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REVIEW ARTICLE

Craving in gambling disorder: A systematic review

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ABSTRACT

Background and objectives: Craving is one of the main criteria for the diagnosis of substance use disorder according to the DSM-5; however, it is not included in the main criteria for gambling disorder (GD). In the present systematic review, we aimed to evaluate the available body of knowledge regarding gambling craving to help step forward to a consensus regarding this topic. *Data sources:* PsycINFO/PsycARTICLES and PubMed/Medline were used. *Study eligibility criteria, participants, and interventions:* (1) individuals of both genders who had a clinical diagnosis of GD in which the presence of gambling craving were studied by means of tasks or self-report tools; (2) we included three types of studies: (a) validation articles of craving psychometric tools in which GD was assessed; (b) articles in which craving–GD association was explored; and (c) treatment articles for GD in which craving was assessed. *Results:* $n = 63$ studies were finally included in the systematic review. Some studies described an association between craving- and gambling-related factors, and craving was also described as a predictor of GD severity, gambling episodes, chasing persistence and income-generating offenses. Gambling craving also seems to be associated with emotional states and negative urgency. Finally, some studies implemented specific interventions for GD and assessed its impact on reducing gambling craving. *Conclusions:* There is a growing body of knowledge on the relevant role of craving in gambling behavior and GD. Further studies are needed to reach a consensus on the diagnostic criterion for GD.

KEYWORDS

gambling disorder, craving, diagnosis, treatment, assessment

INTRODUCTION

Craving plays an important role in addictive behaviors (Tiffany & Wray, 2012), and due to a large body of evidence (Hasin et al., 2013; Romanczuk-Seiferth, Van Den Brink, & Goudriaan, 2014), it is one of the main criteria for the diagnosis of substance use disorders (SUDs) in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013). According to the DSM-5, craving is defined as an intense urge or desire for a drug, which is usually triggered in a context where the drug was previously used but can also independently occur. Following the diagnosis criteria, when assessing SUDs, it should be asked if the urge to consume drugs is strong enough to distract a person from everything else in their life (Hasin et al., 2013). In addition, there are several self-reported measures to assess craving that are appropriate in specific settings (Sayette et al., 2000) and can complement the DSM-5 criteria if needed. Following its publication in 2013, the new DSM-5 diagnosis (including craving as a main criterion) has demonstrated good validity results across several substances (Shmulewitz et al., 2021).

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In addition to SUDs, evidence shows that craving plays a role in non-substance-related behavioral addictions (e.g., gambling disorder (GD), internet gaming disorder; Antons, Brand, & Potenza, 2020). In this regard, GD was the only behavioral addiction reflecting enough evidence to be included in the chapter on substance-related and addictive disorders in the latest version of DSM-5 (APA, 2013). GD is defined as a persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress. GD shares clinical and neurobiological characteristics with SUDs, such as craving and loss of control (Romanczuk-Seiferth et al., 2014). That is, individuals suffering from GD tend to present a pattern of trying to regain their losses with an urgent need to keep gambling (APA, 2013; Petry et al., 2014). However, unlike in substance-related disorders, craving per se is not a main criterion for the diagnosis of GD; therefore, further consensus is needed.

In order to understand the nature of craving and its impact on addictive behaviors, theoretical models have been proposed. In this sense, the interaction of the Person–Affect–Cognition–Execution model (I-PACE, Brand & Potenza, 2021) describes different factors that can lead to craving through a theoretical framework that conceptualizes the development and maintenance of addictive behaviors. According to this model, the presence of craving and inhibitory control deficits may play pivotal roles in addiction, especially in face of behavior-specific triggers. However, as stated by a recent revision of this model (Antons et al., 2020; Brand & Potenza, 2021), research on this topic remains in its early stages regarding non-substance addictive behaviors, and no studies have systematically reviewed all of the current literature on gambling craving.

In light of all the points mentioned above, we aimed to evaluate the large available body of knowledge regarding gambling craving to determine the role of gambling craving in GD.

METHODS

Protocol and registration

The present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The systematic review was registered in PROSPERO, the international prospective register of systematic reviews of the National Institute for Health Research (registration number: CRD42021240504; registration date: 03/04/2021; registration website: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=240504).

Eligibility criteria

Study characteristics. Following the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework (Methley, Campbell, Chew-Graham, McNally, & Cheraghi-Sohi, 2014), we included the following. (1) Population: Individuals of both genders who had a clinical diagnosis of GD (or who were the subject of an interview/instrument to assess the presence of problematic gambling/GD) in whom the presence of gambling craving had previously been explored (or even induced) by means of tasks or self-report tools. (2–4) Regarding intervention, comparison and outcomes, and since we wanted to explore the construct of craving in GD globally, we included three types of studies: (a) validation articles of craving psychometric tools in which GD was assessed; (b) articles in which the craving-GD association was explored; and (c) treatment articles for GD in which gambling craving was assessed; and (5) study design: both longitudinal and cross-sectional. We excluded studies that employed non-human participants, as well as those implementing a qualitative design or not directly assessing gambling craving or GD.

Report characteristics. We included in-press peer-reviewed empirical studies (randomized controlled trials and research studies) written in English and published prior to March 2, 2021. Studies with a quantitative methodology or an observational or descriptive design were eligible. The following publication types were excluded: meta-analysis, systematic reviews, clinical practice guidelines, case report or series, pilot studies and grey literature. Moreover, articles without an abstract were excluded.

Information sources and search strategy

Two electronic databases (PsycINFO/PsycARTICLES and PubMed/Medline) were used. The search strategy included the keywords “gambling AND craving”. The filter “academic publications” was used in the PsychINFO search engine. The search included articles published up to March 2, 2021. Reference lists of the articles finally included in the systematic review were checked manually for possible additional studies.

Study selection

We used a two-step process to assess the results of our search. In the first step, two reviewers (NMB and GMB) individually screened all of the potential articles, taking into account titles and abstracts, prior to the retrieval of full texts. In the second step, those studies identified for full review were screened by the same reviewers according to the eligibility criteria. Differences of opinion between both reviewers were resolved through consensus. The entire process was performed using the Covidence software.

Data collection process and data items

We extracted several data, including the reference of articles, aims, study design, sample characteristics and sample size, GD tools, craving tools, results and treatment interventions. The quality of the included studies (see Table S1 in Supplementary Material) was assessed using the Effective Public Health Practice Project quality assessment tool (EPHPP; National Collaborating Centre for Methods and Tools, 2010), which is applicable across multiple study

designs. EPHPP rates studies as strong, moderate, and weak in terms of their data collection methods, confounders, study design, selection bias, blinding, dropouts, and global study quality score.

RESULTS

Study selection

A total of 437 records were retrieved from the literature search in both databases. After removing 145 duplicates, 192 of the 292 remaining articles were excluded regarding their titles and abstracts. The remaining 100 studies were screened at a full-text level. From the 100 articles screened, 62 were finally included in the present systematic review: 5 validation articles of craving psychometric tools in which GD was assessed, 23 articles in which craving–GD association was explored, and 34 treatment articles for GD in which gambling craving was assessed.

The remainder of the articles was excluded for reasons including: (1) assessment of craving and/or GD unclear, (2) article language not included in the inclusion criteria, (3) study design not included in the inclusion criteria (see Fig. 1).

Study characteristics

Overview of studies. Twenty-three studies included in the systematic review had a cross-sectional design, 5 were instrument validation studies, and 34 had a longitudinal design. Sample sizes ranged from 19 to 55. One study included only females, 13 studies included only males, and 48 studies included both males and females (see Table 1).

Samples. Most studies included adults with different degrees of gambling involvement: **non-gamblers** (Brevers et al., 2018, 2011; Ciccarelli, Nigro, Griffiths, Cosenza, & D'Olimpio, 2016a; Côté, Tremblay, Jiménez-Murcia, Fernàndez-Aranda, & Brunelle, 2020; Crockford, Goodyear, Edwards, Quickfall, & El-Guebaly, 2005; Geisel, Hellweg, Wiedemann, & Müller, 2018; Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Kober et al., 2016; Koehler et al., 2013; Limbrick-Oldfield et al., 2017; Pallanti, Bernardi, Allen, & Hollander, 2010; Quintero, Navas, & Perales, 2020; Sztainert, Hay, Wohl, & Abizaid, 2018; Takeuchi et al., 2016; Wölfling et al., 2011), **gamblers** (Cornil et al., 2018; Caillon et al., 2019; Canale, Cornil, Giroux, Bouchard, & Billieux, 2019; Ciccarelli, Nigro, Griffiths, Cosenza, & D'Olimpio, 2016b; Cornil et al., 2019;

