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IMPULSE CONTROL DISORDERS (D MCGRATH, SECTION EDITOR)

Examining Neural Reactivity to Gambling Cues in the Age of Online Betting

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Abstract

Purpose of Review The goal of this review is to provide new insights as to how and why functional magnetic resonance imaging (fMRI) research on gambling cue reactivity can contribute to significant progress toward the understanding of gambling disorder. After having offered a detailed description of experimental paradigms and a comprehensive summary of findings related to gambling cue reactivity, the present review suggests methodological avenues for future research.

Recent Findings The fMRI literature on problem gambling has identified the main neural pathways associated with reactivity to gambling cues. Yet, the current knowledge on the key factors underlying cue reactivity in gambling is still very incomplete. Here, we suggest that the recent expansion of online sports betting calls for a new line of research offering a fine-grained and up-to-date approach of neural cue reactivity in gambling disorder.

Summary Experimental designs that investigate individual-specific and study-specific factors related to sports betting have the potential to foster progress toward efficient treatment and prevention of gambling disorder.

Keywords fMRI · Cue reactivity · Addiction · Gambling disorder · Sports betting

Introduction

Gambling is on the rise [1, 2]. Not only is it possible to engage in such activity at any time and place, but the omnipresence of gambling-related cues (e.g., advertising, cellphone notifications, witnessing others' thrilling experiences) constantly promotes gambling temptations [3–6]. With this around-the-clock availability and omnipresence of cues, the evolving landscape of (online) gambling and betting raises important public health questions (e.g. [2, 7, 8•]).

Neural reactivity to addiction-related cues, as assessed with functional magnetic resonance imaging (fMRI), has repeatedly been identified as a key biomarker of disorder severity, treatment outcome, and relapse risk in cocaine, alcohol, and nicotine use disorder (e.g., [9, 10]). In this paper, we propose that in a context where online gambling opportunities are blooming, research on gambling cue reactivity could also offer a fertile ground to advance current knowledge about the cognitive and motivational determinants of gambling disorder. To reach this objective, we first present an overview of the learning processes and brain pathways underlying cue reactivity. Then, we comprehensively describe the main cue reactivity paradigms traditionally used in fMRI studies to examine cue reactivity in problem gamblers, before detailing findings from these imaging studies. Finally, by taking into account the main strengths and weaknesses of past methods and findings and capitalizing on previous model-based reviews on neural cue reactivity in substance use disorder [9–12], we identify and characterize the factors that should guide future directions for fMRI studies on gambling cue reactivity.

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BOX 1. A chronological synthesis of the fMRI literature on neural cue reactivity to gambling cues

- 2003: Potenza et al. [40]. fMRI was used to examine the brain correlates triggered by the viewing of videos related to gambling, sad or happy scenarios in a sample of PrGs and a group of healthy controls (HCs). The scenarios were being played by actors talking directly to the camera to increase participants' immersive experience. Another strength of Potenza et al. [40] design is that each type of video was divided into three temporal epochs of interest. Specifically, the gambling video started with an individual describing a stressful situation, such as problem at work or at home (i.e., first epoch of interest). Then, the video depicted the individual driving to and entering a casino, obtaining chips, going to a table, emphasizing the excitement (i.e., second epoch of interest). Lastly, the gambling video described the "rush" and "thrill" triggered by the action of gambling (i.e., third epoch of interest). The sad and happy videos were made so that it progressively increased emotional responses of the participants, with epochs of interest corresponding to either the initial, middle and final period of viewing.

This procedure allowed Potenza et al. [40] to observe different patterns of brain activation between PrGs and HCs across the temporal epochs. Specifically, during the initial period of viewing of the gambling scenarios, PrGs displayed decreased brain activity in the lateral orbitofrontal cortex, the caudate nucleus, basal ganglia and thalamus. No difference was observed for the happy and sad videos. By contrast, during the middle period of viewing, PrGs exhibited increased activity within the cuneus and middle occipital gyrus for the gambling videos, and within the VS and posterior OFC for the happy videos. In the final period of viewing, PrGs displayed decreased activity within the for the gambling videos and within the superior frontal gyrus for the sad videos.

As a whole, findings from Potenza et al. [40] suggest that patterns of neural cue reactivity in PrGs differ according to the temporal dynamics of the action of gambling and of an emotional response. However, one main limitation of these reported findings is that contrast images were computed using uncorrected thresholds (ranging from $p < .001$ to $p < .01$) across the whole brain. Besides, within-group activity maps were not reported. Specifically, within-group activity maps were only used to check and elucidate the nature of the between-group differences, and were examined at a threshold of $p < 0.05$.

- 2005: Crockford et al. [43]. A group of PrGs and a group of HCs viewed nature and gambling-related videos. Three different runs of visual gambling cues were selected and divided into four 30-second segments. The first video run (Casino Gambling Run) displayed individuals gambling in casino settings playing blackjack, craps, roulette, and slot machines/ VLT and receiving cash payouts. The second run (Gambling Venues Run) displayed four 30-second segments of gambling venues involving the exteriors of Las Vegas casinos. The third run (VLT Run) displayed four novel 30-second segments of a VLT being played where viewers could observe the strategies being used. The nature video was also divided into 30-second segments and consisted of wildlife and nature scenes. Subjects' craving for gambling was assessed via a 7-points Likert scale (0 = absent, 7 = maximal) prior to the imaging session and at the end of each run. Importantly, participants were informed that they would have the opportunity to gamble (i.e., play a slot machine game) within the scanner and after all video sequences.

