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Anatomical and Functional Bases Underlying Cognitive Distortion Processes in Pathological Gambling

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I. Summary

Gambling disorder is characterized by an excessive involvement in gambling behavior, with negative consequences and significant functional impairment of the individual who suffers from it. Diagnosis is established from the presence of a number of criteria, similar to the ones used for other addictive disorders, and referring in one way or another to interference or conflict with important activities or relationships, abstinence symptoms, progressive tolerance, mood modification (i.e. coping), lack of control over the addictive activity, and relapse.

In spite of the fact that gambling-related beliefs, and, specifically, distortions relative to prediction, control or attribution of gambling outcomes, are a salient feature of problematic gambling, these are not customarily considered for its diagnosis. Nevertheless, evidence shows that they are essential for the understanding of vulnerability for the disorder, the escalation that marks the transition between recreational and problematic gambling, and maintenance of the latter.

The most widely used model for factorizing gambling-related cognitions, crystalized in the Gambling-Related Cognitions Scale (GRCS), postulates five categories of cognitions. Gambling expectancies refer to perceived consequences of gambling that can directly or indirectly work as reinforcers for gambling maintenance, and include both monetary and non-monetary (e.g. social or affective) outcomes. Inability to stop refers to feelings of low self-efficacy regarding one's capacity to resist urges and to reduce gambling. Control illusion stands for the belief that one can influence gambling outcomes by means of strategies or rituals. Predictive control denotes the belief that gambling outcomes follow a logic or pattern, and are thus predictable (for example, a series of losses is bound to be followed by wins, or gambler's fallacy). Finally, the interpretative bias denotes the proneness to attribute losses to external causes or bad luck, and wins to ability. This classification serves as framework for the present thesis.

In its first study, we review the available evidence regarding the neurocognitive mechanisms potentially involved in these gambling-related cognitions. On the one hand, we assess the possibility that gambling expectancies are linked to reward processing mechanisms. In this regard, evidence is mixed, but seems to suggest that problematic gamblers show increased reactivity in reward-related brain areas during expectancy of gambling-related rewards, and diminished reactivity during both expectancy and experience of natural, non-gambling related rewards (as predicted by the reward deficiency hypothesis). A clearer pattern of results emerges from the study of reactivity to non-winning events that fall close or are perceptually similar to wins (i.e. near-misses). In this case, studies show a neater overactivation of limbic and frontal structures in patients

relative to controls.

Inability to stop, in turn, is conceptually and clinically linked to intense gambling cravings triggered by gambling-related cues. In functional fMRI studies, the most widely used methodology has been to observe brain reactivity to such cues. Several studies show the central role of the insular cortex in such reactivity, and in subjective craving experiences that could be related to perceived lack of control over gambling behavior and inability to stop.

Finally, the other gambling-related cognitions, i.e. control illusion, predictive control, and interpretative bias (jointly categorized as cognitive biases), have been scarcely studied using brain imaging techniques. On the one hand, the studies mentioned above relate the structures involved in near-miss effects also with the gambler's fallacy. On the other hand, the available evidence does not suggest that cognitive biases are associated to generalized cognitive alterations. Quite the opposite, these biases are especially characteristic of a neuropsychologically preserved gambler's profile. Our interpretation of these results, reinforced by the other studies in this thesis, is that these cognitive biases are caused, at least in part, by motivated reasoning, aimed at reducing the impact of losses and justifying the desire to keep on gambling. In this way, gambling-related cognitive biases would be tightly related to the motivational and learning mechanisms involved in the other cognitions previously described.

The second study of this thesis used structural imaging techniques to estimate grey-matter volumes (GMV) in cortical areas of the brain. In a first analysis, comparing GMV between gambling disorder patients and matched controls, a reduction was observed in the dorsomedial prefrontal cortex of patients.

A second analysis, restricted to patients, unveiled an inverse association between GMV in the polar part of the ventrolateral prefrontal cortex and negative urgency. Negative urgency refers to the tendency to commit impulsive acts under the influence of strong negative affect (that has been proposed as a transdiagnostic alteration of emotion regulation process, common to several externalizing disorders, including other addictions).

In a third and last analysis, more directly related with the aims of this thesis, we found an inverse association between GMV in the dorsal cingulate (dACC) and interpretative bias scores, which seems to suggest that an alteration of that area (also linked to other psychopathologies) could be somewhat related to gambling-related biases. However, a complementary analysis showed that GMV of controls was more similar to that of high-bias gamblers that to the one of low-bias ones, which jeopardizes that interpretation. Tentatively,

our interpretation of this result is that increased GMV in low-bias gamblers signals some kind of neuroadaptation characteristic of a gambler profile with less marked biases, and that the profile of gambler with stronger biases would be, in that particular characteristic, more similar to controls.

The third study seems to corroborate the observation that gambling-related cognitive biases are not rooted in an alteration of domain-general learning or reasoning. In this study, participants — either gambling disorder patients or matched controls — were instructed to carry out an associative learning task in which they had to estimate the strength of the causal relationship between their response and an arbitrary (non-monetary) outcome, in a computerized task. The task consisted of two experimental conditions with positive or null contingency between the response and the outcome. Patients did not show an illusion of control (they did not perceive a relationship between their behavior and the outcome when there was not any), but they did show a worse discrimination between contingency conditions. The most relevant and puzzling result, however, was the finding that among patients, those with stronger cognitive biases, as measured by the GRCS scale, where the ones who best discriminated between the two contingencies in the causal learning task.

Finally, in the fourth study, we analyzed the relationships between gambling cognitions and variables related to emotion regulation (impulsivity and cognitive emotion-regulation strategies), in a large sample of gamblers with different degrees of involvement in gambling activities (in a wide range). On the one hand, we found that cognitive biases were more tightly associated with emotional dimensions of impulsivity (and, specifically, positive urgency and sensation seeking), than to other, more strictly cognitive, dimensions (lack of premeditation and perseverance). Most interestingly, however, cognitive biases (again measured with the GRCS) were significantly associated with emotion regulation strategies (especially reappraisal), customarily considered adaptive and systematically linked to positive outcomes and weaker clinical symptomatology in a variety of affective disorders. In other words people with a more marked tendency to use such strategies were more prone to gambling-related cognitive biases.

As a whole, these results are compatible with the general approach to cognitive biases advocated by the Gambling Space Model. In that model, cognitive biases are not considered to arise from a generalized neuropsychological malfunctioning, or from weakness of domain-general processes (e.g. causal learning, probabilistic reasoning, or intelligence), but, at least in part, from motivated reasoning. In other words, they would be causally related to the gambler's motivation to reduce the impact of negative consequences of gambling, and/or to justify the desire to keep on gambling. Such motivation would materialize in a reduction of cognitive

dissonance that does not affect self-concept and, additionally, allows the individual to keep on gambling intensively. This would account for the fact that cognitive biases tend to be more intense in a subgroup of gamblers of younger age, more intelligence and education in the normal-high range, and a marked preference of skill-based games over pure-chance ones.

These findings also have clinical implications. If our approach is correct, standard cognitive restructuration would not be expect to be sufficient to modify resistant beliefs. In that sense, metacognitive and motivational interventions emerge as a necessary complements in specific interventions for the cognitive facet of gambling disorder.

II. Resumen

El trastorno por juego de azar se caracteriza por una involucración excesiva en un comportamiento de juego con apuestas que conlleva consecuencias negativas y un deterioro funcional significativo de la persona que lo sufre. Su diagnóstico se establece habitualmente a partir de la corroboración de una serie de criterios, en su mayor parte similares a los de otros trastornos adictivos, y que hacen referencia a la saliencia de la actividad, la interferencia o conflicto que provoca, los síntomas de abstinencia, la progresiva tolerancia, el uso de dicha actividad como modificador del estado de ánimo (i.e. afrontamiento), la pérdida del control de la actividad, y la propensión a las recaídas.

A pesar de que las creencias relacionadas con el juego y, particularmente, las distorsiones relativas a la predicción, control y atribución de los resultados del mismo son una característica particularmente saliente del juego problemático, éstas no se consideran criterios para su diagnóstico. Ello no es óbice para que la evidencia disponible las señale como esenciales en la vulnerabilidad al trastorno por juego, la escalada que marca la transición entre el juego recreativo y el problemático, y el mantenimiento de éste último.

En el modelo más extendido para describir factorialmente las cogniciones relacionadas con el juego, cristalizadas en la Gambling-Related Cognitions Scale (GRCS), se incluyen cinco tipos de cogniciones. Las expectativas hacen referencia a las consecuencias percibidas del juego que pueden actuar como reforzadores para el mantenimiento del mismo, entre las que se incluyen consecuencias tanto monetarias como no monetarias (e.g. afectivas o sociales). La incapacidad para parar se refiere a la una sensación de baja autoeficacia en la propia capacidad para reducir o eliminar la conducta de juego. La ilusión de control hace referencia a la creencia de que uno puede influir sobre los resultados del juego usando estrategias o rituales. El control predictivo indica la creencia de que existen formas de predecir dichos resultados (por ejemplo, que una racha de pérdidas irá seguida de otra de ganancias, o falacia del jugador). El sesgo interpretativo, por último se refiere a la tendencia a reinterpretar los resultados del juego, una vez que ya se han producido, como atribuibles a la propia habilidad, si son positivos, o al azar u otras causas externas, si son negativos. Esta clasificación sirve de marco para los estudios de la presente tesis.

En el primer estudio de la misma, revisamos la evidencia disponible sobre los posibles mecanismos neurocognitivos que podrían estar relacionados con dichas cogniciones. Por una parte evaluamos la posibilidad de que las expectativas estén vinculadas a alteraciones de los mecanismos de procesamiento de recompensas. A este respecto, la evidencia es confusa, pero parece apuntar que los jugadores problemáticos tenderían a mostrar una reactividad cerebral mayor a la expectativa de reforzadores directamente relacionados con el juego, y menor

tanto a la expectativa como a la experiencia de reforzadores naturales, no relacionados con el juego (en la línea de las predicciones del hipótesis de deficiencia del reforzador, reward deficency hypothesis). Más clara parece la sobrerreacción de estructuras frontales y límbicas a los eventos que, sin ser realmente ganancias, se perciben como cercanos o similares a las mismas (near-misses).

La incapacidad para parar, por su parte, aparece vinculada a la presencia de cravings intensos elicitados por claves relacionadas con el juego. En estudios de resonancia magnética funcional, la metodología más utilizada ha sido observar la reactividad cerebral a esas claves. Distintos estudios muestran la importancia central de la ínsula en dicha reactividad elevada, así como en la experiencia de craving que podría estar relacionada con la sensación de pérdida de control de la conducta de juego y de incapacidad para parar.

Por último, el estudio del resto de cogniciones relacionas con el juego, a saber, la ilusión de control, el control predictivo y el sesgo interpretativo (categorizadas juntas como sesgos cognitivos) mediante técnicas de imagen cerebral ha sido mucho más escaso. Por una parte, los estudios antes mencionados relacionan las estructuras implicadas en la reacción a los near-misses también en la falacia del jugador. Por otra, sin embargo, la evidencia disponible no parece indicar que los sesgos cognitivos se asocien a una disfunción cognitiva generalizada. Más bien al contrario, estos sesgos parecen ser especialmente característicos de un perfil de jugador neuropsicológicamente preservado. Nuestra interpretación de estos datos, que viene reforzada por posteriores estudios de esta tesis, es que los sesgos cognitivos estén causados, al menos en parte, por mecanismos de razonamiento motivado, orientados a reducir el impacto de las pérdidas o justificar el deseo de seguir jugando. De esta forma, los sesgos cognitivos estarían estrechamente vinculados a los mecanismos motivacionales y de aprendizaje implicados en las cogniciones descritas con anterioridad.

El segundo estudio de la tesis utiliza técnicas de imagen estructural para estimar el volumen de materia gris (GMV) en distintas zonas de la corteza cerebral. En un primer análisis, que compara el GMV de pacientes de trastorno por juego con controles sanos, encontramos una reducción de materia gris en el córtex prefrontal dorsomedial.

En un segundo análisis, encontramos una reducción de materia gris en el polo de la corteza prefrontal ventrolateral asociada a una mayor urgencia negativa en el grupo de pacientes. La urgencia negativa se define como la tendencia a cometer actos impulsivos cuando se está bajo el efecto de emociones negativas intensas (y que se ha corroborado como una alteración de la regulación emocional común a varios trastornos externalizan-

tes, incluidas otras adicciones).

En un tercer y último análisis, más directamente relacionado con los objetivos de esta tesis, encontramos una relación inversa entre el volumen de materia gris en el cíngulo dorsal (dACC) y los valores de sesgo interpretativo, que parece indicar una que alteración de dicha área (que también se ha vinculado a otras psicopatologías) podría estar vinculada de una forma u otra a los sesgos cognitivos relacionados con el juego. Sin embargo, un análisis complementario mostró que los controles tenía valores de GMV similares a los de los jugadores de alto sesgo, lo que complica dicha interpretación. De forma tentativa, nuestra interpretación es que el GMV incrementado en el dACC podría ser un marcador de alguna neuroadaptación propia del perfil de jugador que tiende a mostrar menores sesgos cognitivos, y que el perfil de jugador que tiende a mostrar mayores sesgos es, en esa característica particular, más similar a los controles.

El tercer estudio de la tesis abunda en la observación de que los sesgos cognitivos relacionados con el juego no parecen estar enraizados en una alteración general de los procesos de razonamiento o aprendizaje. En este estudio, las personas — pacientes con trastorno por juego y controles emparejados — fueron sometidas a una tarea de aprendizaje asociativo en la que tendían que estimar la fuerza de la relación causal entre su propia conducta y un resultado arbitrario (no monetario), en una tarea computerizada. La tarea contaba con dos condiciones, en una de las cuales existía una alta correlación, y en la otra una correlación nula, entre la conducta y el resultado. Los pacientes con trastorno con juego no mostraron una ilusión de control significativa (no percibían una relación causal entre su conducta y el resultado cuando no había ninguna), pero si mostraron una peor discriminación entre la contingencia positiva y la nula. Lo más relevante, sin embargo, es que, en el grupo de pacientes, las personas con sesgos cognitivos más intensos, medidos con la escala GRCS, eran precisamente los que mejor discriminación mostraban en la tarea de aprendizaje causal.

Por último, en el cuarto estudio, analizamos las relaciones entre sesgos cognitivos y variables relacionadas con la regulación emocional (impulsividad y estrategias cognitivas de regulación emocional) en un grupo de jugadores de azar con distintos grados de implicación en conductas de juego, en un rango amplio. Por una parte, encontramos que los sesgos cognitivos están más estrechamente vinculados a las dimensiones emocionales de la impulsividad (y, más concretamente) a la búsqueda de sensaciones y la urgencia positiva, que a otras dimensiones de la impulsividad más puramente cognitivas (falta de premeditación y perseverancia). Lo más interesante, sin embargo, es que los sesgos cognitivos (de nuevo medidos con la escala GRCS) estaban significativamente correlacionados con estrategias de regulación emocional (fundamentalmente reappraisal o rein-

terpretación) normalmente consideradas adaptativas, y asociadas a una menor sintomatología clínica en una variedad de trastornos afectivos. Dicho de otra forma, las personas con mayor tendencia a usar esas estrategias son también las más propensas a mostrar sesgos cognitivos relacionados con el juego.

En su conjunto estos resultados son compatibles con la visión general de los sesgos cognitivos planteada por el modelo espacial de juego (Gambling Space Model). En dicho modelo, los sesgos cognitivos no se consideran fruto de una alteración neuropsicológica generalizada, ni de una debilidad de los procesos independientes de dominio (como el aprendizaje causal, el razonamiento probabilístico o la inteligencia), sino que son, al menos en parte, el resultado de un tipo de razonamiento motivado, esto es, están causalmente vinculados a la motivación del jugador para reducir el impacto de las consecuencias negativas del juego y/o justificar el deseo de seguir jugando. Dicha motivación se traduciría en una reducción de la disonancia cognitiva que no afecte al al propio autoconcepto y permita, a la vez, continuar jugando de forma intensa. De esta forma se explica que los sesgos cognitivos aparezcan de forma más intensa en un perfil de jugador normalmente más joven, con educación e inteligencia en el rango normal (o incluso alto), y con una preferencia marcada por los juegos de habilidad.

Ello también tiene implicaciones clínicas, en tanto que la mera restructuración cognitiva se dibuja como un acercamiento poco eficaz en la modificación de creencias para la cual el paciente mostrará un alto nivel de resistencia. En este sentido, las técnicas metacognitivas y basadas en intervenciones motivacionales aparecen como un complemento necesario para el abordaje específico de las cogniciones relacionas con el juego.

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1. Introduction

1.1 Definition, diagnosis, and main features of gambling disorder

Gambling disorder (GD) is characterized by loss of control over gambling behavior, with a progressive and recurrent pattern of maladaptive gambling involvement despite adverse consequences, and a prevalence in European countries estimated between 0.12 and 3.4% (Black & Shaw, 2019; Calado & Griffiths, 2016). Although gambling represents a leisure activity for most of the population (Gainsbury et al., 2014; LaPlante et al., 2009; Olason et al., 2006; Volberg et al., 2010), a small proportion of gamblers develop a pattern of excessive gambling behavior with severe negative consequences (Currie et al., 2006; Hodgins et al., 2011).

Initially labeled as pathological gambling[1] (PG), GD was firstly recognized as a mental disorder in 1980 by the American Psychiatric Association, and included as an impulse control disorder in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, American Psychiatric Association, 1980). The DSM-III definition emphasized the progressive loss of control over gambling that causes a significant disruption of the individual's functioning, including familiar, social, occupational, and financial problems. In the fourth edition of DSM (DSM-IV), diagnostic criteria were revised in an attempt to reflect increasing evidence suggesting its similar neurobiological and clinical correlates to substance use disorders (SUD, Clark, 2014; Clark & Limbrick-Oldfield, 2013; Fauth-Bühler et al., 2017; Grant & Chamberlain, 2015; Potenza, 2008; Romanczuk-Seiferth et al., 2014). For example, criteria resembling tolerance ('A need to gamble with increasing amounts of money in order to achieve the desired level of excitement'), and withdrawal symptoms ('Feels restless or irritable when attempting to cut down or stop gambling') were included, together with inability to stop ('Repeated, unsuccessful efforts to control, cut back or stop gambling'). Nevertheless, since its publication date, DSM-IV diagnostic criteria for PG have received some criticism. First, PG definition is mostly based on clinical principles, with limited empirical support (Lesieur & Rosenthal, 1991; Rosenthal, 1989; Shaffer et al., 1997; Stinchfield et al., 2005). Second, the dichotomous character of the diagnosis neglects evidence suggesting that PG should be conceptualized dimensionally as a continuum (Slutske et al., 2011; Strong & Kahler, 2007). Accordingly, the identification of individuals at risk of PG can help to delineate vulnerability factors observed at early stages, and isolate etiological variables contributing to the development of the disorder. Third, many researchers emphasized the fundamental differences between PG and impulse-con-

[1]Despite the change in terminology, Pathological Gambling and Gambling Disorder refer to the same condition, and they will be considered equivalent in the remainder of this thesis.

trol disorders' main clinical manifestations, related to impulsive and compulsive symptoms, questioning its inclusion in the category (Shaffer & Korn, 2002).