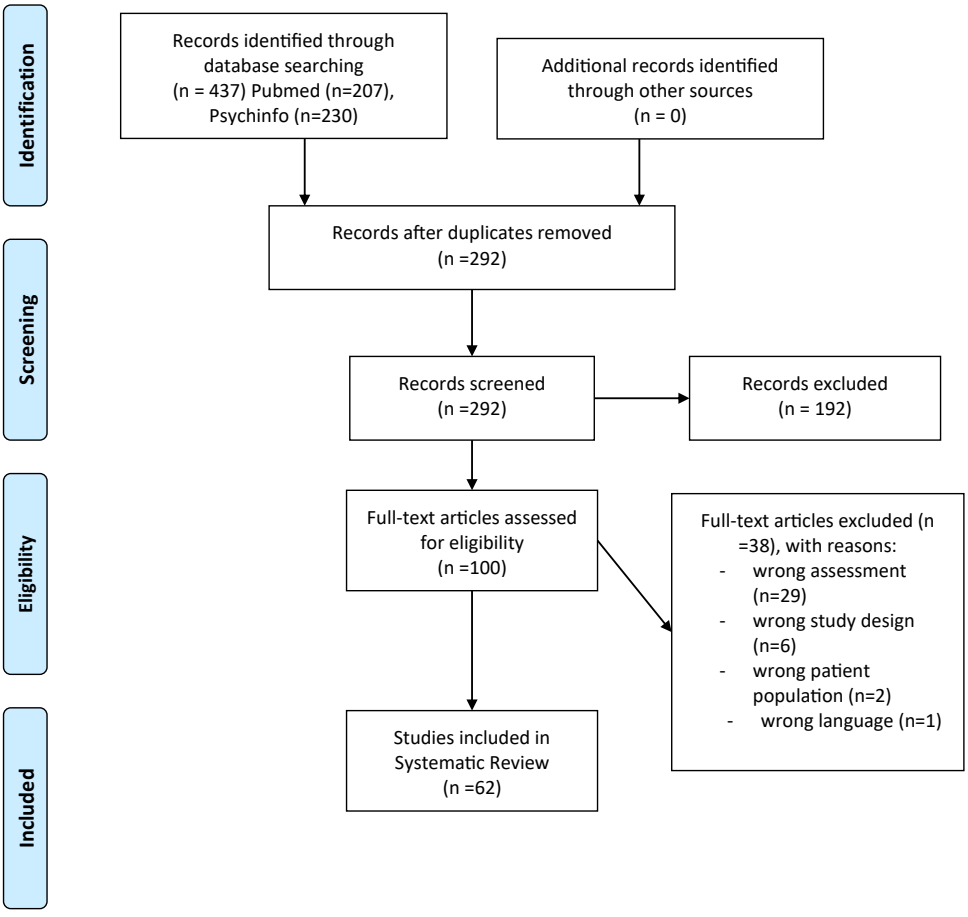

Fig. 1. PRISMA flow diagram. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6 (7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org

Table 1. Characteristics of the studies

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Albein-Urios et al. (2014)	To test if impulsivity can describe transdiagnostic subgroups of individuals who suffer from addiction with different clinical presentations and outcomes based on craving, psychosocial adjustment, and quality of life.	CS	Clinical	GD, CUD	M/F	96	DSM-IV criteria	WCS
Angelo et al. (2013)	To evaluate the efficacy of a physical activity program as adjuvant therapy to treat pathological gambling.	L	Clinical	GD outpatients	M/F	63	DSM-IV criteria, GFS	PCS, WCS
Ashrafioun et al. (2012)	To test the effect of exposure to gambling-related cues on the Gambling Urge Scale (GUS); to assess the convergent validity of the GUS with others craving measures; and to measure the associations between the GUS and social desirability bias and personality traits.	V	Non-clinical	University students	M/F	48	SOGS-RA, GRSQ, GBQ	GUS, PCS, GAS, PG-YBOCS
Ashrafioun et al. (2013)	To assess the psychometric proprieties of the Gambling Urge Scale university students who gamble regularly.	V	Non-clinical	University students	M/F	250	SOGS-RA, GRSEQ, GPS, GBQR	GACS
Bouchard et al. (2017)	To evaluate the safety and the potential clinical usefulness of virtual reality to induce cravings in the frame of cognitive behavioral therapy for gambling disorder.	L	Clinical	GD patients, individuals familiar with video lottery terminals	M/F	Study 1: 64; Study 2: 34	SOGS	GCS
Brevers et al. (2011)	To compare problem gamblers with controls on the attentional bias for gambling-related cues using a flicker paradigm; and to measure the association between gambling self-reported craving and maintenance of attention toward gambling cues.	L	Clinical	GD, HC	M/F	75	SOGS	GACS
Brevers et al. (2018)	To test if addiction-related cues impact proactive inhibition (the limitation of actions in preparation for stopping) in participants who are motivated to quit gambling or cannabis use.	CS	Clinical	Quitting-motivated individuals with GD who were not in treatment	M/F	75	PGSI	GACS
Caillon et al. (2019)	To test the effectiveness of an online temporary and voluntary 7-day self-exclusion program for at-risk gamblers compared to a control group, and to evaluate the impact of the program on gambling severity, cognitive distortions and craving.	L	Non-clinical	Community at-risk gamblers	M/F	60	PGSI	GACS

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Canale et al. (2019)	To assess the psychometric properties of the GACS French version in two independent samples of community gamblers.	V	Non-clinical	Community gamblers	M/F	421	PGSI	GACS
Caselli and Spada (2015)	To test the fit of a metacognitive model of desire thinking and craving in community sample and clinical population.	CS	Clinical and non-clinical	GD, AUD, Tabaco users, problematic internet users	M/F	493	DSM5, SOGS	GACS
Ciccarelli et al. (2016a)	To compare attentional bias in problem gamblers with controls using a modified Posner task; and to measure its associations with craving, emotional dysregulation, depression anxiety and stress.	CS	Non-clinical	Problem gamblers and HC	M	108	SOGS	GACS
Ciccarelli et al. (2016b)	To compare non-problem gamblers, problem gamblers, and abstinent pathological gamblers on attentions bias and craving; and to measure associations between attentional processing, craving and emotional distress in each group.	L	Clinical and non-clinical	GD, non-problem gamblers, problem gamblers	M	75	SOGS, DSM5	GACS
Ciccarelli, Cosenza, D'Olimpio, Griffiths, and Nigro (2019)	To measure the associations between chasing, delay discounting and craving in gamblers; and to determine predictors of chasing, controlling for gambling severity.	L	Non-clinical	Non-problem gamblers, problem gamblers and pathological gamblers	M/F	128	SOGS	GACS
Ciccarelli, Cosenza, Griffiths, et al. (2019)	To compare attentional bias for gambling stimuli between adolescents problem gamblers and non-problem gamblers; and to measure the association of attentional bias with craving and alcohol consumption.	CS	Non-clinical	Problem and non-problem gamblers	M/F	87	SOGS-RA	GACS
Ciccarelli, Cosenza, Griffiths, et al. (2019)	To measure the associations between gambling severity, craving, maladaptive personality traits, and alcohol use among adolescents.	CS	Non-clinical	Gamblers and non-gamblers	M/F	550	SOGS-RA	GACS
Cornil et al. (2018)	To test if the elaborated intrusion theory of desire (a cognitive model of craving) fits gambling craving.	L	Non-clinical	Community regular gamblers	M/F	31	PGSI	Adaptation of a questionnaire developed to assess the component of the EIT related to substance craving (May et al., 2004)

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Cornil et al. (2019)	To assess the psychometric properties of a gambling-adapted version of the CEQ that measures the strength of craving, and the frequency of cravings over time.	V	Non-clinical	Recreational gamblers from general community	M/F	274	PGSI	g-CEQ-F
Cosenza et al. (2020)	To determine predictors of chasing behaviors in Italian adolescents, considering variables of craving, temporal perspective, alcohol use, and gambling severity.	CS	Non-clinical	Problem gamblers and non-problem gamblers	M/F	364	SOGS-RA	GACS
Côté et al. (2020)	To measure the impact of the coping strategies used by the partners of pathological gamblers on their gambling habits, the mechanisms that account for the impact of these coping strategies and the perceptions of their effectiveness.	CS	Clinical	GD patients and their partners	M/F	19	PGSI	Non-validated scale
Crockford et al. (2005)	To compare the neural response to visual gambling cues between pathological gamblers and controls.	L	Non-clinical	HC, gamblers, heavy smokers	M	20	SOGS, SCID-I-PG	Non-validated self-reported questionnaire
de Brito et al. (2017)	To evaluate the effectiveness of treating gambling disorder with topiramate concomitant to a brief cognitive intervention	L	Clinical	GD patients	M/F	30	PG- YBOCS, GBQ	G-SAS,
de Castro et al. (2007)	To measure craving and emotional states correlations separately for alcoholics and pathological gambling.	CS	Clinical	GD, AUD	M/F	92	SCI-PG	WCS, PACS for GD
Dickler et al. (2018)	To evaluate the effectiveness of transcranial direct current stimulation (TMS) over the DLPFC on neural metabolites levels in gambling disorder.	L	Clinical	GD patients	M/F	16	DSM 5 criteria for GD, SOGS	VAS, GCS
Donati, et al. (2021)	To compare treated GD patients pre COVID-19 to the lockdown period, in terms of gambling behaviors and craving.	CS	Clinical	GD patients	M/F	135	SOGS, DSM5	N/S
Dunsmuir et al. (2018)	To test the temporal stability in measure of craving and cognition-oriented constructs; and to measure if baseline symptom severity in gambling urge is associated with change in gambling-related cognitions and how this relationship is moderated by gender.	L	Clinical	Treatment seeking GD	M/F	223	VGS, DSM-IV criteria	GUS

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Duvarci and Varan (2000)	To compare Turkish pathological gamblers to non-pathological gamblers in various gambling behaviors, including craving.	CS	Clinical	Gamblers and GD and HC	M	73	SOGS, DSM-IV criteria	Non-validated self-reported questionnaire
Fernie et al. (2014)	To test the role of desire thinking in gambling in a cohort of participants recruited from community and clinical settings.	CS	Clinical and Non-clinical	Community gamblers	M/F	95	SOGS	GACS and DTQ
Gaetti and Tavares (2017)	To assess psychometric proprieties of the Gambling Follow-up Scale, Self-Report version (GFS-SR) in individuals with gambling disorder; and to determine predictors of gambling remission among the measures obtained from the GFS-SR.	V	Clinical	GD patients	M/F	120	DSM5, SOGS	GFS-SR
Gay et al. (2017)	To evaluate the efficacy of active HF-rTMS over the left dorsolateral prefrontal cortex (DLPFC) on craving and gambling behavior in adults seeking treatment for GD.	L	Clinical	Treatment-seeking patients with GD	M/F	22	SOGS, PG-YBOCS	VAS
Geisel et al. (2018)	To compare leptin blood levels between patients with Pathological Gambling, Internet Gaming Disorder, Alcohol Use Disorder and healthy controls; and to measure the associations between leptin and craving.	CS	Clinical	AUD, GD, IGD, HC	M	76	PG-YBOCS	PG-YBOCS
Goudriaan et al. (2010)	To compare cue reactivity in problem gamblers, heavy smokers and healthy controls.	L	Clinical	Problematic gambling, smokers, HC	M	52	SOGS, DSM-IV-TR	Non-validated self-reported questionnaire
Hawker et al. (2021)	To measure associations between real-time gambling cravings and self-efficacy with gambling behavior, and the moderating role of gambling, mental health, and addiction-related variables.	L	Non-clinical	Gamblers	M/F	97	PGSI, SGHS	Six items measuring gambling cravings (occurrence, frequency, intensity), self-efficacy (craving self-efficacy, Gambling self-efficacy) and gambling episodes.