Crockford et al. [43] observed that mean change in subjective craving was significantly in PrGs than in HCs. At the brain level, within-group analyses revealed that PrGs and HCs showed significant activity in several overlapping regions in response to the gambling stimuli, including right inferior and medial frontal gyrus, and bilateral (pre)cuneus, parietal lobule, medial/inferior occipital gyrus, lingual gyrus, and fusiform gyrus. Between-group analyses revealed that PrGs exhibited higher activation in the right medial frontal gyrus, the right inferior frontal gyrus, the right parahippocampal gyrus and left fusiform gyrus. In addition, post-hoc analyses revealed that PrG participants exhibited increased activation in the dorsal visual processing stream (bilateral precuneus and right inferior parietal lobule) in response to viewing a VLT video, whereas HCs activated the ventral visual processing stream (right medial occipital gyrus, right cuneus, right lingual gyrus and left lingual gyrus) when viewing the video depicting gambling venues. No correlation analyses were reported between craving scores and brain imaging data.

- 2008: Potenza et al. [41]. This review paper included supplementary brain imaging analyses on data from past studies from Potenza et al. [41] in PrGs, from Wexler et al. [54] in CDs during gambling or drug video scenarios, respectively, and for the entire period of viewing of the addiction videotapes. These analyses showed increased activity within ACC while viewing addiction-related videos in CDs, as compared to PrGs. Nevertheless, similarly as in Potenza et al. [41], the low sample size (PrG: $n = 10$; HC: $n = 11$) and the uncorrected thresholds of brain imaging analyses the statistical validity of these findings.

- 2010: Goudriaan et al. [44]. This study used a cue-reactivity task where participants were required to press a response button with their left index finger when a face was present in the picture and had to press a response button with their right index finger when no face was present. There was no time limit to answer. The pictures were either neutral, smoking-related or gambling-related. In addition, low-level baseline pictures with arrows pointing to the left or right were presented, and a left or right response had to be given. The participants were either PrGs in treatment for gambling problem, current HSs or HCs. Importantly, PrGs had to be at least one week abstinent from gambling, and HSs had to be overnight smoking abstinent (16-18 hours of abtinentce). Participants filled out the gambling and smoking urge questionnaires before and immediately after fMRI scanning.

This study highlighted that viewing gambling pictures (as opposed to neutral pictures) is related to brain activation in left occipital cortex, bilateral parahippocampal gyrus, right amygdala and right in PrGs relative to HSs and HCs. Importantly, within the PrG group, a positive relationship was found between gambling-related craving (only post-scan scores were used) and activation in the VLPFC, left anterior insula and left caudate head when viewing gambling pictures, as compared to neutral pictures. In addition, Goudriaan et al. [44] observed increased brain activity to smoking cues (VMPFC, rostral ACC and left VLPFC) in HSs with high levels of nicotine dependence, as compared to HSs with lower levels of nicotine dependence (left precuneus, right insula, left middle and superior temporal gyri) and with PrGs and HCs (VMPFC, rostral ACC and left VLPFC). Moreover, higher smoking urge in HSs was associated with increased activity in the VLPFC and left amygdala during viewing of smoking-related pictures versus neutral pictures. Nevertheless, no significant difference was observed between pre-scan and post-scan scores of gambling or smoking urge in PrGs and HSs, respectively.

- 2012: Balodis et al. [42]. This study aimed to examine the association between emotion and motivational ratings and neural cue reactivity. The data was the same as in Potenza et al. [40]. Indeed, another interesting aspect from the task design in Potenza et al. [40] is that participants were asked to rate the intensity of their emotional or motivational responses triggered by the video scenarios of sadness, happiness or gambling. For each scenario, participants were instructed to push a button when they started to feel sadness, happiness or an urge to gamble, respectively. Then, following each video, participants described the quality of their emotional or gambling urge responses and rated them on a 10-points Likert scale. In Potenza et al. [40], subjective reports and brain imaging data were analyzed separately, with the PrG group reporting stronger emotional responses and gambling urges when viewing the gambling scenarios, as compared to the HC group. Therefore, Balodis et al. [42] extended the findings from

Box 1 *Notes. CD* cocaine dependent; *HC* healthy control; *HS* heavy smoker; *PrG* problem gambler; *ROI* regions of interest; *ACC* anterior cingulate cortex; *DLPFC* dorsolateral prefrontal cortex; *DS* dorsal striatum; *MPFC* medial prefrontal cortex; *OFC* orbitofrontal cortex; *PFC* prefrontal cortex; *VMPFC* ventromedial prefrontal cortex; *VLPFC* ventrolateral prefrontal cortex; *VS* ventral striatum

Potenza et al. [40], by examining the association between brain imaging data (according to the three scenario types and to the three epochs of interest) and participants' subjective ratings of the video scenarios.

Balodis et al. [42] observed that correlations between self-reported responses and brain activations were strongest during the epoch corresponding to the middle viewing period, and more robust in PrGs than in HCs for all conditions. During this epoch, subjective ratings of gambling urges in the PrG group were negatively correlated with MPFC activation and positively correlated with middle temporal gyrus and temporal pole activations. Sadness ratings in the PrG group correlated positively with activation of the medial orbitofrontal cortex, middle temporal gyrus, and retrosplenial cortex, while self-reported happiness during the happy videos demonstrated mainly inverse correlations with activations in the temporal poles. However, although this study employed a significance threshold of 0.7 for the correlational analyses altogether with an extent threshold of 25 contiguous voxels for selecting clusters of activation, Type I errors remain an issue due to the high numbers of correlations undertaken (not reported). The use of a single rating of subjective urges to gamble is another caveat, as it does not disentangle levels of gambling urge felt prior and after the viewing of the gambling scenario.

- 2012: Balodis et al. [45]. This study used a "monetary incentive delay task" (adapted from [45]), which consisted of (i) a reward prospect, (ii) a motor-action, (iii) an anticipation phase, and (iv) an outcome phase. In the reward prospect phase, participants (a group of PrGs and a group of HCs) viewed a cue signaling the potential to win or lose money. In the motor-action phase, participants had to simply press a button when a target appeared. Participants won (or avoided losing) money by pressing a button before the target disappeared. In the anticipation phase, participants waited for feedback notifying whether they had won or lost the trial. In the outcome phase, participants received feedback on whether they had won or lost the trial as well as on their cumulative earnings. Task difficulty (i.e., the length of target presentation during the motor-action phase) was based on reaction times collected during a pre-scan practice session, such that participants won on 66% of trials.

