Games in the Brain: Neural Substrates of Gambling Addiction

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Abstract

As a popular form of recreational risk taking, gambling games offer a paradigm for decision neuroscience research. As an individual behavior, gambling becomes dysfunctional in a subset of the population, with debilitating consequences. Gambling disorder has been recently reconceptualized as a "behavioral addiction" in the *DSM-5*, based on emerging parallels with substance use disorders. Why do some individuals undergo this transition from recreational to disordered gambling? The biomedical model of problem gambling is a "brain disorder" account that posits an underlying neurobiological abnormality. This article first delineates the neural circuitry that underpins gambling-related decision making, comprising ventral striatum, ventromedial prefrontal cortex, dopaminergic midbrain, and insula, and presents evidence for pathophysiology in this circuitry in gambling disorder. These biological dispositions become translated into clinical disorder through the effects of gambling games. This influence is better articulated in a public health approach that describes the interplay between the player and the (gambling) product. Certain forms of gambling, including electronic gambling machines, appear to be overrepresented in problem gamblers. These games harness psychological features, including variable ratio schedules, near-misses, "losses disguised as wins," and the illusion of control, which modulate the core decision-making circuitry that is perturbed in gambling disorder.

Keywords

decision making, risk taking, problem gambling, dopamine, video games

Introduction

Gambling is a diverse behavior that is found in nearly every world culture and has existed for thousands of years (Binde 2005). Broadly speaking, a gamble involves a decision to place a wager on an uncertain event that offers the potential for a larger prize. This article confines itself to forms of gambling where money is the commodity, for both the wager and the prize. In Western culture, most forms of gambling are offered by commercial organizations such as casinos or bookmakers, who maintain a "house advantage" by configuring the games to have a negative expected value, so that a gambler's continued play will inexorably result in a net loss. One or two games provide exceptions to this rule—in poker, for example, the player's skill level can influence their expected return (Reber 2012)—but for the purposes of this review, we will focus on games of pure chance, which include lotteries, roulette, and slot machines.

Gambling can be considered a prototypical example of a risky decision, and as such, the psychology of gambling can be readily situated within the broader context of decision neuroscience or "neuroeconomics" (Clark and others 2013). To decompose a gamble into its cognitive elements, there is an initial decision phase that includes the placing of the bet (e.g., buying a lottery ticket) and typically some kind of deliberative selection, for example, which slot machine to play on, or which lottery numbers to choose. After the bet is placed, there is an anticipatory period in which the gambler waits to find out whether or not she/he has won. The length of anticipation varies from the order of days in the case of lotteries, to mere seconds in the case of a slot machine or scratchcard. Last, the outcome phase is the "big reveal" in which the gambler finds out whether they have won or lost. In the next section, we summarize a substantial body of research from the larger field of decision neuroscience that delineates the core neural circuitry involved in these three stages.

Whereas gambling represents a harmless form of entertainment for most consumers, it has the capacity to become dysfunctional in a minority. In these individuals, the

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negative consequences are severe, and include financial debt, bankruptcy, family dissolution, and criminal behavior (Shaffer and Martin 2011). Research from decision neuroscience provides a lens for examining the clinical dimensions of gambling behavior. "Compulsive gambling" (later termed "pathological gambling") was first recognized in the *DSM-III* (American Psychiatric Association 1980) and was classified as an Impulse Control Disorder. Following a program of research describing the substantial overlap between patients with gambling problems and substance use disorders, in neurocognitive functioning and neurobiological sequelae (see Potenza 2006), the condition—now termed "gambling disorder"—was recently reclassified in the *DSM-5* (American Psychiatric Association 2013) into the "Substance-Related and Addictive Disorders" category. As such, gambling disorder has become the first recognized "behavioral addiction" (Clark 2014). The third section summarizes recent data on this biomedical approach to problem gambling as a form of addiction, and highlights some of its shortcomings. We note, for example, that there are no accepted biomarkers for addictions (as for other mental disorders) (Hall and others 2015). Gambling involvement also exists on a continuum from casual, recreational gambling to severe gambling disorder, and gamblers who do not meet full diagnostic threshold can nevertheless experience significant gambling-related harms (Toce-Gerstein and others 2003).

These kinds of arguments have nurtured a public health approach to gambling that emphasizes the need for a range of strategies with the objective of reducing the harms associated with a behavior (Korn and Shaffer 1999). In describing the causes of these harms, the public health framework highlights the complex interactions between individual vulnerabilities and the product that is used or abused (e.g., gambling or drugs of abuse). In the case of gambling, we refer to this as the interplay between "the gambler and the game," or "the player and the product." In our opinion, this formulation represents a step forward from the narrow biomedical approach (the "brain disease model"), which focuses predominantly on the individual vulnerabilities (see also Schüll 2012). Certainly, there is overwhelming evidence that such vulnerabilities exist, such that two individuals can undergo a similar degree of gambling exposure, but only one develops a gambling problem—the risk of developing addiction is not a "level playing field" (Heyman 2010). At the same time, two dispositionally similar individuals may play two different forms of gambling (e.g., a lottery vs. a modern electronic gambling machine [EGM]), and again, only one individual might develop a gambling problem, highlighting the potential influence of the specific game. In research on gambling and gambling addiction, the neuroscience of the games themselves has received limited attention. The fourth section of the article will review the evidence that some forms of gambling have a higher addictive potential, concentrating on the case of EGMs, which have received the most empirical scrutiny to date. The final section will consider the cognitive neuroscience underlying the psychological properties ("structural characteristics"; Griffiths 1993) of these games, with the aim of outlining the neural bases of the player–product interaction.