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Hollander et al. (2005)	To evaluate the efficacy of sustained-release lithium carbonate in the treatment of patients with pathological gambling and bipolar spectrum disorders.	L	Clinical	GD and Bipolar Disorder	M/F	29	SOGS, Y-BOCS-PG, CGI, pathological gambling improvement scale, pathological gambling Behavioral Self-Report Scale	VAS
Hollingshead et al. (2016)	To determine if the motivation to play social casino games predicts changes in self-reported gambling behaviors in a community sample of gamblers.	CS	Non-clinical	Gamblers who play social casino games	M/F	140	PGSI	Non-validated six-item scale
Jacoby et al. (2013)	To compare gamblers migrants in Germany with Germans regarding their gambling problems, motivation and craving to gamble; and to determine predictors of vulnerability to pathological gambling among migration-related factors (i.e.: gambling patterns, severity of gambling, motivation and craving, acculturative stress, cultural and religiosity factors and family/peer gambling related differences).	CS	Non-clinical	Gamblers (migrants vs Germans) with varying degrees of gambling problems	M/F	106	KFG	PG-YBOCS
Kober et al. (2016)	To compare brain activity in individuals with gambling disorder, cocaine use disorder and healthy controls during exposure to cocaine, gambling and sad scenarios	L	Clinical	GD, CUD, HC	M/F	103	SCID-I, SCI-PG, SOGS	1–10 scale for craving (1 = not at all, 10 = a lot).
Koehler et al. (2013)	To compare functional connectivity in the prefrontal and the mesolimbic system between pathological gamblers and controls; and to measure the associations between function connectivity and impulsivity, smoking and craving.	CS	Non-clinical	Non-treatment seeking individuals with GD and HC	M	38	KFG, G-SAS	VAS
Limbrick-Oldfield et al. (2017)	To compare cue-related brain responses to gambling-related appetitive stimuli between gambling disorder patients and controls.	L	Clinical	GD, HC	M	38	DSM-IV criteria, PGSI	VAS

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Linnet et al. (2017)	To evaluate the efficacy of CBT in gambling disorder patients with a comorbid diagnosis of depression compared with gambling disorder patients without comorbidity.	L	Clinical	GD patients	M/F	61	SOGS, SCID-I	VAS
McGrath et al. (2013)	To test if acutely administered nicotine can affect gambling craving in gamblers who smoke.	L	Non-clinical	Regular gamblers, smokers	M/F	30	CPGI	GACS, VAS
Miedl et al. (2014)	To test if gambling-related cues modulates striatal reward signals and impulsivity in gamblers.	L	Non-clinical	Gamblers	M	22	SOGS	VAS
Pallanti et al. (2006)	To compare the behavioral and neuroendocrine responses to an oral single dose of m-CPP to placebo in pathological gamblers and controls.	L	Clinical	GD and Controls	M/F	52	Y-BOCS-PG	VAS
Pallanti et al. (2010)	To compare pathological gamblers to controls in their neuroendocrine and behavioral responses to Sumatriptan.	L	Clinical	GD, HC	M/F	41	SOGS	PG-YBOCS, CGI, VAS
Penna et al. (2018)	To evaluate the efficacy of exercise as treatment for gambling disorder on gambling severity, psychiatric comorbidities and craving.	L	Clinical	GD patients	M/F	59	DSM-5 criteria, GFS-SR	G-SAS
Petry and Kiluk (2002)	To compare gamblers with or without suicidal ideations in psychiatric, social/family, and gambling problems.	CS	Clinical	Treatment seeking GD	M/F	342	ASI, SOGS (Life-time and past-month versions)	One item 10-point Likert scale
Petry and Oncken (2002)	To compare treatment-seeking gamblers who smoke to treatment-seeking gamblers who do not smoke in different gambling related variables.	CS	Clinical	Gamblers (smokers/non-smokers)	M/F	317	ASI, SOGS (Life-time and past-month versions)	Non-validated self-reported questionnaire
Quintero et al. (2020)	To test if negative urgency is linked to resistance to extinction in an emotional associative learning task; and to measure the association between these two variables and gambling severity and craving.	CS	Non-clinical	Gamblers and non-gamblers	M/F	70	SOGS	GACS
Sauvaget et al. (2018)	To evaluate the efficacy of rTMS over the right DLPFC on reducing cue-induced cravings in treatment-seeking patients with pathological gambling.	L	Clinical	GD seeking treatment	M/F	30	DSM-IV criteria, GRCS	VAS, GACS
Shead et al. (2019)	To evaluate the feasibility of a mindfulness-based meditation intervention and its efficacy in changing gambling cravings and/or delay discounting.	L	Non-clinical	Gamblers	M/F	40	GAQ, PGSI	GACS

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Stewart and Wohl (2013)	To test di effectiveness of monetary limit pop-up messages in increasing adherence to self-proclaimed monetary limits.	L	Non-clinical	People with varying degrees of gambling problem	M/F	59	10-item gambling checklist from DSM	GACS
Sztainert et al. (2018)	To determine if plasma ghrelin concentrations are linked to higher gambling motivation and more gambling behaviors.	L	Non-clinical	Gamblers with different gambling degrees	M/F	101	PGSI	GACS
Takeuchi et al. (2016)	To compare loss aversion between pathological gambling and controls; and to measure the associations between loss aversion and craving in GD.	CS	Clinical	GD, HC	M	57	SOGS, SCI-PG	GACS
Tavares e tal. (2005)	To compare cravings in individuals with pathological gambling to individuals with alcohol-dependence; and to measure the associations between craving, negative emotional state, and temperament factors.	CS	Clinical	GD seeking treatment	M/F	150	SCID-I-PG	WCS
van der Tempel et al. (2019)	To evaluate the efficacy a 10-week group mindfulness-based intervention in treatment-seeking women with GD.	L	Clinical	Treatment-seeking women with GD	F	9	NODS	GACS
Melero Ventola et al. (2020)	To test the effectiveness of a mindfulness-based cognitive therapy (MBCT) group therapy in reducing craving to gamble.	L	Clinical	GD patients	M	33	NORC Diagnostic Screen for Gambling Disorders	Non-validated questionnaire
Wemm et al. (2020)	To compare heavy smokers and problem scratch-off lottery gamblers on psychological and hormonal reactions under conditions of high stress, and to see the impact of a stressor on craving.	L	Non-clinical	Controls, gamblers, and 30 heavy smokers	M/F	100	SOGS, DSM5	VAS
Wölfling et al. (2011)	To compare pathological gamblers to healthy on emotional processing of gambling-relevant and -irrelevant stimuli.	L	Non-clinical	GD, HC	M/F	30	SOGS, DSM-IV-TR	VAS
Wulfert et al. (2009)	To test if heart rate, subjective excitement, and urge to gamble are cue-specific and triggered by the preferred gambling activity cues or if they are generalized and triggered by any gambling-related cue.	L	Clinical	GD	M/F	94	SOGS, NODS	VAS
Yokotani et al. (2020)	To determine if gambling craving predicts income-generating, drug-related and violent offenses among inmates Japanese prisoners.	CS	Non-clinical	Inmates in prison	M	332	SOGS	GACS

(continued)

Table 1. Continued

Article	Aims	Design	Population	Sample	Gender	N	GD assessment tool	Craving assessment tool
Young and Wohl (2009)	To assess the psychometric properties and validate the multidimensional gambling craving scale (GACS) and to examine if GACS scores are persistent in the face of continued loss.	V	Non-clinical	Study 1: university students; Study 2: gamblers; Study 3: university students	M/F	Study 1: 220; Study 2: 145; Study 3: 46	PGSI	GACS
Zack et al. (2016)	To evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) and continuous theta burst stimulation (cTBS) on gambling reinforcement and associated responses.	L	Non-clinical	Community non-treatment-seeking men with GD	M	9	SOGS, NODS	VAS
Zack et al. (2019)	To evaluate the efficacy of D1activation and the moderating effect of impulsivity on GD individual.	L	Clinical	GD patients with varying degrees of impulsivity	M/F	30	SOGS	VAS