In response to these concerns, the fifth version of the DSM introduced a number of changes in GD diagnosis. First, pathological gambling was renamed as gambling disorder and reclassified from the Impulse Control Disorders Not Elsewhere Classified section to the new category Substance-Related and Addictive Disorders (Mann et al., 2016; Petry et al., 2014). This recategorization represents the formal recognition of the existence of behavioral addictions, where the main characteristic includes the absence of any exogenous chemical agent. In addition, the novel clinical description of GD eliminates the 'Commitment of Illegal Acts' criterion and lowers the threshold for GD diagnosis from five to four criteria to improve diagnostic accuracy (Jiménez-Murcia et al., 2009; Stinchfield et al., 2005; 2016).

The change in disorder category was mainly driven by accumulating evidence that highlights the overlap of symptomatology and neurobiology, and the common patterns of comorbidity between GD and Substance-Related Disorders (Fauth-Bühler et al., 2017; Romanczuk-Seiferth et al., 2014). Specifically, emotion dysregulation, altered reward processing, imbalanced decision-making, craving, and impaired cognitive control seem to be involved in the etiology of both disordered gambling and drug abuse (Goudriaan et al., 2019). Although the reclassification is timely, it has not been accompanied by a clear theoretical account of the mechanisms driving the transition between recreational and disordered gambling (Clark et al., 2019; Grant & Chamberlain, 2016; Kardefelt-Winther et al., 2017).

Epidemiological investigations have demonstrated that GD is frequently associated with severe negative consequences, such as substantial economic adversities, personal and social interference, occupational and legal difficulties and a generalized impairment in life functioning (Currie et al., 2006; Hodgins et al., 2011; Raylu & Oei, 2002; Shaw et al., 2007). Nevertheless, GD patients are usually incapable to regulate gambling behavior and tend to 'chase losses' in an effort to retrieve financial losses (Linnet et al., 2006). In addition, psychiatric comorbidities are frequent in GD. Specifically, almost three-quarters of GD patients experience at least one comorbid syndrome (Hodgins et al., 2005; Petry et al., 2005). In this context, the most common comorbid conditions are mood and anxiety disorders (Ibáñez et al., 2001; Shaffer & Korn, 2002), substance-use disorders (Petry & Oncken, 2002; Bischof et al., 2013; French et al., 2008) and general health problems (Morasco et al., 2006). Interestingly, comorbidities appear to combine with specific psychological traits to define different GD profiles characterized by more severe gambling problems (Hodgins et al., 2005; Hodgins &

el-Guebaly, 2004; Quigley et al., 2015; Yip & Potenza 2014).

1.2. Neurocognitive approaches to gambling disorder

Over the last years, there has been a significant increase in GD research, integrating different theoretical frameworks with recent developments in neuroscience techniques (Blaszczynski & Nower, 2002; Clark et al., 2019; Clark & Limbrick-Oldfield, 2013; Goudriaan et al., 2014; Griffiths & Delfabbro, 2001; Limbrick-Oldfield et al., 2013; Luijten et al., 2017; Navas et al., 2019; Sharpe, 2002; Yücel et al., 2017). Important advances have occurred in delimitating clinical and brain correlates of GD, and defining different subtypes with distinct clinical profiles and complications (Álvarez-Moya et al., 2010; Blaszczynski & Nower, 2002; Chamberlain et al., 2017; 2020; Devos et al., 2020; Jiménez-Murcia et al., 2020; Ledgerwood & Petry, 2010; Milosevic & Ledgerwood, 2010; Nower et al., 2013; Stewart et al., 2008). Similarly, substantial effort has been dedicated to elucidate etiological and vulnerability factors associated with GD (Blanco et al., 2015; Goudriaan et al., 2004; Hodgins et al., 2012; MacLaren et al., 2011; Myrseth et al., 2009; Shaffer et al., 2004), which would be useful to guide prevention and intervention programs. In line with established evidence from Substance-Use Disorders (Kendler et al., 2003; Krueger et al., 2002; Stone et al., 2012; Swendsen et al., 2010; Verdejo-García et al., 2008), the etiology of GD is a complex and multifactorial phenomenon (Blaszczynski & Nower, 2002; Griffiths, 2005; Sharpe, 2002), influenced by a variety of risk factors, including genetic dispositions (Ibáñez et al., 2000; Lobo & Kennedy, 2009; Xuan et al., 2017), sociodemographic variables (Volberg et al., 2001; Welte et al., 2004), comorbidities with psychiatric disorders (Slutske et al., 2001; Potenza et al., 2005), personality factors (MacLaren et al., 2011; Blanco et al., 2009), family antecedents of GD or SUD (Slutske et al., 2010; Blanco et al., 2012) and adverse events during childhood (Petry & Steinberg, 2005; Petry et al., 2005).

Vulnerability factors tend to co-occur, and recent investigations are integrating diverse predictive variables in theoretical models to analyze interaction effects in their contribution to GD etiology (Hodgins et al., 2012; Navas et al., 2019). Converging evidence is showing the key relevance of individual processes to determine the etiology of GD (Ledgerwood & Petry, 2010; Milosevic & Ledgerwood, 2010; Slutske et al., 2005; Vachon & Bagby, 2009). Specifically, a large body of research has identified gambling-related cognitive distortions (Fortune and Goodie, 2012; Johansson et al., 2009; Cosenza & Nigro, 2015), impulsivity (Verdejo-Garcia et al., 2008; MacKillop et al., 2014; MacLaren et al., 2011), emotion regulation deficits (Blaszczynski & Nower, 2002) and cognitive control problems (Moccia et al., 2017; Sharpe, 2002) among the most critical

variables contributing to GD etiology.

Individual dispositions and heterogeneity in neurobiological traits and neurocognitive processes can predispose individuals to develop GD (Shenassa et al., 2012; Slutske et al., 2012), and function as predictors of gambling relapse (Goudriaan et al., 2008). Accordingly, a bidirectional interaction has been suggested between neurocognitive functions and gambling behavior, where neurobiological processes influence how the gambler experiences the rewarding properties of gambling, and simultaneously recurrent gambling behavior can induce neuroadaptations and shape neurobiological functions to subserve gambling aims (Potenza, 2013; Sharpe, 2002).

Within this framework, where addiction can emerge in the absence of any external agent, GD can be considered as a learning disorder, where certain gambling games' features interact with neurocognitive functions to induce a deviation of adaptive instrumental learning processes (Clark et al., 2019; Navas et al., 2019; Perales et al., 2020; Yücel et al., 2017). Still, the high worldwide prevalence of the gambling phenomenon constitutes an ongoing puzzle for researchers, due to the widespread acceptance of the negative expected value of gambling behavior in the long term (Clark, 2010). Nevertheless, there are various games' structural characteristics that foster gambling allurement (Linnet et al., 2010; Parke & Griffiths, 2007). For instance, near-miss events, multiline betting, 'stop' buttons, or high frequency of reinforcement increase gambling motivation, involvement and expenditure (Clark et al., 2009; Harrigan et al., 2014; Linnet et al., 2010; Parke & Griffiths, 2007)

The two main pillars of the neurocognitive definition of GD as an addictive disorder are thus the alterations of reward-based learning (that underlie imbalanced motivation) and dysfunction of cognitive processes (Brevers et al., 2019; Clark & Limbrick-Oldfield, 2013; Fauth-Bühler et al., 2017; Luijten et al., 2017; Moccia et al., 2017; Potenza, 2014; van Timmeren et al., 2018). Likewise, biobehavioral models of substance addiction describe these mechanisms as key elements in the etiology of substance use disorders (Koob and Volkow, 2010).

Reward-based learning

Extensive evidence from decades of experimental human and animal research on reinforcement learning shows the impact of diverse reinforcement programs and conditioning paradigms on different variables related to acquisition and extinction of instrumental responses, including the modeling of gambling behaviors

(Fester & Skinner, 1957; Hurlburt et al., 1980; Schoenfeld et al., 1956; Skinner, 1969). Notably, reinforcement schedules characterized by an intermittent and variable pattern of reinforcement generate behavioral perseverance, as shown by enduring responses in extinction learning processes (Adams & Dickinson, 1981; Hilgard & Bower, 1975; Sharpe, 2002). In addition, uncertainty is proposed as a key factor that attracts attention and motivation, thus influencing gambling persistence (Fiorillo, 2011; Niv et al., 2006; Young et al., 2005). Specifically, it has been demonstrated that sustained activation of midbrain dopamine neurons signals uncertainty of motivationally-relevant stimuli in animals (Fiorillo et al., 2003). In humans, fMRI ventral striatal activity during reward anticipation has been shown to reflect reward uncertainty (Preuschoff et al., 2006) and ventral striatal dopamine release correlates with performance in the Iowa Gambling Task (IGT; Linnet et al, 2012).

Drugs of abuse exert their hedonic effects by hijacking the normal functioning of reward systems (Koob & Le Moal, 2005; 2008; Volkow & Li, 2004). In natural environments, dopaminergic prediction error signals elicited by unexpected rewards attenuate as the learning process advance, and reward can be predicted by external cues (Berridge, 2012). However, over-stimulation of the dopamine system by drugs of abuse prevents habituation of mesolimbic prediction error signals, overriding the incentive value of natural rewards, and generating a prevalent cue-triggered impulse for drug consumption (Robinson & Berridge, 2008), a process customarily known as incentive sensitization.

Notably, human and animal research suggests that a similar mechanism may be involved in the brain response to uncertain reinforcers (Anselme et al., 2013; Fiorillo et al., 2003, Preuschoff et al., 2006), stimulating dopamine release coupled with prediction error signals (Schultz, 2016). In gambling, current games operate under random ratio reinforcement schedules, where independence between trials determines the inherent uncertainty of the game (Haw, 2008; Lagorio & Winger, 2014). Recent proposals on the potential motivational value of uncertainty in gambling are indeed grounded on this idea (Navas et al., 2019).

The investigation of imbalanced motivational processes in GD is epitomized by three different lines of research. First, neurocognitive studies of attentional processes in gamblers showing biased attention towards gambling-related stimuli, compared to non-gambling stimuli. Second, reward processing and cue-reactivity paradigms suggesting an increased reward sensitivity of mesocorticolimbic regions to gambling-related stimuli. And finally, a diminished sensitivity to natural rewards, compared to gambling rewards.

Attention processes

The process of incentive sensitization is responsible for the acquired salience of gambling cues, which become capable of eliciting urge responses. Parallel to the imbalance in incentive motivation, sensitization also causes a preponderant attentional bias toward gambling cues, which gradually generalizes to a variety of contexts (Berridge & Kringelbach, 2015). These altered attentional processes have been extensively studied using neurocognitive paradigms (see Hønsi et al., 2013; van Timmeren et al., 2018; for reviews and meta-analysis). Although the measuring paradigms to assess attentional processes are heterogeneous, overall, these studies report a facilitation effect and reduced reaction time in detecting gambling stimuli, compared to neutral stimuli (Boyer & Dickerson, 2003; Brevers et al., 2011a; Ciccarelli et al., 2016; Molde et al., 2010). Moreover, studies implementing research procedures with direct measures of attentional bias, including Event-Related Potentials (ERP) and eye-tracking techniques, also report findings suggesting attentional bias in GD (Brevers et al., 2011b; McGrath et al., 2018; Wölfling et al., 2011).

Reward-processing

Evidence on reward processing mechanisms in GD patients is heterogeneous, showing a mixed pattern of hyper- (Sescousse et al., 2016; Gelskov et al., 2016; Miedl et al., 2012; van Holst et al., 2012a) and hypo-responsiveness (Balodis et al., 2012a; Choi et al., 2012; de Ruiter et al., 2009; Reuter et al., 2005; Tsurumi et al., 2014) of striatal, medial prefrontal and insular regions. Preliminary reports found evidence of reduced striatal activity in GD patients (de Ruiter et al., 2009; Reuter et al., 2005), however, recent studies using computerized gambling games have revealed increased anticipatory responses to gambling rewards in mesocorticolimbic regions, including striatum and medial PFC (Gelskov et al., 2016; van Holst et al., 2012a; Worhunsky et al., 2014).

Beyond the altered reward sensitivity in response to gambling rewards, imbalanced motivational processes in GD may also manifest in impaired reward sensitivity to natural rewards (Sescousse et al., 2013). Specifically, reward deficiency syndrome (RDS) theory predicts a diminished sensitivity to natural reinforcers (Blum et al., 2000), a result that has been substantiated for opiate (Lubman et al., 2009), cocaine (Asensio et al., 2010; Wexler et al., 2001) and nicotine dependence (Jastreboff et al., 2015). Similarly, in a seminal article, Sescousse et al. (2013) examined the hypothesis of diminished reward sensitivity to non-gambling rewards in GD patients using an incentive delay task. This investigation compared sensitivity to monetary and erotic

rewards between GD patients and healthy controls in non-gambling contexts. GD patients showed blunted ventral striatal reactivity to cues predicting erotic stimuli, when compared to cues signaling a monetary reward. Nevertheless, they did not find differences in reactivity to monetary cues between groups.

Moreover, a recently published meta-analysis on this issue examined brain reward processing during reward anticipation and outcome delivery in GD and substance-use disorder (SUD) patients (Luijten et al., 2017). A common pattern of decreased striatal activity during reward anticipation was found for both clinical groups. In contrast, GD and SUD patients showed a distinct response to outcome delivery, with reduced dorsal striatal activity in GD patients and increased VS activity in SUD patients. Consequently, the pattern of results in GD patients was interpreted as evidence supporting the reward deficiency syndrome (RDS) hypothesis in GD.

Cue-reactivity

Research on GD using the cue-reactivity paradigm yields more consistent results, with findings providing support for the incentive sensitization hypothesis in GD. Accordingly, an augmented BOLD response to gambling-related stimuli has been reported in the insula, dorsomedial PFC, anterior and posterior cingulate cortex, parahippocampal gyrus and amygdala (Limbrick-Oldfield et al., 2017; Goudriaan et al., 2010; Crockford et al., 2005; Kober et al., 2016). Notably, the association between gambling cue-reactivity and craving measures (Balodis et al., 2012b; Limbrick-Oldfield et al., 2017; Goudriaan et al., 2010), emphasizes their potential role as an indicator of gambling craving and inability to stop gambling.

Furthermore, a recent study compared cue reactivity in GD patients and controls to individually-tailored gambling cues, as well as responses to appetitive food cues (Limbrick-Oldfield et al., 2017). This investigation did not explicitly compare gambling versus food cues, but with matched neutral cues. They found an increased cue-reactivity response in the insula and ACC to gambling cues, but responses to food cues did not differ significantly between groups (Limbrick-Oldfield et al., 2017). Therefore, heterogeneity of findings precludes any straightforward conclusion on GD patients reward deficits.

This body of evidence thus reflects the impact of GD in a motivational shift, where cues associated with gambling become increasingly salient, and overshadow the importance of natural rewards. This process enables gambling-cues with the capacity of eliciting craving responses.

Cognitive control mechanisms

In addition, loss of control over the urge to engage in gambling activities is a defining feature of GD (Hodgins et al., 2011; O'Connor & Dickerson, 2003) and substance-use disorders (Goodman, 2008; Volkow & Li, 2005). This component of GD can be partially attributed to a failure of cognitive control mechanisms to inhibit gambling behavior and has been studied using diverse neurocognitive paradigms (Moccia et al., 2017). Cognitive control represents a multifaceted construct and entails different sub-domains, including response inhibition, conflict monitoring and cognitive flexibility. Moreover, impulsivity is not strictly considered a component of cognitive control, but a manifestation of impaired top-down regulatory processes (Bari & Robbins, 2013; Dalley et al., 2011) and represents a vulnerability factor to develop addictive disorders (Perry & Carroll, 2008; Verdejo-García et al., 2008). Similarly, recent theoretical accounts differentiate between choice impulsivity, the tendency to discount delayed rewards, and action impulsivity, the inability to suppress preponderant motor responses (Moeller et al., 2001; Wang et al., 2016).

The differential recruitment of prefrontal control regions in GD patients, including dorsolateral PFC, ventromedial PFC, orbitofrontal cortex and ACC (Brevers et al., 2015; de Ruiter et al., 2009; 2012; Miedl et al., 2012; 2015; van Holst et al., 2012b), and associated impairment of cognitive control measures using different procedures (Brevers et al., 2015; de Ruiter et al., 2009; Miedl et al., 2012; 2015; van Holst et al., 2012b), may partially explain attentional bias in gamblers, and contribute to core clinical manifestations.

1.3 Specific features of gambling disorder

From the literature reviewed above, and even considering the variability between studies and some inconsistent findings, we can conclude that GD shares main hallmarks of the neurocognitive profile that define the Substance-Related and Addictive Disorders category (Clark, 2014; Goudriaan et al., 2006; Lawrence et al., 2009; Limbrick-Oldfield et al., 2013; van Holst et al., 2010). Nevertheless, beyond these common aspects, disordered gambling is also defined by unique features that differentiate them from substance-related disorders, namely, the specific procedural characteristics absent in substance addiction.

In gambling, a defining feature is the involvement of risk. In a typical gambling scenario, people usually wager an amount of money, with the expectation of obtaining a larger reward. In addition, gambling games potentiate the uncertain nature of the process. Specifically, the inherent uncertainty in gambling games generates recurrent physiological responses in gambling situations (Meyer et al., 2000; 2004; Studer & Clark, 2011),

reflected in increased cortisol, epinephrine and cardiovascular activity during real gambling sessions. Moreover, problem gamblers reported a heighted heart-rate and epinephrine baseline levels compared to occasional gamblers, a result that denotes an increased anticipatory physiological arousal and expectancy in GD patients (Meyer et al., 2004).

