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Neural cue-reactivity in pathological gambling as evidence for behavioral addiction: a systematic review

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Abstract

Increasing incidence of problem gambling has led to prioritizing the problem from the point of view of public health. Additionally, gambling disorder has been recently classified as a behavioral addiction, with implications for both its diagnosis and treatment. However, the shared neural substrate of addictions, to substances and behavioral, is still discussed. Thus, this systematic review aims to provide up-to-date knowledge from the past five years (2017–2022) concerning the neural correlates of gambling related stimuli (cue-reactivity) on the basis of a previous review (Brevers et al., Cognitive, Affective and Behavioral Neuroscience 18:718–729, 2019). A total of five studies were included in the review. Activation of brain areas related to memory, reward and executive functions could be the underlying mechanism of this behavioral addiction. Specifically, nucleus accumbens and striatum (ventral and dorsal), parahippocampal regions, the right amygdala and several prefrontal cortex regions have systematically been found more active in those subjects exposed to gambling-related cues. Also, the insula could play a pivotal role connecting these three systems in a highly integrated neural network with several implications for reward processing modulation, associative learning and top-down attentional regulation to improve saliency of addiction-related cues. These results are consistent with previous findings on other substance addictions, such as alcohol, tobacco, marijuana or cocaine. The study of neural reactivity to stimuli related to addiction could be useful as a biomarker of the severity of the disorder, the efficacy of the treatment, the risk of relapse, in addition to being an objective criterion to measure the effectiveness of prevention campaigns.

Keywords Behavioral addiction · Gambling disorder · Neural reactivity · Neuroimaging · Systematic review

Pathological gambling (PG) was earlier described as a "chronic and progressive failure to resist impulses to gambling and gambling behavior, a failure that compromises, disrupts, or damages personal, family or vocational pursuits" (Lesieur & Custer, 1984, p. 147). Long before, in the nineteenth century, gambling was viewed from a moral perspective, with the gambler being likened to a sinner or criminal (Bell, 1974). However, a series of social and clinical developments occurring in the 1970s and 1980s caused a shift towards a medical model. As a consequence, PG was first included by the American Psychiatric Association in the third edition of its Diagnostic and Statistical Manual (DSM) (APA, 1980) as an impulse-control disorder. This classification extended further to DSM-IV and the International Classification of Diseases, 10th edition (ICD-10), (WHO, 1992). However, both its diagnostic criteria and classification have been criticized. In the first place, the description was originally clinical and non-empirical based. Theories about PG from psychology and sociology abounded before its classification in the most frequently used nosology systems (Devereux, 1949; Frey, 1974). Although evidence coming from these approaches suggests that problem gambling was distributed on a continuum, past editions of DSM and ICD recognized only the presence or absence of a categorical diagnosis of PG, without considering degrees in its severity. Furthermore, many authors have questioned the nature of PG as an impulse-control disorder. Contrary to this clinical population, pathological gamblers find their

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activity enjoyable and do not feel distress until the gambling is finished and losses become a problem (Shaffer & Korn, 2002). Along with these inconsistencies, brain imaging studies and neurochemical tests have provided support to the resemblance between PG and substance abuse disorders (SADs). In fact, there is increasing evidence that both types of addictions, to substances and behavioral, could share the same underlying brain circuits as found in neural cue-reactivity studies. In these studies, a cue is any neutral stimulus that has been repeatedly paired with the effects of the addictive behavior (Crockford et al., 2005; Fauth-Bühler et al., 2017; Holst et al., 2010; Kober et al., 2016). As in the case of substance addictions, evidence has shown distinct brain activation in subjects with a gambling disorder (GD) in prefrontal and mesolimbic areas. These brain areas are typically involved in executive control functioning as well as reward processing, respectively. Traditionally, gambling research paradigms have used immediate versus delayed rewards to explore reward processing and inhibition (Alessi & Petry, 2003). Also, natural (i.e., sex, food) versus gambling-conditioned (i.e., lights, roulette, lottery tickets) rewards have been employed to compare different brain responses to those stimuli (Noori et al., 2016). Finally, economic rewards have been used particularly in the context of cognitive heuristics, decision making and risk assessment (Kahneman & Tversky, 1979). In addition, impaired decision-making, planning or inhibition have been pointed out earlier in GD (Conversano et al., 2012; Genauck et al., 2017; Wiehler & Peters, 2015) along with special sensitivity to gambling-related stimuli compared to natural rewards (Quester & Romanczuk-Seiferth, 2015). This special sensitivity to addiction-related cues has also been linked to substance addictions (Cummings & Blum, 2000; Robinson & Berridge, 2001; Volkow et al., 2003). Furthermore, increased brain activity in parts of the mesolimbic dopamine system has been reported in visual gambling-related cues experiments (Fauth-Bühler et al., 2017), suggesting a dopaminergic dysfunction during reward anticipation as a common feature of both kinds of addiction. Notwithstanding, other neurotransmitters such as noradrenaline, serotonin and opioids have been related to GD, which could contribute to arousal/excitement, impulse control and urges/craving, respectively (Potenza, 2014).