Note. Addiction Severity Index (ASI), Canadian Problem Gambling Index (CPGI), Clinical Global Impression Severity of Illness Scale (CGI), Cocaine Use Disorder (CUD), Cognitive Behavioral Therapy (CBT); Cross-sectional (CS), Desire Thinking Questionnaire (DTQ), Gamblers' Beliefs Questionnaire (GBQ), Gamblers' Beliefs Respond Questionnaire (GBRQ), Gambling Activity Questionnaire (GAQ), Gambling Craving Experience Questionnaire – Frequency (g-CEQ-F), Gambling Craving Scale (GACS), Gambling Disorder (GD), Gambling Follow-up Scale (GFS),Gambling Follow-up Scale Self-Report Version (GFS-SR),Gambling Passions Scale (GPS), Gambling Refusal Self-Efficacy Questionnaire (GRSEQ), Gambling Symptom Assessment Scale (G-SAS), Gambling Symptom Assessment Scale (G-SAS), Gambling Urge Scale (GUS), Gambling-Related Cognitions Scale (GRCS), German Questionnaire For Gambling Behavior "Kurzfragebogen zum Glücksspielverhalten" (KFG), Longitudinal (L), National Opinion Research Center DSM Screen for Gambling Problems (NODS), Pathological Gambling Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), Penn Alcohol Craving Scale (PACS), Pennsylvania Craving Scale (PCS), Problem Gambling Severity Index (PGSI), Short Gambling Harms Scale (SGHS), Short Questionnaire on Gambling Behaviour (KFG), South Oaks Gambling Screen (SOGS), South Oaks Gambling Screen-Revised Adolescents (SOGS-RA), Structured Clinical Interview for DSM-IV for pathological gambling (SCID-I-PG), Structured Clinical Interview for Pathological Gambling (SCI-PG), Validation of an instrument (V), Victorian Gambling Screen (VGS), Visual analog scale (VAS), Weiss Craving Scale (WCS).

Duvarci & Varan, 2000; Fernie et al., 2014; Hawker, Merkouris, Youssef, & Dowling, 2021; Hollingshead, Kim, Wohl, & Derevensky, 2016; Jacoby et al., 2013; McGrath, Dorbeck, & Barrett, 2013; Miedl, Büchel, & Peters, 2014; Petry & Oncken, 2002; Quintero et al., 2020; Wemm, Cao, Han, & Wulfert, 2020; Wulfert, Maxson, & Jardin, 2009), and **individuals with GD** (Albein-Urios, Pilatti, Lozano, Martínez-González, & Verdejo-García, 2014; Angelo, Tavares, & Zilberman, 2013; Linnet, Jeppsen Mensink, de Neergaard Bonde, & Winterdahl, 2017; Bouchard et al., 2017; Brevers et al., 2018, 2011; de Brito et al., 2017; Caselli & Spada, 2015; de Castro, Fong, Rosenthal, & Tavares, 2007; Cornil et al., 2019; Côté et al., 2020; Crockford et al., 2005; Dickler et al., 2018; Donati et al., 2021; Dunsmuir, Smith, Fairweather-Schmidt, Riley, & Battersby, 2018; Duvarci & Varan, 2000; Gaetti & Tavares, 2017; Gay et al., 2017; Geisel et al., 2018; Goudriaan et al., 2010; Hollander, Pallanti, Allen, Sood, & Rossi, 2005; Kober et al., 2016; Koehler et al., 2013; Limbrick-Oldfield et al., 2017; Melero Ventola, Yela, Crego, & Cortés-Rodríguez, 2020; Morasco, Weinstock, Ledgerwood, & Petry, 2007; Pallanti et al., 2010; Pallanti, Bernardi, Quercioli, DeCaria, & Hollander, 2006; Penna, Kim, de Brito, & Tavares, 2018; Petry & Kiluk, 2002; Quintero et al., 2020; Sauvaget et al., 2018; Sztainert et al., 2018; Takeuchi et al., 2016; Tavares, Zilberman, Hodgins, & El-Guebaly, 2005; van der Tempel et al., 2019; Wemm et al., 2020; Wölfling et al., 2011; Yokotani, Tamura, Kaneko, & Kamimura, 2020; Zack et al., 2019, 2016). 5 studies included individuals with alcohol use disorder (de Castro et al., 2007; Caselli & Spada, 2015; Duvarci & Varan, 2000; Geisel et al., 2018; Tavares et al., 2005), 2 included individuals with cocaine disorder (Albein-Urios et al., 2014; Kober et al., 2016), and 7 studies included samples of adolescents and young adults (Ashrafioun, McCarthy, & Rosenberg, 2012; Ashrafioun, Rosenberg, Cross, & Brian, 2013; Ciccarelli, Cosenza, Griffiths, Nigro, & D'Olimpio, 2019; Cosenza, Matarazzo, Ciccarelli, & Nigro, 2020; Shead, Champod, & MacDonald, 2019; Stewart & Wohl, 2013; Young & Wohl, 2009).

Assessment of GD. Multiple validated psychometric instruments and clinical interviews were used in the different studies to assess GD severity. The most commonly used tools were the South Oaks Gambling Screen (SOGS; Lesieur & Blume, 1987), and the Problem Gambling Severity Index (PGSI; Ferris & Wynne, 2001). Some other psychometric instruments used were: the South Oaks Gambling Screen Revised for Adolescents (SOGS-RA; Winters, Stinchfield, & Fulkerson, 1993), the Short Gambling Harms Scale (SGHS; Browne et al., 2016), the Short Questionnaire on Gambling Behaviour (KFG; Petry, 1996), the Addiction Severity Index (ASI; McLellan et al., 1985), the Canadian Problem Gambling Index (CPGI; Ferris & Wynne, 2001), the Gambling Symptom Assessment Scale (G-SAS; Kim & Grant, 2001), the Victorian Gambling Screen (VGS; Ben-Tovim, 2001). Moreover, some questionnaires measuring aspects related to GD, such as the Gambling-Related Cognitions Scale (GRCS; Raylu & Oei, 2004a), the Gamblers' Beliefs Questionnaire (GBQ; Steenbergh, Meyers, May, & Whelan, 2002), the Yale Brown Obsessive Compulsive Gambling Scale (Y-BOCS-PG; Pallanti, DeCaria, Grant, Urpe, & Hollander, 2005), the Gambling Passions Scale (GPS; Rousseau, Vallerand, Mageau, & Provencher, 2002), the Gambling Refusal Self-Efficacy Questionnaire (GRSEQ; Casey, Oei, Melville, Bourke, & Newcombe, 2008), and the Clinical Global Impression (CGI) Pathological Gambling Improvement Scale (Guy, 1976), among others, were included in different studies. There is no clear consensus on whether the craving construct should be assessed as a state (a transient and context-determined phenomenon) or as a trait. For example, the g-CEQ has two forms: frequency (more in a trait perspective) and strength (in a state perspective).

The main clinical interview used in the studies included in this review was the Structured Clinical Interview for DSM-IV–Patient Edition (SCID; First, Spitzer, Gibbon, & Williams, 1995).

Assessment of gambling craving. In the studies assessed, the Gambling Craving Scale (GACS; Young & Wohl, 2009) was the most widely used validated instrument to assess gambling craving. Specifically, 26 studies in the systematic review used this instrument, either alone or in combination with other craving assessments. Other validated instruments used to measure craving were: the Weiss Craving Scale (WCS; Weiss, Griffin, & Hufford, 1995), the Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999) adapted to evaluate craving for gambling (de Castro et al., 2007), the Pathological Gambling Yale-Brown Obsessive Compulsive Scale (PG-YBOCS; Pallanti et al., 2005), the Gambling Urge Scale (GUS; Raylu & Oei, 2004a, b), the Desire Thinking Questionnaire (DTQ; Caselli & Spada, 2011), the Gambling Symptom Assessment Scale (G-SAS; Kim, Grant, Potenza, Blanco, & Hollander, 2009), and the Gambling Craving Experience Questionnaire—Frequency (g-CEQ-F; Cornil et al., 2019).

The questionnaires measuring gambling craving are adapted from questionnaires developed in the substance use field. For example, the GACS is adapted from the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991), the GUS is adapted from the alcohol urge questionnaire (Bohn, Krahn, & Staehler, 1995), the Penn Gambling Craving Scale is adapted from the PACS (Flannery et al., 1999), and the g-CEQ is adapted from the Craving Experience Questionnaire (May et al., 2014).

In addition, some studies did not use validated questionnaires to assess gambling craving, but rather visual analogical scales (used by 16 studies) or item/s specifically designed for a particular study (8 studies) (see Table 2).