In addition, risk and uncertainty elements of gambling, together with certain structural features of the games' design, establish a propitious scenario to develop cognitive distortions. Likewise, distorted gambling cognitions represent an additional unique aspect that distinguishes GD from other addictive disorders. Gambling cognitions, although not integrated in the GD diagnostic criteria, have been associated with the gambling phenomenon from early descriptions (Gaboury & Ladouceur, 1989). They are thus considered core elements of GD (Clark, 2010; Johansson et al., 2009) and have been identified as relevant vulnerability factors (Cosenza et al., 2014; Leonard & Williams, 2016; Yakovenko et al., 2016). In the following section we will delineate the main gambling cognitions described in the literature, articulated in the model behind the Gambling-Related Cognitions Scale (GRCS, Raylu & Oei, 2004). Then, we have made an effort to integrate different lines of research on distorted cognitions to identify three distinct etiological pathways to the development of gambling cognitions that will be tested in the investigations included in this thesis.

Gambling cognitions

As noted earlier, one of the defining characteristics of gambling is the involvement of uncertainty and risk, and gambling behavior is considered itself as a risk-taking activity (Hellberg et al., 2019). Thus, the analysis of cognitive factors associated with risky decision-making is essential to understand the gambling phenomenon (Goodie & Fortune, 2013). Randomness is an inherent feature in gambling games (i.e., slot-machines, roulette, craps), where skill-involvement is an exception (i.e., blackjack, poker). In this context, individuals incur in dysfunctional beliefs and erroneous cognitions, as delusive cause-effect inferences and perception of illusory patterns, when they process events only determined by chance (Clark, 2014).

In relation to a constantly changing environment, where patterns and regularities occur in many distinct forms and their detection has adaptive value, human brains have evolved to perform higher order cognitive functions. Nevertheless, the processes that facilitate these elaborated functions are prone to errors (Tversky & Kahneman, 1973). The vast amount information one should consider in any decision-making situation make the use of shortcuts and cognitive heuristics frequent (Kahneman et al., 1982; Toplak et al., 2011). However,

in contrast with mental shortcuts and heuristics, which function is to select and discard irrelevant information, gambling cognitions reflect a collection of cognitive bias and pervasive beliefs that represent dysfunctional assumptions and misperceptions about gambling (Raylu & Oei, 2004).

Humans learn to identify contingencies in probabilistic environments, in order to predict the occurrence of future events. As a result, in a context where outcomes are determined mostly by chance, individuals tend to develop illusory associations between unrelated events (Gaboury & Ladouceur, 1989). These individual dispositions to anticipate future situations have evolutionary value. Nevertheless, in artificial contexts dominated by uncertainty, where outcomes cannot be predicted, this tendency would facilitate the development of false contingencies between independent elements of the situation (Delfabbro & Winefield, 1999). Therefore, the implementation of associative learning principles in random situations would promote the emergence of cognitive distortions and could be a contributing factor explaining biases as predictive and illusory control (Gaboury & Ladouceur, 1989).

In general, gambling cognitions refer to dysfunctional beliefs concerning exaggerated expectancies about the reinforcing properties of gambling, perceived difficulties in controlling gambling behavior, and a collection of gambling-related cognitive distortions more specifically associated with how the gambler interprets gambling outcomes and his ability to influence these outcomes (Clark & Limbrick-Oldfield, 2013; Goodie & Fortune, 2013; Raylu & Oei, 2004), such as illusion of control and other biased attributions or misbeliefs about gambling (Toneatto, 1999).

Gambling cognitions are defining attributes of GD (Johansson et al., 2009), and have been identified among the most important GD risk factors (Delfabbro et al., 2009; Cosenza et al. 2014). GD patients report significantly higher scores on gambling distortions than non-problem gamblers and healthy controls (Joukhador et al., 2003), and studies have demonstrated that maladaptive beliefs are significantly associated with gambling severity (Oei et al., 2007; Raylu & Oei, 2004; Grall-Bronnec et al., 2012; Iliceto et al., 2015; Taylor et al., 2014), and frequency (Arcan & Karanci, 2015). Additionally, reductions in biased cognitions have been associated with gambling recovery (Fortune & Goodie, 2012).

In their pioneering work, Gaboury and Ladouceur (1989) introduced the first systematic qualitative research approach applied to the investigation of gambling cognitions in pathological gamblers, labeled as the 'think aloud' method. In this procedure, participants are requested to verbalize their thoughts while gambling.

In this procedure, the investigator records the verbalizations derived from thinking processes and examines them to classify according to the distinction between rational and irrational expressions (Ladouceur et al., 1988). Results from this early study demonstrated that 70% of gambling-related statements were irrational, and even low frequency gamblers communicate erroneous thoughts (Gaboury & Ladouceur, 1989). Using this approach, similar results were replicated in different samples (problem versus social gamblers), conditions (winning versus loosing), scenarios (real versus laboratory) and gambling activities (slot-machine, roulette, blackjack) by diverse and independent research groups (Coulombe et al., 1992; Delfabbro & Winefield, 1999; Griffiths, 1994; Ladouceur & Dube, 1994; Ladouceur, et al., 1991; Walker, 1992).

Early studies applied this procedure in regular gamblers while playing slot-machines in real gambling scenarios (Delfabbro & Winefield, 1999; Walker, 1992). Results showed that 70-80% of gamblers produced irrational statements while gambling (Delfabbro & Winefield, 1999; Walker, 1992), and this tendency was more pronounced in frequent gamblers (Griffiths, 1994). The more frequent biases reported by gamblers in these studies included illusion of control (Coventry & Norman, 1998; Dixon, 2000), attribution biases (Gilovich, 1983), the availability heuristic (Wagenaar, 1988) and the gambler's fallacy. From this early evidence came the first descriptions of gamblers' cognitions that would be later articulated in validated structured psychometric tools and recent theoretical accounts (Raylu & Oei, 2004).

Definition and description of main gambling cognitions

The human ability for adaptive decision-making rests on the capacity to assess the expected value of rewards and estimate outcome probability (Hélie et al., 2017). Gambling machine games are programmed to maximize uncertainty and unpredictability, effectively exploiting the human's bounded rationality and reward system. The cognitive literature on gambling has revealed a number of cognitive distortions and irrational beliefs that affect decision making in gambling scenarios, and promote excessive confidence and overestimation of winning probability (Goodie & Fortune, 2013). In this framework, cognitive distortions constitute central etiological processes in disordered gambling (Clark et al., 2014), reliable indices of GD severity (Joukhador et al., 2003; Xian et al., 2008), and predictors of future gambling involvement (Yakovenko et al., 2016). Thus, cognitive bias could be the missing piece to complete the GD puzzle, that is, how a behavior with a widely known overall negative expected value can become pervasive and recurrent.

Cognitive distortions are substantial contributors in the development of GD (Fortune & Goodie, 2012),

since gamblers' irrational beliefs and distorted cognitions about the ability to influence gambling outcomes alter their perceptions about the probabilistic nature of the events and promote gambling persistence despite negative consequences (Johansson et al., 2009; Oei, Lin, & Raylu, 2008). Consequently, these misbeliefs can shape a biased confidence on their capacity to recover economic losses, and result in loss-chasing (Studer et al., 2015).

Considering the compelling evidence that demonstrates the central importance of cognitive bias in GD (Clark et al., 2014), the development of reliable instruments to measure cognitive distortions have attracted significant research attention (Goodie & Fortune, 2013). The predominant structured approach to study cognitive distortions in gambling is the hierarchical 5-factor model developed by Raylu and Oei, and materialized in the Gambling-Related Cognitions Scale (GRCS; Raylu & Oei, 2004). The five dimensions of this model are: illusion of control, predictive control, interpretative bias, gambling expectancies and inability to stop. The first three dimensions came from early analysis on gambling erroneous perceptions (Gaboury & Ladouceur, 1989; Toneatto et al., 1997), and are grouped in the category of causal biases, while the remaining dimensions are considered pervasive beliefs and adapted from substance addiction research (Lee et al., 1999). Illusion of control refers to the biased belief that certain strategies or rituals can influence gambling outcomes, and also includes the control of random gambling outcomes by skills or knowledge. Predictive control reflects different strategies used by gamblers to predict gambling outcomes. For example, illusory contingencies between cues and outcomes, past history of loses followed by wins (gamblers' fallacy) or "loss chasing". Interpretative bias alludes to reformulations of gambling outcomes to mitigate their negative impact, that is, the attribution success to personal skills and failure to external influences, and selective memory bias. Gambling expectancies refers to a variety of expectations and motivations to gamble, including social approval, cope with negative emotions or feelings of excitement. Lastly, inability to stop gambling denotes a subjective perception of difficulties to control gambling urges.

Moreover, recent evidence shows that GRCS score is a robust GD predictor (Taylor et al., 2014; Tang & Wu, 2012; Cosenza et al., 2014), and accounts for a significant amount of disorder variance (Cosenza & Nigro, 2015; Donati et al., 2015; Ciccarelli, Griffiths, et al., 2016).

Among these cognitions, control illusion and predictive control can be considered as instances of distorted causal learning, namely an overestimation of the perceived causal link between one's behavior (or environmental cues) and gambling outcomes. The overestimation can be promoted by rewards, but also by events

that are considered as causally informative. This is the case of near-misses: non-wins that are subjectively perceived as being close to wins, and thus indirectly rewarding and contributing to illusory mastery (Clark et al., 2009; Sescousse et al., 2016). Given the detrimental impact that cognitive distortions have on GD patients, the study of their neurobiological basis have received little attention in gambling research. Hitherto, investigations on brain substrates of cognitive distortions have addressed the illusion of control (Clark et al., 2009; Clark et al., 2014), interpretative biases (Ruiz de-Lara et al., 2018), the gamblers' fallacy (Clark et al., 2014), and near-miss effects (Chase & Clark, 2010; Clark et al., 2009; Dymond et al., 2014; Habib & Dixon, 2010; van Holst et al., 2014). In the next section, we will analyze the most relevant gambling cognitions from different perspectives.

Illusion of Control

Illusion of control refers the general tendency to believe that individual actions can influence events only determined by chance (Langer, 1975). In the context of gambling, this cognitive distortion manifests in the conviction that using particular betting strategies or rituals in random gambling games can help to achieve success, and the perception that the use of certain skills of knowledge can affect random gambling outcomes (Goodie, 2005; Ladouceur & Sévigny, 2005). According to the proposal of GD as an associative learning disorder (Clark et al., 2019; Navas et al., 2019; Perales et al., 2020), illusion of control can emerge as a result of displaying dysfunctional instrumental learning processes in random situations.

The phenomenon of illusion of control can affect motivation and generate unrealistic judgments of increased probability of winning (Xue et al., 2013), thus promoting high risk-taking behaviors in gamblers (Davis et al., 2000). In addition, when individuals perceive the existence of an element of control in a gambling context, they tend to accept more and higher bets (Davis et al., 2000; Dixon, 2000; Goodie, 2003; Xue et al., 2013). Accordingly, gamblers with preference for gambling games that involve a skill component demonstrate stronger illusions of control, compared with gamblers with preference for games based on chance (Myrseth et al., 2010). Moreover, at the neural level, neuroimaging studies using different methodological manipulations of active choice to model illusory control have shown an increased activation in striatum and medial prefrontal cortex in GD (Clark et al., 2009) and community samples (Xue et al., 2013).

Gambler's Fallacy

The gambler's fallacy is the prototypical example of the predictive control cognitive bias, and due to its

easiness to implement in laboratory settings, have been one of the most studied, both at the behavioral (Ayton & Fischer, 2004; Burns & Corpus, 2004; Croson & Sundali, 2005) and neural level (Xue et al., 2011, 2012a, 2012b). In a random context, the gambler's fallacy refers to the belief that a sequence of the same event would be corrected by the occurrence of an alternative event. The gamblers' fallacy has been extensively studied in gambling situations, where gamblers tend to take higher risks after a series of loses than wins (Croson & Sundali, 2005; Xue et al., 2011). In behavioral terms, gamblers tend to predict the cease of a sustained sequence of results with the same outcome, as this sequence is extended in time.

The etiology of this cognitive bias has been related with an inaccurate understanding of randomness, where subsequent events are independent from previous ones. Accordingly, it represents a concrete example of the representativeness heuristic (Kahneman & Tversky, 1972) that consist in the idea that any part of a succession of random events should epitomize the general statistical distribution where it belongs (i.e. the law of small numbers; Tversky & Kahneman, 1971; Kahneman & Tversky, 1972; Rabin, 2002). Specifically, in the context of slot-machine playing, gamblers are susceptible to think that after a jackpot, the machine is not expected to deliver another win combination in a period of time. Moreover, gambler's fallacy can contribute to the phenomenon called 'chase loses' in GD, and explain the recurrent gambling behavior despite accumulating loses. In this situation, the gambler may anticipate a jackpot is more likely to happen after a series of loss trials (Sharpe, 2002).

In addition, the study of neurocognitive substrates of the gambler's fallacy has recently attracted increasing attention in neuroscience research (Xue et al., 2011, 2012a, 2012b). In particular, the investigations of gambler's fallacy-like behaviors in community samples have shown an involvement of lateral prefrontal regions (Xue et al., 2011; Xue et al., 2012b) and have suggested a relationship with dysfunctional affective processes (Xue et al., 2011; Xue et al., 2012a).

Interpretative Bias

Interpretative bias (IB) refers to the reconstruction of gambling outcomes to make them fit into to one's interests and motivations. Accordingly, gamblers tend to attribute success to their abilities and losses to bad luck, thus selectively remembering wins over losses, which in turn helps them maintain an illusory expectancy of wining (Raylu & Oei, 2004). It is one of the most informative cognitive biases from the GRCS, as it enables discrimination both between GD patients and healthy control groups, and between different clinical and

behavioral patterns in GD patients (Del Prete et al., 2016; Navas et al., 2016). Importantly, biased cognitions assessed by IB were highly and independently predictive of gambling severity and clinical status (Del Prete et al., 2017; Donati et al., 2015; Grall-Bronnec et al., 2012; Navas et al., 2016). So far, however, the study of neural bases of this distortion has been scarce. Specifically, results from a structural Voxel-Based Morphology study indicate that higher IB scores were associated with diminished grey matter volume in dorsal anterior cingulate cortex (Ruiz-de Lara et al., 2018).

Near-Misses

As a mechanism boosting delusive expectancies, brain response to near-misses has received increasing attention in GD research (Chase & Clark, 2010; Clark et al., 2009; Clark et al., 2014). Near-misses occur when the display of a negative outcome is perceptually similar to a win. In their seminal article from 2009, Clark and collaborators showed that the ability of near-miss events to promote gambling motivation occurs by recruiting reward system regions (anterior insula and ventral striatum, VS) that mimic win-related responses. Furthermore, using the classical lesion-studies paradigm, Clark et al. (2014) showed that focal brain lesions on the insula abolish gambling-related cognitive biases (specifically the gambler's fallacy and near-miss effect). In regular gamblers, near-misses, when compared to full-misses, were also associated with significant VS response, and higher gambling severity predicted increased responses in the midbrain area to near-misses (Chase & Clark, 2010). In response to near-misses, it has been also reported an association between bilateral VS connectivity to the insula and gambling severity (van Holst et al., 2014). In addition, Sescousse et al. (2016) compared responses between GD patients and controls, showing a heightened striatal response to near-miss outcomes in gamblers.

Therefore, research on the brain responses to near-misses in GD patients has shown a consistent amplified response in VS and insula (Chase & Clark, 2010; Clark et al., 2014; Clark et al., 2009; Dymond et al., 2014; Sescousse et al., 2016; van Holst et al., 2014), associated with an increased motivation to gamble. The rewarding properties of near-misses in GD patients have a direct effect on gambling expectancies, and reflecting outcomes closely matching a win, they can function as information on skill acquisition or strategy improvement, thus also contributing to illusory control (Clark et al., 2014).

1.4 The origin of gambling cognitions

Gambling distortions as alterations of domain-general cognitive functions

The body of literature on the study of cognitive errors in the processing of probabilistic information has not emerged within GD studies. Instead, it has a long tradition that dates back to the study of cognitive heuristics in decision making under uncertainty (Tversky & Kahneman, 1971; Kahneman et al., 1982). Combining decision theory with psychophysiology principles, Amos Tversky and Daniel Kahneman translated psychological experiments on decision making processes to real-life situations, and found systematic deviations in people's decisions that questioned objectivity of individual perceptions of reality (Kahneman, & Tversky, 1973). They found that, when confronted with complex tasks that require the assessment of probabilities and expected values, individuals base their decisions on a number of heuristic rules that can lead to systematic errors (Tversky & Kahneman, 1973). In a series of investigations during the seventies, they described a set of heuristics and biases that people use in the subjective evaluation of probabilities and judgments associated with uncertain situations (Kahneman, & Tversky, 1972; Tversky & Kahneman, 1973). From these investigations, they conclude that cognitive biases were not associated with external motivations or influences, since participants were requested to be accurate and correct responses were rewarded (Kahneman, & Tversky, 1972). On the contrary, these mistaken estimations were grounded on unreliable information and biased intuitive judgments (Kahneman, & Tversky, 1979).

Although their research was not circumscribed to gambling scenarios, the results from these investigations yield to the description of logical errors comparable to cognitive distortions found in gambling research (Tversky & Kahneman, 1974). Moreover, these erroneous beliefs were present in different populations, as psychologists, flight instructors, lawyers, nurses, and even in individuals with experience in statistics (Tversky & Kahneman, 1971; Kahneman, & Tversky, 1973). Accordingly, in the representativeness heuristic, the misunderstanding of random processes would bias individuals to think that a segment of a random sequence would be representative of the entire sequence (Kahneman, & Tversky, 1972).

Relatedly, in gambling scenarios, the observation of a series of trials with black outcomes on roulette, would lead individuals to think that a red outcome is more likely (gamblers' fallacy). Further, one of the manifestations of the availability heuristic is the bias in memory retrieval (Tversky & Kahneman, 1973). The effect of familiarity, salience and recency affect judgments of probability, and games' structural features exploit these

mechanisms, for instance, by the association of infrequent wins with intense audiovisual stimuli that facilitate memory retrieval (i.e. interpretative bias). A related example of the availability heuristic is the illusory correlation, which refers to judgments of the frequency of co-occurrence of distinct events. Thus, the subjective estimation of a strong association between a specific ritual or charm with success, would bias gamblers to think these strategies can have an influence on a random game (illusion of control).