Risk, Reward, and the Brain

Much of the evidence supporting gambling disorder as a behavioral addiction came from research comparing problem gambling to substance use disorders. Drugs of abuse act on neural circuitry that is normally tuned for signaling and predicting reward. This network is colloquially termed the "brain reward system," comprising the medial and orbital aspects of the prefrontal cortex (PFC), ventral striatum (VS), dopaminergic midbrain, and affiliated regions including the amygdala and insula (see Haber and Knutson 2010). The dominant model posits that by driving this circuitry in a way that is markedly more potent than natural rewards, drugs of abuse act to "hijack" this system (Clark 2014; Wise 2004).

The involvement of the medial and orbital PFC was recognized initially from examination of neurological case studies with damage to this region, who display marked changes in decision making, impulse control, and social behavior (Damasio 1994). These changes have some curious parallels with problem gambling (Cavedini and others 2002) and indeed problem gambling has been described as a secondary consequence of ventromedial PFC pathology (Manes and others 2010). The influential "somatic marker" framework for decision making emphasizes connectivity between the ventromedial PFC and the amygdala (Bechara and others 1999). During real-time experiences, the amygdala codes emotional valence to "primary inducers," such as the appetitive response to winning a horse race bet. The ventromedial PFC retrieves these emotional associations during subsequent decisions, for example, the memory of the excitement felt when winning a horse race bet will bias decisions taken on the next visit to the racetrack. This emotional input further includes a bodily component, communicated to ventromedial PFC via the interoceptive functions of the insula (Bechara 2003).

Recent work has complimented a neuropsychological approach to decision making with an economic perspective that presents "utility" as a common currency for judging the relative desirability of different goods. Meta-analysis of functional MRI studies illustrates how these "valuation" signals are represented in ventromedial PFC, with overlapping responses across tasks that varying

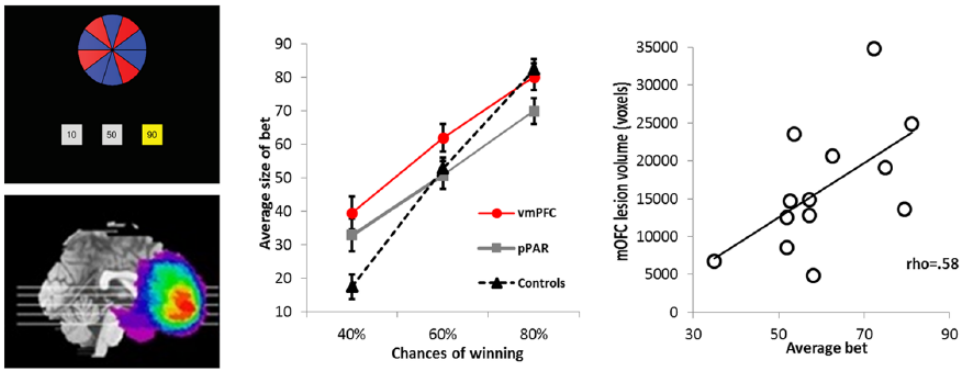

Figure 1. On the roulette betting task, the participant views a roulette wheel with 10 blue and red segments. Blue is automatically designated as the winning color, and the number of blue segments varies systematically across trials (likelihood of winning: 40%, 60%, 80%). On each trial, the participant must select between three available bets (10, 50, 90 points). Patients with damage to the ventromedial prefrontal cortex (vmPFC, n = 13; lesion overlap shown with red indicating damage across all 13 cases) placed higher bets than control participants. Both vmPFC and patients with damage to posterior parietal cortex (pPAR) showed diminished sensitivity to the level of uncertainty. Within the vmPFC group, volume of damage within the medial portion of the orbitofrontal cortex was positively correlated with the average bet on the task. Data from Studer and others (2015).

multiple decision parameters including basic preference, uncertainty, the delay to reward, and effort (Bartra and others 2013; Levy and Glimcher 2012). Such data implicate the ventromedial PFC in the "decision" phase of the gambling cycle. Using tasks that specifically capture betting decisions within a gambling context, ventromedial PFC is recruited during relatively higher stakes bets in healthy volunteers (Studer and others 2012), and patients with focal damage to ventromedial PFC show elevated betting tendencies (Clark and others 2008; Studer and others 2015; see Fig. 1). Comparable effects are described in problem gamblers as well as in patients with alcohol dependence (Lawrence and others 2009). Nevertheless, other brain regions likely contribute to this kind of decision making: patients with damage to the insula (Clark and others 2008) and posterior parietal cortex (Studer and others 2015) also showed changes in betting behavior, primarily in the adjustment of bet size in response to changing reward probability.