Taking into account all this evidence, PG has been reclassified as a behavioral addiction, within the substance-related and addictive disorders in the fifth edition of DSM (APA, 2013). This shift is coherent with symptom similarities (dependence, tolerance, craving and withdrawal symptoms) (Potenza, 2006), neurobiological evidence, treatment efficacy as well as with social learning theories (Brown, 1987) and the principles of operant and conditioned learning. Therefore, the name "Gambling Disorder" seems to be the most appropriate for this mental health condition (Petry et al., 2014).

Additionally, gambling is on the rise. Several countries like China (Long et al., 2018), United Kingdom, Australia or the USA have reported increases in gambling behavior, which have been exacerbated due to the Covid-19 pandemic (Håkansson, 2020). This growth in gambling has been especially observed in those countries with liberalized markets, including Australia, Canada, Croatia or Spain (Gavriel-Fried et al., 2021; Ministerio de Sanidad, 2021). There is convincing evidence that greater availability of gambling is correlated with PG (Binde, 2014; Lesieur & Custer, 1984), a question that also affects online gambling (Chóliz, 2016; Hubert & Griffiths, 2018). In fact, various distribution and placement strategies used on digital platforms to boost the exposure of gambling advertisements among online audiences have been reported in different studies (Syvertsen et al., 2022). These social media platforms may give operators the chance to drastically boost brand recognition, draw in new clients and offer effective customer relations management (Houghton et al., 2019). These data are especially worrisome in a young population, given that the period of increased vulnerability to the GD onset is between 18 and 24 years old (Hing et al., 2016). In addition, we must consider that GD is related to severe disturbances of personal, social, economic as well as family-related areas of a person's life. For example, economic costs of GD can range from bad credit, legal problems or work absenteeism to complete bankruptcy (Abbott et al., 1995). Furthermore, an observational study found that the children of compulsive gamblers were more likely to smoke, drink and use drugs (Jacobs et al., 1989). Finally, damage to health and relationships, along with psychological distress, are typically among the main burden of harm related to gambling (Abbott, 2020). Thus, many experts are beginning to talk about the *online gambling epidemic* (Choliz & Marcos, 2019), due to the increase in this gambling modality (Hing et al., 2014). As a consequence, sociological factors concerning gambling behavior must be taken into account regarding legislation, prevention campaigns, advertising regulation, social networks and accessibility (Bestman et al., 2016; Frey, 1974). These factors should be based on evidence from empirical work. In particular, it is of special importance to study which features of gambling cues currently used in the social media platforms are more prone to produce favorable attitudes towards gambling or behavioral intentions, or to increase the risk of developing PG.

For all these reasons, further increasing our knowledge about the neurobiological correlates of GD has the following benefits: firstly, the study of neural reactivity to stimuli related to addiction has shown its usefulness as a biomarker of the severity of the disorder, efficacy of the treatment, and risk of relapse (Brevers et al., 2019). In fact, it has been demonstrated that there is a stimuli-specific response depending on the type of game the subject

is addicted to, and the type of stimuli employed. For example, Limbrick-Oldfield et al. (2017) found a distinct response to gambling-related cues and natural reinforcers, showing the specificity of this kind of stimuli over natural rewards. Furthermore, it has been suggested that both the range and specificity of associated cues could be greater and more varied in GD compared with substance abuse disorders. In particular, regular horse race bettors exposed to lottery cues showed only modest changes in craving compared to cues associated with the preferred activity (Wulfert et al., 2009). These could be used to design and improve more effective psychological treatments in the future, along with empirical-based prevention campaigns. Furthermore, these studies allow us to have more reliable and objective measures of craving, specify the underlying brain mechanisms of psychological therapies or help to improve responsible gambling advertising policies (Clark & Goudriaan, 2018). In this sense, early detection and prevention could be better assessed and designed on the basis of brain reactivity measures. Finally, this could serve to strengthen the categorization of this clinical entity into the addictive disorders group. In fact, as it has been suggested, both PG and SADs could respond to similar treatments. Particularly, cognitive-behavioral therapy has proved to be efficacious for both GD and SADs (Echeburúa & Fernández-Montalvo, 2005; Rash & Petry, 2014; Ribeiro et al., 2021; Zamboni et al., 2021). With reference to pharmacological therapy, although there is no drug treatment approved for GD (Victorri-Vigneau et al., 2018), three types of psychiatric drugs are recommended in clinical practice guidelines: antidepressants, opioid antagonists and mood stabilizers (Menchon et al., 2018). Antidepressants, most commonly serotonin reuptake inhibitors (SSRIs), have shown to be superior to placebos in five randomized, double-blind, placebo-controlled trials. Opioid antagonists such as naltrexone have been used to reduce cravings, with promising results. The findings are mixed about mood stabilizers such as lithium or topiramate being helpful for GD. What definitely seems not to be recommended is the use of antipsychotic drugs in GD (Kraus et al., 2020). In essence, a clear conceptualization of a mental disorder has several implications for its early detection, diagnosis and intervention that could affect both clinical and public health practices.