Moreover, GD research has also shown that even non-problem recreational gamblers manifest cognitive distortions (Gaboury & Ladouceur, 1989; Griffiths, 1994; Joukhador et al. 2003). Whereas it is an established result that gambling cognitions are over-represented in GD patients (Cunningham et al., 2014; Jacobsen et al., 2007; Joukhador et al. 2003; MacKay & Hodgins, 2012; Miller & Currie, 2008; Myrseth et al., 2010; Navas et al., 2016, 2017; Wohl et al., 2007; Xian et al., 2008; Yakovenko et al., 2016; for a review, see Goodie & Fortune, 2013), variability in the expression of such cognitions across different levels of gambling involvement is not trivial (Joukhador et al. 2003; Myrseth et al., 2010; Yakovenko et al., 2016). However, GD patients differ from recreational gamblers and non-gamblers not only in the intensity of gambling cognitions expression, but also in the relationships with different clinically-relevant variables (Wohl et al., 2007). For instance, in GD patients, gambling cognitions are associated with gambling severity (Cunningham et al., 2014; Xian et al., 2008), and are robust predictors of future gambling involvement in longitudinal studies (Yakovenko et al., 2016).

Therefore, different research lines demonstrate that heuristics and biases are not exclusive of pathological gamblers, as they are also expressed by social gamblers and non-gamblers (Joukhador et al. 2003; Tversky & Kahneman, 1974). Cognitive distortions constitute a shared aspect of human decision making, and can thus be considered as an alteration of domain-general cognitive functions involved in judgment and decision-making situations characterized by uncertainty. As previously mentioned, the ability to detect patterns and regularities in the environment, and discern real contingencies from illusory correlations is an adaptive ability resulting from years of evolution in relation with natural contexts. In these contexts, perseverance of unrewarded responses has a learning function, and provides useful information about the likelihood of potential future rewards. However, the unique structural features that characterize gambling games turns these behavioral tendencies dysfunctional, since uncertainty and statistical independence between trials is inherent to gambling (Haw, 2008).

Despite the fact that biases are generalized, people can differ in their expression. So, the possibility exists that such individual differences could make individuals more or less vulnerable to GD. In other words, a

first etiological hypothesis regarding the origin of distorted gambling cognitions is that individual differences in the domain-general functions underlying cognitive processes could make people more or less prone to their manifestation in gambling scenarios and thus contribute to develop disordered gambling behavior.

Gambling cognitions derived from the exposition to gambling games

In recent years, the emergence of novel gambling opportunities has turned gambling into a widespread phenomenon (Gainsbury et al., 2014). For example, the legalization and regulation of different forms of online gambling has had a substantial impact, with a rapid increase of internet gambling participation (Gainsbury et al., 2014). Investigations on online gambling behavior report higher problem gambling prevalence rates among internet gamblers (Ladd & Petry, 2002; Griffiths et al., 2009; Olason et al., 2011) and a profile characterized by younger age, higher educational level and being employed (Griffiths et al., 2009; Wood & Williams, 2011). Moreover, the most common motives to gamble reported by online gamblers is the accessibility and convenience (McCormack & Griffiths, 2012).

Beyond the generalized availability and easy accessibility that facilitate gambling involvement, research has identified specific structural features from games' design that facilitate GD escalation (Linnet et al., 2010; Parke & Griffiths, 2007; Yücel et al., 2017). Many of these features represent different factors associated with how the reward is delivered, and promote delusive expectancies and perceived illusory control (Harrigan et al., 2014). For instance, the frequency of near-miss events (Barton et al., 2017; Murch & Clark, 2016) has been associated with augmented physiological responses and increased gambling motivation and persistence (Clark et al., 2009; 2012; Côté et al., 2003; Kassinove & Schare, 2001). Intense sensory stimulation, in the form of different manipulations of sounds and light, can be used as feedback on the occurrence of significant events, facilitating future memory retrieval, or as an environmental characteristic, drawing attention to the location of gambling machines (Yücel et al., 2017). In addition, high frequency of betting and reinforcement ratio (Harris & Griffiths, 2018) produce increased gambling persistence, excitement and desire to play (Linnet et al., 2010). Multiple-line betting machines (Harrigan et al., 2014) and superficial features of the game as 'stop' or 'hold' buttons (Parke & Griffiths, 2007) are designed to induce a delusive element of skill, which has no real impact on reward probability (Ladouceur & Sévigny, 2005). Also, random ratio (RR) reinforcement schedules (Haw, 2008; James & Tunney 2017; Nolan, 1970), were developed and refined to maximize reward uncertainty, that in turn stimulates reward system regions and dopamine release (Fiorillo et al., 2003; Preuschoff et al., 2006; Schultz, 2016).

In reinforcement learning literature, it is acknowledged that variable schedules of reinforcement produce stable and resistant responses, compared to fixed-ratio programs (Fester & Skinner, 1957). In variable ratio (VR) schedules, the reinforcement is delivered after a set number of responses, and the number of responses required oscillates from one, until a specified number (i.e., 4), in a variable order, with a specific mean ratio (i.e. 2,5). In addition, random ratio (RR) schedules are a particular case of VR schedules, where the specific responses required to obtain the reward respond to a specific ratio (i.e. 1:4), but responses can fluctuate from one to an undetermined number, and thus variability in the sequence of responses for reinforcement is higher (Catania & Reynolds, 1968; Millenson, 1963).

Moreover, an essential distinction between both schedules is that, in VR schedules, the probability of reward increases with each unreinforced response, whereas in RR schedules, probability does not depend in the number of previously unreinforced responses. Thus, reward probability in every single trial is independent from previous trials (Lagorio & Winger, 2014). As noted above, reward uncertainty can stimulate DA release associated with prediction error signals (Ross et al., 2008; Schultz, 2016), and promote incentive sensitization. But, in addition to that, as programmed in RR schedules, it can also make the development of illusory contingencies particularly disadvantageous for the gambler.

In summary, ambling games' features facilitate the development of cognitive distortions, through exploiting human sensitivity to detect contingencies in probabilistic environments (Clark, 2014). The structural characteristics of gambling games design, as RR schedules, multiline betting, false feedback, near-miss events, and 'stop' or 'hold' buttons can interact with human cognitive control and decision-making processes to promote gambling distorted cognitions (Ladouceur & Sévigny, 2005; Wohl & Enzle, 2003). Hence, gambling cognitions can develop as a consequence of gambling behavior, specifically, by the interaction between the gambler neurocognitive functions and specific features of games' design, by capitalizing on human tendencies to make intuitive judgments based on insufficient information (Tversky & Kahneman, 1974). In this realm, recent longitudinal investigations have studied the prospective course of gambling cognitions in gamblers (Leonard & Williams, 2016; Nicholson et al., 2016). These studies have suggested a bidirectional relationship between gambling bias and problematic gambling, where gambling biases are etiologically related with subsequent problem gambling, but gambling involvement also promotes the development of gambling bias.

Gambling cognitions as motivated reasoning: The Gambling Space Model

As previously described, the concept of causal biases refers to the subset of gambling cognitions that reflect altered processes of causal learning, and includes control illusion, predictive control and interpretative bias. These causal biases represent an overestimation of the perceived causal association between individual behavior or environmental cues, and gambling outcomes. The complexity of gambling cognitions emerges from their associations with constructs from different nature, for instance, impulsivity and emotion regulation processes (Michalczuk et al., 2011; Navas et al., 2019). In turn, these interactions define specific gamblers profiles with unique combinations of personality and sociodemographic characteristics, and particular clinical complications.

According to Michalczuk and collaborators (2011), the association between impulsivity and gambling biases can help to explain their etiology. They argue that causal biases are associated with impulsivity in GD patients because impulsive behavior in decision making contexts can predispose gamblers to accept distorted beliefs without questioning. Therefore, cognitive biases would develop as a consequence of an impulsive cognitive style. However, this interpretation cannot account for the finding that cognitive biases correlate more robustly and systematically with emotional and motivational aspects of impulsivity (sensation seeking, positive urgency and negative urgency) than with its purely cognitive facets (lack of perseverance and premeditation) (Del Prete et al., 2016). In addition, higher cognitive distortions characterize a subgroup of gamblers with younger age, higher education attainment and preference for skill-based games (Myrseth et al., 2010).

An alternative explanation that tries to integrate the triadic relationships between gambling cognitions, impulsivity and emotion regulation is proposed by the Gambling Space Model (GSM, Navas et al., 2019). Within this framework, cognitive distortions (and particularly outcome-related cognitive biases) are defined as hallmarks of a self-deceptive cognitive style, characterized by a disposition to distort reality with a self-centered motivation. In essence, cognitive biases emerge as manifestations of motivated reasoning (Kunda, 1990), and can reflect an attempt to mitigate negative emotions resulting from adverse gambling outcomes and promote positive emotions to justify excessive gambling. Hence, as instances of an intention to regulate gambling-derived emotions, cognitive biases should overlap with elaborated emotion regulation strategies. Accordingly, two recent studies found evidence supporting this assertion (Jara-Rizzo et al., 2019; Navas et al., 2016). The first study by Navas and colleagues (2016) showed that a subgroup of GD patients with higher cognitive distortions were more likely to use putatively adaptive emotion regulation strategies (i.e. putting into

perspective, from the Cognitive Emotion Regulation Questionnaire, CERQ; Garnefski & Kraaij, 2007) than healthy controls. Similarly, Jara-Rizzo et al., (2019) have recently found an association between cognitive distortions and the dispositional use of reappraisal (from the Emotion Regulation Questionnaire, ERQ; Gross & John, 2003) to cope with negative emotions. Thus, the Gambling Space Model makes the counterintuitive prediction that 'adaptive' emotion regulation strategies used by healthy individuals to modulate negative emotions (i.e. different forms of reappraisal, re-attribution or refocusing, generally associated with positive outcomes) can be used by GD patients to manage negative events (i.e. losses) and enhance positive emotions that help them justify their excessive gambling involvement (Navas et al., 2019).

In summary, the GSM proposes that gambling cognitions have a motivational basis, and in combination with elaborated emotion regulation strategies, including those considered as adaptive, contribute to gambling behavior maintenance despite accumulating losses. In addition, the relationship between cognitive distortions and elaborated emotion regulation mechanisms can help to explain the inconsistent results on executive dysfunction in GD patients (Goudriaan et al., 2006; 2014). If cognitive biases are motivated, it would not be necessary a dysfunction in basic cognitive mechanisms or numerical abilities in GD patients to manifest those biases. In contrast, the implementation of elaborated emotion regulation mechanisms with a self-centered motivation would require preserved cognitive functions (Navas et al., 2019).

1.5 Rationale for the studies included in the thesis

GD represents a serious public health concern, and is characterized by loss of control over gambling behavior despite negative consequences (American Psychiatric Association, 2013). From early descriptions of GD to current theoretical conceptualizations, gambling cognitions have been considered as hallmarks of GD symptomatology (Blaszczynski & Nower, 2002, Clark, 2014; Gaboury & Ladouceur, 1989; Navas et al., 2019; Sharpe, 2002). Uncertainty and risk, inherent features of gambling games, have been analyzed in terms of their motivational value, and how in interaction with specific neurocognitive functions and psychobiological traits promote gambling cognitions. In turn, gambling cognitions have been considered as emerging from insufficient statistical abilities and unreflective and rush behavioral tendencies (Michalczuk et al., 2011). However, recent findings demonstrate that this assumption may be an oversimplification of the complex nature of cognitive bias (Del Prete et al., 2016; Myrseth et al., 2010; Navas et al., 2016; Perales et al., 2017).

Compelling preliminary magnetic resonance imaging studies reported associations of gambling cogni-

tions with insular, orbitofrontal and striatal regions (Chase & Clark, 2010; Clark et al., 2009; Clark et al., 2014; Dymond et al., 2014; van Holst et al., 2014). However, these studies have essentially focused on the near-miss effect, and thus cannot generalize to other cognitions featuring alterations associated with inferential and causal learning processes. Thus, replication of these findings on distinct gambling cognitions is warranted.

Complementary, how these specific gambling cognitions translate into general deficits on causal learning processes have received little attention in GD research. The identification of alterations on general-domain causal learning functions associated with cognitive biases would help to understand their etiology and thus promote improved and evidence-based intervention approaches for GD. In addition, the investigation of interactions between gambling cognitions and other clinical manifestations of GD is important for two reasons. First, it can help to understand the nature and origins of gambling cognitions. In addition, it can define specific GD profiles with unique characteristics and complications, to identify distinct pathways to GD vulnerability.

Further research is needed to better characterize gambling cognitions in GD. Moreover, the integration of different research approaches in the study of gambling cognitions would be particularly useful given the complexity of the phenomenon and relationships with gambling clinically-relevant variables. This thesis is built on previous knowledge and accumulating evidence from our laboratory, integrated in the GSM, a comprehensive approach to understand GD development and associated key vulnerability factors.

1.6 Aims and hypotheses

General aims

The overarching aim of the present thesis is to provide new insights into the etiology of gambling cognitions and its central relevance as a unique manifestation of GD clinical picture. We attempt to achieve a better understanding of the neurocognitive processes underlying gambling cognitions, and how specific structural characteristics of gambling games' design interact with such processes to promote cognitive distortions. We integrated different research approaches, from neuroimaging techniques to psychometric instruments and neuropsychological tasks, to disentangle the internal structure of gambling cognitions and interactions with other clinical hallmarks of GD, namely, emotion regulation strategies and impulsivity measures. We sought to characterize structural correlates of GD, and how variability of individual traits in GD patients interact with brain morphometric measures. Further, we aimed to ascertain if the dysfunctional processes measured by gambling cognitions psychometric tools generalize to domain-general causal learning deficits in gamblers. Finally,

we attempt to shed some light on the triadic relationships between gambling cognitions, emotion regulation strategies and impulsivity, to identify the inner nature of gambling cognitions and how these constructs interact to define specific gamblers' profiles with unique characteristics and associated vulnerability factors. Ultimately, we expect that our findings can serve as a significant contribution to expand knowledge and understanding of neurocognitive alterations in GD, and eventually provide novel approaches for individualized interventions on the diverse clinical manifestations of GD.

Specific aims and hypothesis

Study 1. Psychobiology of gambling-related cognitions in gambling disorder.

Aims

- The aim of this review is to describe the psychobiological substrates of gambling-related cognitive bias to promote a better understanding of the development of compulsive gambling.
- First, we outline the main gambling-related cognitive distortions described in GD literature, articulated in the theory behind the Gambling-Related Cognitions Scale (GRCS; Raylu & Oei, 2004).
- Then, we delineate the key neurocognitive processes that underlie gambling cognitions, and summarize recent investigations using validated research paradigms on GD patients. We analyze these cognitions in terms of neurocognitive components that can be explored using neuroimaging techniques
- Finally, we describe how interactions between causal biases and adaptive emotion regulation mechanisms in gamblers contribute to a self-deceptive reasoning style that promotes gambling maintenance.

Study 2. Regional grey matter volume correlates of gambling disorder, gambling-related cognitive distortions, and emotion-driven impulsivity.

Aims

- In the first experimental study, we apply morphometric methods to explore regional structural differences between GD patients and healthy controls (HC).
- In addition, we explore potential relationships between regional volumetric measures and individual variability in two hallmarks of GD symptomatology, identified by previous research to be key markers of clinical status and prognosis: the interpretative bias (IB) and negative urgency (NU).
- The specific aims of this study are:

- To explore potential differences in grey matter volume between GD patients and a sociodemographically-matched group of HCs, using a VBM approach.
- To analyze the involvement of two specific measures of gambling-related cognitive distortions and affect-driven impulsivity (IB and NU) in individual GM variability.

Hypotheses

- The heterogeneity of previous findings on structural differences between GD patients and HC prevents an unambiguous prediction on specific anatomical areas; nevertheless, methodologically sound studies suggest GMV reductions in control and regulation structures (Grant et al., 2015; Zois et al., 2017).
- Considering the lack of direct evidence on relationships between structural measures and clinically relevant variables in GD, we should refer to functional MRI studies. Accordingly, studies in GD patients report associations between gambling cognitions and insular and striatal regions (Clark et al., 2014), and involvement of striatum, amygdala and ventral prefrontal cortex in affect-driven impulsivity (Contreras-Rodríguez et al., 2016). Moreover, compelling evidence highlight the transdiagnostic nature of NU, contributing to externalizing psychopathology and as a marker of increased complications in GD (Navas et al., 2019). Thus, we hypothesized that relationships between this impulsivity domain and structural measures will not overlap with case-control differences, and converge towards general-domain regulatory regions.

Study 3. Causal Learning in Gambling Disorder: Beyond the Illusion of Control.

Aims

- In the second empirical study, we use an instrumental causal learning task to examine performance differences between GD patients and healthy controls, matched in relevant sociodemographic and intelligence variables. With this experimental protocol, we aim to corroborate if cognitive biases as measured with self-report instruments are grounded in general-domain cognitive functions. In addition, we analyze potential influences of clinically relevant factors (gambling cognitions and severity) on individual differences in behavioral performance. In this investigation, we manipulate the contingency in the two versions of the task, and program null and positive contingencies for each one. We attempt to discern if differences in the degree of contingency influence behavior and judgments in gamblers.

Hypotheses

- We predict that, in GD patients, general-domain illusion of control bias in the instrumental learning task will be associated with GRCS illusion of control and predict gambling severity.
- More pronounced deviations in the estimation about contingency in GD patients, compared to HC, particularly in the null contingency condition, which would reflect illusion of control bias.
- We expect that deviations in contingency estimation will be significant predictors of gambling status and severity.
- We also expect that deviations in contingency estimation will hold predictive value over causal biases, assessed with the GRCS (Raylu & Oei, 2004)

Study 4. The paradoxical relationship between emotion regulation and gambling-related cognitive biases.

Aims

- The last empirical study from this thesis investigate impulsivity and emotion regulation predictors of gambling-related cognitions in a sample of gamblers with different levels of gambling involvement (from occasional to disordered gamblers).
- Given previous literature on associations between cognitive distortions, emotion regulation strategies and impulsivity measures, we aim to harness a methodologically sound approach to examine the associations between these measures, controlling for the effect of clinically-relevant variables, as gambling severity.

Hypotheses

- Anchored on the assumption that causal biases in gamblers have a motivational basis, we can derive two overarching predictions on the associations of emotion regulation strategies and impulsivity measures with gambling-related cognitions.
- The first prediction is based on the notion that affect-driven impulsivity dimensions and cognitive bias shared a common emotional and motivational foundation. In particular, we propose that emotions involved in eliciting affect-driven impulsivity also contribute to development of cognitive bias. Accordingly, we expect a closer relationship of gambling cognitions with emotional/motivational dimensions of impulsivity (positive and negative urgency, and sensation seeking) than with its cognitive compo-

nents (lack of perseverance, and lack of premeditation).