The role of the VS is more linked to the processing of the anticipatory phase and outcome of reward-based decisions, mediated by the ascending dopamine projection from the ventral tegmental area. Electrophysiological recording from dopamine cells in this pathway during appetitive Pavlovian conditioning illustrate how these neurons initially fire (at outcome) to unexpected rewards. Over the course of learning, their firing tracks back in time to conditioned stimuli that predict the rewarding outcome (Schultz and others 1992). These cells continue to fire to "prediction errors" when there is a mismatch between the expected and delivered outcomes (Schultz and others 1997): phasic dopamine activity increases to unpredicted reward (a positive predictive error), is unchanged to expected reward, and is actually depressed when an expected reward is withheld (a negative predictive error). Translational research in humans using a wheel-of-fortune gambling task in combination with functional MRI showed that the hemodynamic response in VS tracked the relative magnitude of monetary rewards (Breiter and others 2001). The Monetary Incentive Delay task developed by Knutson and colleagues demonstrates activity in the same region during reward anticipation (Knutson and others 2001). In this capacity, VS responds to both unexpected rewards and conditioned stimuli that predict the imminent delivery of reward.

It is thought that these VS signals in functional MRI at least partly reflects changes in dopamine neurotransmission. Indeed, dopamine release measured using positron emission tomography (PET) with the [^{11}C]raclopride ligand was significantly correlated with fMRI activation of dopaminergic midbrain nuclei during the anticipation of monetary reward (Schott and others 2008). Using high-resolution fMRI optimized to these subcortical responses, both VS and the ventral tegmental area were significantly activated following unexpected monetary rewards (D'ardenne and others 2008).

The insula may contribute to this processing in two distinct ways. With a crucial role in interoception (i.e., awareness of bodily states), the anterior insula is posited to represent the subjective experience of emotional responses, both appetitive and aversive (Craig 2009). Gambling is known to be highly physiologically arousing, and as such, the insula should be recruited in the sensory processing of these visceral signals. The insula plays

a further role in representing the risk of decisions; for example, using fMRI, bilateral insular responses scaled linearly with the degree of risk on a trial, as informed by the participant's past experience on the task (Preuschoff and others 2008). Our observation that patients with focal insular lesions are less sensitive to the degree of uncertainty in a gambling task (Clark and others 2008) supports the assertion that the insula plays a necessary role in guiding risk-sensitive decision making. Whether these interoceptive and decision-making functions of the insula are dissociable, or whether the role of the insula in physiological and affective signaling underlies its involvement in risk processing, remains an open question (Singer and others 2009).

Gamblers' Brains

Having described the neural circuitry that underlies gambling-related decision making, we can next investigate whether pathophysiology in this circuitry distinguishes those who develop gambling disorders from those who do not. The biomedical model asserts that a neurobiological abnormality of either genetic or environmental origin predisposes some individuals to react to gambling exposure with escalating, uncontrolled play (Schüll 2012). In support of this argument, genetic variations affecting dopamine transmission in particular show altered frequency in groups of problem gamblers (Lobo and others 2014). Brain imaging studies indicate characteristic changes in the brain reward circuitry outlined above (Miedl and others 2012; Reuter and others 2005). Trait impulsivity—the tendency toward unplanned or hasty responses that often result in poor outcomes and negative consequences—is an important component of this liability. Groups of problem gamblers display increases in behavioral measures of impulsive responding and impulsive decision making (Lawrence and others 2009), as well as on self-report impulsivity scales (Michalczuk and others 2011).

There are at least two qualifiers to this liability. First, the vulnerability for problem gambling appears to be a generalized disposition that is also associated with the risk of developing substance use disorders, and most likely a range of other risky behaviors. In a twin study, 64% of the estimated genetic liability for gambling disorder was shared with alcohol dependence (Slutske and others 2000), and the clinical comorbidity between problem gambling and substance use disorders is high (Petry and others 2005). Prospective studies demonstrate that impulsivity predates the development of both gambling and substance-related problems (Slutske and others 2005; Slutske and others 2012). As a second (albeit related) point, this generalized vulnerability is continuously distributed throughout the population: single individuals cannot be categorically identified as "at risk" or "not at risk"; rather there is a varying level of disposition.

Within cognitive neuroscience, a major program of research has used fMRI in combination with increasingly sophisticated gambling simulations, to elucidate pathophysiology in the core decision-making circuitry described in the second section. A number of influential studies have reported *hypo*-activity in the VS and ventromedial PFC, primarily during the anticipation and receipt of monetary rewards (Balodis and others 2012; Reuter and others 2005; Sescousse and others 2013). These observations are consistent with a reward deficiency syndrome that is posited to drive the continual engagement in high-stimulation, risky behaviors (Hommer and others 2011; Leyton and Vezina 2012). Conversely, an increasing number of studies also describe *hyper*-activity within the exact same regions, implying some sensitization of the reward system (Miedl and others 2012; Van Holst and others 2012). The experimental factors that moderate these effects are unclear at the present time, but likely include the task's ability to temporally separate decision-, anticipation-, and outcome-related brain responses (Van Holst and others 2012), and the degree to which the task draws on realistic gambling cues (Sescousse and others 2013).