Therefore, the aim of this study is to systematically review research focusing on the neural correlates of gambling cue exposure. In particular, this research will analyze data associated with psychological variables as well as brain functional connectivity. Thus, we aim to explore the role of different brain areas commonly associated with key cognitive processes involved in GD as a behavioral addiction such as executive functions, memory and reward processing.

Method

For the purpose of this research a systematic review was conducted following PRISMA method guidelines (Moher et al., 2009). This type of review provides the following advantages: a structured methodology which reduces the risk of bias and subjectivity; a rigorous method to condense a range of studies, allowing readers to access the achieved results in a single format; a transparent process for reaching conclusions; and its flexibility for regular updating (Khan et al., 2003). Also, SPIDER tool was used to determine the research question and to make a more efficient strategic search (Cooke et al., 2012). The databases Web of Science, Scopus, Medline and PsycInfo were consulted through the EBSCO Discovery search engine tool. Within the search strategy, we created operational definitions for the key terms: "gambling", "neuroimaging" and "cue-reactivity". "Gambling" was defined as any kind of game where the person risks something for the possibility of making a profit; "Neuroimaging" was defined as a technique that allows us to have images of brain functioning based on the exchange between oxyhemoglobin and deoxyhemoglobine within the neurons of a particular brain region; finally, "cue-reactivity" paradigms are based on the exposure of any neutral stimulus that has been repeatedly paired with the effects of the addictive behavior, in this case, with any activity related to gambling, more typically, visual. The following terms were combined with Boolean operators (AND/OR) as part of the search strategy: 'gambl*' AND ('cue-reactivity' OR 'neuroimaging'). The inclusion criteria were: a) articles concerning gambling behavior/disorder and neuroimaging; b) the article must be empirical, data-based and peer reviewed; c) articles from the past five years (2017–2022), since there is a previous review on this topic (Brevers et al., 2019); d) written in English; e) comprising human subjects f) all age groups. Studies including subjects with other comorbid mental diagnoses apart from GD were excluded. Database searching was carried out on January 20, 2022. Additionally, the references of articles selected were consulted to identify additional studies, but none were found.

The first database search generated 1.470 articles. A total of 1.102 duplicate records were removed, resulting in a total of 368 articles. Then, two members of the team (AC y JGC) screened these 368 articles checking their title and abstracts and applying the inclusion criteria. After this phase, a total of 363 articles were excluded with reasons (see Fig. 1). Thus, only five articles were selected to finally be included in this review. Subsequently, another team member (MAC) reviewed and recorded all full-text articles selected following the content analysis technique, used to systematically categorize qualitative data (Berelson, 1952).