Association between gambling craving and gambling-related factors

Several studies included in the present systematic review explored an association between gambling craving and gambling-related factors, such as gambling or gambling episodes (Fernie et al., 2014; Hawker et al., 2021), GD severity (Quintero et al., 2020), high-risk positive reinforcement

Table 2. Craving assessment instruments

Full name	Acronym	Reference	Description
Gambling craving scale	GACS	Young and Wohl (2009)	9 items, 3 subscales: desire, anticipation, relief *The structure of the GACS is questioned by Canale et al. (2019) who established a two-factor structure, in line with the Questionnaire of Smoking Urges
Weiss Craving Scale	WCS	Weiss et al. (1995)	5 items, craving in the 24h before the assessment: strength and frequency of urges, response to craving cues, and likelihood of relapsing if facing the environment where the addictive behavior usually takes place
Penn Alcohol Craving Scale adapted to evaluate craving for gambling	PACS	Original: Flannery, Volpicelli & Pettianati, (1999) Adaptation to GD: de Castro et al. (2007)	5 items (adapted from alcohol to GD): frequency and time spent thinking about gambling, difficulty in resisting relapse opportunities, and strength of craving episodes
Pathological Gambling Yale-Brown Obsessive–Compulsive Scale	PG-YBOCS	Pallanti et al. (2005)	10 items: Gambling Thoughts/Urges subscale (the strength of urges to gamble), and Gambling Behaviors subscale
Gambling Urge Scale	GUS	Rousseau, Vallerand, Ratelle, Mageau, and Provencher (2002)	6 items to assess current craving to gamble
Desire Thinking Questionnaire	DTQ	Caselli and Spada (2011)	10 items to assess desire thinking. 2 sub-factors: verbal perseveration and imaginal prefiguration
Gambling Symptom Assessment Scale	G-SAS	Kim et al. (2009)	12 items to assess GD severity. A craving sub-score is derived from the sum of items 1 to 7 that assess desire to gamble and gambling related thoughts
Gambling Craving Experience Questionnaire	g-CEQ	Cornil et al. (2019)	Two forms: frequency (more in a trait perspective) and strength (in a state perspective) with 9 items each. Each form includes 3 subscales: intensity, (quality of the) imagery and intrusiveness (of the thoughts) with 3 items each

situations (Hawker et al., 2021), chasing (Ciccarelli, Cosenza, D'Olimpio, Griffiths, & Nigro, 2019; Cosenza et al., 2020), attentional bias for gambling-related cues (Brevers et al., 2011; Ciccarelli, Nigro, Griffiths, Cosenza, & D'Olimpio, 2016a), loss aversion (Takeuchi et al., 2016), income-generating offenses (Yokotani et al., 2020) and adolescent gambling involvement (Ciccarelli, Nigro, Griffiths, D'Olimpio, & Cosenza, 2020).

On the one hand, some authors have described an association between craving and gambling-related factors. For example, Fernie et al. (2014) highlighted that craving, among other factors, correlates with gambling. Moreover, a positive association between craving and facilitation bias for gambling-related cues in the early orientation of attention was described (Ciccarelli et al., 2016a), although Brevers et al. (2011) did not find an association between these factors in the problematic gambling group. In addition, an association between higher gambling craving and lower loss aversion levels was described (Takeuchi et al., 2016). Finally, different factors, such as emotional states (de Castro et al., 2007) and negative urgency (Quintero et al., 2020), have been associated with gambling craving. More specifically, gambling craving seems to be negatively correlated with positive emotional states (de Castro et al., 2007).

On the other hand, some studies have identified gambling craving as a predictor. For example, Quintero et al. (2020) stressed that greater craving levels would predict greater GD severity and stressed that greater gambling craving was predicted by negative urgency (understood as the tendency to carry out impulsive behaviors under conditions of negative affect). Similarly, Hawker et al. (2021) observed that gambling cravings were predictors of gambling episodes, and that high-risk positive reinforcement situations exacerbated the intensity of gambling craving levels. Ciccarelli, Cosenza, D'Olimpio, et al. (2019) found that cravings could predict the decision to chase and chasing persistence. Yokotani et al. (2020) observed that craving predicted income-generating offenses and suggested that craving may be related with financial issues. Finally, in the specific case of adolescents, the anticipation and desire subscales of the GACS may be one of the best predictors of adolescent gambling involvement (Ciccarelli et al., 2020).

Gambling craving according to different populations

On the one hand, some studies compared the levels of gambling craving in individuals with and without GD. Problem gamblers, in comparison with non-problem gamblers (Ciccarelli, Cosenza, D'Olimpio, et al., 2019; Ciccarelli et al., 2016a; Wölfling et al., 2011) or social gamblers (Wulfert et al., 2009) seem to report higher levels of craving. Similarly, Duvarci and Varan (2000) also observed a higher percentage of craving in the group of individuals with GD (58.1–67.7%),

compared to the non-pathological group (14.6–21.4%), and the authors suggested that craving may play an essential role in the maintenance of the disorder.

On the other hand, some authors have compared gamblers or gamblers with GD according to different characteristics. For example, compared to non-daily-smoker gamblers, the daily-smoker gamblers showed a higher gambling craving. Moreover, in a study comparing migrant gamblers and German gamblers, it was observed that migrants presented higher levels of craving (Jacoby et al., 2013). Petry and Kiluk (2002) compared individuals with GD with or without a history of suicidal ideation, observing that those with suicidal ideation presented higher levels of gambling craving.

Finally, some authors compared craving levels in individuals with GD and other clinical conditions. For example, Tavares et al. (2005) observed higher craving in individuals with GD compared to individuals with alcohol dependence.

Craving in GD treatment

Several studies implemented some specific intervention in GD and assessed its impact in reducing gambling craving (see Table 3).

Pharmacological interventions. Four studies implemented pharmacological interventions and explored their impact on gambling craving. One study reported that topiramate had a greater efficacy than a placebo in reducing craving when concomitant to a brief cognitive intervention (de Brito et al., 2017). Two studies tested the hypothesis of serotoninergic system impairment in GD with mixed results. The first one tested a single-dose administration of partial 5-HT agonist m-CPPmg/kg and compared it with a placebo both in GD and healthy controls. The results show no significant craving variation after placebo and m-CPP in GD or controls. The authors hypothesized that, contrary to alcohol abuse craving, gambling cravings, as well as cocaine use, may be more related to other monoaminergic systems and dopamine (Pallanti et al., 2006). However, in a later study, results of exploring craving responses to Sumatriptan (a selective 5-HT1B/1D agonist) in patients with GD compared to healthy controls led the authors to state towards the presence of a serotonergic alteration in GD similar to the one observed in alcohol use disorder (Pallanti et al., 2010). Additionally, medications that activate D1 could restrain chasing in high-impulsivity gamblers, and the D1 blockade could be effective for high impulsivity gamblers concerned with craving, as suggested in one study with a placebo-controlled, double-blind, counterbalanced design (Zack et al., 2019). Finally, one study was conducted with individuals suffering from GD and bipolar spectrum disorder and reported the efficacy of sustained-release lithium carbonate on reducing craving as well as other clinical measures (Hollander et al., 2005).

Psychological and behavioral interventions. Nine of the studies implemented psychological- or behavioral-related interventions and explored their impact on craving. Most of these studies reported some impact on reducing craving.

Regarding behavioral-related interventions, a randomized clinical trial for at-risk online gamblers (Caillon et al., 2019) reported the effectiveness of a 7-day self-exclusion measure to specific websites on reducing craving after a window time of two months. The authors suggest the 7-day intervention should have a longer duration to have greater impact on reducing craving. Two studies explored the benefits of physical exercise on reducing gambling craving with significant results. One study reported the benefits of physical exercise on reducing gambling craving in GD, with no significant differences regarding the type of exercise (i.e.: stretching or a more structured exercise program; Penna et al., 2018). The other study found a significant decrease in craving after each exercise session and at the end of the physical exercise program (Angelo et al., 2013).

Three studies were based on mindfulness approaches. Two of the studies were conducted with clinical samples. The first study specifically focused on treatment-seeking women with GD and reported that a 10-week mindfulness-based intervention was effective in significantly reducing craving in 75% of the individuals (van der Tempel et al., 2019). The second study compared effectiveness in reducing gambling craving through a mindfulness-based cognitive therapy (MBCT) and a mutual-aid group intervention (treatment as usual; Melero Ventola et al., 2020). In this study, both interventions had an impact on the participants' craving; however, the mutual-aid group intervention reduced the intensity of cravings, whereas the MBCT intervention decreased all craving-related scores (i.e., intensity, frequency, urgency, total craving). Lastly, one study was performed in a non-clinical population (i.e., university students with some gambling experience) and reported that a brief audio-guided mindfulness-based intervention was effective in reducing gambling craving in contrast to the comparison control task (audiobook listening), which did not present any significant impact on craving (Shead et al., 2019).

Additionally, one study described a virtual reality tool to safely trigger the craving to gamble as an exposure exercise during cognitive behavioral therapy (CBT) for GD. This virtual reality tool was no more effective than the standard CBT protocol, and the authors suggest that more research should be conducted to further increase its efficiency (Bouchard et al., 2017). Another study focused on craving and comorbidity by exploring differences in individuals suffering from GD with and without depression (Linnet, Jeppsen Mensink, de Neergaard Bonde, & Winterdahl, 2017). According to this study, craving was not significantly different between groups in both pre- or post-treatment assessments, and both groups (with and without depression) significantly decreased their craving at the end of treatment.

Finally, one study found that baseline (pre-treatment) craving had no effect on gambling-related cognitions at the end of CBT treatment and vice versa (Dunsmuir et al., 2018). However, in this study, with time, craving was found to be significantly stronger in men compared to women when adjusted for cognition paths.