Other work has focused on the neurochemistry of problem gambling. Here, the dopamine system has been investigated most extensively, inspired in part by the well-documented syndrome in Parkinson's disease, where problem gambling has been described as a side-effect arising from treatment with dopamine agonist medications (Gallagher and others 2007). Patients with substance use disorders also show robust reductions in dopamine D2/D3 receptor availability in the striatum, using [^{11}C]raclopride PET imaging (Nutt and others 2015; Volkow and others 2001). In problem gamblers, no such differences in dopamine D2/D3 receptor binding have been observed, across four independent studies (Boileau and others 2013; Clark and others 2012; Joutsa and others 2012; Linnet and others 2011). Some of these studies did observe individual differences, such that reduced dopamine receptor levels were correlated with mood-related impulsivity (Clark and others 2012; see Fig. 2) and gambling severity (Boileau and others 2013), which again reinforces the continuous nature of these putative neurobiological markers.

PET imaging can also be used to quantify amphetamine-induced dopamine *release*. A recent study using the alternative dopamine (D3-preferent) tracer [^{11}C]PHNO showed compelling increases in striatal dopamine release in problem gamblers, as well as positive correlations between dopamine release and gambling severity (Boileau and others 2014). Similar protocols in stimulant users have described an "attenuation" of

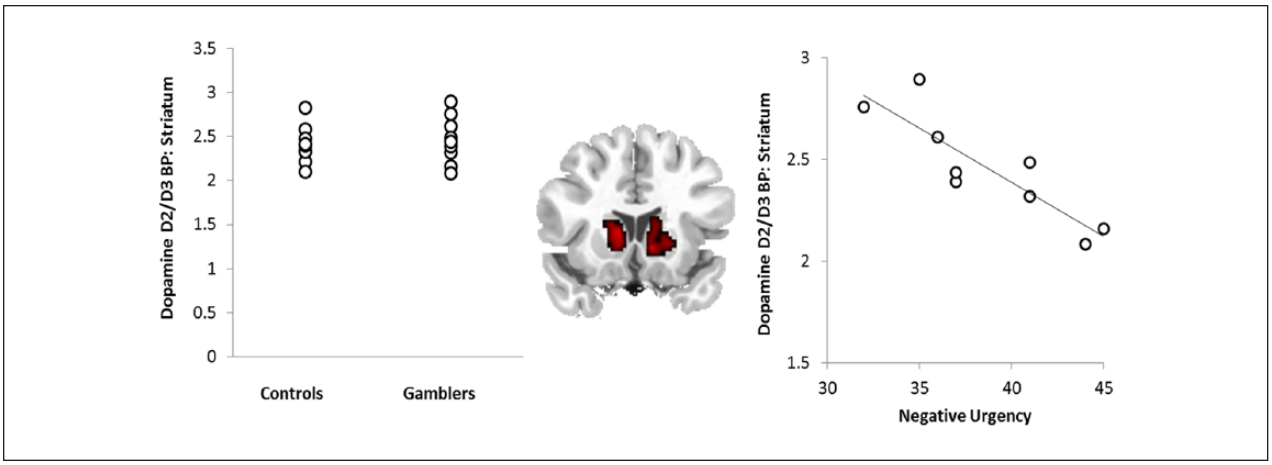

Figure 2. Using positron emission tomography with the [11C]raclopride ligand, nine males with problem gambling were compared against nine healthy males. There were no group differences in dopamine receptor binding in the overall striatum, or striatal subdivisions, but within the group of gamblers, dopamine receptor binding was negatively correlated with self-report measures of mood-related impulsivity (shown for Negative Urgency, on the UPPS-P). The central figure shows the voxel-wise correlation between the regression of Negative Urgency against raclopride binding, showing (negative) correlations in right ventral putamen and bilateral caudate. Data reprinted from Clark and others (2012).

dopamine release (Martinez and others 2009; Volkow and others 1997). Thus, in this instance, there is an intriguing disparity between the profiles observed in problem gamblers and drug addiction, which raises the further possibility that some of the effects described in substance use disorders may be induced by long-term drug exposure.

The main conclusion to draw from this extensive body of research on the neurobiology of problem gambling is that group differences are apparent between problem gamblers and non-problem gamblers, and consistently implicate the core circuitry underpinning reward-based decision making. However, any vulnerability appears to be general across many risky behaviors (besides gambling) and is highly distributed. This raises a critical question of how this vulnerability leads to gambling disorder: besides the obvious requirement for environmental exposure, how might the psychological properties of specific games interact with these dispositional variables and underlying neural substrates? Approaching this question with a more even-handed interest in both the player and the product may also help resolve some of the discrepancies in the neuroimaging literature as to when hypo- versus hyper-activity should be observed within the brain reward system.

Are All Forms of Gambling Equal in Addictive Potential?