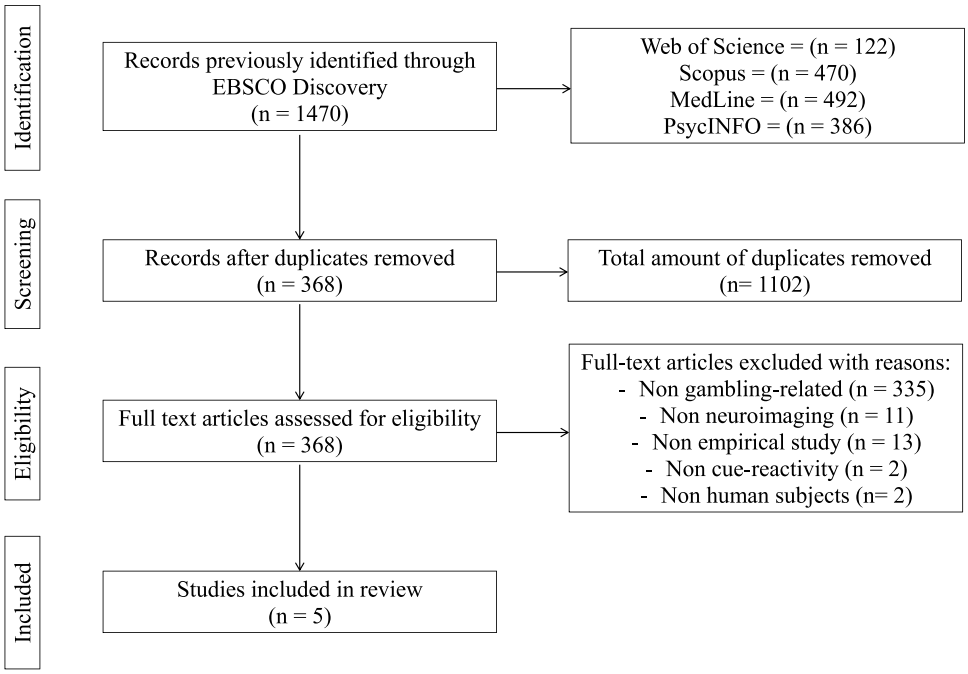

Fig. 1 PRISMA flow-chart of search strategy results

Results

From the total of 5 articles finally selected, the number of participants in each study ranged from 40 to 111, with a total of 296. The average age of the participants was 32 years-old and more than half were men. Of the total participants, 94% completed the experimental tests and questionnaires.

Altogether, the evidence analyzed in this systematic review reveals the involvement of three brain systems when GD subjects are exposed to gambling-related cues: the reward system, learning and memory, and the executive prefrontal cortex. In order to provide a more structured exposition of the main findings, results will be grouped into these brain systems referred to above. Also, two extra subsections have been added: one of them is related to the basal brain functioning while in resting state to compare with the neural correlates of gambling-related cues processing; the other concerns the proposed pivotal role of the insula into the addiction neural dynamics. For further details about the main findings of each study finally selected for this review see Table 1.

The reward system

Previous studies have found structural brain impairment in subcortical regions related to the reward system and motivation in GD. Specifically, several works have highlighted the role of nucleus accumbens and striatum on reward processing while gambling and craving (Limbrick-Oldfield et al., 2017; Quester & Romanczuk-Seiferth, 2015). Besides, activation of the ventral and dorsal striatum, as well as the nucleus accumbens, has also been linked to the anticipation of economic rewards in GD, as well as reduced sensitivity of the same regions to erotic stimuli (Sescousse et al., 2013). These data give support to a *sensitizing theory of addiction* (Robinson & Berridge, 2001), which predicts a decreased brain response in reward brain areas to natural reinforcers (i.e. sex or food) compared to addiction-related stimuli.

Regarding the implication of reward brain areas in GD, Brevers et al. (2018) found in a sample of 42 male sports fans that when exposed to sports cues (soccer games that would occur either the same day or the following day after the scanning session), and having the availability to bet, caudate nucleus was more highly activated compared to a control condition (only watching the game). Although in this study participants were not clinically diagnosed with GD, problem gambling was assessed with the *Problem Gambling Severity Index* (PGSI; Ferris & Wynne, 2001), which has proved its validity to assess the degrees of problem gambling severity (Holtgraves, 2009). In another study, Limbrick-Oldfield et al. (2017) scanned and compared 20 GD with 22 healthy controls (HC), all males, while viewing gambling (i.e. slots), gambling-matched neutral (i.e. ticket vending machine), food (i.e. donut) or food-matched neutral pictures (i.e. colorful bath towels). Gambling-related pictures elicited increased brain activity in the reward system in GD compared to HC, including nucleus accumbens and ventral striatum. Also, they found that brain activation in nucleus accumbens and insula was associated to craving in GD. Moreover, craving to gamble was negatively correlated with connectivity between ventral striatum and the medial prefrontal cortex; this means that craving could be

Table 1 Article summary

Study	n	Study design	Key Findings
Genauck et al. (2021)	30 GD (20% females) 30 HC (20% females)	Affective decision-making task combined with functional magnetic resonance imaging (fMRI)	Subjects with GD showed stronger PIT-related functional connectivity between nucleus accumbens, amygdala and lateral orbitofrontal cortex Increase connectivity between amygdala and anterior OFC was inversely correlated with accepting a gamble in HC compared to GD
Takeuchi et al. (2019)	53 GD (100% males) 58 HC (100% males)	MRI while performing a risky choice task	Reduce grey matter volume was observed in the GD group compared to HC. Moreover, there was a negative correlation between regional grey matter volume and the *elevation parameter* in the gain domain in GD This correlation was not found in striatum
Brevers et al. (2018)	42 soccer fans (90,5% males)	fMRI imaging while exposing participants to soccer cues and gambling availability in a cue exposure task	Significant activations in the right middle frontal gyrus and right frontal orbital cortex were observed when participants have a gambling availability option Insula is more strongly activated when subjects are exposed to football cues associated with a gambling prospect. Particularly, insula was highly connected to parahippocampal gyrus, lingual gyrus, lateral occipital gyrus and occipital pole
Timmeren et al. (2018)	20 GD (80% males) 20 HC (85% males)	fMRI in a resting state preceded by gambling pictures	GD patients showed increased functional connectivity strength within right middle insula and right middle prefrontal cortex Gambling-related cognitive distortions correlated positively with brain activation in amygdala, insula, right temporal lobe and right middle prefrontal cortex
Limbrick-Oldfield et al. (2017)	20 GD (100% males) 22 HC (100% males)	Brain response (fMRI) in gamblers compared to healthy controls using both gambling-tailored cues and appetitive non-gambling stimuli	GD showed greater brain activity in ACC and insula when exposed to gambling-cues. Craving was associated to brain activation in bilateral insula and accumbens nucleus. The greater the abstinence, the lower the craving There was a decreased connectivity between PFC and nucleus accumbens, which was inversely correlated with craving