During the reward prospect phase (i.e., signaling a potential win or loss), between-groups contrast revealed decreased brain activity in PrGs relative to HCs in the medial PFC, the VMPFC, the insula, the ACC, the left VS, and in the left inferior frontal gyrus. During the anticipation phase (win condition only), PrGs exhibited decreased brain activity in the left VMPFC extending to the VS. PrGs also demonstrated decreased activations in multiple regions of when receiving a monetary win or loss during the outcome phase.

- 2012: Van Holst et al. [48]. This study used a "guessing task" (adapted from [56]), which consisted of three phases: (i) expectation, (ii) anticipation, and (iii) outcome. In the expectation phase, participants (a group of treatment-seeking PrGs and a group of HCs) viewed a cue signaling a probability to receive a monetary reward and had to indicate with a button press whether they expected to win or lose. Then, participants had to wait 4 seconds (i.e., the anticipation phase) to receive a win or loss feedback (i.e., the gambling outcome phase).

In the brain imaging analyses, van Holst et al. [40] merged the expectation and anticipation phase (total epochs length = 6 seconds). Between-group analyses revealed that, as compared with HCs, PrGs exhibited increased activations in the bilateral DS and the left orbitofrontal cortex (OFC) when they expected and anticipated a monetary gain. Importantly, within the PrG group, gambling problem severity was negatively associated right amygdala when expecting and anticipating a monetary gain. van Holst et al. [53] did not report the findings regarding brain activations in the outcome phase.

- 2012: van Holst et al. [46]. This study examined the interaction between gambling cue reactivity and motor response inhibition in PrG. Specifically, a group of treatment-seeking PrGs and a group of HCs performed a Go/No-go task that required to press a button when a certain type of stimulus (neutral, positive, negative or gambling pictures) was shown (Go trials) and to inhibit pressing the button when a neutral stimulus appeared (No-Go trials). Hence, the Go/No-go task consisted of four blocks containing pictures that were positive, negative, neutral, or gambling-related. Because all pictures were neutral in the neutral block, participants were instructed to respond to all neutral pictures, but not to respond when a vehicle was shown in the picture.

van Holst et al. [46] observed higher DLPFC, ACC and VS activations for the gambling cues (i.e., go trials from the gambling block) minus control cues (i.e., go trials from the neutral block) contrast in PrGs, as compared with HCs. Importantly, PrGs were also better than HCs at inhibiting their motor response in blocks featuring neutral pictures (i.e., no/go trials) and gambling pictures (i.e., go trials). Moreover, as compared with HCs, PrGs showed lower activation of the DLPFC and ACC regions during no-go trials (i.e., neutral pictures) of the gambling blocks than during no-go trials of the neutral blocks. One explanation for this result is that this sample of gamblers was recruited from addiction treatment centers, where they received cognitive behavioral therapy. This could have lowered their motivational-approach tendencies when embedded into a gambling context (see also [57]).

- 2012: van Holst et al. [47]. This functional connectivity study relied on the dataset from van Holst et al. [46]. Group interactions showed that during neutral inhibition, HCs exhibited greater functional connectivity between the left caudate and occipital cortex compared with PrGs. In contrast, during inhibition in the positive condition, PrGs showed greater functional connectivity between the left caudate and occipital cortex compared with HCs. During inhibition trials in the negative condition, a stronger functional connectivity between the left caudate and the right ACC in PrGs relative to HCs was present.

- 2013: Sescousse et al. [49]. A group of PrGs and a group of HCs participated to an "incentive delay task" [101]. Each trial consisted of an (i) anticipation, a (ii) discrimination, and (iii) an outcome phase. During the anticipation phase, participants saw a cue announcing the type (either monetary or erotic), probability (0/25/50/75%) and intensity (low/high) of an upcoming reward. In the next phase, participants were asked to perform a visual discrimination task (left button press for a triangle; right button press for a square) within a maximum time of 1 second. Success on this task preserved the participants' chance to obtain the probabilistic reward. In the outcome phase of the rewarded trials, participants saw an erotic image (with high or low erotic content) or a cue mentioning the amount of money won (high or low amount). In addition, following each reward outcome, participants were asked to provide a hedonic rating on a 1–9 continuous scale (1 = very little pleased; 9 = very highly pleased). In non-rewarded and control trials, participants were presented with "scrambled" pictures.

In the anticipation phase, the monetary versus erotic cues contrast revealed an increased response in PrGs relative to HCs in the VS, which appeared largely driven by a reduced sensitivity to erotic cues. Moreover, within the PrG group, the intensity of the differential response to monetary versus erotic cues in the VS was associated with problem gambling severity.

In the outcome phase, between-group analyses highlighted increased OFC activation in PrGs when receiving a monetary gain. Sescousse et al. [49] also examined the modulation of brain activation by the hedonic ratings. For monetary rewards, they found that activity in the VS correlated with hedonic ratings in both HC and PrG participants. By contrast, VS activation in HCs, but not in PrGs, varied according to the hedonic ratings of erotic rewards. This finding suggests that the VS of PrGs failed at encoding the hedonic value of erotic rewards.

- 2016: Kober et al. [50]. This study followed prior work from Potenza et al. [40] and Wexler et al. [54] with participants viewing videos depicting cocaine, gambling, or sad scenarios. As compared to previous work from this research group, this study examined neural cue reactivity in larger

Box 1 (continued)

samples of CDs, PrGs and HCs. Participants viewed six videos depicting cocaine, gambling, and sad scenarios presented in a counter-balanced order. After each video, participants were asked to rate their urge to use cocaine or to gamble on a 1–10 scale (1 = not at all, 10 = a lot). Each functional run was divided into two periods of video viewing: the initial 45 seconds of video viewing (to examine the emergence of craving/emotional responses), and the final 45 seconds of video viewing (to examine more developed or protracted craving/emotional responses).