It is widely accepted that drugs of abuse vary in their capacity to promote dependence in regular users. These "capture rates" are higher in epidemiological data for tobacco users (31.9%) compared with cocaine users (16.7%), which, in turn, are higher than in cannabis users (9.1%) (Anthony and others 1994). Of course, drugs of abuse vary widely in their pharmacological actions. Is it possible that different forms of gambling also vary in their potential for harm? Lotteries are consistently found to be the most prevalent form of gambling but are less related to problematic engagement than various other forms (Short and others 2015). EGMs, by contrast, show lower rates of overall engagement in the general population but appear more associated with problematic use. For example, in individuals seeking treatment for problem gambling, EGMs rank highly in the preferred and/or problematic form of gambling (Meyer and Hayer 2005; Michalczuk and others 2011). When EGMs were removed from all Norwegian gambling establishments in 2007, rates of gambling-related problems dropped considerably, with little evidence of substitution toward other available forms (Lund 2009). Other work describes an accelerated trajectory from beginning regular EGM play to meeting diagnostic criteria for problem gambling disorder in EGM gamblers (mean 1.1 years) compared with non-EGM gamblers (mean 3.6 years) (Breen and Zimmerman 2002). Whereas these strands of research support the addictive potential of EGMs, critics point out that these studies do not constitute definitive proof of a causal link (Blaszczynski 2013; Dowling and others 2005).

The popular forms of gambling vary along a number of important psychological dimensions that may determine this apparent potential for harm. One variable is the pace of play (Griffiths and Auer 2013). Lotteries, by

their nature, enforce delays (often of several days) between purchasing a ticket, finding out the results of the draw, and being able to purchase a ticket for the next draw. EGMs, in contrast, are continuous games that allow rapid play and the ability to initiate the next bet immediately. Pace of play is one of many distinguishing features of EGMs. Movement from analog technology to a computerized game format has enabled the incorporation of an array of further game features that optimize the schedules of reinforcement and sensory feedback properties in order to keep gamblers playing. The sections below consider four psychological features of gambling games, which are each present in modern EGMs, and which have begun to be examined in relation to their effects on underlying brain reward circuitry.

The Variable Ratio of Reinforcement

Central to the function of slot machines is the manner in which wins are delivered randomly on a small proportion of plays. Traditional accounts of this Variable Ratio schedule highlight the exceptional persistence of such responding (see Skinner 1953). Skinner (1963) once remarked that gamblers and dedicated scientists may both persist ad infinitum in pursuit of such exceptionally rare events as slot machine jackpots or breakthrough scientific discoveries. How does the brain respond to unpredictable rewards? In a [^{11}C]raclopride PET study in healthy volunteers using a card selection game with monetary rewards, there was a significant increase in dopamine release in left medial caudate in the variable ratio condition (Zald and others 2004), with no change in a fixed ratio condition where the same overall amount of reward was delivered.

Converging results come from electrophysiological work on non-human primates. In addition to midbrain dopamine neurons coding unexpected rewards in phasic burst firing, the tonic firing rate of these cells varies with uncertainty. In a Pavlovian conditioning task, Fiorillo and others (2003) found that these sustained responses were highest under conditions of maximal reward uncertainty, when the probability of reward delivery following the conditioned stimulus approached chance levels ($P = 0.5$). It is, perhaps, no coincidence that reinforcement schedules that produce greater dopamine release in the reward network are the same ones found in slot machines. In instrumental responding tasks where the true contingency between the behavioral response and a desired outcome is held at zero, healthy volunteers also reliably overestimate their degree of control, and these judgments are heightened in problem gamblers (Orgaz and others 2013). This "illusion of control" in relation to EGM play is considered further below.

Near-Misses

Near-misses, perhaps better called "near wins," occur across most if not all gambling situations, when a favorable outcome is nearly achieved, but falls just short. In a slot machine, a near miss would occur if the first two jackpot symbols lined up on the pay-line, and the third match narrowly missed the pay-line. Electronic forms of gambling enable the controlled delivery of near-misses (Harrigan 2008) as well as opportunities for novel types of near-misses (e.g., bonus features, see Parke and Griffiths 2006), and the empirical research on these events is mostly in the context of slot machine gambling. A moderate rate of near-misses was seen to encourage persistent slot machine play (Côté and others 2003; Kassinove and Schare 2001). In a simplified slot machine task, near-misses also increased the subjective motivation to continue gambling, compared with "full-miss" events (Clark and others 2009). Translating these data to the cognitive neuroscience realm, near-misses elicited significant signal change in VS and anterior insula—areas that were also recruited by the jackpot wins on the task (Clark and others 2009) (see Fig. 3). As such, reward-related brain responses can be driven by this game feature in the absence of objective reinforcement. This finding has been replicated in a number of subsequent studies, and brain responses to near-misses have been shown to scale positively with symptoms of problem gambling (Chase and Clark 2010; Dymond and others 2014; Shao and others 2013). The ingenious study by Shao and colleagues also manipulated past experience with the slot machine game: participants with extended practice showed enhanced activation in reward-related regions to the anticipatory reel spins, and decreased activation to the spin outcomes, consistent with the transfer of dopamine cell firing from the unconditioned stimulus to the conditioned stimulus in electrophysiological studies (Schultz and others 1992).