GD Gambling disorder, *HC* Healthy controls, *fMRI* functional magnetic resonance imaging, *PIT* Pavlovian to instrumental transfer, *ACC* anterior cingulate cortex, *PFC* Prefrontal cortex

dependent on the force of the connectivity between cognitive control and reward processing areas.

These subcortical brain regions could be very important to understand the transfer between gambling cues and actual gambling behavior. For example, Genauck et al. (2021) studied the pavlovian to instrumental transfer (PIT) in a group of 30 GD and 30 matched HC through an affective decision-making task and cue exposure. PIT is an experimental paradigm that allows researchers to assess how conditioned stimuli influence instrumental behavior. In the affective mixed-gambles task used in this study, subjects had to indicate their willingness to accept a gamble after being exposed to a randomly set of images, which could be either neutral, with positive consequences of gambling, with negative consequences of gambling or only gambling-related. Results showed that they could distinguish the GD from the HC based on the differential brain activation in nucleus accumbens, the amygdala and their connections with orbitofrontal cortex (OFC). In particular, one of the top-four predictors of being classified as GD was the connectivity between nucleus accumbens and amygdala, being stronger for GD compared to HC. That means that the more strongly the acceptance of the gamble during presentation of gambling cues was associated with an increase in correlation between reward and affective processing areas, the more likely the subject was a GD.

Learning and memory systems

Brain structures related to memory and learning such as the hippocampus or the amygdala are systematically found impaired or involved in brain responses of GD during gambling cue exposure (Goudriaan et al., 2010). Accordingly, affective processing of stimuli by the amygdala or learning mechanisms mediated by the hippocampus, such as episodic memory, along with pavlovian and instrumental conditioning, could be related to maintaining factors that prevent prolonged abstinence.

In this sense, Takeuchi et al. (2019) studied the *distortion parameter* applied to GD. According to *prospect theory* of decision-making, individuals asymmetrically appraise their losses and gains perspectives (Kahneman & Tversky, 1979). The probability weighting function, which is commonly depicted as an S-shaped curve, shows subjectively biased cognition, where the *distortion parameter* shows an overestimation for lower probabilities and an underestimation for higher probability, steeper for losses than gains; this means that individuals are risk-averse when faced with a risky choice that results in gains, preferring solutions that result in lesser predicted value but better certainty, while when faced with a risky decision that could result in losses, people are risk-seeking, preferring solutions that have a lower expected utility, as long as they can prevent losses. In addition, the *elevation parameter* reflects the overall elevation of the function, in which a highly elevated probability weighting function implies overestimated probabilities for gains (more optimism) and overweight probabilities relative to the objective probabilities of gaining; this *elevation parameter* is also modeled by individual differences and is assumed to reflect impulsivity (Trepel et al., 2005). In the Takeuchi et al. (2019) study, 53 GD subjects and 58 age-matched HC underwent MRI scans while performing a risky choice task, in which subjects were presented with options between a gamble and a sure option, with both gain and loss domains. Results revealed significant grey matter volume reduction in the amygdala, but not in the striatum in GD subjects compared to HC. Moreover, there was a negative correlation between the *elevation parameter* in the gain domain and regional grey matter volume in the amygdala. These results have been interpreted as subjects with GD generally overestimating probability in the gain domain compared to HC. Possible explanations relate grey matter volume in the amygdala with impaired decision-making processes, in such a way that the probability overestimation may be related to disrupted decision-making and result in risk-taking behaviors. Curiously, recent studies have found similar grey matter alterations in several brain regions related to behavioral addictions besides GD, including the amygdala (Rahman et al., 2014; Zhou et al., 2022).

However, not all cues must be external; cognitive distortions, such as illusion of control, predictive control, inability to stop or interpretive bias (Wu et al., 2018) could count as internal cues that boost behavioral intention to gamble. In fact, Timmeren et al. (2018) found that cognitive distortions in GD subjects correlated positively with the limbic system activation, specifically in the right amygdala. Furthermore, a strong connectivity has been observed between the amygdala and anterior OFC in HC compared to GD in an affective decision-making task in trials with a negative cue (Genauck et al., 2021), suggesting a possible disconnection between affective and cognitive processes in GD, which would lead to cognitive distortions as well as impaired decision-making. Finally, these two brain structures showed close activation with nucleus accumbens and right middle insula, which seems to be connecting reward, learning and executive control systems into a more highly integrated network.

