 5.39$, df = 1, $P = 0.02$
Alcohol (AUDIT)[b]	9.23 (5.32)	8.67 (4.47)	$t(26) = 0.31, P = 0.76$
Handedness (left)	2	4	$\chi^2 = 0.14$, df = 1, $P = 0.71$
Neuropsychological data			
WAIS subtests:			
"Vocabulary"	10.36 (2.50)	13.47 (1.25)	$t(27) = 4.29, P < 0.001$
"Information"	10.00 (2.08)	12.80 (2.01)	$t(27) = 3.69, P < 0.001$
Depression (BDI)	17.00 (10.57)	3.47 (2.95)	$t(27) = 4.77, P < 0.001$
Impulsiveness (BIS-11)[b]	74.93 (7.25)	58.36 (8.63)	$t(26) = 5.50, P < 0.001$
"Attention"	2.25	2.14	$t(26) = 1.57, P = 0.13$
"Motor"	2.47	1.95	$t(26) = 4.35, P < 0.001$
"Non-planning"	2.8	2.71	$t(26) = 5.63, P < 0.001$
Anxiety (GAD-10)	12.57 (9.02)	8.27 (5.89)	$t(27) = 1.53, P = 0.14$
Risk-taking (DOSPERT)			$t(27) = 1.57, P = 0.13$
"Perceived risk"	-0.25 (0.25)	-0.51 (0.20)	$t(27) = 3.14, P = 0.004$
"Expected benefit of risk"	0.46 (0.41)	0.40 (0.31)	$t(27) = 0.49, P = 0.63$
Behavioral data			
Loss aversion, Lambda (λ)	1.45 (0.49)	1.83 (0.83)	$t(27) = 1.47, P = 0.077$[c]
Response time (ms)	927 (240)	959 (122)	$t(27) = 0.45, P = 0.66$

Abbreviations: SOGS, South Oaks Gambling Screen; AUDIT, Alcohol Use Disorders Identification Test; WAIS, Wechsler Adult Intelligence Scale; BDI, Beck Depression Inventory; BIS-11, Barratt Impulsiveness Scale, 11th ed., GAD-10, Generalized Anxiety Disorder test; DOSPERT, Domain-Specific Risk-Taking scale.

[a] Highest educational level (scoring): 1 = Lower/general secondary school, 2 = vocational education and training, 3 = upper secondary school, 4 = professional college degree, 5 = bachelors degree or similar, 6 = masters degree.

[b] One gambler did not complete the AUDIT screen, one did not complete the smoking and educational screen. One control subject did not complete the BIS-11 questionnaire.

[c] Non-parametric permutation test used due to non-normal distributions.