• According to our proposal, where the combination of elaborated cognitive strategies of emotion regulation considered as adaptive and cognitive bias could reflect gamblers' intention to misinterpret gambling outcomes and mitigate their negative impact, we hypothesize a counterintuitive relationship between adaptive emotion regulation strategies (putting into perspective, reappraisal) and cognitive bias.

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2. Psychobiology of gambling-related cognitions in gambling disorder

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2.1 Highlights

- We outlined key psychobiological processes associated with biased gambling cognitions
- Games' structural features maximize uncertainty and promote cognitive distortions
- Sensitivity to gambling-related rewards promotes delusive gambling expectancies
- Unsuccessful attempts to control craving foster perceived inability to stop gambling
- Mechanisms of emotion regulation contribute to cognitive biases

2.2 Abstract

The aim of this review is to explore the psychobiological substrates of gambling-related cognitions, and their relationship with motivational and emotional processes, to contribute to the understanding of this important facet of disordered gambling. These cognitions promote gambling initiation and maintenance, and gambling games' structural features are designed to foster them. According to our proposal, individual psychobiological features modulate gambling distortions vulnerability. Abnormal sensitivity to gambling-related rewards promotes the development of unrealistic expectancies, facilitating gambling escalation. As gambling behavior becomes recurrent, gambling cues acquire incentive salience, capable of triggering craving responses. Unsuccessful attempts to control craving generate the perceived inability to stop gambling. A proportion of gamblers use emotion regulation strategies to cope with gambling-related emotions, which fuels cognitive biases.

2.3 Introduction

Gambling disorder (GD) is characterized by excessive and maladaptive gambling behavior, and its prevalence ranges between 0.12 and 3.4% [1,2]. In the fifth Diagnostic and Statistical Manual of Mental Disorders, GD, previously considered as an Impulse Control Disorder, has been reclassified in the new category Substance-Related and Addictive Disorders [3]. This recategorization was driven by evidence highlighting the overlap in neurobiology and symptomatology, and the substantial degree of comorbidity between GD and Substance-Related Disorders [4,5]. Imbalanced reward sensitivity, decision-making alterations, impaired cognitive control and craving, seem to be similarly relevant for compulsive gambling and drug use [6]. In spite of these similarities, the mechanisms driving the transition from recreational to addictive behaviors remain controversial (see Figure 1) [7,8].

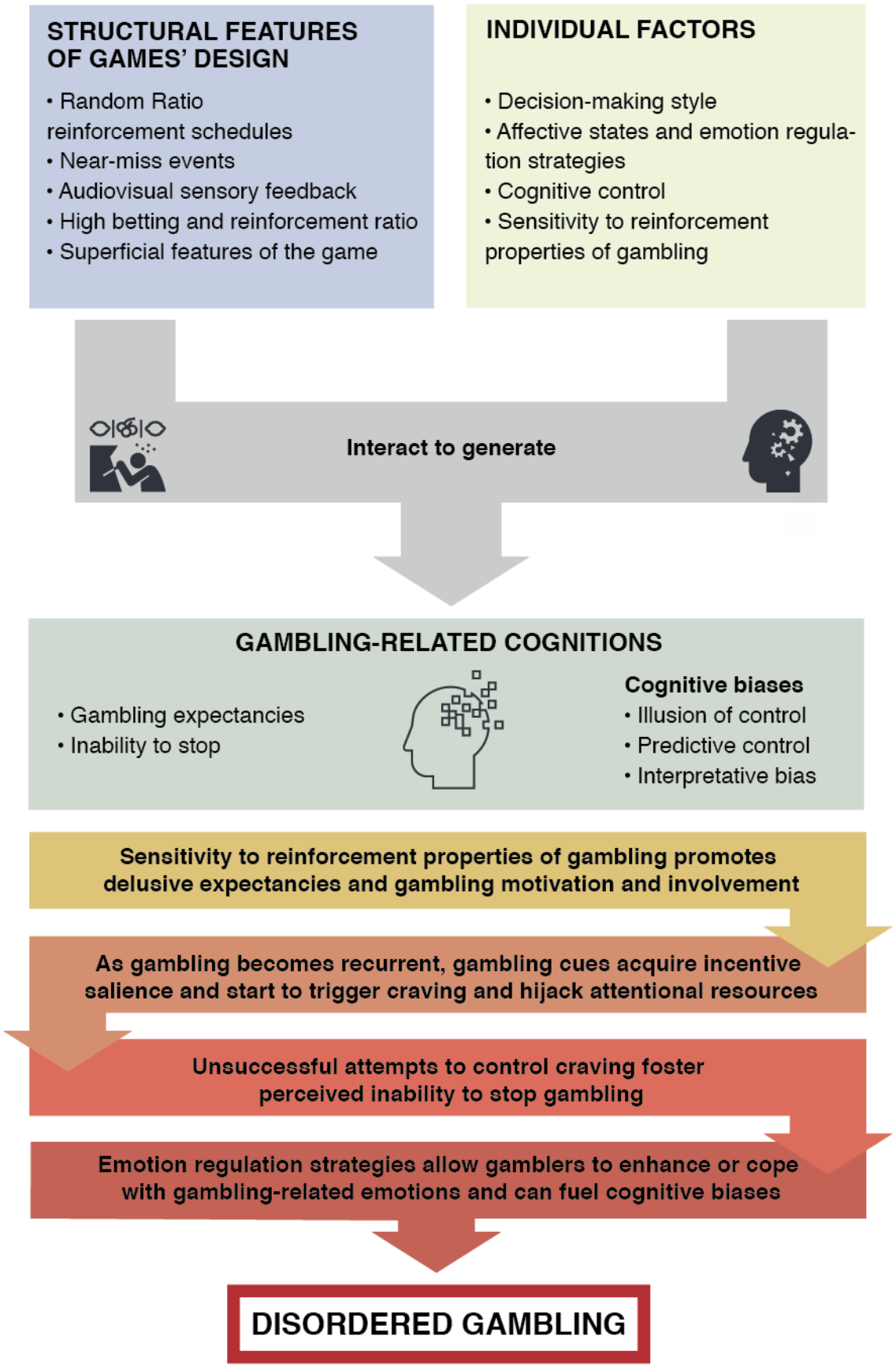

Figure 1: Graphical abstract

Addictive agents exert their effects by over-stimulating the systems involved in learning adaptive responses to probabilistic natural reinforcers. Evidence shows that unexpected rewards evoke dopaminergic prediction error signals [9]. By recurrent association, reward becomes predictable by external cues, and discrepancy between expected and experienced reward eventually disappear [10]. Crucially, drugs of abuse are not only hedonically rewarding, but also activate dopamine (DA) release in the mesolimbic pathway, mimicking prediction error signals, which precludes their attenuation as instrumental learning progresses [11]. By this mechanism, cues associated with drug consumption override the incentive value of natural rewards (i.e. incentive sensitization, IS), and generate a prevailing motivational impulse to use the drug [12]. This approach may help to explain the transition from recreational to compulsive gambling, in the absence of a chemical agent influencing DA activity. Most gambling devices operate under random ratio (RR) schedules [13,14], where reward probability in every single trial is independent from previous trials [15], and uncertainty cannot be reduced. Evidence suggests that reward uncertainty can mimic drug effects by triggering DA release associated with prediction error signals [16–19]. In parallel, animal research has shown that overtraining under similar partial reinforcement schedules facilitates the development of habits [20]. This process seems to depend on a gradual shift in the involvement of the striatum (from its ventral to its dorsal part) in behavior control, and is also likely involved in the generation of compulsive drug use habits [21,22].

Complementarily, gambling games' features facilitate the development of cognitive distortions, by exploiting human sensitivity to detect contingencies in probabilistic environments [23]. When faced with reward uncertainty and randomness of games of chance, gamblers try to make sense of the ambiguity, for instance, by searching patterns [24]. Gambling disorder patients (GDP) are particularly susceptible to experience cognitive distortions [11,25].

This review is aimed at exploring the psychobiological substrates of gambling-related cognitions. First, these cognitions are outlined, articulated in the model behind the Gambling-Related Cognitions Scale (GRCS) [26]. Secondly, we analyze these cognitions in terms of neurocognitive components that can be explored using neuroimaging techniques. And finally, we review recent available evidence on how emotion regulation mechanisms contribute to a self-deceptive reasoning style that promotes gambling maintenance.

2.4 Gambling cognitions: an overview

Our ability for adaptive decision making rests on the capacity to assess the expected value and to esti-

mate the probability of significant outcomes [27]. Yet, the cognitive literature on gambling has revealed a number of cognitive distortions and pervasive beliefs that affect gambling decision making [24]. These cognitions contribute to the etiology of disordered gambling [23,28]**, and predict future gambling involvement [25].

The best-known approach to study gambling cognitions is Raylu and Oei's 5-factor model, materialized in the GRCS [26]. The five dimensions in this model are: control illusion, predictive control, interpretative bias, gambling expectancies and inability to stop. The first three dimensions, extracted from early analyses of gambling-related misperceptions [29,30], are grouped in the category of causal biases, whereas the remaining dimensions are dysfunctional beliefs adapted from substance addiction research [31]. Control illusion refers to the biased belief that certain strategies or rituals can influence gambling outcomes. Predictive control reflects the belief that gambling outcomes are predictable, based on illusory contingencies between cues and outcomes, or a perceived history of loses followed by wins (gamblers' fallacy). Interpretative biases allude to hindsight reformulations of gambling outcomes to attribute success to personal skills, and failure to external influences. Gambling expectancies refers to a variety of motives to gamble, including socializing, coping with negative emotions or excitement-seeking. Lastly, inability to stop gambling denotes the perceived difficulty to control gambling urges.

Among these cognitions, control illusion and predictive control can be considered instances of distorted causal learning, namely an overestimation of the perceived causal link between one's behavior (or environmental cues) and gambling outcomes. This over-estimation can be fueled by actual rewards, but also by non-rewards that are seen as causally informative. This is the case of near-misses: non-wins that are subjectively perceived as being close to wins, and thus indirectly rewarding and contributing to illusory mastery [28]**.

Despite the validated relationships between outcome-related perceptions and beliefs, and general-domain decision making processes, in general (and gambling-related decision-making in particular) [26,32], the study of their neurobiological bases has received relatively little attention. Hitherto, investigations on brain substrates of cognitive distortions have addressed the illusion of control [28,33]**, interpretative biases [34], the gamblers' fallacy [28], and near-miss effects [33,35–38]. In the next sections, we try to link the neurobiological findings described in these studies to the cognitions described above.

2.5 Gambling expectancies – Reinforcing properties of gambling

Substance addiction literature has shown that expectations on the potential effects of drugs are relevant

in the development of substance-related problems [39–41], and modulate brain reactivity to substance-related cues [42]. Similarly, in gamblers, expectancies about the reinforcing properties of gambling have been associated with gambling-related motivation, problems, and persistence [26,43]. Moreover, an expected reward from placing a bet (compared to passively viewing a competition) triggers increased activity in insular, striatal and prefrontal regions [44]. Thus, although gambling expectations include diverse motives to gamble, psychobiological research has mostly focused on the processing of in-game rewards.

Recently, the emergence of novel gambling opportunities [45] has been accompanied by parallel increases in the number of gambling modalities and games' structural features that facilitate gambling escalation [14,46]. Many of these features are associated with reward delivery and involved in expectancies formation, i.e. reinforcement schedules [47], frequency of near-miss events [48,49], intense sensory feedback as audiovisual stimuli [14], high frequency of betting and reinforcement ratio [50], or superficial features as stop buttons with no real impact on reward probabilities [51].

As a mechanism boosting delusive expectancies, brain response to near-misses has received increasing attention [28,33,35]. In a seminal article, Clark and collaborators [33]** showed that, by recruiting reward system regions (anterior insula and ventral striatum, VS) that mimic win-related responses, near-misses promote gambling motivation. Furthermore, Clark et al. [28]** showed that insular lesions abolish the gambler's fallacy and near-miss effects. In regular gamblers, near-misses, when compared to full-misses, were also associated with significant VS response, and higher gambling severity predicted increased responses in the midbrain area to near-misses [35]*. Gambling severity was also associated with bilateral connectivity between VS and insula in GDP in response to near-misses [38]*. Similarly, Sescousse et al. [52]** compared responses between GDP and controls, showing a heightened striatal response to near-miss outcomes in gamblers. Results from experimental paradigms examining near-miss effects are summarized in Table 1.

With regard to actual rewards, etiological theories of addiction can help to explain how exaggerated expectancies emerge. More specifically, according to the reward deficiency syndrome (RDS) , the reward system turns increasingly hyposensitive to natural rewards as the addictive process progresses, which can indirectly boost drug-reward-related expectancies [53]. However, in GD research, evidence regarding these putative reward processing anomalies remains inconsistent [54]. The mixed pattern of hyper- [52,55–57] and hypo-responsiveness [58–62] of striatal, medial prefrontal and insular regions found in reward processing research in GD may be due to the intrinsic limitations of case-control studies, as well as samples characteristics and

methodological shortcomings [63,64].

Cognition category	Neuroimaging paradigm	Summary of results	Studies
Gambling expectancies	Reactivity to near-misses	Consistent hyperactivation of ventral striatum, insula	Clark et al. [33] (↑); Chase & Clark [35] (↑); Habib & Dixon [37] (↑); van Holst, Chase & Clark [38] (↑); Clark et al. [28] (↑); Dymond et al. [36] (↑); Worhunsky et al. [101] (↓); Sescousse et al. [52] (↑)
	Reward anticipation	Mixed evidence of hyper- and hypoactivation in medial PFC, ventral and dorsal striatum, insula	Sescousse et al. [65] (=); Balodis et al. [58] (↓); Choi et al. [59] (↓); van Holst et al. [57] (↑); Tsurumi et al. [62] (↓); Worhunsky et al. [101] (); Fauth-Bühler et al., [105] (=); Romanczuk-Seiferth et al, [73] (=); Brevers et al. [44] (↑ expectancy bet)
	Reward delivery	Mixed evidence of hyper- and hypo- activity in medial and lateral PFC, ventral striatum, insula, OFC	Reuter et al. [61] (↓); de Ruiter et al. [60] (↓); Balodis et al. [58] (↓); Sescousse et al. [65] (↑); Worhunsky et al. [101] (=)
INABILITY TO STOP	Cue-reactivity and craving induction	Consistent hyperactivation of insula, dorsomedial and dorsolateral PFC, ACC, PCC, parahippocampal gyrus and amygdala, and associations with craving measures	Crockford et al. [83] (↑); Goudriaan et al. [80] (↑); Balodis et al. [85] (=); van Holst et al. [106] (↑); Kober et al. [84] (↑); Limbrick-Oldfield et al. [72] (↑)
CAUSAL BIASES (control illusion, predictive control, interpretative bias)		Interpretative bias predicted reduced dorsal ACC grey matter volume. Personal control modulated neural reactivity and connectivity in response to gambling outcomes	Clark et al., [33]; van Holst et al., [38]; Clark et al., [28]; Ruiz de-Lara et al., [34]

Table 1. Summary of Magnetic Resonance Imaging studies exploring neurocognitive processes associated with gambling cognitions. (↑) increased reactivity in gambling disorder patients (GDP), compared to controls; (↓) decreased reactivity in GDP, compared to controls; (=) no significant differences in neural reactivity between GDP and controls; PFC, prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

Table 1 presents a detailed description of results from studies using reward-processing paradigms in GD with functional Magnetic Resonance Imaging (fMRI). To clarify these discrepancies, Sescousse et al. [65] compared sensitivity to monetary and erotic rewards between GDP and healthy controls in non-gambling contexts. GDP showed blunted VS reactivity to cues predicting erotic stimuli, when compared to cues signaling a monetary reward. However, reactivity to monetary cues did not differ between groups. Extending this result, a recent meta-analysis compared brain reactivity to different types of rewards, including natural (food, erotic) and addiction-related (drug, gambling), and found a common network that responds to rewards from different types, including bilateral insula, striatum, frontal and anterior cingulate cortex (ACC) [66].

Another important methodological distinction regards the focus on reward anticipation or delivery. Reward anticipation, where acquired expected value is central, is specifically involved in coding expectations and motivational processes [67]. Conversely, outcome evaluation is implicated in updating previously learned expected value when confronting novel information [68]. According to this delimitation, a recently published meta-analysis examined brain reward processing during reward anticipation and outcome delivery in GD and substance-use disorder (SUD) patients [69]**. A common pattern of decreased striatal activity during reward anticipation was found for both clinical groups. In contrast, GD and SUD patients showed a distinct response to outcome delivery, with reduced dorsal striatal activity in GDP and increased VS activity in SUD patients. Consequently, the pattern of results in GDP was interpreted as evidence supporting the RDS hypothesis in GD.

2.6 Inability to stop – Craving control

Recurrent unsuccessful attempts to control gambling cravings foster the belief of inability to stop gambling [70]. Craving, in turn, arises from the repeated association between external cues and rewarding effects of the addictive agent, and progressive neuroadaptations in distinctive brain networks [12,38,57,60,71–73].

As noted above, most drugs of abuse exert their rewarding properties by stimulating the DA system [74]. Thereby, ventral tegmental area projections trigger DA release to different regions of mesocorticolimbic system, including nucleus accumbens, VS, insula, hippocampus, amygdala, prefrontal and ACC [75]. The recurrent activation of DA system with repeated drug use -or gambling-, sensitizes reward circuits and generates increased responses to cues associated with the addictive agent [67].

Sensitization is responsible for cue-triggered urges to gamble, but also causes attentional bias toward

gambling cues that gradually generalizes to a variety of contexts [76]. The relocation of attentional resources manifests in the differential recruitment of cognitive control regions in GDP [71], and can generate cognitive control problems in the absence of a substantive alteration on executive functions [77]. Consistent with this hypothesis, structural differences between GDP and controls in cognitive-control structures have been difficult to identify [34,78]. Moreover, the insular cortex has been implicated in craving and addiction motivation, as it underpins motivationally relevant interoceptive representations of addiction-related outcomes, and has been shown to divert cognitive resources toward gambling-related goals [79]. Accordingly, insular reactivity to gambling-cues is associated with craving states in GD [72,80].