Executive functions system

Impaired executive functions have also been raised as an important issue in behavioral addictions. Distorted decision-making in favor of risky choices, impaired planning, lack of consequence anticipation or failure to inhibit unsuitable behaviors are some of the main features related to impaired executive function and commonly observed in addictions, both to substances and behavioral. In general,

OFC, dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex are found to be more active in GD subjects when exposed to gambling-related cues, as well as when performing anticipation, processing and decision-making tasks related to rewards (Holst et al., 2010; Starcke et al., 2018). Also, higher craving scores when GD subjects are exposed to gambling-related cues were associated with lower connectivity between regions of the nucleus accumbens and frontomedial prefrontal cortex (Quester & Romanczuk-Seiferth, 2015), reinforcing the hypothesis of an impaired connectivity between the reward system regions and prefrontal executive cortex (Volkow et al., 2003).

Most of the studies reviewed in this article have found altered prefrontal activation in GD in connection with other brain areas. For example, reduced loss aversion in GD was associated with reduced loss-related functional connectivity from the amygdala to ventral medial prefrontal (Genauck et al., 2021). Also, when GD have the opportunity to gamble ('betting condition') significant activations in the right middle frontal gyrus and right frontal orbital cortex were observed, along with significant activation in the right hippocampus, OFC, anterior insula, medial frontal gyrus, and caudate nucleus (Brevers et al., 2018). Furthermore, in their study, Limbrick-Oldfield et al. (2017) found a decreased connectivity between PFC and the nucleus accumbens. In addition, this connectivity was inversely correlated with craving; that is, the more the craving, the lower the connectivity between PFC and the reward system.

Finally, Genauck et al. (2021) found that increased functional connectivity between the nucleus accumbens and amygdala could modulate the value representation in the OFC, and this could be related to impaired decision making, increasing the likelihood of choosing riskier options.

Resting state functional connectivity

To correctly interpret the neuroimaging data, a baseline of GD patients in a resting state is needed. This could bring us the opportunity to know if the brain alterations found are due to structural brain damage (cause) or to learning mechanisms (effect). Even though studies examining resting-state functional connectivity have been scarce, evidence has shown a strong connectivity between right middle frontal gyrus and right striatum in GD patients compared to controls (Koehler et al., 2013), the OFC to the amygdala, and the amygdala and the insula in the resting state. This evidence points to an increased connectivity between mesolimbic regions and the frontostriatal circuit in GD patients, that is, strong connectivity between reward processing and cognitive control (Timmeren et al., 2018). Although these results are congruent with those found by the studies previously reviewed in this research (see, for example, Genauck et al., 2021), more longitudinal and premorbid studies are needed to elucidate the directionality of this brain activation pattern.

A possible key role for the insula

All the articles selected for this review mentioned the association between the insula and some other brain area. This is consistent with the triadic models of addiction (Noël et al., 2013), which have highlighted the role of the insula as a switch responsible for executive disruptions in certain situations (i.e., homeostatic imbalance, deprivation, stress or lack of sleep) in favor of motivation and drive to seeking immediate rewards (Naqvi et al., 2014). This network switching could affect the identification of salient stimuli, modulating the interaction between default (ventromedial prefrontal cortex (VMPFC) and Posterior Cingulate Cortex) and executive functioning (DLPFC and posterior parietal cortex). In fact, gambling-related stimuli could be more salient due to top-down attentional mechanisms mediated by prefrontal cortex associations with the insula (Timmeren et al., 2018). Thus, the insula could play a key role by connecting learning systems with top-down control of attention. In addition, previous cue-reactivity studies already found an increased activity in the insula while watching gambling cues compared to neutral cues, which also correlates with between-subject craving scores (Limbrick-Oldfield et al., 2017). Finally, lesions to the insula have been associated with a reduced withdrawal to a substance (nicotine) and attenuated gambling-related cognitive distortions (Clark et al., 2014). All this evidence, together with the previously exposed, point to a key role of the insula in behavioral addictions such as GD, probably by modulating attentional processing, selective reward enhancement and conditioned learning.

Discussion and conclusions

The present systematic review aimed to provide an up-to-date state of the art concerning the brain response when GD subjects are exposed to gambling-related cues. Although previous research had collected some evidence regarding this topic, the rapid and constant development of cue-reactivity studies about GD demands continuous updating. In addition, the cumulative evidence will serve both for the consolidation of GD into the behavioral addiction diagnostic category and for developing more objective measures of treatment and prevention campaigns effectiveness.