Neuromodulation interventions. Four studies explored the effect of a neuromodulation intervention on gambling

Table 3. Type of intervention used and principal results regarding craving

Article	Intervention	Results for craving
Albein-Urios et al. (2014)	x	- The subgroup of addicted patients classified in Class 1 showed greater trait impulsivity and poorer cognitive impulsivity. This group was characterized by increased levels of craving, worse psychosocial functioning, and lower perceived quality of life.
Angelo et al. (2013)	Physical activity program	- The reduction in craving following each session and at the end of the program. - The post-session reduction in craving was accompanied by a post-program reduction in anxiety but not by a post-program reduction in depressive symptoms. - The craving reduction was associated with a variation in prolactin levels but not with variations in levels of cortisol or adrenocorticotropic hormone.
Ashrafioun et al. (2012)	Cue exposure to gambling stimuli to elicit subjective craving using two formats (photographic format versus imagery scripts)	- Self-reported craving (GUS) increased following exposure to gambling stimuli in both presentation formats. However, a greater change in craving was shown with the inclusion of images compared to the photographic format. - The post-cue exposure GUS correlated with other questionnaires assessing craving to gamble, and other variables associated with gambling (e.g., gambling-related problems, preoccupation with gambling, distorted gambling beliefs, gambling refusal self-efficacy, sensation seeking). - No correlation between GUS and social desirability bias.
Ashrafioun et al. (2013)	Cue exposure to induce craving was tested using two types of stimuli (gambling versus non-gambling activity), and two types of presentation format (photographic versus imagery scripts)	- Convergent validity was shown by the correlation between the GUS and the GACS scores. - GUS scores increased significantly following exposure to gambling cues, but not following exposure to non-gambling cues, regardless of the format by which cues were presented. - After exposure to gambling cues, GUS craving scores were significantly correlated with all three subscales of another measure of craving to gamble, gambling-related problems, passionate attachment to gambling, distorted gambling beliefs and gambling refusal self-efficacy.
Bouchard et al. (2017)	CBT and 2 imaginal exposure exercises (imagination condition) or CBT with the 2 exposure exercises conducted using VR immersion (VR condition)	- VR can be used to induce cravings in gamblers. - The feasibility and usefulness of integrating VR in CBT to identify more high-risk situations and dysfunctional thoughts; inducing craving during relapse prevention exercise related to treatment outcomes. - Compared to inducing craving in imagination, using VR does not lead to stronger, longer or more out-of-control craving.
Brevers et al. (2011)	The attentional bias was measured using the flicker paradigm with gambling-related or neutral items	- In the GD group, measures of gambling-related attentional bias were not associated with craving for gambling and gambling dependence severity.
Brevers et al. (2018)	Motivational state of gambling was induced by a personalized mental imagery script to re-experience a recent craving situation, compared to a control condition (relaxation mental imagery script)	- Script imagery-induced changes in gambling craving (GACS). This change was higher in the personalized mental imagery compared to the relaxation mental imagery script. - Proactive response inhibition decrease as a function of the change in craving anticipation scale of GACS: the greater the anticipated positive outcomes of gambling, the less the proactive response inhibition.
Caillon et al. (2019)	Self-exclusion procedure on favorite website	- After 2 months of self-exclusion procedure, the gambling-related cognitions and the subscale "desire" of the GACS decreased.
Canale et al. (2019)	A craving induction procedure by audio-guided imagery was used to test the GACS	- The structural validity of the original 3-factor solution (anticipation, desire, relief) was not confirmed. Additional exploratory analysis showed the good fit of a 2-factor solution: an intention and desire for gamble dimension and a relief dimension. - The 2-factor structure of the GACS was confirmed in the second independent sample (cross validation).

(continued)

Table 3. Continued

Article	Intervention	Results for craving
Caselli and Spada (2015)	x	- The path models where examined within each sample, showing that positive metacognitions about desire thinking are associated with imaginal prefiguration and verbal perseveration. Verbal perseveration is then associated with negative metacognitions about desire thinking and craving. - The metacognitive model of desire thinking and craving is suggested as innovative transdiagnostic lines of treatment for addictive behaviors.
Ciccarelli et al. (2016a)	A modified version of Posner Task (attentional bias task) with gambling-related stimuli	- Compared to non-problem gamblers, problem gamblers showed higher levels of craving. - Positive correlations between facilitation bias at 100 ms and craving were observed.
Ciccarelli et al. (2016b)	A modified version of Posner Task with gambling-related stimuli	- A relationship between craving and facilitation bias in the early orientation of attention emerged. - Problem gamblers reported a higher level of craving compared to the other groups.
Ciccarelli, Cosenza, Griffiths, et al. (2019)	x	- Regression analyses indicated that heightened levels of craving and the inability to tolerate delay in gratification, along with gambling severity, predicted both the decision to chase and chasing persistence.
Ciccarelli, Cosenza, Griffiths, et al. (2019)	x	- Problem gamblers displayed facilitation bias for gambling cues and reported higher levels of craving (GACS).
Ciccarelli, Cosenza, Griffiths, et al. (2019)	x	- At-risk gamblers and problem gamblers scored higher on GACS, PID-5-BF and AUDIT compared to both non-gamblers and non-problem gamblers. - Antagonism and Disinhibition PID-5-BF dimensions, Anticipation and Desire GACS subscales, and AUDIT total score were the best predictors of adolescent gambling involvement.
Cornil et al. (2019)	x	- Six triggers for craving were classified as relevant: external cues, associated thoughts, positive affect, visual imagery, boredom and spontaneous thoughts. - Regarding craving characteristics, seven descriptors were classified as relevant: self-control, thoughts about mood improvement, tactile imagery, comfort expectation, context, visual imagery and distraction.
Cornil et al. (2019)	A craving induction procedure using an audio-guided imagery scenario was used to test the structure of the g-CEQ-S	- The confirmatory factor analyses supported the validity of the expected three-factor model of the strength and frequency forms of the g-CEQ and showed a better model fit than a one-factor solution. - Moderate to strong correlations between the g-CEQ-S and the GACS supporting its construct validity. - All subscales of both versions of the g-CEQ significantly correlated with problem gambling symptoms, gambling motives (except financial motives), and gambling cognitions. - Various subscales of the g-CEQ-F correlated gambling frequency. - The imagery subscale of the g-CEQ-F correlated with sensation seeking. - The intensity subscale of the g-CEQ-S showed significant correlation with positive affect of the PANAS.
Cosenza et al. (2020)	A chasing task using two experimental conditions (control vs loss)	- The choice to continue or to stop playing did not vary as a function of experimental condition (control vs. loss). - The decision to chase depended mostly on craving, whereas chasing propensity was affected by craving and alcohol misuse.
Côté et al. (2020)	x	- Eight strategies were shown to have a considerable impact (moderate to high) that helped reduce gambling cravings.

(continued)

Table 3. Continued

Article	Intervention	Results for craving
		- Eight strategies that mostly reduced considerably (moderate to strong impact) gambling cravings, but that also had the reverse effect in certain circumstances. - Three strategies have a considerable impact on increasing gambling craving.
Crockford et al. (2005)	fMRI during visual presentations of gambling-related video alternating with video of nature scenes	- Mean baseline craving for gamblers was higher than controls, and gamblers reported a significant increase in mean craving after the experiment. - Gamblers and controls exhibited overlap in areas of brain activity in response to the visual gambling cues. However, gamblers showed a greater activity in the right dorsolateral prefrontal cortex and left occipital cortex.
de Brito et al. (2017)	Randomized, double-blind placebo-controlled, flexible dose topiramate	- Topiramate proved superior to a placebo in reducing gambling craving.
de Castro et al. (2007)	x	- Craving for gambling was inversely correlated with positive affect (PASAS-X), whereas craving for alcohol was directly correlated with negative affect (PASAS-X). - Compared to alcohol, gambling craving seems more dependent upon environmental contingencies (e.g., poor social adjustment).
Dickler et al. (2018)	Two tDCS/MRS sessions separated by 7 days, receiving active and sham tDCS conditions	- Positive correlation between metabolite levels during active, but not sham, stimulation and levels of risk taking, impulsivity and craving - Higher craving level correlated with greater effects of active tDCS in the striatal neural metabolite.
Donati, et al. (2021)		- Low levels of craving, as assessed by telephone semi-structured interviews during the lockdown. - The reduction of the problems related to gambling from the period pre quarantine to the lockdown was related to reduced craving.
Dunsmuir et al. (2018)	The treatment program comprised predominantly CBT and CT	- There was no significant association between baseline GUS scores and post-treatment gambling-related cognitions, or vice versa. - Gambling craving had a significantly stronger tracking correlation across time for men than women when adjusting for cognition paths.
Duvarci and Varan (2000)	x	- The percentages of pathological gamblers who reported craving ranged between 58.1 and 67.7%, as compared to 14.6 ± 21.4% in the non-pathological group. Thus, pathological gamblers experienced craving more often compared to the non-pathological gamblers.
Fernie et al. (2014)	x	- Correlation analyses revealed a relation between the GACS and the SOGS. - However, regression analysis revealed that both recruitment source and desire thinking were the only independent predictors of SOGS when controlling for all other study variables, including craving.
Gaetti and Tavares (2017)	The patients entered a 6-month program (intervention) that comprised a medical assessment, aimed at diagnosis and treatment of psychiatric comorbidities, and a brief cognitive intervention targeting cognitive distortions regarding randomness and games of chance. A follow-up assessment was conducted after treatment completion	- Factor analysis presented a three-factor solution: gambling behavior (factor 1), social life (factor 2), and personal hardship (factor 3). - Factor 1 comprised the gambling frequency of the items, time spent gambling, money spent on gambling and gambling craving. - Convergence validity: the GFS-SR item for gambling craving correlated with a reference scale assessing gambling symptoms. - The GFS-SR scores showed excellent sensitivity to change (factor 1), predictive validity for treatment response (factor 2), and ability to distinguish recovered from unrecovered patients after treatment (factor 3).