Between-group analyses related to in-scanner subjective ratings revealed that CDs reported highest cocaine urges in response to cocaine videos and PrGs reported highest gambling urges in response to gambling videos. Neuroimaging data revealed that the initial period of video viewing activated the ACC and VMPFC, and predominantly to cocaine videos in CDs. In the last period of video viewing the DLPFC and the dorsal ACC were most strongly activated for cocaine videos in CDs, gambling videos in PrGs, and for sad videos in HCs. No correlation analyses were reported between craving scores and brain imaging data.

- 2017: Limbrick-Oldfield [52..]. In this study, a group of PrGs in treatment and a HC group were scanned while viewing gambling, gambling-matched neutral, food, or food-matched neutral pictures. There were four subtypes of gambling cues: photographs of the shop-fronts of bookmakers, as well as 'action' images from electronic roulette, sports betting and slot machines. For each PrG participant, Limbrick-Oldfield et al. [52..] selected the two forms most relevant to PrGs' personal game preferences, as well as the shopfronts. To control for the potential impact of fasting on neural responses to food and gambling cues, participants were instructed to eat a light meal ~ 2 h before the scan.

Stimuli were presented in a blocked design. Each block contained five images from the same category. Participants were instructed to imagine that they were in the place pictured in each photograph or interacting with the item shown. Moreover, to maintain attention, participants were asked to press a button with each new image. At the end of each block, participants gave a craving rating ("I crave gambling right now") on a 1-9 scale (1 = strongly disagree, 9 = strongly agree). They were also asked to rate their craving to gamble before they entered the scanner.

Within the PrG group, brain imaging analyses on the contrast of gambling minus gambling-matched neutral cues revealed increased activity within the left posterior cingulate gyrus, the left superior frontal gyrus, the left frontal pole and extended to multiple regions including the bilateral VS, MPFC, left angular gyrus and right lateral occipital cortex. For the same contrast, and compared with HCs, PrGs showed increased activity in the left insula, the left frontal operculum, ACC and superior frontal gyrus.

Limbrick-Oldfield et al. [52..] also undertook brain connectivity analyses between the nucleus accumbens and ROI including the PFC, insula and VS. Within PrGs, the contrast of gambling minus gambling-matched neutral cues revealed increased functional connectivity between the nucleus accumbens and the right inferior frontal gyrus. Between-group analyses showed increased functional connectivity, compared with HCs, between the nucleus accumbens and the left insula cortex (extending to left putamen), and the superior frontal gyrus.

PrGs also exhibited higher mean craving scores than HCs after the viewing of gambling-related pictures. PrGs also showed a significant craving increase following gambling cues relative to both neutral cues and rest blocks. At the brain level, for the gambling minus gambling-matched neutral cues contrast, mean craving ratings in the PrG group were associated with greater activity within the right insula, the left central operculum/left insula, the cerebellum, and the ROI mask in the nucleus accumbens. For the functional connectivity analysis, higher craving ratings were associated with reduced connectivity between nucleus accumbens and medial PFC. No region showed a significant correlation with problem gambling severity.

- 2017: Brevers et al. [51]. This study examined whether the viewing of gambling-related pictures impacts on proactive (the restrain of actions in preparation for stopping) and reactive (outright stopping) inhibition. A group of high-frequency poker players, and one group of matched non-gambler controls, performed a modified version of the stop-signal paradigm, which required participants to inhibit categorization of poker or neutral pictures. The probability that a stop-signal occurs (0%, 17%, 25%, 33%) was manipulated across blocks of trials, as indicated by the color of the computer screen.

Behavioral analyses revealed that poker players were faster than controls in categorizing pictures across all levels of proactive motor response inhibition (go trials). Brain imaging analyses highlighted higher dorsal ACC activation in poker players, as compared with controls, during reactive inhibition. Taken together, findings from Brevers et al. [51] suggest that, due to their faster rates of stimulus discrimination (i.e., go responses), poker players might have recruited more cognitive resources than controls when required to stop their response (reactive inhibition). In other words, these findings suggest that frequent gamblers need to trigger additional cognitive resources, when required to stop their motor response, while being embedded in an environment featuring gambling stimuli. Nevertheless, Brevers et al. [51] did not observe any significant effect of stimulus type (control vs. poker-related), at both behavioral and neural levels. This suggests that the observed effects were due to a familiarity bias (e.g., high expertise in discriminating poker cues) rather than to salient-motivational processes.

Box 1 (continued)

Processes Underlying Cue Reactivity

Increased reactivity to addiction-related cues is assumed to result from the activation of specific associative pathways in long-term memory [13]. These associations are built and strengthened gradually through classical conditioning processes, that is, by the learning history of temporal or spatial coactivation between external (e.g., environmental cue) or internal (e.g., affective state) cues and reward consumption effects [14, 15]. In line with this account, the incentive sensitization theory predicts that the repeated pairing of environmental cues with substance consumption leads these cues to acquire increased salience and to capture attention, over and above primary natural rewards (e.g., food, sex; [16–18]). At the cerebral level, a wealth of fMRI studies has shown that the incentive salience of substance-related cues (triggering so-called "wanting") is generated by a large and distributed brain system involving the ventral and dorsal striatum, amygdala, hippocampus, insula, anterior cingulate cortex, orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPFC), as well as sensory, visual, and motor cortices [9–12].