Although three principle brain systems have been identified, the overall shared and strong connection between different brain areas clearly shows that we have to understand these brain correlates in a more dynamic and systemic manner when studying addictions. For example, reward areas such as nucleus accumbens may act via connections with

prefrontal regions, which may be related to subjective craving in these patients. Conversely, the amygdala might be associated to risk evaluation, but empirical data suggests that this subcortical region must be associated both to the insula and the OFC. In fact, several works have highlighted the neural network formed by the amygdala, the OFC and VMPFC in decision-making and consequence anticipation (Bechara, 2005). Likewise, these prefrontal brain regions along with DLPFC may be responsible for impaired consequence anticipation, disadvantageous decision-making or disinhibited behaviors (Quoilin et al., 2020). In turn, these areas may be connected to 'wanting' dorsal striatum functioning, reward anticipation and regulatory top-down control of attention to make addiction-related stimuli more salient.

Accordingly, the insula has been singled out as a possible key brain region that connects all the three commented systems. As we mentioned earlier, the anterior insular cortex could exert a crucial influence over the loss of control in several addictions, including for example heroine consumption and its associated relapse tendency (Joshi et al., 2020).

As expected, the evidence collected in this review supports the classification of GD as a behavioral addiction. This is because similar brain activation patterns have been found in both types of addiction, to substances and behavioral. In fact, a previous series of studies has shown greater activation in the prefrontal cortex, parahippocampal regions, and occipital cortex when GD subjects are exposed to gambling-related cues, along with other behavioral addictions (Crockford et al., 2005; Holst et al., 2010; Miedl et al., 2010). Likewise, a recent meta-analysis found a shared grey-matter alteration in both substance use disorders (SUDs) and behavioral addictions (BAs). More specifically, reduced grey matter was found in bilateral prefrontal cortex and bilateral insula in two types of BAs such as *Internet Gaming Disorder* (IGD) and GD, in accordance with our results (Qin et al., 2020). Furthermore, in opioids addiction, functional connectivity between the OFC and dorsal striatum could predict the force of craving after a period of a voluntary abstinence (Fredriksson et al., 2021). Interestingly, these variations in OFC were also observed in other BAs, such as the *Compulsive Sexual Behavior Disorder* (Golec et al., 2021). Finally, a shared neurofunctional alteration has been observed both in frontal and ACC in BAs such as IGD along with all SUDs (Klugah-Brown et al., 2021). All these questions are important for the advance in comorbidity and nosological clarification in the BAs. For example, although not recognized in DSM and ICD classifications yet, both *internet addiction disorder* (IAD) and IGD pose challenges for the conceptualization and delimitation of GD, especially in the online modality. However, evidence available at present, albeit scarce, points to a distinct nature between these entities. For example, Choi et al. (2014) found that both *alcohol use disorder* (AUD) and IGD showed more impulsivity traits measured through the *Barratt Impulsiveness Scale* version 11 (BIS-11) compared to the GD group, suggesting a more compulsive tendency in the first two groups. In the same vein, Tonioni et al (2014) found differences in temperamental, coping and social patterns between GD and IAD. More recently, Mallorquí-Bagué et al. (2017) found some similarities between GD and IGD in relation to emotional and personality traits, but differences in novelty seeking, body mass index and food addiction. However, high comorbidities have been highlighted between online GD and IAD (Ford & Hakansson, 2020). Although we have to take these results with caution due to their novelty and paucity, it seems that both disorders, GD and IAD, could be different in their underlying mechanisms. An important question for future research would be to determine the similar or different natures of online GD, IGD and IAD and if one could be a subgroup of another. Precisely, neural cue-reactivity paradigms could serve to compare brain activation patterns when exposed to addiction-related cues in order to find underlying neurophysiological differences.

Additionally, the findings reported in this study have remarkable implications for BAs treatment. The common neurobiological mechanisms between SUDs and BAs will allow us to develop new psychotherapies and treatments aligned with the transdiagnostic approach common to all types of addiction (Barlow et al., 2020). Likewise, new neurophysiological therapies such as direct transcranial magnetic and direct current stimulation have begun to show promising results in reducing craving in patients with both substance and behavioral addiction (Lapenta et al., 2018; Spagnolo et al., 2019). Furthermore, biomarkers of current clinical status of patients will allow us to measure their evolution and to reduce the risk of future relapse. Finally, prevention campaigns should be empirically-based to prove their effectiveness and to avoid the common backfire effect observed in these messages (Cárdaba et al., 2016; Newall et al., 2022). The neural correlates of gambling-related cue exposure can account for all of these implementations and improvements.

In conclusion, the results found in this systematic review are compatible with those found in the previous scientific literature (Balodis et al., 2012; Crockford et al., 2005; Fauth-Bühler et al., 2017; Goudriaan et al., 2010; Holst et al., 2010; Kober et al., 2016; Miedl et al., 2010; Potenza, 2008; Sescousse et al., 2013). As we can see in Fig. 2, almost two decades of research concerning the brain correlates of cue-reactivity in GD clearly show the implication of the three brain systems above discussed. We have included in this picture the results found in a previous review (Brevers et al., 2019) to complement our own results.