In cognitive neuroscience, the most common approach to study neural responses to craving is the cue-reactivity paradigm [81], where participants are exposed to cues previously associated with gambling, and responses are measured using fMRI techniques. These studies have reported an abnormal recruitment of mesocorticolimbic networks [82], but also of regions devoted to cognitive control (dorsolateral PFC) and salience attribution (insula, ACC) [72,83,84]. Specifically, the most consistent finding is an increased activation in mesocorticolimbic regions in GDP, including insula, dorsomedial PFC, ACC, posterior cingulate cortex, parahippocampal gyrus and amygdala [72,80,83,84] (see Table 1 for a summary of main findings from cue-reactivity studies). Interestingly, gambling-cue reactivity studies show an association between cue-related brain activity and craving scores [72,80,85]. Lastly, in an attempt to integrate available fMRI literature on gambling cue-reactivity, Meng and colleagues [82] published a meta-analysis reporting an increased activation in putamen and globus pallidus in GD patients.

In summary, available evidence supports the idea that the imperative motivational impulse generated by incentive sensitization defines the development of craving, and perceived inability to stop gambling. This process also marks the initiation of compulsive gambling behavior and detachment of "wanting" from gambling hedonic properties, and precipitates negative consequences derived from recurrent gambling.

2.7 The motivated nature of causal biases

Compared to reward processing and cue-reactivity, psychobiological research on gambling-related cognitive biases (control illusion, predictive control and interpretative bias) has received little attention. It could be tentatively hypothesized that these biases originate in poor reasoning or probabilistic abilities. However, a recent study has shown that gamblers with stronger biases perform better than gamblers with weaker biases

in a causal learning task [86]. Moreover, causal biases are unrelated to lack of premeditation and perseverance [87], and stronger cognitive distortions characterize a subgroup of young gamblers with higher education level and preference for skill-based games [88].

Consequently, it has been recently proposed that causal biases have a motivational basis. In other words, gambling-related biases can reflect an attempt to justify gambling motivation, or temper negative emotions resulting from adverse gambling outcomes. Although cognitive biases are often depicted as automatic or mindless [89], people can also elaborate on them, and they can result from overthinking rather than 'underthinking' [90]. In accordance with a reflective view of gambling biases, the dispositional use of intentional emotion regulation strategies customarily considered as adaptive (putting into perspective, reappraisal), has been associated with stronger gambling-related cognitive distortions [91–93]. According to the recently proposed Gambling Space Model [11], this association is mostly driven by a specific subtype of gamblers characterized by a self-serving reasoning style, oriented towards deluding themselves about their higher gambling abilities. This proposal could account for the inconsistent results regarding executive dysfunction in GDP [77]. Although the understanding of neurocognitive bases of emotion regulation in GD is preliminary [94,95], their study in the general population is reasonably well-developed, with dominant models distinguishing between incidental (model-free) and intentional (model-based) emotional regulation mechanisms, anatomically associated with, respectively, lateral prefrontal/parietal, and ventral/medial prefrontal cortices [96–98]. Further research on the possible involvement of the former in gambling-related cognitive distortions is warranted.

2.8 Summary and conclusions

The development of distorted cognitions contributes to gambling behavior initiation, and is associated with gambling escalation and development of gambling problems [25,28,99,100]. In this review, we outlined how structural features of gambling games interact with human bounded rationality to develop these distorted gambling-related cognitions, and explore the psychobiological basis of this interaction.

Gambling expectancies are associated with how the gambler processes the rewarding properties of gambling outcomes. However, evidence regarding reward processing in GDP is mixed, which precludes any simple interpretation. Although compelling preliminary evidence supports striatal hyporesponsivity in GDP [69]**, consistent with the RDS hypothesis, studies using simulated gambling have also revealed an increased anticipatory activity to gambling rewards in mesocorticolimbic regions, including striatum and medial PFC

[52,55,57,101]. A plausible interpretation of this pattern of results is the potential complementary roles of reward deficiency and incentive sensitization in distinct phases of disorder progression. According to the RDS framework, initially blunted activity of the reward system and the ensuing less pleasurable experience from natural rewards may turn the individual vulnerable to gambling [54]. Subsequently, incentive sensitization caused by repeated exposure to gambling opportunities may render the reward system hypersensitive to gambling-related cues, which contributes to gambling expectancies, that are however detached from actual hedonic value [102].

Research on the brain responses to near-misses in GDP has yielded more consistent results, showing an augmented response in VS and insula [28,33,35,38,52] associated with an increased motivation to gamble. The rewarding properties of near-misses in GDP have a direct effect on gambling expectancies, and can function as information on skill acquisition or strategy improvement, thus also contributing to illusory control [28]**.

The perceived inability to stop gambling is proposed to originate from repeated unsuccessful attempts to control craving. The incentive sensitization hypothesis holds that craving is mostly cue-triggered, and results from learning-driven neuroadaptations. More specifically, repeated exposure to environmental cues associated with gambling reinforcement endows initially neutral stimuli with incentive salience, detaching "wanting" from gambling hedonic properties, and diverting attention towards them.

Research on gambling craving using the cue-reactivity paradigm supports the incentive sensitization hypothesis. Augmented response to gambling-related stimuli has been reported in the insula, ACC, dorsomedial PFC, posterior cingulate cortex, parahippocampal gyrus and amygdala [72,80,83,84]. Notably, the consistent association between gambling cue-reactivity and craving measures [58,72,80], emphasizes the potential role of cue-reactivity as an indicator of gambling craving and inability to stop gambling. Complementarily, diverted attentional resources towards gambling-related stimuli can generate cognitive-control problems, in the absence of manifest alterations on executive functions [77,103,104].

Further, the attempts to explore the psychobiological underpinnings of cognitive biases have been spare. However, (a) the unsuccessful attempts to find an association between causal biases and poor probabilistic or general reasoning [86,88]; and (b) the association between gambling biases and supposedly adaptive emotion regulation strategies, suggest that these biases can be motivated by the desire to continue gambling or the attempts to cope with negative gambling outcomes [91–93]. If this hypothesis is correct, it could also help to

elucidate the seemingly puzzling results on executive dysfunction in GDP [77]. More importantly, it could redirect psychobiological research on gambling biases towards the structures and networks involved in emotion regulation [97,98].

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3. Regional grey matter volume correlates of gambling disorder, gambling-related cognitive distortions, and emotion-driven impulsivity

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3.1 Abstract

Reports of regional grey-matter volume (GMV) anomalies in patients with gambling disorder (PGD) are inconsistent, which can be attributed to methodological disparity and inattention to individual variability.

Voxel-based morphometry was used to compare GMV between 25 PGD and 25 healthy controls. Additionally, we explored the associations of interpretative bias (IB, the tendency to reinterpret gambling outcomes ad hoc) and negative urgency (NU, the tendency to act rashly under negative affect) with GMV in patients. These measures were chosen based on their sound association with gambling disorder in related studies. GMV tests were corrected across the whole brain (using a combination of voxel and cluster-level thresholds for a clusterwise-equivalent $p \leq 0.05$ criterion).

GMV was smaller in PGD than in controls in the dorsomedial prefrontal cortex. In PGD, a stronger cognitive distortion (higher IB) was associated with reduced GMV in the dorsal anterior cingulate; and patients with higher levels of impulsivity (higher NU) presented reduced GMV in the right ventrolateral prefrontal cortex.

These findings are consistent with recent studies exploring individual differences in GD. However, the area discriminating between groups showed no overlap with the ones associated with IB and NU. These traits are thus unlikely to be responsible for between-group GMV differences.

Keywords: gambling disorder, neuroimaging, structural differences, cognitive bias, impulsivity

3.2 Introduction

Gambling disorder (GD) is characterized by persistent gambling behavior despite adverse consequences (Hodgins, Stea & Grant, 2011). In view of its overlap with substance use disorders, a new category has been created in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatry Association, 2013) for substance-related and addictive disorders, including gambling disorder as the only behavioral addiction currently recognized as such.

Structural magnetic resonance imaging (MRI) studies in substance use disorders have shown that regular drug use causes extensive morphological brain changes (Cousijn et al., 2011; Daumann et al., 2011; Fritz et al., 2014; Tolomeo, Gray, Matthews, Steele, & Baldacchino, 2016), and these alterations are difficult to disentangle from etiological substrates of addiction vulnerability. GD, on the contrary, does not necessarily

involve brain exposure to addictive substances. Hence, if samples are carefully selected, comparisons between patients with gambling disorder (PGD) and controls are free of neurotoxic effects, which make GD a valuable model to understand addiction neurobiology.

In spite of this, literature investigating grey matter (GM) alterations in GD is scarce, and results inconsistent. Some studies (Joutsa, Saunavaara, Parkkola, Niemelä, & Kaasinen, 2011; van Holst, de Ruiter, van den Brink, Veltman, & Goudriaan, 2012) found no differences in GM between clinical samples and control groups, whereas others (Grant, Odlaug, & Chamberlain, 2015; Koehler, Hasselmann, Wüstenberg, Heinz, & Romanczuk-Seiferth, 2015; Rahman, Xu, & Potenza, 2014; Zois et al., 2017) found a mixed pattern of increases and decreases in frontal, parietal, and superior medial cortices, the hippocampus, the amygdala, and ventral striatum.

These studies vary in methodology, and are not directly comparable. The present study tries to overcome some limitations of previous research by considering a large array of potential confounders (including drug use and psychiatric status) and matching the two groups as closely as possible. Given that most previous studies have used voxel-based morphometry (VBM) to explore regional grey matter volume (GMV), the same measure will be used here, while implementing a number of methodological improvements in order to reliably isolate the specific tissue of interest and better control for false positives1.

A related question is whether grey matter alterations in PGD, if they exist, are related to variability among PGD. Gamblers have been classified according to personality traits (e.g. Billieux et al., 2012), clinical features (e.g. Blaszczynski & Nower, 2002), and game modality preferences (e.g. Navas et al., 2017a). However, structural differences associated with gambling-related traits remain unexplored. The potential association between brain structure and individual differences among PGD is relevant in two domains. First, an overlap between group differences and areas associated with specific personality traits would help to understand how sample selection can account for different results across studies. And second, a lack of correspondence between group differences and regions related to personality traits could be relevant to understand how individual variability is integrated into underlying GD mechanisms to generate individual clinical profiles. Accordingly, this study focuses on traits that 1) have consistently been associated with GD development or complication mechanisms, 2) are easily and reliably measurable with instruments validated for our samples, and 3) can help to establish connections between brain dimensions and behavioral manifestations of GD.

Gambling-related cognitive biases meet these criteria. They are relevant for GD etiology (Clark, Studer, Bruss, Tranel, & Bechara, 2014), and are involved in gambling persistence and severity (Joukhador, MacCallum, & Blaszczynski, 2003; Subramaniam, Chong, Browning, & Thomas, 2017; Xian et al., 2008). With regard to their operationalization, the Gambling-Related Cognitions Scale (GRCS; Raylu & Oei, 2004) has shown good psychometric properties and is clinically informative (Michalczuk, Bowden-Jones, Verdejo-Garcia, & Clark, 2011). The scale covers three cognitive biases (illusions of prediction and control, and interpretative bias), along with subjective expectancies of reward and perceived inability to stop gambling.

In a previous study with a related sample, we identified interpretative bias (IB; the ad hoc attribution of gambling successes to ability and losses to bad luck) as the most informative cognitive bias in the GRCS to discriminate both between PGD and healthy control (HC) groups, and between different clinical and behavioral patterns in PGD. Importantly, biased cognitions assessed by IB were highly and independently predictive of gambling severity and clinical status (Del Prete et al., 2017; see also Donati, Ancona, Chiesi, & Primi, 2015; Grall-Bronnec et al., 2012; Navas, Verdejo-García, López-Gómez, Maldonado, & Perales, 2016). In order to avoid multiple testing with different subscales, IB was thus selected a priori as the most promising measure among GRCS cognitions.

Recent research exploring the associations between brain function and gambling-related biases has focused on the near-miss effect –the tendency to interpret losses perceptually similar to wins as if they were almost wins. Near misses have been shown to maintain motivation to gamble, and to recruit structures also responding to real monetary wins (Clark, Lawrence, Astley-Jones, & Gray, 2009). Functional MRI (fMRI) studies have reported increased striatal response to near-misses in gamblers compared to controls and associations between midbrain and insula activity and/or connectivity during near-misses and gambling severity (Chase & Clark, 2010; Sescousse et al., 2016, van Holst, Chase, & Clark, 2014). Beyond these areas, an fMRI study found that the influence of gambler's fallacy on responses in a card-guessing task correlated with a stronger activation of the lateral prefrontal cortex (lPFC; Xue, Juan, Chang, Lu, & Dong, 2012). Despite these precedents, literature on brain structure associations with individual differences in gambling cognitions is scarce (Clark et al., 2014), and to our knowledge, there are no previous studies linking trait-like gambling-related cognitions to brain structure.

The second trait meeting our criteria, impulsivity, is actually linked to all addictive processes (Perry & Carroll, 2008; Verdejo-García, Lawrence, & Clark, 2008; Pattij & De Vries, 2013). Among the question-

naires proposed to operationalize impulsivity, the UPPS-P (Whiteside & Lynam, 2001) has been shown to be particularly informative. This model includes five dimensions: negative urgency, positive urgency, sensation seeking, lack of perseverance, and lack of premeditation (Cyders & Smith, 2008), with the first three factors representing facets of motivation and affect-driven impulsivity, and the last two corresponding to cognitive impulsivity.

For reasons similar to the ones described above regarding IB, Negative Urgency (henceforth NU, the tendency to act rashly under the influence of strong negative emotions; Whiteside Lynam, Miller, & Reynolds, 2005) was selected as the best candidate index of impulsivity-related individual variability.

Recent research does support the decisive relevance of NU in GD, with PGD exhibiting particularly high scores in this aspect of impulsivity (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Billieux et al., 2012; MacLaren, Fugelsang, Harrigan, & Dixon, 2011; Michalczuk, et al., 2011). A recent integrative meta-analysis (MacLaren et al., 2011) confirms NU as an important vulnerability factor in the etiology of GD. Beyond addictive processes, NU has been observed to be a major determinant of externalizing behavior (Berg, Latzman, Bliwise, & Lilienfeld, 2015), and a recent theoretical model (Navas et al., 2018) suggests its contribution to gambling complications. In neurofunctional terms, available studies link NU in addicted individuals to anomalies in the functioning of cortico-striatal and cortico-amygdalar circuits (e.g. Clark et al., 2012; Contreras-Rodríguez et al., 2015). However, no previous studies have investigated the association of NU with brain structure in PGD.

Summing up, the aims of the present study were to explore potential differences in GMV between PGD and a well-matched group of HC, using a VBM approach; and to analyze the involvement of two specific measures of gambling-related cognitive distortions and affect-driven impulsivity (IB and NU) in individual grey matter variability.

With regard to the first aim, previous studies seem compatible with a reduction of GMV in PGD in control and regulation structures (Grant et al., 2015; Zois et al., 2017), but concordance is insufficient to make hypotheses about specific anatomical areas. Similarly, studies point out to the involvement of insular and dorsal prefrontal cortices in gambling-related cognitive distortions, and of ventral prefrontal cortex, striatum, and amygdala in affect-driven impulsivity (e.g. Clark et al., 2012; Contreras-Rodríguez et al., 2015), but no direct structural evidence is available. This makes whole-brain analysis with appropriate control of α-error

growth necessary. However, with regard to NU, previous research has found its involvement in psychopathology and externalizing behavior, adding upon and complicating GD symptomatology (see also Navas et al., 2018). Therefore, our specific hypothesis regarding this impulsivity dimension is that its association with GMV anomalies will extend beyond the areas showing differences between groups, towards areas involved in general-purpose regulatory processes.

3.3 Materials and methods

Sample characteristics

Socio-demographic and clinical information for the two groups is shown in Table 1. PGD were recruited a behavioral addictions rehabilitation center in Andalusia, Spain (Granadian Association of Rehabilitated Gamblers, AGRAJER). HC participants were selected using purposive sampling, based on characteristics of PGD regarding age, gender, education level, socioeconomic status, intelligence quotient (IQ), and smoking severity. All PGD were men; therefore, only male participants were included in HC group.

Exclusion criteria for both groups were: current or past history of psychiatric disorders or serious neurological condition (including past or current substance abuse), current use of psychoactive medication, IQ below 80, and any contraindication for MRI procedures. Participants who did not meet the study criteria were excluded from further assessments (9 PGD, 3 HC). PGD were abstinent (as part of their treatment commitment), and none of them reported any relapses throughout the study. Although abstinence is not always a selection criterion in gambling research, it is not uncommon either (de Ruiter et al., 2009; Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010), and it is among the inclusion criteria in other areas of addiction research (Bolla et al., 2004; Eldreth, Matochik, Cadet, & Bolla, 2004; Fu et al., 2008; McBride, Barrett, Kelly, Aw, & Dagher, 2006).

As part of their admission protocol, all PGD underwent a semi-structured interview based on DSM IV for axis I and II disorders with their therapist, comprising all the necessary information to check for exclusion criteria. GD diagnosis was established by the therapist on the basis of such an interview, and was confirmed by a score equal to or above 5 in the South Oaks Gambling Screen (SOGS; Lesieur & Blume, 1987). For HC, an equivalent interview was carried out by an experienced clinician, and took place at the beginning of the first assessment session.

Table 1. Demographic information and clinical characteristics from patients with gambling disorder (PGD) and healthy controls (HC).

	PGD	**HC**			
	Mean (SD)	***Mean (SD)***	***t (1, 48)***	***p***	***BF10***
Age	31.68 (8.22)	31.10 (7.06)	0.277	0.783	0.292
Years of education	13.40 (3.49)	13.60 (3.27)	-0.209	0.835	0.288
Monthly income	1,560.00 (689.50)	1,440.00 (744.00)	0.591	0.557	0.326
Handedness*	22(R)/3(L)	21(R)/4(L)	-	0.684	-
WAIS Matrix reasoning	97.40 (12.00)	101.80 (13.38)	-1.224	0.227	0.521
WAIS Vocabulary**	100.21 (13.47)	104.80 (15.71)	-1.096	0.279	0.456
WAIS IQ	98.60 (9.19)	103.30 (11.24)	-1.618	0.112	0.818
Months in treatment	2.00 (1.12)	-	-	-	-
SOGS gambling severity	10.08 (3.45)	0.56 (0.96)	13.287	<0.001	$2.953 \cdot 10^{14}$
MC excessive gambling	2.56 (0.82)	0.04 (0.200)	14.918	<0.001	$2.263 \cdot 10^{16}$
MC alcohol misuse	0.72 (1.10)	1.00 (0.91)	-0.979	0.332	0.419
MC substance misuse	0.40 (0.76)	0.44 (0.65)	-0.199	0.843	0.287
Smoking severity**	2.50 (2.73)	2.64 (2.08)	-0.202	0.842	0.290
Dysphoric mood	8.68 (8.33)	6.20 (4.97)	1.277	0.209	0.550
Interpretative bias	17.96 (6.16)	7.00 (4.62)	7.117	<0.001	$1.726 \cdot 10^{6}$
Negative urgency	2.68 (0.83)	2.20 (0.73)	2.167	0.035	1.855

Note: Monthly income is expressed in Euros. Smoking severity and dysphoric mood were measured with the Fagerström test and the Beck Depression Inventory. Significant differences are indicated in bold. * χ^2 instead of t-tests was used for handedness. Due to data loss from one participant in PGD group, degrees of freedom for variables marked with ** are (1,47). Abbreviations: R, right-handed; L, left-handed; WAIS, Wechsler intelligence scales; MC, MultiCAGE CAD-4, SOGS, South-Oaks Gambling Screen.