This extended brain pathway likely reflects the complex nature of the interactions between the so-called bottom-up *impulsive* and top-down *reflective* systems. Specifically, the fMRI literature on cue reactivity suggests that the motivational salience carried by substance-related cues may (i) sensitize or exacerbate the activity of the amygdala-striatal "impulsive" system, which generates positive affective associations and fast approach behavior toward addiction-related stimuli and (ii) subvert attention, reasoning, planning, and decision-making resources of the prefrontal "reflective" system to seek and reach rewards. Importantly, substance cue reactivity does

not necessarily lead to weaker or hypoactive cognitive control (as commonly described by dual-process models of addictions; [14, 19, 20]), but instead redirects attention and executive control resources toward goals related to substance consumption [21–24]. In line with this account, triadic models of addiction advance that, under certain circumstances (e.g., homeostatic imbalance, reward deprivation, stress, sleep deprivation), the insular cortex plays a pivotal role in promoting the drive and motivation to get a reward by "hijacking" goal-oriented processes toward addiction-related cues at the expense of inhibitory control resources [25–35]. Taking into account these dynamic patterns of neural cue reactivity is of critical importance for studies that aim at modulating brain processes to decrease subjective states of craving. For instance, Hayashi et al. [36] highlighted that the strong craving elicited by the immediate availability of cigarettes was diminished by transiently reducing DLPFC activity through transcranial magnetic stimulation. This further suggests that brain regions commonly associated with reflective processes do not only support inhibitory control, but more generally modulate mesolimbic value signals up or down based on goals and context.

In the past decade, research has shown that gambling-related cues can foster the development of strong attentional biases and positive memory associations among problem gamblers (for a review, see [37–39]). The pivotal role of incentive salience-related processes in gambling disorder is further evidenced by the fMRI literature on gambling cue reactivity, covered in the next section.

Gambling Cue Reactivity Paradigms in Neuroimaging Research

Box 1 and Table 1 offer a comprehensive account of the experimental paradigms used in fMRI studies to examine gambling cue reactivity. Despite the limited literature in comparison with the one available for substance use disorder (e.g., [53]), a high-diversity of experimental designs been used to examine the neural correlates of gambling cue reactivity. These studies have been undertaken in sub-clinical individuals as well as individuals with severe gambling disorder (collectively referred to here as problem gamblers; PrGs), being either active or abstinent PrGs at testing time, and usually compared with groups of non-gambler healthy controls (HCs; excepted in [40, 50] where a group of PrGs was compared with a group of individuals with cocaine addiction and a group of healthy controls).

Table 1 Overview of fMRI studies on gambling cue reactivity

Study	Sample	Task	Tesla	Software	Statistical threshold
Potenza et al. [40, 41]; Balodis et al. [42]	10 PrG; 11 HC; (9 CD; 6 HC)*	Exposure to gambling, sad and happy videos	1.5 T	Yale	Uncorr; whole brain
Crockford et al. [43]	10 PrG; 10 HC	Exposure to nature and gambling videos	3.0 T	Stimulate	Corr; whole brain
Goudriaan et al. [44]	17 non-smoking PrG under treatment; 18 HS; 17 HC	Exposure to gambling, smoking and neutral pictures	3.0 T	SPM2	FWE; whole brain
Balodis et al. [45]	14 PrG; 14 HC	Monetary incentive delay task	3.0 T	SPM5	FWE; ROI
van Holst et al. [46, 47]	16 PrG under treatment; 15 HC	Go/No go task featuring neutral, positive, negative and gambling pictures	3.0 T	SPM5	FWE; ROI
van Holst et al. [48]	15 PrG under treatment; 16 HC	Guessing task, involving monetary reward	3.0 T	SPM5	FWE; ROI
Sescousse et al. [49]	20 PrG; 20 HC	Incentive delay task, involving monetary reward, sexual reward, and neutral trials	1.5 T	SPM2	FWE; whole brain, ROI
Kober et al. [50]	30 CD; 28 PrG; 45 HC	Exposure to gambling, sad and happy videos	3.0 T	SPM5	FWE; whole brain
Brevers et al. [51]	14 frequent gamblers; 14 HC	Stop-signal paradigm featuring gambling and neutral pictures	3.0 T	FSL/Randomize	TFCE; whole brain
Limbrick-Oldfield [52]	19 PrG under treatment; 19 HC	Exposure to gambling, food and neutral pictures	3.0 T	FSL/Flame	FWE; whole brain, ROI

Notes. Studies between brackets present supplementary analyses and findings from a previously published database. *CD* cocaine dependent, *Corr* corrected for multiple comparisons, *FSL* FMRIB Software Library, *FWE* family-wise error, *HC* healthy control, *HS* heavy smokers, *PrG* problem gamblers, *ROI* region of interest, *SPM* statistical parametric mapping, *uncorr* uncorrected for multiple comparisons TFCE Threshold-free cluster enhancement. *only in Potenza [41]

Similarly to what has been done in the field of substance use disorder (e.g., [9, 12]), a key feature of cue reactivity paradigms is that they expose participants to gambling-related cues, depicting real-life gambling-related situations through auditory and/or visual stimulations [40, 41, 43, 44, 46, 50–52]. These gambling cues are matched either to control cues [41, 43, 44, 46, 51, 52] or to other types of motivationally-salient (e.g., food, smoking) or emotionally-laden (e.g., happy, sad) cues [40, 41, 44, 46, 49, 50, 52••]. In some studies, gambling pictures were customized according to participants' gambling preferences [51, 52••]. Gambling-related pictures were used either as task-irrelevant (i.e., distracting) [44] or as task-related targets during stimulus discrimination task [46]. Several studies instructed participants to picture themselves experiencing the gambling situation [40, 41, 50, 52••] or to passively watch the gambling cues while being informed that they will have the opportunity to gamble after the scanning session [43]. As outlined in Box 1, this high-diversity of methodological approaches likely plays a role in the inter-studies variability of the activation maps reported.

Another important aspect of neural cue reactivity studies is that brain activation patterns were generally correlated with subjective self-reports. In the fMRI literature on gambling cue reactivity, these ratings are supposed to measure gambling-related craving [43, 44, 50, 52••], and/or emotional and motivational responses [40–42, 50]. This type of measure is usually collected after each task run/block [40–42, 50], before the scanning session and after each task block/run [43, 52••], or pre- and post-scanning session [44].