(continued)

Table 3. Continued

Article	Intervention	Results for craving
		- A cutoff score of 33 was found to have an 87% sensitivity and 80% specificity for gambling recovery.
Gay et al. (2017)	Real or sham treatment with high frequency rTMS over the left DLPFC with interval of 1-week Cue-induces craving by presentation of gambling-related videos	- As compared to sham, real rTMS significantly decreased cue-induced craving. - No significant effect of rTMS was observed on gambling behavior.
Geisel et al. (2018)	x	- There was no correlation of leptin blood levels with craving in patients with GD.
Goudriaan et al. (2010)	fMRI event-related cue reactivity paradigm, consisting of gambling, smoking-related and neutral picture	- Increased regional responsiveness to cue-induced craving (gambling pictures) in brain regions linked to motivation and visual processing was present in problematic gamblers.
Hawker et al. (2021)	A 4-week Ecological Momentary Assessment (EMA)	- Gambling craving predicted gambling episodes, and craving self-efficacy predicted gambling expenditure. - Moderation analyses showed the following: craving self-efficacy exacerbated craving frequency with gambling expenditure; high-risk positive reinforcement situations exacerbated craving intensity and gambling self-efficacy with gambling episode; and substance use exacerbated gambling self-efficacy with duration, and buffered gambling expenditure with craving intensity.
Hollander et al. (2005)	Sustained-release lithium carbonate (10 weeks treatment)	- Patients significantly improved while taking sustained-release lithium carbonate compared to placebo, on pathological gambling and reduced Y-BOCS including thoughts/urges and behavior. - A self-estimate of feeling able to control gambling (VAS) showed significant improvement with sustained-release lithium compared to placebo at week 10.
Hollingshead et al. (2016)	x	- Gamblers who used social casino games to reduce their craving to gamble reported an overall decrease in gambling.
Jacoby et al. (2013)	x	- Migrants have higher motivation and craving (PG-YBOCS) compared to Germans.
Kober et al. (2016)	fMRI during presentation of videos with cocaine, gambling, and sad scenarios	- GD participants reported strong craving to gambling videos. - Neuroimaging showed a dorsal mPFC region that was most strongly activated by cocaine videos in cocaine-dependent participants, gambling videos in GD participants, and sad videos in control participants. - Female GD but not males showed an increased response to gambling videos in dorsal mPFC and a region in posterior insula/caudate.
Koehler et al. (2013)	Functional connectivity resting-state fMRI	- GD patients showed an increased connectivity from the right middle frontal gyrus to the right striatum as compared to controls, which was also positively correlated with craving scores in the GD group. - The increased connectivity to the cerebellum was shown in GD compared to controls and positively correlated with craving for gambling in GD.
Limbrick-Oldfield et al. (2017)	fMRI during presentation of gambling-related, neutral and food images	- Craving ratings in GD increased following gambling cues compared with non-gambling cues. - fMRI analysis revealed group differences in left insula and anterior cingulate cortex, with the GD showing a greater reactivity to the gambling cues but no differences to the food cues. - In GD, gambling craving positively correlated with gambling cue-related activity in the bilateral insula and ventral striatum, and negatively correlated with functional connectivity between the ventral striatum and the medial prefrontal cortex.

(continued)

Table 3. Continued

Article	Intervention	Results for craving
Linnet et al. (2017)	Evidence-based treatment program based on CBT	- Treatment outcomes were associated with reductions in SOGS, craving, and gambling control.
McGrath et al. (2013)	Exposure to gambling-related cues before and after the administration of nicotine or placebo	- A low dose of acutely administered nicotine does not increase cue-induced craving for gambling in at-risk video lottery terminal gamblers who smoke.
Miedl et al. (2014)	fMRI and a temporal discounting task with gambling-related cues	- Gamblers increasingly discounted delayed rewards in the presence of high-craving gambling cues compared to low-craving cues. - Neuroimaging results revealed a positive correlation with a value in low-craving in midbrain and bilateral ventral striatum that was reversed in high craving.
Pallanti et al. (2006)	Placebo-controlled crossed administration of orally dose of meta-chlorophenylpiperazine (m-CPP) 0.5 mg kg^{-1}	- No significant craving variation after placebo and m-CPP in GD or controls.
Pallanti et al. (2010)	Sumatriptan (100 mg) and placebo were administered orally under identical, double-blind conditions	- The GD group demonstrated a higher score for all items in VAS for craving than the HC group. - No significant differences in the scores obtained for placebo and Sumatriptan conditions were obtained, and there were no correlations between biological and behavioral measures.
Penna et al. (2018)	Exercise program (50-min sessions with six to eight individuals per session, twice a week for eight weeks)	- GD patients undergoing an exercise program experience clinical improvement on gambling severity, psychiatric comorbidity and gambling craving. - However, the main hypothesis was only partly confirmed, as participants in the exercise program did not report greater reductions in gambling severity and craving compared to the stretching group
Petry and Kiluk (2002)	x	- Compared with pathological gamblers with no history of suicidal ideation, those with suicidal ideation reported greater cravings for gambling.
Petry and Oncken (2002)	x	- Compared to non-daily smokers, the daily smokers 'craved' gambling more and had a lower perceived control over their gambling.
Quintero et al. (2020)	Associative learning laboratory task with gambling-related cues	- Acquisition of conditioned-elicited responses remained unaffected by negative urgency, whereas extinction was hampered in individuals with a high negative urgency, especially for conditioned stimuli associated with erotic and gambling-related pictures. - Negative urgency predicted higher craving scores, and these predicted more severe gambling-related symptoms. - Extinction was not independently related to craving.
Sauvaget et al. (2018)	Low-frequency rTMS session to the right DLPFC on cue-induced craving	- The rTMS sessions were associated with a significant decrease in the gambling urge, regardless of whether the session was active or sham. - After controlling for cue-induced craving level, no effects were observed for active rTMS on craving. - Results failed to demonstrate the specific efficacy of one session of LF rTMS to decrease cue-induced craving, which may be partially explained by a strong placebo-effect and rTMS.
Shead et al. (2019)	Mindfulness-based meditation exercise condition (MBCT) or control condition (audiobook recording), delivered 10 min a day for 7 days	- MBCT with meditation condition showed to reduce gambling craving which highlights the potential benefits of meditation practice to reduce gambling cravings.
Stewart and Wohl (2013)	Playing a slot machine in a virtual reality casino environment with or without the support of a pop-up	- Participants who received a monetary limit pop-up reminder were significantly more likely to adhere to monetary limits than participants who did not.

(continued)

Table 3. Continued

Article	Intervention	Results for craving
	reminder when they hit their monetary limit	- Multiple logistic regression showed that as gambling symptomatology and dissociation increased, the likelihood that participants adhered to preset monetary limits decreased. However, craving to gamble did not predict adherence to preset monetary limits.
Sztainert et al. (2018)	Presentation of gambling-related cues or neutral cues in faster or satiated conditions	- Cues that predict the opportunity to gamble have an acute effect on ghrelin concentrations that is facilitated by fasting, and that ghrelin concentrations are a significant predictor of gambling persistence. - However, neither fasting nor the cues were effective in increasing subjective measures of gambling cravings, including measures of anticipation, desire, or relief.
Takeuchi et al. (2016)	Behavioral economics task to measure loss aversion	- The distribution pattern of loss aversion parameters of patients significantly differed from that of controls. - GD with low loss aversion showed higher scores of GACS and excitement-seeking compared to GD with high loss aversion.
Tavares et al. (2005)	x	- GD scored higher than alcohol dependence individuals for craving measures. - Gambling craving positively correlated with depression (BDI) and negatively correlated with length of abstinence and reward dependence scale of the TCI
van der Tempel et al. (2019)	Mindfulness-based intervention (MBI) in 10 group treatment sessions (90-min)	- Significant reduction in craving from the beginning to the end of the MBI. - These changes were clinically significant in 75% of participants.
Melero Ventola et al. (2020)	Mutual-aid vs MBCT	- Mutual-aid group intervention produced only moderate reductions in craving intensity. - the MBCT program significantly increased the scores of the mindfulness-related variables and reduced the craving intensity, frequency, and urgency - craving-related scores were low at the end of the MBCT intervention and at the one-month, three-month, and six-month follow ups.
Wemm et al. (2020)	Stress induction procedure consisted of a job interview in front of judges and an arithmetic task	- Following a stressor, subjective craving in smokers increased whereas gamblers' craving decreased. - In gamblers, higher subjective stress was associated with decreased craving, whereas changes in cortisol levels were unrelated to craving.
Wölfling et al. (2011)	Exposure to gambling-related stimuli by an EEG cue-reactivity paradigm	- Compared to HC, GD showed significantly stronger gambling-relevant stimulus-induced psychophysiological cue reactivity, as demonstrated by larger late positive potential, higher arousal and more positively toned valence ratings as well as higher stimulus-induced craving for gambling cues. - However, GD did not show the expected increase in general craving over time and after stimulus presentation.
Wulfert et al. (2009)	Cue-exposure presenting video-clips of preferred and non-preferred gambling activity	- Compared to social gamblers, individuals with probable GD reported overall significantly higher craving. - Cue-specific reactivity was shown in the urge to gamble. Both horse race and lottery gamblers reported the highest urges when they were exposed to cues of their preferred gambling activity.
Yokotani et al. (2020)	x	- Craving for gambling predicted income-generating offenses, but not drug-related and violent offenses.
Young and Wohl (2009)	x	- In Study 1, a factor analysis revealed the emergence of a 9-item scale with 3 factors: Anticipation, Desire, and Relief. The GACS predicted problem gambling severity, depression, and positive and negative affect. - In Study 2, the factor structure of the GACS was confirmed using a community sample of gamblers.

(continued)

Table 3. Continued

Article	Intervention	Results for craving
		- In Study 3, GACS scores significantly predicted persistence to play on a virtual slot machine in the face of continued loss. Specifically, the more participants craved gambling, the longer they engaged in it.
Zack et al. (2016)	Three treatment sequence with (rTMS, cTBS, sham), with intervals of 1-week	- Relative to sham, rTMS reduced post-game increases in desire to gamble (VAS), whereas cTBS reduced amphetamine-like effects, and decreased diastolic blood pressure.
Zack et al. (2019)	Preferential D2 antagonist haloperidol (HAL; 3 mg) or the mixed D1–D2 antagonist fluphenazine (FLU; 3 mg).	- HAL and FLU led to linear increases and decreases, respectively, in a desire to gamble across increasing levels of impulsivity. - GD patients with high impulsivity for whom craving is the primary concern may benefit more from medications that attenuate D1 activation.