A recent study in patients with focal brain injury highlighted a causal role for the insula in coding near-miss events (Clark and others 2014) (see Fig. 4). Patients with lesions affecting the insular region failed to show the typical motivational response to near-miss outcomes, compared with groups of patients with damage to the amygdala or ventromedial PFC. On a second task involving a long series of red/black decisions on a roulette wheel, patients with insula damage also showed an abolition of the Gambler's Fallacy effect, wherein players are less likely to choose either color following apparent runs of that outcome (e.g., red, red, red, red, ____). The absence of these two gambling-related "cognitive distortions" following insula damage mirrors other data in nicotine dependence: smokers who sustained insula damage via a stroke were more likely to quit smoking compared

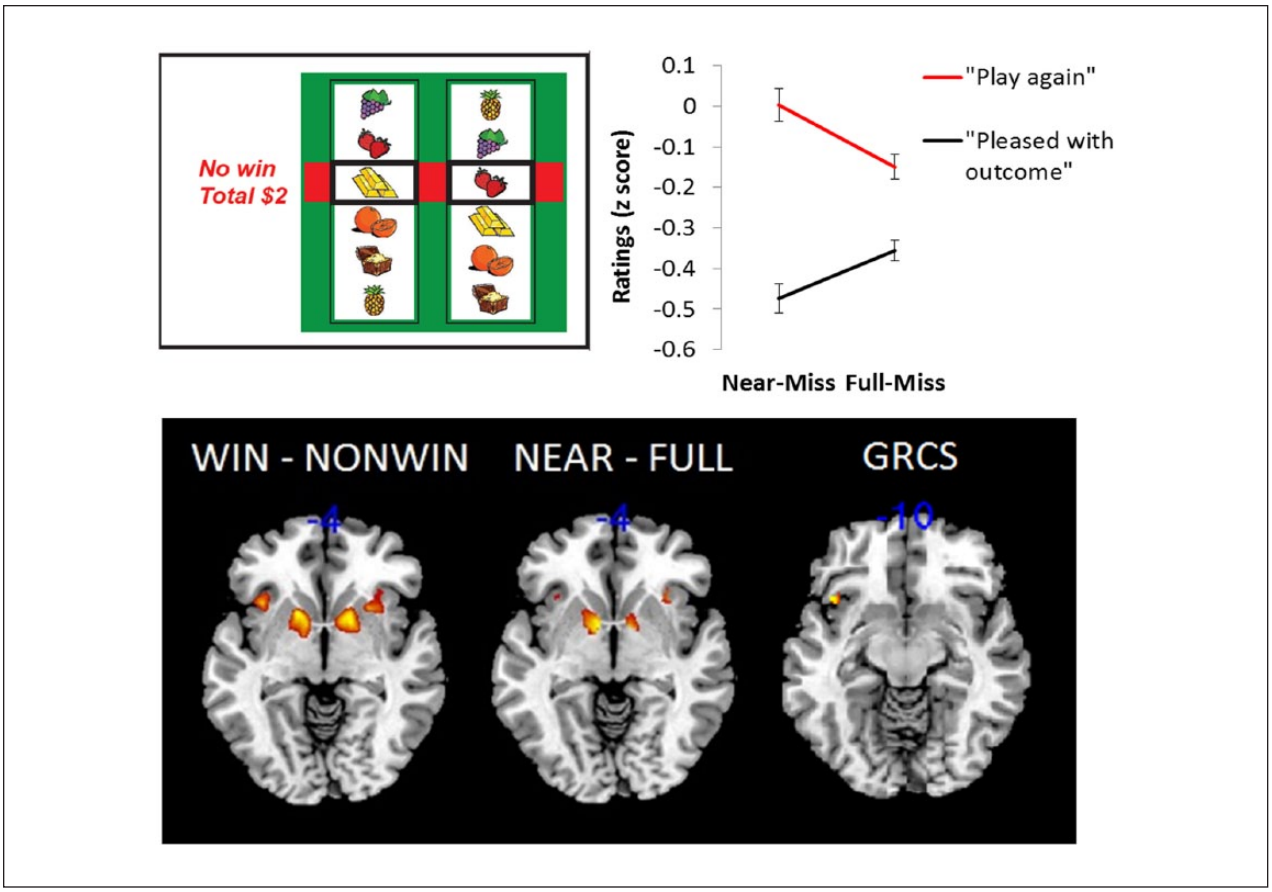

Figure 3. On the two-reel slot machine task, a win was signaled if the two reels aligned, and if the right reel stopped one position from a match (as shown), this was considered a near-miss. Trial by trial ratings in healthy participants (n = 40) indicate that near-misses (compared to full-misses) were experienced as unpleasant but increased the motivation to continue to play the game. Using functional MRI in 15 participants, the contrast of a monetary wins against all non-win outcomes was associated with significant signal change in ventral striatum and anterior insula (left). In these win-responsive regions, the contrast of near-misses and full-misses (two objectively equivalent events) was associated with significant activity to near-misses (middle), and the brain response to near-misses in anterior insula was predicted by higher scores on a trait gambling scale, the Gambling-Related Cognitions Scale (right). Data reprinted from Clark and others (2009).

with cases with strokes elsewhere in the brain, and purportedly experienced a loss of the urge to smoke (Naqvi and others 2007). Given that gambling near-misses and drug cravings both involving substantial physiological activation, these effects may be driven by the insula's established role in interoceptive processing (Craig 2009) and generate a clinical prediction that hyper-activity of the insula may underlie the susceptibility to gambling-related distortions in problem gamblers.