In addition to studies using classical cue reactivity tasks, fMRI was also used to examine the neural correlates of motor response inhibition toward gambling-related cues [46, 47, 51]. This type of studies allowed to identify how effortful and cognitive control processes impact upon neural gambling cue reactivity. Lastly, brain imaging studies also involved cues signaling the occurrence of probabilistic monetary rewards, allowing to probe anticipation-related brain activity [45, 48, 49].

fMRI Evidence of Gambling Cues Reactivity

Findings summarized in Box 1 outline that exposure to (audio)visual gambling cues elicit increased brain activations in individuals with problem gambling relative to non-gambler matched controls. Only Potenza et al. [40] (see also [41, 42] using the same dataset) and Balodis et al. [45] observed diminished neural gambling cue reactivity in PrGs relative to HCs.

One potential explanation for this discrepancy is that, in Potenza et al. [40], both within-subject and between-group contrast images were computed using uncorrected thresholds across the whole brain. Hence, while Potenza et al. [40] provided preliminary evidence of gambling cue reactivity, it cannot be excluded that type I errors occurred due to the relatively lenient statistical threshold used (e.g., [59]). Interestingly, using a similar task design as in Potenza et al. [40], Kober et al. [50] observed opposite results, i.e., increased activation in the dorsomedial prefrontal cortex and dorsal anterior cingulate cortex of PrGs while exposed to gambling-related videos. The larger sample size and the whole-brain-corrected thresholds used in this latter study make the results potentially more reliable. Balodis et al. [45] observed that PrGs exhibit decreased striatal activations when viewing cues indicating potential monetary gains or losses. These findings differ from those obtained by van Holst et al. [48] and Sescousse et al. [49], which highlighted increased patterns of striatal activations when PrGs were exposed to such cues. Nevertheless, the experimental tasks used in these fMRI studies differed according to the level of uncertainty associated with monetary outcomes. Specifically, in van Holst et al. [48] and Sescousse et al. [49], the monetary reward was probabilistic (i.e., explicit win/loss ratio followed by a random draw), which is comparable to a real-life gambling (e.g., [60]). By contrast, in Balodis et al. [45], participants viewed a cue signaling the potential to win or lose money, which was entirely contingent on a button press (i.e., participants had control over the reward delivery process). As such, the decreased pattern of brain activation observed in PrGs by Balodis et al. [45] might be due to less realistic and ecological gambling scenarios (for additional discussions, see [61–63]). This suggests that PrGs attribute high incentive salience toward cues that are intimately related to gambling, but show decreased interest toward cues signaling the availability of a conventional monetary reinforcement. In other words, the processes of incentive salience attribution may be restricted to a narrow set of cues intimately related to gambling (e.g., [64, 65]). However, one should note that this reasoning is based on a reverse inference and should thus be taken with caution.

A central finding of past fMRI studies is the consistent association, within the PrG group, between cue-induced brain activations, disordered gambling symptoms [49], and gambling craving (task-induced craving change [52••]; post-task craving scores [44]; gambling craving rating scores obtained after the viewing of gambling video [42]). These findings are of critical importance as they suggest that brain reactivity to gambling cues is a valid biomarker of gambling-related craving and of gambling disorder severity. Noteworthy, Kober et al. [50] and Crockford et al. [43] did not report analyses on the association between brain activation and gambling craving ratings, despite having reported group differences regarding craving scores in PrGs relative to HCs.

Available fMRI literature on gambling cue reactivity also shows that integrating different types of hedonic cues, within the same task design, impacts on the magnitude of the main and interactive effects of brain imaging results [44, 46, 49, 52••]. For instance, findings from Sescousse et al. [49] suggest that the concurrent availability of monetary and erotic rewards

triggered a motivational hierarchy favoring monetary rewards over erotic ones in PrGs. Similar findings were found in a study comparing patients with gambling disorder or substance use disorder with regard to gambling versus cocaine cue reactivity [50]. Specifically, this study showed that the dorsomedial prefrontal cortex and the dorsal anterior cingulate cortex were most strongly activated for cocaine-related videos in cocaine-dependent participants, and for gambling videos in PrGs, which clearly suggests a specificity of brain reactivity to the cues associated with the addictive behavior.

As a whole, given the robust evidence that brain activity in PrGs is strongly modulated by gambling cues, we believe that the examination of the neural reactivity toward gambling cues represents a promising tool for clinical neuroscience of gambling disorder.

An Integrative Framework for Examining Neural Cue Reactivity in the Age of Online Gambling

In comparison to the literature on neural cue reactivity in substance use disorder, available knowledge on the key factors underlying cue reactivity in gambling disorder is still very incomplete. Specifically, it is currently unclear how individual-specific factors (symptom severity, duration/intensity of use, active user vs. trying to quit, treatment outcomes) and study-specific factors (e.g., craving induction, reward availability, personalized cues) impact on gambling cue reactivity. Therefore, our aim here is to provide direct research directions for enhancing current knowledge on how specific factors impact on gambling cue reactivity, and by extension on its predictive power regarding clinical status and treatment outcome of gambling disorder.

Capitalizing on influential model-based reviews on neural cue reactivity in substance use disorder [9, 11, 12, 66], the following sections describe a conceptual and methodological framework that attempts to integrate both individual-specific and study-specific factors known to modulate neural cue reactivity in cocaine, alcohol, and nicotine users (see also Table 2 for a summary of the proposed research directions). While implementing this integrative approach in experimental research presents important challenges, we argue that the recent expansion and popularization of online sports betting services calls for the development of more comprehensive and specific models of neural cue reactivity in gambling disorder.

Exploring the Clinical Validity of Gambling Cue Reactivity

There is currently a rapid proliferation of sports betting opportunities. One striking feature of this new offer of online gambling is the advent of in-play betting that allows sports bettors to place bets during the game (e.g., on the final outcome of the game, on key events within the game, or on a particular discrete event during a game; [67]). As such, a countless number of sport events continuously promote gambling opportunity, a phenomenon that has already been linked to an increased willingness to bet in sport fans (including children; [8•, 68–71]). Moreover, in contrast to other types of gambling activities, sports betting is not negatively connoted in our society (e.g., [72]). Hence, both the hyper-accessibility and the increase level of social acceptance of this conduct can be expected to expand the spectrum of gamblers within the population, with specific samples of gamblers (i.e., sport bettors) at both extreme ends of the spectrum of gambling frequency and severity.