Note. Alcohol Use Disorders Identification Test (AUDIT), Beck Depression Inventory (BDI), Cognitive Behavioral therapy (CBT), Cognitive therapy (CT), Continuous theta burst stimulation (cTBS), Dorsolateral Prefrontal Cortex (DLPFC), Electroencephalography (EEG), Functional magnetic resonance (fMRI), Gambling Craving Experience Questionnaire – Frequency (g-CEQ-F), Gambling Craving Experience Questionnaire – Strength (g-CEQ-S), Gambling Craving Scale (GACS), Gambling Disorder (GD), Gambling Follow-up Scale, Self-Report version (GFS-SR), Gambling Urge Scale (GUS), Medial prefrontal cortex (mPFC), Pathological Gambling Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), Personality Inventory for DSM-5-Brief Format (PID-5-BF), Positive and Negative Affect Scale Extended Form (PASAS-X), Positive and Negative Affect Schedule (PANAS), Repetitive transcranial magnetic stimulation (rTMS), South Oaks Gambling Screen (SOGS), Temperament and Character Inventory (TCI), Transcranial direct current stimulation/magnetic resonance spectroscopy (tDCS/MRS), Virtual Reality (VR), Visual Analog Scale (VAS).

craving. Of these studies, one was conducted in a non-clinical population in which repetitive transcranial magnetic stimulation (rTMS) proved to reduce the short-term craving to gamble (Zack et al., 2016). The other three studies were conducted in clinical samples; one of them reported a significant decrease in cue-induced craving with a single application of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) vs. sham in GD treatment-seeking patients (Gay et al., 2017). Another study, also conducted with GD treatment-seeking patients and rTMS but on the right DLPFC, reported a significant decrease in craving regardless of the session being active or sham rTMS (Sauvaget et al., 2018). The third study with a clinical population described how craving level correlated with greater effects of transcranial direct current stimulation (tDCS) on striatal glutamate + glutamine co (Glx; Dickler et al., 2018).

Neuroimaging

Four studies explored brain activity in cue-induced craving tasks in GD clinical samples reporting associations in four main areas: midbrain, striatum, insula and prefrontal cortex (PFC; dorsolateral and medial PFC). In one study, the right DLPFC was more activated with higher mean craving scores in GD than in healthy controls (Crockford et al., 2005). In another study, gambling craving was positively correlated with activity in the bilateral insula and ventral striatum and negatively correlated with the functional connectivity between the ventral striatum and the medial prefrontal cortex (Limbrick-Oldfield et al., 2017). Additionally, a positive correlation in midbrain and striatum was found in low-craving trials, and this correlation was reversed in high-craving trials Miedl et al. (2014). Finally, in GD and SUDs, one study reported an increased regional responsiveness to cue-induced craving (i.e., gambling pictures) in brain regions linked to motivation and visual processing (Goudriaan et al., 2010).

DISCUSSION

For years, in the field of addictions, the constructs "control" and "self-control" have been considered essential, and encompass concepts such as craving (Dickerson & Baron, 2000). Craving has been considered a key indicator in the development and maintenance of SUDs, given that it is associated with alterations in the control of substance use and, consequently, the likelihood of this use (Serre, Fatseas, Swendsen, & Auriacombe, 2015; Sayette, 2016). Therefore, craving was included as a new diagnostic criterion for SUDs in the DSM-5 (APA, 2013). There seems to be a scientific consensus that the inclusion of craving provides a more valid and clinically relevant diagnosis of SUDs and aids in the identification of possible risk factors for SUDs (Shmulewitz et al., 2021).

GD shares multiple similarities with SUDs, such as craving. It has been suggested that, both in substance addictions and in behavioral addictions such as GD, craving may be the result of cue-reactivity based on conditioning processes (Antons et al., 2020). These responses, both cognitive and affective, may be associated with reductions in inhibitory control and, consequently, in the presence of repetitive behaviors (Antons et al., 2020). Multiple experts consider that craving is an essential feature in GD that is

reflected in aspects such as unsuccessful efforts to stop gambling behavior and chasing one's losses, among others (Ashrafioun & Rosenberg, 2012; Blaszczynski & Nower, 2002; van Holst, van den Brink, Veltman, & Goudriaan, 2010; Sharpe, 2002). However, craving has not yet been proposed as a diagnostic GD criterion in the DSM, nor does it explicitly appear in the most common GD screening instruments, such as the South Oaks Gambling Screen (SOGS; Lesieur & Blume, 1987).

The present systematic review aimed to develop the specific role of craving in GD. From the 100 articles screened, 62 were finally included. All the articles included in the present review are convergent and none of them refute the relevance of craving in GD. In fact, craving has been associated with multiple aspects related to gambling, such as GD severity, gambling episodes, and chasing, among others (Brevers et al., 2011; Ciccarelli, Cosenza, D'Olimpio, et al., 2019; Ciccarelli et al., 2016a; Ciccarelli et al., 2020; Cosenza et al., 2020; Fernie et al., 2014; Hawker et al., 2021; Quintero et al., 2020; Takeuchi et al., 2016; Yokotani et al., 2020). Thus, there is evidence on the core component of craving on GD, and there may be some support for the inclusion of gambling craving as a diagnostic criterion in the DSM.

In this context, several studies found a direct association between gambling craving and emotional states. More specifically, gambling craving may be negatively linked with positive emotional states and positively associated with negative urgency (de Castro et al., 2007; Quintero et al., 2020). Both craving and (negative) emotions appear to be central features of addictions; hence, there is a growing interest in understanding how the two factors interact (Oliver, MacQueen, & Drobes, 2013). Different theoretical models have attempted to explain this association, hypothesizing, for example, that different affective states may generate craving which, in itself, is a type of affect that is modified according to the context (Sayette, 2016).

Of special interest are the seventeen studies, which implemented some specific interventions for GD and assessed its impact on reducing craving. To date, pharmacological interventions still yield inconclusive results. Two studies focused on the hypothesis of serotoninergic system impairment (de Brito et al., 2017; Pallanti et al., 2006) with some limited evidence of efficacy of medications that activate D1 in high-impulsive gamblers (Zack et al., 2019), and one study focused on the efficacy of sustained-release lithium carbonate on reducing craving and affective instability, but only in individuals who present pathological gambling when bipolar spectrum disorder is present (Hollander et al., 2005). The results for psychological interventions are more promising, with a special emphasis on the proven effectivity of MBCT on reducing craving compared to other psychological interventions or behavioral-related interventions (Melero Ventola et al., 2020; Shead et al., 2019; van der Tempel et al., 2019). Finally, the four studies exploring neuromodulation interventions on gambling craving are somewhat effective, yet these interventions are brief, and craving is so far proven to be reduced in short-term (Dickler et al., 2018; Gay et al., 2017; Sauvaget et al., 2018; Zack et al., 2016).

It is worth highlighting the main limitations of the studies included in the review were the following: (1) A psychometric instrument or visual analog scale was exclusively used to assess craving in most cases, which could lead to a desirability bias. (2) Most studies do not include a specific definition of craving or use heterogeneous definitions. (3) In most studies a clinical diagnosis of GD was not made, only a self-administered questionnaire was used to determine the presence/severity of GD. (4) Many studies predominantly included male samples and/or small sample sizes, especially of the clinical samples, and therefore the generalizability of the results obtained is limited. (5) Most studies were cross-sectional, and thus a causal association between GD and craving cannot be established. (6) Most studies did not explore the presence of psychiatric comorbidities, medication or gambling preferences, as well as other factors that could interfere with craving–GD association. (7) In most cases, a comparison group was not included. (8) The samples of subjects with GD not seeking treatment may be underrepresented. (9) Some of the studies were retrospective in nature. (10) Most of the treatment studies did not include follow-ups or these were very short. (11) In most studies, the sample was either constituted of only males or had a much bigger representation of males than females; females with GD and the gender differences in craving were understudied. More longitudinal studies with larger sample sizes and more representative samples are needed to facilitate the generalization of the results obtained and to test for possible treatment possibilities (still scarce and not yet well-established). Similarly, future studies could explore in greater depth the factors that could condition the association between GD and craving to determine why some subjects report experiencing craving to a greater extent than others.

The limitations of the present systematic review should be highlighted. The central limitations were: (a) due to the scarcity of studies in this field, all studies evaluating GD and craving were included. This implies a remarkable heterogeneity of samples (both in terms of sociodemographic variables, such as age, and clinical variables, such as GD severity). (b) It was decided to include articles that mentioned the term "craving" at least once. Since craving is defined as "an intense urge or desire", some experts have used the terms "desire" or "urge" to refer to it. However, these terms were not included in the search for the present systematic review, and by using only the term "craving" we missed a non-significant number of publications. (c) In this systematic review, qualitative studies, which can also provide very relevant information in this framework, were excluded.

CONCLUSIONS

The findings of the different studies included in this systematic review suggest that gambling craving is a relevant factor in gambling behavior and GD. The possible association of craving with GD severity would support the proposal of some authors to consider craving as a diagnostic criterion for GD, as it is contemplated in the SUDs. However, more

longitudinal research is needed in this regard, assessing both constructs in a comprehensive and less biased manner than current studies.

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SUPPLEMENTARY MATERIALS

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