Losses-Disguised-as-Wins

The advent of multiple pay-lines in modern slot machines opened the door to a number of new game features. Instead of solely aiming to line up symbols across a single central pay-line, players can now place concurrent bets across numerous pay-lines that include diagonal and zig-zag configurations. One consequence of this feature is that players can win back an amount of money that is less than the total amount that was wagered on that spin. For example, a player could bet 10 cents across 20 pay-lines for a total of $2.00 wagered. They may then find that they have won $0.50 because one of their 20 pay-lines produced a win. Critically, this net *loss* of $1.50 triggers win-related feedback from the machine, including joyful melodies, flashing lights, and the sight of money counting up in the "cash remaining" window. These events are known as "losses-disguised-as-wins" (LDWs) because they obscure the fact that money has been lost on a given bet.

Behavioral research indicates that the majority of gamblers prefer this multiline style of play to the traditional one-line games (Templeton and others 2014). Following games with a high rate of LDWs, gamblers

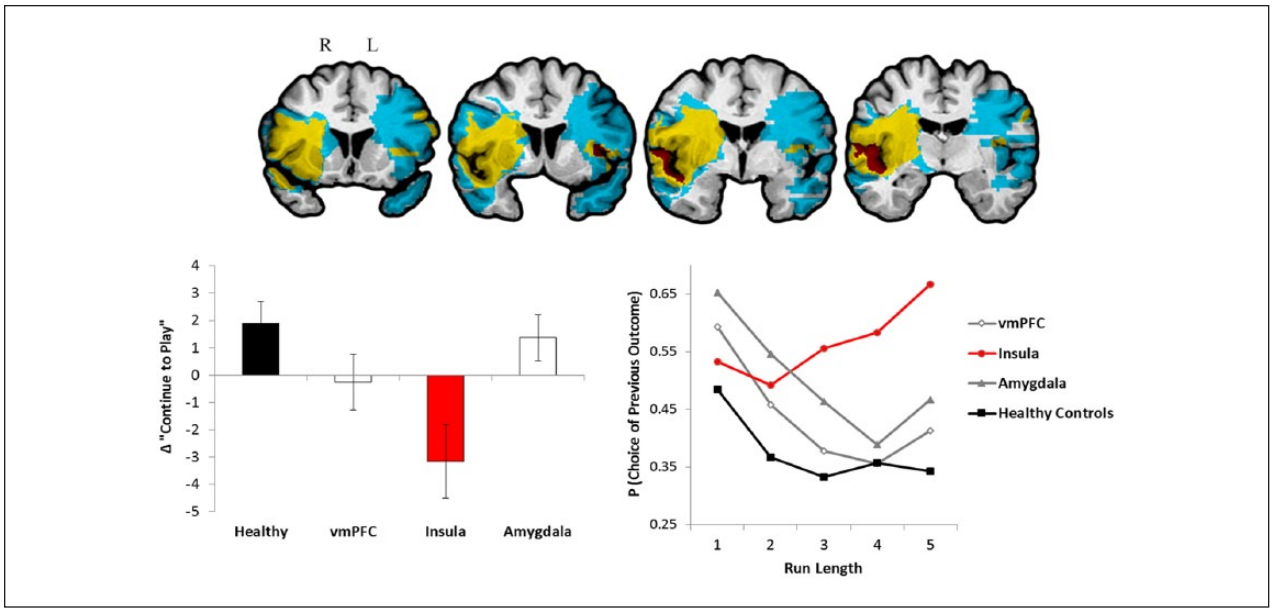

Figure 4. Effects of insula damage on gambling-related cognitive distortions. The coronal slices show lesion overlap in the insula group; e.g. in the right insula cases, red indicates the overlap (in insula) across all 4 cases. Participants gave trial-by-trial ratings of their motivation to continue. The bar chart (left) displays a change score (Δ) for this motivational ratings following near-misses compared to "full-misses": the well-replicated increase in motivation following near-misses was abolished in the group with insula damage. In the roulette task (right), participants made 90 consecutive red/blue predictions: the "gambler's fallacy" is seen as a decrease in the likelihood of choosing either color as a function of the preceding run length of that color. This effect was also absent in the group with damage to the insula region. Data reproduced from Clark and others (2014).

tend to overestimate the number of actual wins that were received (Jensen and others 2012). These events also drive significant responses in the sympathetic nervous system, assayed via skin conductance responses: the increase following LDWs is comparable to that following a real win, and scales closely with the amount "won" (Dixon and others 2010; Dixon and others 2014). These psychophysiological effects to LDWs were abolished when auditory accompaniment to the LDWs was muted (Dixon and others 2015). This result implies that the sensory feedback ordinarily associated with gambling wins has become sufficient to drive conditioned physiological responses, even when money is actually being lost. Research on the LDW effect and the broader impact of sensory features in gambling games is in its nascence and the application of further neuroscience methods is likely to be fruitful.