Table 2 Summary of the proposed integrative framework for examining neural cue reactivity in the age of online gambling

Identified challenges	Potential research directions
Exploring the clinical validity of gambling cue reactivity	=> Identify how neural cue reactivity varies as a function of the duration/intensity of gambling behavior, the degree of gambling disorder severity, and the current status (active user, trying to quit, abstinent)
Establishing the predictive value of gambling cue reactivity	=> Examine whether neural reactivity to gambling cues, measured before an attempt to quit, could identify problem gamblers with heightened relapse vulnerability => Examine whether neural reactivity to gambling cues, measured before the actual initiation of gambling habits, could predict later problematic gambling behaviors
Integrating new measures of gambling involvement	=> Examine how neural reactivity to gambling cues varies as a function of harmonious versus obsessive passion for gambling
Using cues associated with gambling availability	=> Examine how the prospect of actual gambling impacts on neural reactivity to gambling cues => Examine the interactions between cue-elicited feelings (e.g., enjoyment, winning confidence) and pre- versus post-task changes in gambling craving
Renewing measures of key variables	=> Examine whether gambling cues associated with ubiquitous touchscreen smartphone apps impact on neural cue reactivity during motor response inhibition

From the standpoint of the present review, this variation in gambling participation and severity calls for a new line of research for further establishing the clinical validity of gambling cue reactivity with indices of duration/intensity of use, addiction severity, and current clinical status (active user, trying to quit, abstinent). All these individual-specific factors are known to modulate neural reactivity to psychoactive substance cues in substance use disorder. For instance, while reviewing fMRI studies of drug cue reactivity, Wilson et al. concluded that drug-related cues trigger increased brain activation in individuals who are actively using drugs and not seeking treatment at testing time, as compared with treatment-seeking drug users [11]. Moreover, several studies observed that levels of hedonic/incentive cognitive association [73] and motor approach tendency toward alcohol cues [74–78] are lower in individuals who are motivated to quit, as compared with heavy alcohol users. These patterns can be accounted for if one assumes that quitting-motivated individuals, in contrast to active users, develop an active avoidance strategy toward cues to support their abstinence/moderation goals [76]. Taken together, these experimental approaches contrast with fMRI studies on gambling cue reactivity, which have often compared one sample of PrGs (either active or treatment-seeking) with a group of non-gambler HCs, eventually failing to identify brain pathways that vary according to frequent (but non-problematic) and problematic gambling habits.

Establishing the Predictive Value of Gambling Cue Reactivity

One main challenge for future research is to establish whether neural reactivity to gambling cues (not only related to sports betting but also to other gambling types), measured before an attempt to quit, could identify gamblers with heightened relapse vulnerability. Previous research on substance use disorder have already shown that relapse-vulnerable individuals can be identified before quit attempts based on their brain reactivity to substance-related cues (for a review, see [9]). For instance, Janes et al. [79] highlighted that the insular cortex response to smoking cues before trying to quit was a significant predictor of relapse in quitting-motivated smokers.

This line of research should not only focus on treatment outcomes, but also on examining whether neural cue reactivity to gambling cues predicts problematic gambling behaviors. This type of studies appears especially relevant to the field of sports betting. Specifically, recent research findings have highlighted that despite having never gambled, some young sports fans displayed technical knowledge of sports betting, including being able to discuss and describe "odds," different gambling markets, and how to place bets [69]. This betting-related knowledge could be predominantly traced back to the abiding marketing they were faced with (e.g., pop-up messages occurring during live sports events that feature dynamic betting ratios; [80]), inducing increased recall and awareness of sports betting brands, or perceptions of promotional strategies [68, 69, 81, 82]. As such, this ubiquity of cues might increase the incentive salience of sports betting in young individuals long before they reach the minimum legal age for gambling. In this context, neuroimaging research could prove useful to examine whether neural cue reactivity at time 1 (e.g., in young people who are sport fans but are not legally authorized to bet) predicts the problematic involvement in sports betting at time 2 (e.g., 1 year after being legally authorized to bet on sports). Ultimately, this type of research should enable the creation of personalized prevention and treatment programs on problematic sports betting.

Integrating New Measures of Gambling Involvement

Brain imaging studies on gambling cue reactivity will also benefit from alternative measures of gambling habits. One important aspect is to characterize samples of gamblers according to their actual involvement in gambling, as "high involvement" is not necessarily associated with negative consequences or disordered gambling symptoms (e.g., [83]). Indeed, past research has shown that it is possible to distinguish harmonious passion (i.e., a strong inclination to engage in the activity willingly and with a sense of volition) from obsessive passion (i.e., an uncontrollable urge to engage in the activity; [84–86]) toward sports (e.g., with the "Sports Fans Passion Scale"; [87]) and sports betting (e.g., with a sports betting adaptation of the "Gambling Passion Scale"; e.g., [88]). Considering this critical difference between harmonious and obsessive passion is of major importance when examining cue reactivity processes in individuals who aim at controlling or stopping sports betting. Specifically, one key aspect of sports betting is that it binds gambling to watching sport, that is, a popular, enjoyable, and valorized activity. Hence, a challenge for these quitting-motivated sports bettors is to restore an interest in sports events watching per se, that is, without betting on it. This view echoes qualitative studies that examined trajectories of recovery from gambling problems [89–91, 92•]. Specifically, these studies highlighted that processes of behavioral change revolve around shifting from a "gambling self" to a self-identity that is reshaped in harmonious and appropriate ways. In terms of brain-related clinical outcome, one would expect such a shift to be accompanied by diminished brain reactivity to sports betting cues combined with increased brain activity toward sports watching cues in abstinent sports bettors, as compared with active problem sports bettors.

Using Cues Associated with Gambling Availability

Since every sporting event is available to bet on, merely viewing cues related to sporting events (e.g., advertisements featuring betting odds) has the potential to drastically increase

gambling temptation [5, 6, 93–95]. In other words, exposure to sports betting cues signals gambling availability.