One of the most difficult issues to elucidate when studying the neural correlates of gambling-related cues refers to distinguishing learned brain functioning from basal brain

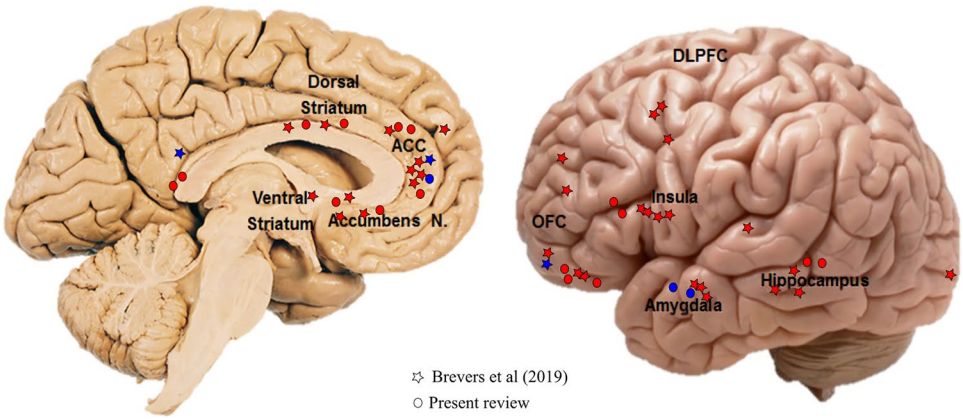

Fig. 2 Neural gambling-related cue reactivity summary. Note: Although the insula, the amygdala and the hippocampus are represented superimposed to enable a better understanding, these are cortical internal regions behind dorsal and lateral view. Increased brain activation is represented in red; Decreased brain activation is represented in blue. DLPFC: Dorsolateral prefrontal cortex; OFC: Orbitofrontal cortex; ACC: Anterior cingulate cortex

dysfunction (Timmeren et al., 2018). To remedy this problem, more studies investigating the brain's functional activity in resting states in GD are needed to compare with the gambling-cues condition, combined with longitudinal studies. Also, the limited number of articles found hinders the scope of our conclusions. The scarcity of recent research about this topic is surprising. Evidence has proved that GD patients show an increased brain activity when exposed to gambling related stimuli in certain brain areas. Furthermore, the results obtained by Genauck et al (2021) allow to distinguish between gamblers and non-gamblers based on gambling-cue PIT-related functional connectivity. This could be very helpful for the clinical characterization of the neural disturbances related to this behavioral addiction.

In addition to being in accordance with the previous evidence, the results presented in this review add new insights and provide novel directions for future research. Since the most recent review of neural cue-reactivity in GD claims that the current knowledge is still very scarce (Brevers et al., 2019), there is a requirement for more qualitative and quantitative scientific production in this field. In the first place, new cognitive paradigms must be added to explore different brain responses to gambling-related cues. For example, the articles consulted in this review combine affective decision-making with risky choice tasks that are absent in previous works. The inclusion of new investigations studying higher cognitive processes such as executive functioning, planning, decision-making and emotional responses could increase our knowledge, providing a more complete picture of the gambler's responses to key stimuli. Also, the addition of resting states as a baseline to compare with neural cue reactivity could provide new insights for understanding the brain's distinct responses to gambling-related cues in both non-gamblers and pathological gamblers. This could be fundamental to look into the question of whether the neural impairment commonly found in PG subjects is structural or acquire by experience. Finally, the focus on the insula is clearly increasing in recent years due to its possible key role as a neural node that connects a more integrated neural network, critical for the processing of information, conditioned learning and final behavior observed in subjects with GD.

To conclude, studies such as that of Zhou et al. (2022) show that new methodological tools should be added, such as connectome-based predictive modelling (CPM), as well as new cognitive paradigms, to further increase our knowledge of the underlying neurobiological basis of gambling behavior and its risk associated factors. Likewise, the dynamic nature of brain regions involved in GD addiction demand a more systemic approach. Because of this, connectivity studies are needed to clarify the relations and brain dynamics between different regions in these disorders as opposed to the study of isolated brain areas activity. We hope this evidence will contribute to both increase our knowledge about neural correlates of GD as a behavioral addiction and to provide effective tools to reduce the dangerous tendency of the online gambling epidemic in the near future.

Author contributions

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- **Illustrations, tables and figures:** Javier García-Castro and Ana Cancela.
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- **Writing review and editing:** Ana Cancela and Miguel Ángel Martín Cárdaba.

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Declarations

Compliance with ethical standards This is a systematic review. This article does not contain any studies involving human participants performed by any of the authors.

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