The final study sample consisted of fifty participants (25 HC and 25 treatment-seeking PGD) All of them were at least 18 years old and spoke fluent Spanish. Participants were informed about all aspects of the study and were required to sign informed consent prior to participation. The procedure was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee of the University of Granada.

Procedure

Assessment was divided in two sessions, with an average two-week inter-session interval. In the first session, lasting for approximately 1 hour and 30 minutes, participants underwent a number of psychometric and neuropsychological tests. For PGD, this session took place in the facilities of their rehabilitation center, whereas for HC it took place in the Mind, Brain and Behavior Research Center at the University of Granada. This session was composed of four counterbalanced blocks of measurements (including questionnaires and experimental tasks), although only intelligence, impulsivity, gambling-related cognitive biases and gambling severity tests are relevant for the aims of the present study. Full questionnaires were administered, although only interpretative bias (IB) from GRCS, and negative urgency (NU) from UPPS-P were considered for the present analyses. Other measures included in the evaluation protocol with partially overlapping samples have been reported elsewhere (see Megías et al., 2017 [88% overlap]; Navas et al., 2016 [52%]; 2017b [52%]).

In the second session, participants underwent a MRI session in the Mind, Brain and Behavior Research Center. The whole MRI protocol consisted of anatomical T1-weighted, Resting-State fMRI, and Diffusion Tensor Imaging sequences. Concerning the aims of the present study, only structural data will be considered. In the same session, they also underwent EEG recording during a learning task that is also unrelated to the aims of the present study (reported in Megías et al., 2017). Participants were compensated with approximately 12€/hour for their participation.

Psychometric instruments

The Gambling-Related Cognition Scale (GRCS, Spanish version, Del Prete et al., 2017) is a self-report measure of gambling-related distorted cognitions. It comprises 23 items, structured in five subscales assessing cognitive biases associated with gambling (gambling expectancies, illusion of control, predictive control, inability to stop gambling, and IB). For all subscales, a higher score indicates a stronger distorted/exaggerated cognition. Only the IB subscale was used in the present study.

UPPS-P Impulsive Behavior Scale. The Spanish short version of the UPPS-P scale (Cándido, Orduña, Perales, Verdejo-García, & Billieux, 2012) is based on Whiteside and Lynam's (2001) model of impulsivity, and assesses five facets of impulsivity, namely, sensation seeking, lack of premeditation, lack of perseverance, NU, and positive urgency. For all subscales, a higher score means higher impulsivity. Only the NU subscale was used in the present study.

The Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV, Wechsler, 2008) was used to assess intelligence. A composite IQ was calculated from the vocabulary and matrix reasoning subtests, according to standard instructions.

The South Oaks Gambling Screen (SOGS, Spanish version, Echeburúa, Báez, Fernández-Montalvo, & Páez, 1994) is the most commonly used and internationally validated gambling severity scale. This 20-item questionnaire is based on DSM-III diagnostic criteria for pathological gambling, and assesses core symptoms and frequent negative consequences of problem gambling.

MultiCAGE CAD-4 (Pedrero Pérez et al., 2007). This is a quick clinical screening tool for alcohol abuse, illegal drug abuse, excessive gambling, excessive Internet surfing, excessive video gaming, hypersexuality, compulsive money spending/shopping, and eating disorders. Each subscale is composed of four yes/no items, checking for subjectively informed craving, relatives', friends', or other acquaintances' complaints about the behavior under assessment, guilt or shame feelings/lack of acknowledgment, and self-reported compensatory behaviors. Only excessive gambling, drug abuse, and alcohol abuse subscales were used here.

The Fagerström Test for Nicotine Dependence (Spanish version, Becoña & Vázquez, 1998) was used to assess smoking severity. The test consists of six items evaluating smoking frequency and quantity, compulsion, and dependence.

Beck Depression Inventory II (BDI-II, Spanish version, Sanz, Perdigón, & Vázquez, 2003) is a self-report measure of dysphoric mood experienced in the week prior to the evaluation and is composed by 4-point scale items. No participants met criteria for depressive disorder.

MRI Acquisition Protocol

MRI data were collected using a Siemens Magnetom TrioTim Syngo MR B17 3T scanner equipped with a 32-channel head coil, located at the Mind, Brain and Behavior Research Center (University of Granada). A high-resolution T1-weighted isotropic image using a 3-Dimensional magnetization prepared rapid

acquisition gradient echo (3D–MPRAGE) sequence was acquired with the following specifications: TR, 2300 milliseconds; TE, 3.1 milliseconds; inversion time (IT), 900 milliseconds; FA, 9°; spatial resolution, 0.8 x 0.8 x 0.8 millimeters; imaging matrix, 256 x 256 pixels; number of slices, 208, field-of-view (FoV), 256 mm.

MRI Preprocessing - Voxel-based morphometry (VBM) analysis

Structural images from each participant were visually inspected to discard subjects with low quality or motion artifacts. Reoriented images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in native space using unified segmentation (New Segmentation Algorithm) in SPM8. The resulting GM tissue maps were imported into DARTEL (Diffeomorphic Anatomical Registration Using Exponentiated Lie Algebra) registration algorithm (Ashburner, 2007) to generate GM tissue maps resliced to an isotropic 1 x 1 x 1 mm voxel size. DARTEL procedure has been shown to improve spatial accuracy by creating a study-specific GM template from the participant's maps, and calculating individual nonlinear transformations to this template. The group GM template was built after six iterations by averaging participants' GM maps. Followed by the preliminary affine registration of GM templates to tissue probability maps from Montreal Neurological Institute (MNI, http://www.mcgill.ca/neuro/), GM segments were warped nonlinearly to MNI space and scaled using Jacobian determinants of the deformations to restore tissue volume changes after normalization process. This process accounts for participant's original brain volume and permits to make inferences on regional volume differences. Finally, normalized and modulated GM maps were smoothed using a 10 mm Full-Width-at-Half-Maximum (FWHM) Gaussian kernel. The decision was made in accordance with previous studies (De Wit et al., 2014; Pujol et al., 2004), and to maintain a balance between the 12 mm standard recommendation for VBM analysis (Ashburner & Friston, 2000; Friston et al., 2004) and the 10 mm-Gaussian kernel that has been shown to increase the signal to noise ratio, and correct potential errors on spatial normalization (Radua, Canales-Rodríguez, Pomarol-Clotet, & Salvador, 2014).

Statistical analyses

Group matching and correlational analyses

Two-tailed Welch's t-tests (implemented on JASP Statistical Package, Love et al., 2015) were used to assess group differences in relevant potential confounders. Complementarily, bilateral Bayesian t-tests with default settings as implemented in JASP software [Cauchy prior width=0.707, prior P(H1)=P(H0)=0.50] were performed in order to evaluate relative evidence for the alternative hypothesis versus the null hypothesis. Pear-

son correlations were used to explore IB and NU associations with clinically relevant indices (SOGS severity, MultiCAGE subscores, and BDI dysphoric mood score).

Significance criterion for group matching t-tests was set a $p \leq 0.05$. Ten r coefficients were tested in correlational analyses. Given there were specific directional predictions for correlations of NU with BDI, MultiCAGE scores, and SOGS, as well as for the correlation between IB and SOGS, the Bonferroni-corrected significance criterion for these analyses was set at $p \leq 0.005$ (one-tailed).

Grey matter volume analyses

Total intracranial volume (TIV) was calculated by summing up the native space volumes of GM, WM and CSF maps in MATLAB. GM segments generated in VBM-DARTEL processes were used to assess regional volume differences between PGD and HC. The modulated, normalized and smoothed images were used to conduct the statistical analyses. Age and TIV were entered as covariates of no interest in all GMV analyses (Good et al., 2001). Absolute masking was used at an estimated optimal threshold of 0.2 to maximize statistical sensitivity by restricting the analysis to GM tissue and overcome potential inaccuracies in the GM-WM edge definition (Ridgway et al., 2009). A combination of voxel- and cluster-level thresholds was used to reach a clusterwise criterion equivalent to $p \leq .05$. The statistical threshold at the voxel-level was $p \leq 0.001$, and the cluster extent threshold for each analysis was determined using AlphaSim function implemented in DPABI software (Data Processing & Analysis for - Resting State - Brain Imaging, http://rfmri.org/dpabi). Cluster extent was determined by 1000 Monte-Carlo iterations that control for type I and type II errors. AlphaSim function has been shown to be a reliable method to correct for multiple comparisons, when implemented with adequate parameters (Bennett, Wolford, & Miller, 2009; Lieberman, Berkman, & Wager, 2009; Lieberman & Cunningham, 2009; Nichols, 2012; Vul, Harris, Winkielman, & Pashler, 2009) as, for example, with smoothness estimation based on the standardized residuals, instead using the smoothing kernel applied to the data (Bennett et al., 2009; Nichols, 2012). AlphaSim input parameters included a cluster connection radius of 18 mm, and the smoothness was estimated directly from the statistical image with full width and half maximum (FWHM) of FWHMx=15.023; FWHMy=14.599; FWHMz=14.810. We used the brain mask generated from the statistical analysis, with a volume of 397470 voxels. The minimum cluster size determined by AlphaSim function to be considered significant was 416 voxels. Cluster extent was further adjusted to account for non-isotropic smoothness of structural images, as described by Hayasaka, Phan, Liberzon, Worsley, & Nichols (2004).

In order to explore potential GMV differences between PGD and HC, GM maps were submitted to a voxel-wise whole-brain two-sample comparison in SPM8 to examine the main effect of group.

To investigate the relationships between the traits of interest and GMV (in the PGD group), GM individual segments from the PGD group were submitted to two voxel-wise whole-brain multiple regression models in SPM8, using IB and NU scores as main independent variables.

Regression analyses were complemented with follow-up tests. These analyses were carried out to visualize how high- and low-NU gamblers (and high- and low-IB gamblers) differed from controls in GMV (that is, to visualize whether high scores in IB/NU made gamblers more similar or dissimilar to controls in GMV in areas previously identified to correlate with such traits). Given that these analyses are mostly illustrative and partially redundant with regression analyses, they are reported in Appendix 1 (Supplemental Material). In these post-hoc analyses, planned comparisons between pairs when exploring the main effect of group were considered significant at $p \leq 0.05$.

3.4 Results

Group matching and correlational analyses

Welch's t-tests yielded no significant differences between groups in any of the potentially confounding variables (see Table 1). As expected, groups differed in gambling measures (SOGS and MultiCAGE), IB, and NU. Bayes factors provided substantial evidence in favor of the null hypothesis ($BF10<1/3$) for age, education years, monthly income, drug misuse, and nicotine dependence; and just anecdotal evidence in favor of the null hypothesis ($1>BF10>1/3$) for IQ measures, MultiCAGE alcohol misuse subscore, and BDI. For none of the potential confounders under consideration the Bayes factor (either anecdotally or substantially) supported the existence of differences between groups, which indicates a good global matching. Additionally, Bayes factors strongly supported the existence of differences between groups in SOGS and MultiCAGE gambling subscores, and IB. Although the difference between groups in NU was statistically significant according to the Welch's t-test, the Bayes factor for this measure only provided anecdotal evidence of a difference between groups.

Additionally, global volume measures were estimated for HC (mean ± SD GMV: 0.75 ± 0.04 l; mean ± SD WM volume: 0.55 ± 0.03 l; mean ± SD TIV: 1.68 ± 0.09 l) and PGD (mean ± SD GMV: 0.74 ± 0.05 l; mean ± SD WM volume: 0.55 ± 0.04 l; mean ± SD TIV: 1.67 ± 0.11 l). Analyses revealed no significant

global differences between groups in GMV [t(48)=-0.46, p=0.32], WM volume [t(48)=-0.38; p=0.35] or TIV [t(48)=-0.49; p=0.31].

Analyses of correlations of IB and NU with clinical measures (SOGS severity, MultiCAGE gambling, alcohol and drug subscores, and BDI dysphoric mood score) yielded a small set of significant associations. NU was associated with BDI and MultiCAGE gambling subscore (Pearson's r=0.52, p<0.005, and r=0.56, p<0.005, one-tailed). IB correlated with total SOGS severity (r=0.50, p=0.005, one-tailed). NU did not significantly correlate with IB, SOGS or non-gambling MultiCAGE subscores; nor did IB with any MultiCAGE or BDI scores (min. p=0.125, one-tailed).

VBM Analysis

Group Differences

Compared to HC, PGD showed a significant decrease in GMV in the dorsomedial prefrontal cortex (dmPFC) (peak x, y, z MNI coordinates=6, 42, 42; T-value=3.94; cluster size=491; Figure 1). Figure A2.1 in Appendix 2 (Supplemental Material) depicts the full T-map for this contrast (and peak coordinates). The full set of T-values can be downloaded from the University of Granada Open Repository: http://hdl.handle.net/10481/48216.

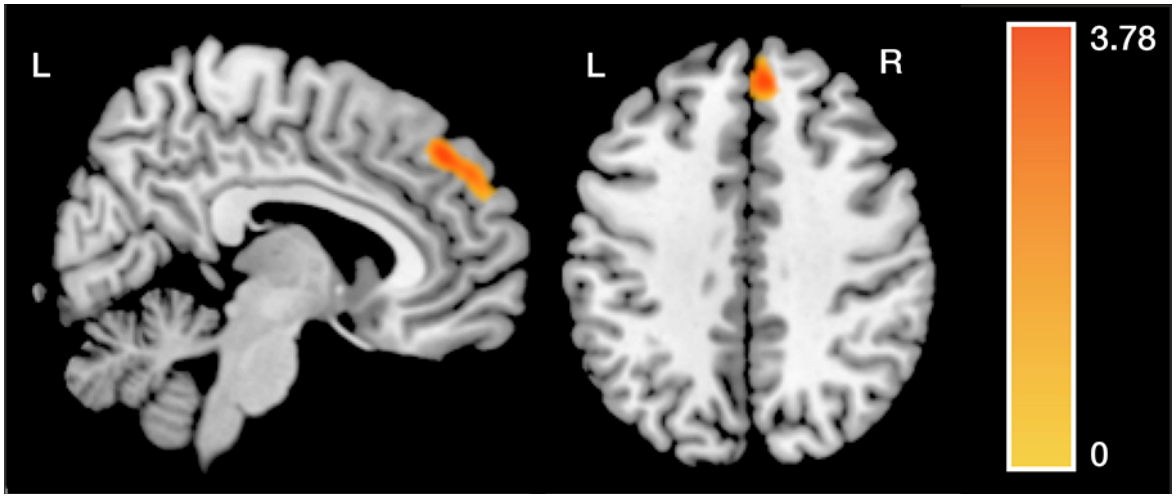

Figure 1. Region showing a significant reduction in grey matter volume in patients with gambling disorder, compared with healthy controls, after controlling for age and total intracranial volume.

Multiple regressions

In the first regression analysis in PGD, GMV in dorsal anterior cingulate cortex (dACC) from a cluster covering both hemispheres correlated negatively with IB scores (peak x, y, z MNI coordinates=-12, 11,

42; T-value=5.21; cluster size=589, Figure 2; see also Appendix 1 in Supplemental Material). Figure A2.2 in Appendix 2 (Supplemental Material) depicts the full T-map for this contrast (and peak coordinates). The full set of T-values can be downloaded from the University of Granada Open Repository. http://hdl.handle.net/10481/48216.

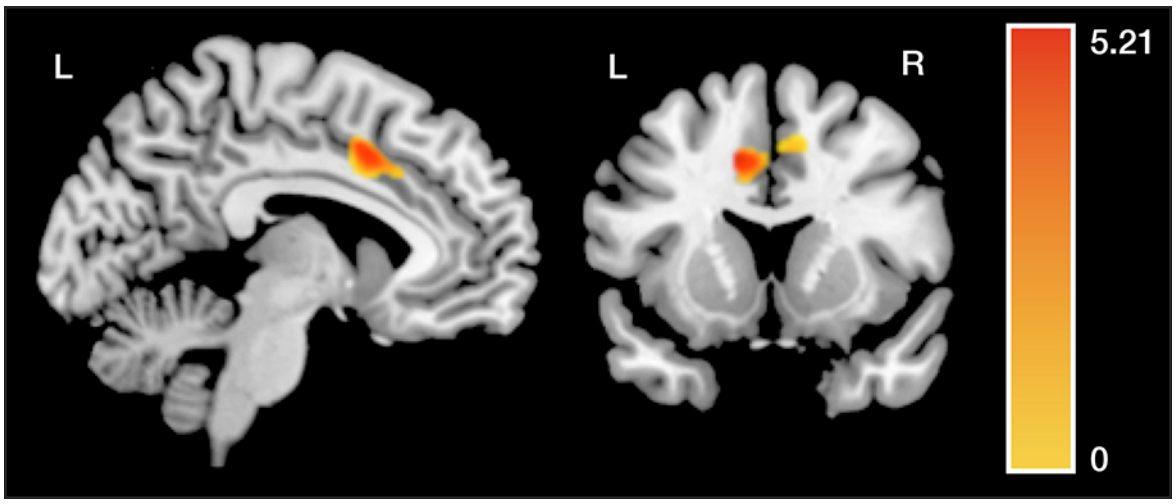

Figure 2. Brain region showing a significant negative association between grey matter volume and Interpretative Bias scores in patients with gambling disorder, after controlling for age and total intracranial volume.