Research is thus warranted to extend previous neuroimaging work on gambling cue reactivity by examining how the prospect of actual betting impacts specific brain pathways. Initial strides toward this research direction have been taken by Brevers and colleagues [96••]. These authors reported, through the use of an fMRI cue exposure task (adapted from a food cue reactivity study; [97]), that thinking about a sporting event with the intention of gambling on the outcome, compared with thinking about it with the mere intention of watching it, triggers higher prefrontal, insular, and striatal activations in a sample of football (soccer) fans. Importantly, Brevers et al. [96••] used ecological cues (i.e., football games that were occurring in real life in the days following the scan, with the logos and names of the two teams facing each other) and manipulated gambling reward availability/expectancy (participants received additional money if the team they chose to bet on eventually won the game). Comparable study-specific factors (e.g., substance availability/expectancy; substance cues as task target; personalized cues) have been shown to modulate neural cue reactivity in substance use disorder (e.g., [9]).

Another interesting feature of the Brevers et al. [96••] study is the inclusion of post-task ratings for individual cues that were regressed against brain responses observed during the experiment. Two ratings were used: the degree of confidence toward the winning team and the degree of enjoyment directed toward a game. Indeed, all sports fan can express a degree of confidence toward the result of a forthcoming sport event (e.g., through "Fantasy Sports Leagues" with or without monetary/material reward involved; [98]). We advance that similar procedures should be used in future studies to complement pre- and post-task (block) craving measures. This would allow to take into account the interaction between the level of interest elicited by the cues and pre- versus post-task craving changes. In addition, including such parametric indices would represent a considerable advantage for experimental tasks that alternate reward availability conditions on a trial-per-trial basis, including exposure to situations known to interact with neural cue reactivity as a potent trigger of impulsive gambling behaviors (e.g., reward-blocking or frustration induction procedures; [98–101]). For instance, individuals are more impulsive in their monetary choices after having experienced "frustration", e.g., when they are denied a gambling opportunity [100]. Accordingly, sports bettors should experience similar heightened frustration when they perceive a cue depicting an attractive yet unavailable betting opportunity. Previous neuroimaging studies have shown that the insular cortex and the amygdala play a key role in evaluating the emotional content triggered by these "frustrating" events [101, 102]. As such, this new line of research may extend current knowledge on the brain pathways underlying situations that fuel gambling temptation.

Renewing Measures of Previously Explored Variables

Another central aspect of the new sports betting offer is that recent technological advances allow for repeated and continuous access to sports betting at the touch of a smartphone screen (i.e., mobile gambling; [79]). As such, the motor response pattern used for opening a sports betting smartphone apps mimics the button press procedures commonly used in the laboratory (e.g., to push the left or the right computer key; go or no-go responses). This opens new avenues for ecological behavioral and brain imaging research examining the interaction between cue reactivity and motor response inhibition in the lab. For instance, the go/no -go task used by van Holst et al. [46] or the stop-signal paradigm chosen by Brevers et al. [51] can easily be adapted with cues depicting print screens from sports betting apps taken from participant's smartphones (with print screens from other apps to be used as control cues; e.g., mail, calendar, notes). Indeed, it has already been shown that cues associated with ubiquitous touchscreen smartphone apps trigger heightened sensorimotor skills and strong motor approach tendencies (e.g., [103, 104]). It follows that the extensive use of online sports betting platforms could impair the ability to stop a motor response when it interferes with updated goal-driven behaviors (e.g., to withdraw or refrain a motor response toward a sports betting cue).

Adopting a Data Driven Approach in the Age of Open Science

Capitalizing on sports betting cues will enhance the validity of cue reactivity tasks. Nevertheless, it is important to methodological considerations while using a stepwise approach (e.g., running behavioral pre-tests and pilot neuroimaging studies before undertaking neuroimaging studies) and integrated levels of data analyses (from whole-brain and functional connectivity analyses to ROI and effective connectivity analyses, respectively). For instance, brain Z-maps from Brevers et al. [96••] could be used as functional masks by future studies when assessing group activation differences in predefined regions of interest. This should be especially helpful for increasing the statistical power of future studies involving participants with high levels of problematic sports betting habits—that is, those who are difficult to recruit, usually resulting in small and underpowered samples. A comparable approach has been adopted in brain imaging research on gambling disorder by Sescousse et al. [49], who used peak voxels from their previous study using the same protocol in healthy controls [58] to draw ROI spheres. This procedure allowed them to identify interactions among the brain networks involved in the processing of salient-motivational cues in PrGs. Another promising avenue is the creation of multicenter brain research projects (e.g., [105•]) and neuroscience-based framework for gambling disorder (such as those already existing in

substance use disorder; [106, 107]). These initiatives can now be more easily implemented by using pilot data for computing the necessary sample size to obtain a certain level of statistical power (e.g., through the use of http://neuropowertools.org and http://fmripower.org) prior to submitting preregistered reports and by sharing research materials online, with the statistical maps that can be uploaded to neurovault.org, the raw data to openfmri.org, and the code to github.com.

Concluding Remarks

Experimental designs investigating individual-specific and study-specific factors related to sports betting have the potential to offer a fine-grained approach to the examination of neural gambling cue reactivity. We are convinced that this integrative approach will not only increase our understanding of the neurobiology of problem gambling severity, treatment outcome, and relapse risk in gambling disorder, but will also help in identifying biomarkers that can disentangle between harmonious and harmful gambling habits. Ultimately, along with inputs from open science initiatives building upon multicenter collaborations, this scientific work should speed up the implementation of efficient public health prevention and treatment programs on new forms of gambling disorder.

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Compliance with Ethics Guidelines

Conflict of Interest Damien Brevers, Guillaume Sescousse, Pierre Maurage, and Joel Billieux declare no conflicts of interest relevant to this manuscript.

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- • Of importance
- •• Of major importance

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