The Role of Control

As games of pure chance, many forms of gambling nevertheless involve opportunities for a choice or instrumental action, such as selecting one's lottery numbers or throwing a dice. While these behaviors have no objective influence over the outcome, they typically instill a sense of skill or mastery that is termed "the illusion of control" (Langer 1975). In classic examples, craps players expressed a conviction that throwing the dice harder would be likely to roll higher numbers (Henslin 1967), and lottery players refused to exchange a ticket that they had personally chosen for a ticket with an objectively higher likelihood of winning (Langer 1975).

Whereas EGMs are fundamentally games of chance, these games employ a variety of interactive features that may heighten one's sense of control over an outcome. Many games offer a "stopping device," whereby pressing the spin button or touch-sensitive display during the reel-spin acts as a brake to slow the reels' motion. This serves the dual purpose of accelerating the pace of play and creating a sense of skill following win (or near-miss) outcomes (Ladouceur and Sévigny 2005). Many modern EGMs also incorporate exhilarating, arcade-style bonus games on additional screens, which often involve skill-based devices such as shooting a plastic gun at a moving target. While these activities are accounted for in the overall-negative "payback percentage" of their machines, it is likely that they also foster illusory control.

Perceived control over an outcome substantially shapes brain responses. In a seminal study, caudate responses to appetitive outcomes were selectively observed in a condition where those outcomes were contingent on participants' button presses (Tricomi and others 2004). In

extending this story from objective contingency to "perceptions" of control, a recent fMRI study showed that VS responses to rewarded outcomes were greater following an initial decision between two response keys, even when the choice was randomly associated with trial success (Leotti and Delgado 2014). Another study used a control manipulation where the participant's choice between three gambles was either approved or vetoed by the computer: medial PFC and posterior cingulate were sensitive to (illusory) control, although striatal regions were not (Kool and others 2013).

Conclusions

This article has contrasted two contemporary approaches to underlying the harmful and potentially addictive aspects of gambling behavior. The biomedical approach posits a brain basis to gambling disorder, where individual vulnerability factors predispose certain individuals to develop a gambling problem. As we have described, significant scientific inroads have been made over the past decade in describing this brain basis, with respect to genetics, neurochemistry, and functional brain systems. A dopamine-innervated brain network comprising VS, ventromedial PFC, dopaminergic midbrain, and insula is recruited during gambling-related decision making and shows evidence of dysregulation in problem gamblers. However, the biomedical approach has been narrowly construed by some as implying that the clinical consequences of gambling are *confined* to a small minority of consumers who are biologically disposed to excessive involvement. This interpretation is sometimes taken as implying that the specific forms of gambling are irrelevant; that is, vulnerable individuals would develop a gambling problem regardless of their precise game preferences (Schüll 2012). However, the available data indicate that vulnerability markers for problem gamblers are generalized markers that convey liability to many risky behaviors, including substance use disorders. This liability is also fully continuous such that the *majority* of the population appear to have *some level of* vulnerability, which becomes manifested as disorder through exposure to the gambling product (effectively, a diathesis-stress model).

A public health approach to problem gambling embraces this more even-handed balance between "the player and the product", recognizing that gambling harms arise through the interaction of individual vulnerabilities (including those of neurobiological origin) with the effects of the gambling game (Korn and Shaffer 1999). By this account, the game is far from an irrelevant or benign "portal" for the development of problem gambling. Ascertaining the addictive potential of different forms of gambling has proven challenging (Blaszczynski 2013); perhaps even more so than for drugs of abuse where intoxication and fatalities are directly quantifiable in relation to pharmacological doses (Nutt and others 2007). Nevertheless, to illustrate the differences between forms of gambling, we summarized evidence that EGMs fall among the most harmful forms of gambling. Ultimately, it is the psychological properties of these games that dictate their addictive potential (Griffiths and Auer 2013). We have concentrated on four psychological properties that are evident in EGM play—the reinforcement schedule, the delivery of near-misses, the phenomenon of the "loss disguised as a win," and the opportunity for irrelevant control—and considered research from decision neuroscience showing that in the healthy brain, these factors also modulate brain activity within the same core reward circuitry.

Building on this separate characterization of the individual vulnerabilities and the multifaceted effects of the games themselves, the next step is to describe the *interplay* between these components. To what extent do individual differences exist in the susceptibility to specific game features (Chase and Clark 2010, Shao and others 2013)? Do these individual differences predict the future development of problem gambling? How do the neurobiological effects of these game properties vary within an individual, in the transitional stages from non-gambling to recreational gambling, or from controlled to uncontrolled gambling? And to what degree can the addictive potential of gambling games be related to single features versus a combination of features, such that the harms for a given form of gambling (e.g., EGMs) may exceed the sum of the parts?

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