In the second regression analysis in PGD, GMV in the right ventro-lateral prefrontal cortex (vlPFC) (i.e. right middle frontal gyrus extending to right orbital gyrus), correlated negatively with NU (peak x, y, z MNI coordinates=45, 54, -2; T-value=5.07; cluster size=1222; Figure 3, see also Appendix 1 in Supplemental Material). Figure A2.3 in Appendix 2 (Supplemental Material) depicts the full T-map for this contrast (and peak coordinates). The full set of T-values can be downloaded from the University of Granada Open Repository: http://hdl.handle.net/10481/48216

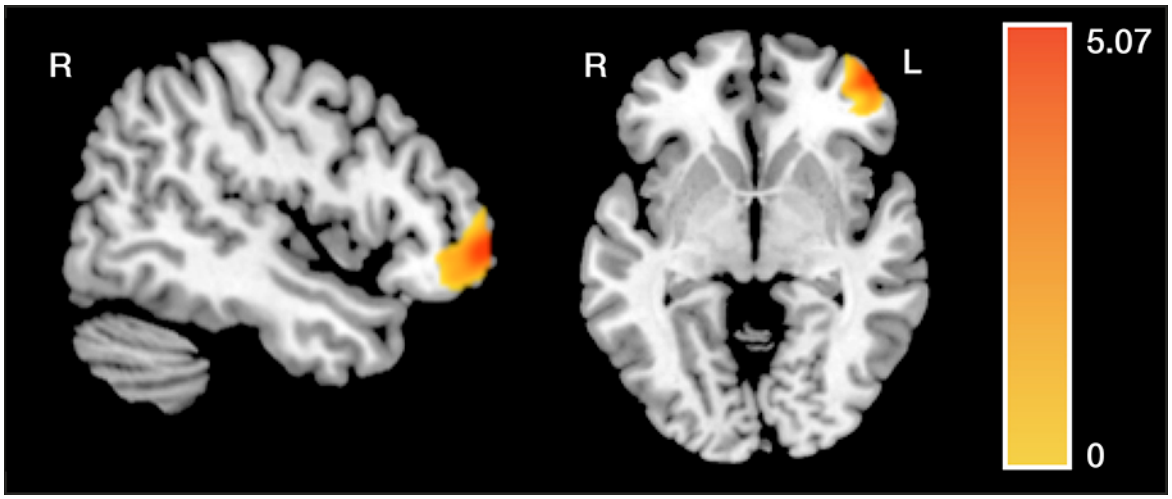

Figure 3. Brain region showing a significant negative association between grey matter volume and Negative Urgency scores in patients with gambling disorder, after controlling for age and total intracranial volume.

3.5 Discussion

In the present study, a voxel-based morphometry (VBM) approach was used to explore regional grey matter volume (GMV) differences between patients with gambling disorder (PGD) and healthy controls (HC). In addition, we examined potential relationships between regional GMV and two gambling disorder-related traits, identified by previous research to be key markers of clinical status and prognosis: the interpretative bias (IB), and negative urgency (NU).

Indeed, associations between these constructs and clinical measures corroborated their clinical significance. NU correlated with BDI dysphoric mood and MultiCAGE gambling scores, whereas IB correlated with SOGS severity scores. NU did not significantly correlate with SOGS severity. However, as we have argued elsewhere (Navas et al., 2018), NU is more directly related to GDP subtyping and the assessment of complications and comorbidity risk than to severity of symptoms as measured by the SOGS2.

With regard to structural measures, dmPFC regional GMV was reduced in PGD, compared to HC. Additionally, in PGD, IB and NU scores were associated with reduced volumes in dACC and right vlPFC, respectively.

Our finding from between-groups contrast is consistent with results reported by Zois et al., (2017). This study investigated GM differences between a sample of PGD without substance use disorder comorbidities, two groups of PGD with substance abuse comorbidities (alcohol and poly-substance abuse), and a group of

controls (including regular gamblers, and participants diagnosed with specific phobias). These results suggest, first, an association between GD and GMV reduction in the same area from prefrontal cortex (dmPFC), and second, that the association occurs independently from substance abuse.

A brief critical revision of studies investigating grey matter anomalies in GD is presented in Appendix 3 (Supplemental Material). In brief, some studies have failed to detect differences between groups, or have found differences in areas not directly related to the ones identified here (Joutsa et al., 2011; van Holst et al., 2012; Rahman et al., 2014); and some others report differences in the opposite direction (Koehler et al., 2015; Fuentes et al., 2015). From the studies reporting prefrontal gray matter reductions (Grant et al., 2015; Zois et al., 2017), Zois et al.'s report is actually the one most directly comparable to ours (if we consider the contrast between pure PGD and controls). Discrepancies with other studies are probably attributable to sample size, the presence of other conditions such as SUD and depression, and methodological aspects (i.e. whole brain versus region of interest analysis or even corrected versus uncorrected results) (Zois et al., 2017, p. 868). Socio-demographic and community sampling differences are also likely to influence in the observed inconsistencies.

The dmPFC is known to participate in a number of different functions (Bechara & Damasio, 2005), which makes difficult to infer the precise link with GD. Tentatively, the observed reduction in dmPFC GMV could compromise its normal functioning in reward-based decision making (Gläscher et al., 2012). dmPFC activation has been observed to mediate the relationship between impulsivity and reward-related dopaminergic release in left NAcc (Weiland et al., 2014), and a network including dmPFC shows increased activity during the representation of the magnitude of potential rewards when individuals decide which gamble to play to maximize benefits (Rogers et al., 2004). These activations have been more consistently observed in decision-making tasks under ambiguity (where uncertainty can be resolved by learning from feedback), than under risk (where probabilities are known beforehand; Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005). The involvement of dmPFC in emotional processes associated with risk-taking (Coombes, Corcos, Pavuluri, & Vaillancourt, 2012; Hsu et al., 2005; Phan et al., 2004; Xue et al., 2009;) could also be relevant for its potential role in gambling behavior.

As noted earlier, neurotoxic effects are absent in PGD without drug abuse comorbidities and, in contrast with some previous studies, the observed between-group structural differences are not attributable to detrimental effects of drugs. Still, structural neuroadaptions caused by gambling-related practice and learning cannot be discarded. This possibility is compatible with the fact that the structural anomalies reported here are

less extensive than the ones reported in drug-addicted individuals (see, for example, Gonçalves, Baptista, & Silva, 2014). Consequently, structural differences between PGD and controls could either precede GD onset (and thus be potential vulnerability markers), or be caused by gambling-related behavior during the course of the disorder. Longitudinal studies are needed to check for the existence of structural differences prior to GD onset and to track neural changes occurring during GD course.

With regard to heterogeneity in our sample of PGD, dACC grey matter volume showed a negative association with a measure of biased gambling-related attributions (IB). We did not observe, however, the relationships with the insula and dlPFC that were suggested by previous fMRI and lesion studies.

Recent models link the dACC to the expected value of exerting control, motivation of effortful behavior, and learning flexibility (see Shenhav Cohen, & Botvinick, 2016). However, the pattern of PGD individual differences in GMV was such that high IB PGD showed reduced dACC GMV compared to low bias PGD, which made the former visually more similar to controls than the latter. The specific pattern makes our results on individual differences in this cognitive bias quite difficult to interpret. In a study with a mostly overlapping sample (Megías et al., 2017), we observed a similar trend in individuals' response to uncertainty. As a group, PGD showed an abnormal electroencephalographic response to uncertain outcomes. However, the sign of the relation between the magnitude of such anomaly and gambling-related cognitive biases (including the IB) was opposite to the hypothesized direction. Patients with stronger biases showed a less abnormal response to uncertainty (which made them similar to controls). Relatedly, in a study with a different sample (Perales, Navas, Ruiz de-Lara, Maldonado, & Catena, 2016), we observed that PGD were less accurate than controls in learning observational contingencies in a causal learning task. However, gamblers with strong gambling-related biases (as measured by the GRCS scale, and including the IB) were more accurate at discriminating the programmed contingencies, and also more similar to controls, than gamblers with weaker gambling-related biases.

Thus, whatever the role of dACC in gambling is, it is plausible that cognitive biases characterize a subgroup of patients in which certain neuropsychological functions are preserved. Specifically, Navas et al., (2017a, 2018) have recently proposed that certain cognitive biases associated with strategic gambling require intact executive control or even overexertion of control, in relation to other gamblers and controls.

Our findings on the relationship between vlPFC and NU in PGD were more in line with our expectations. In PGD, regional GMV in vlPFC decreased as the NU level in gamblers increased. Post hoc analysis

revealed that, although PGD as a group did not show reduced GMV in this area relative to HC, high-NU PGD exhibited lower grey matter vlPFC volume than low NU patients and controls (see Appendix 1). The section from right vlPFC identified to correlate with NU is reliably linked to inhibitory control, an essential ability to optimize adaptive decision making and effectively adjust actions to an uncertain world. Indeed, fMRI studies have consistently show activation of right vlPFC in inhibitory tasks including Stop-Signal, Stroop, and Go/No-Go tasks (Aron, Robbins, & Poldrack, 2014). Specifically, right vlPFC has been consistently linked to regulation of negative emotions (Ochsner et al., 2004; Kim & Hamann, 2007, Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

NU, namely the proneness to lose control of behavior under intense negative emotions (Cyders & Smith, 2008), has been previously associated to failure on inhibitory control (Billieux, Gay, Rochat, & Van der Linden, 2010). More specifically, recent models stress the importance of the vlPFC in inhibitory modulation of negative emotions (Etkin, Büchel, & Gross, 2015). In this view, urgent behaviors occur because these regulatory mechanisms fail to modulate the emotion that triggers them (e.g. frustration or craving; Navas et al., 2018; Wager et al., 2008).

This type of emotion regulation failure could play a crucial role in GD. However, the relation between NU and psychopathology seems to go beyond GD. In general, impulsive behavior is common to diverse neuropsychiatric disorders (Albein-Urios, et al., 2013; Bøen et al., 2015; Dawe & Loxton, 2004; Egan, Dawson, & Wymbs, 2017; Fischer, Settles, Collins, Gunn, & Smith, 2012; Grant, Odlaug, & Chamberlain, 2016; MacLaren et al., 2011; Verdejo-García et al., 2008). NU (and particularly its feelings-trigger-action component; Johnson, Carver, & Joormann, 2013; Johnson, Tharp, Peckham, Carver, & Haase, 2017) has been proposed to be an important factor of a shared endophenotype contributing to an array of externalizing disorders, including GD, other additive processes, conduct problems and aggression (see also Castellanos-Ryan et al., 2014). This is consistent with previous data showing that NU is not only related to gambling severity, but also, and even more consistently, to clinical complications and poor prognosis (Grant et al., 2016; MacLaren et al., 2011; Savvidou et al., 2017; Steward et al., 2017; Torres et al., 2013; Yan, Zhang, Lan, Li, & Sui, 2016). Although associations between NU and drug use in our sample were precluded by the stringent selection of pure, strictly abstinent PGD, the association of NU with poorer mood and current, treatment-resistant symptoms in the clinical group reinforces de role of NU as a complication factor.

The relative unspecificity of NU in GD accounts for the fact that PGD tend to differ in this trait from

controls, but not necessarily from other groups of addicted individuals (Torres et al., 2013). Similarly, it accounts for the discrepancy between the area associated with NU in PGS and the region yielding differences between PGD and controls. Most likely, NU is relevant for GD assessment, but neither specific nor necessary for its diagnosis.

Strengths and limitations

In this work, we tried to overcome the methodological shortcomings of previous research. Samples were selected to ensure comparability and avoid confounding. Presence of frequently comorbid conditions and use of psychoactive medication were evaluated a priori, and purposive sampling for HC was performed based on sociodemographic and clinical information from PGD. Additionally, age was entered, along TIV, as covariate of no interest in GMV analyses.

First, we used VBM settings recommended by Radua et al., (2014), to optimize sensitivity [large smoothing kernels (FWHM=10mm) and voxel-based spatial statistics]. Brain image segmentation was performed using unified segmentation, which has shown higher sensitivity and specificity than other software packages (FSL and Brainsuite; Kazemi & Noorizadeh, 2014). Complementarily, the DARTEL registration procedure has shown to increased spatial accuracy by using a participants-based template (Ashburner, 2007).

Second, with regard to false positive control, AlphaSim correction for multiple comparisons was computed with a voxel-wise threshold of $p<0.001$, and further adjusted using Hayasaka et al.'s (2004) method, to account for non-isotropic smoothness.

And finally, selection of variables of interest (IB and NU) was done in a strictly a priori manner, without considering other dimensions from the questionnaires and based on previous works with samples from the same sociodemographic background.

Despite these considerations, results must be interpreted in light of a number of limitations. First, the cross-sectional nature of the study precludes drawing sound conclusions about causal direction of results. Second, our samples consisted of male participants, and generalization of results to females is not ensured. Third, GD diagnosis was based on DSM-IV criteria for pathological gambling. And fourth, although samples are larger than usual in GD neurobiological research, it is also true that they could be considered not large enough to overcome some recent critiques to neuroimaging research (Button et al., 2013). Small sample size, combined with strict post-hoc alpha-error correction for whole-brain analyses could have rendered the present study

underpowered, that is, insensitive to small-to-medium size effects (especially for within-sample regressions and comparisons). In other words, reported effects are probably strong, but weaker effects could have remained undetected.

Final remarks

In contrast with the recent flourishing of functional MRI research in GD, structural literature has been sparse and the results inconsistent. In the present study, we used a reliable morphometric approach to study structural brain differences between PGD and HC, and potential associations of grey matter structure with individual variation in two traits involved in GD development and putative complications.

Results suggest that maladaptive GD traits –i.e. distorted attributions and recall of gambling outcomes, and the tendency towards rash action under negative emotions– are associated with diminished GMV in dACC and vlPFC, respectively. Further, we demonstrate that GD, despite not entailing the consumption of toxic substances, is associated with structural brain alterations in dmPFC. The functions attributed to these areas by previous research are definitely relevant for gambling behavior. All these areas are involved in executive cognition, and are functionally interconnected, but do not overlap between them, which could be indicating that the processes that are crucial for clinical status and the ones underlying patients' heterogeneity are dissociable.

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3.7 Supplemental material

- **Appendix 1:** Follow-up ROI analyses
- **Appendix 2:** Graphical depiction of T-maps for group, interpretative bias, and negative urgency associations with regional grey matter volume
- **Appendix 3:** A critical review of VBM studies in gambling disorder

Appendix 1: Follow-up ROI analyses

Statistical analyses

Individual grey matter volume (GMV) values were extracted from peak coordinates of significant clusters in regression models (one measure per participant representing GMV in the peak location of the area observed to correlate with negative urgency [NU], and another one representing GMV in the peak location of the area observed to correlate with interpretative bias [IB]), using the MarsBar region of interest toolbox (http://marsbar.sourceforge.net) in SPM8. These measures (henceforth, GMV peak values) were regressed over age and TIV to obtain standardized residuals.

First, we used Welch's t-tests to compare patients with gambling disorder (PGD) against healthy controls (HC) in GMV peak values of the two locations previously observed correlate with NU (vlPFC) and IB (dACC). These analyses were performed to explore the possibility that between-group differences in these areas could have been obscured by lack of power in whole-brain analyses.

Secondly, in order to further characterize grey matter differences among PGD and visualize them in relation to HC, the PGD sample was split by the median IB and NU scores. The median IB score for the PGD group was 18. PGD with IB>18 were assigned to the high-IB subgroup (N=12; mean ± SD, 22.7 ± 3) and PGD with a IB score ≤ 18 were assigned to the low-IB subgroup (N=13; mean ± SD, 13.14 ± 4.3). The median NU score for the PGD group was 2.75. PGD with NU>2.75 were assigned to the high-NU subgroup (mean ± SD, 3.44 ± 0.41) and PGD with NU ≤ 2.75 were assigned to the low-NU subgroup (mean ± SD, 2.1 ± 0.48).

In a first ANOVA, GMV peak values in the vlPFC were compared across the high-NU, the low-NU, and the HC groups. In a second ANOVA, GMV peak values in the dACC was compared across the high-IB, the low-IB, and the HC groups. Main contrasts of interest were the ones of the clinical subgroups against the HC group. For these analyses, a $p \leq 0.05$ was used as significance threshold.

Results

Welch's t-tests for the vlPFC and dACC GMV peak values did not yield significant differences. vlPFC mean (SD) values were -0.17 (1.13) and 0.09 (0.81) for GDP and HC, respectively, t(48)=-0.92, p=0.36. dACC mean (SD) values were 0.15 (1.15) and -0.11 (0.80) for GDP and controls, respectively, t(48)=-0.91, p=0.37.

In the first ANOVA the high-NU (mean ± SD, -0.83 ± 0.91), the low-NU (mean ± SD, 0.62 ± 0.83), and the HC group (mean ± SD, 0.08 ± 0.82) were compared in vlPFC GMV peak values. Homogeneity of variances was checked using Levene's test (Levene's statistic=0.24; p=0.78). A significant between-group effect (F=10.27; p<0.001) emerged from significant differences between high-NU and low-NU (mean difference (MD)=-1.46; p<0.001), and between high-NU and HC (MD=-0.91; p<0.01). The difference between low-NU and HC was not significant (MD=0.55; p=0.13). In other words, the low-NU and HC groups were similar between them, and showed larger GMVs in the target area than the high-NU group.

In the second ANOVA, the high-IB (mean ± SD, -0.41 ± 0.96), the low-IB (mean ± SD, 0.50 ± 1.16), and the HC groups (mean ± SD, -0.06 ± 0.80) were compared in dACC GMV peak values (Levene's statistic=1.27; p=0.29). In this case, the main group effect (F=3.3; p<0.05) emerged only from the difference between the low-IB and the high-IB subgroups (MD=0.91; p=0.04). The HC subgroup was visually closer to the high-IB subgroup than to the low-IB one, but did not significantly differ from any of them (min. p=0.17).

Appendix 2: Graphical depiction of T-Maps for group differences, interpretative bias, and negative urgency associations with regional grey matter volume

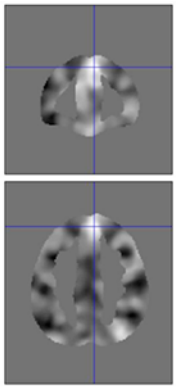

Figure A2.1. T-Map for group differences in Grey Matter between PGD and HC

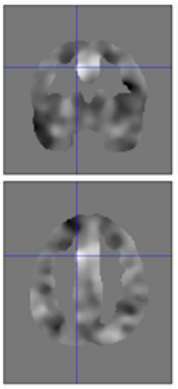

Figure A2.2. T-Map for Interpretative Bias - Grey Matter association in PGD

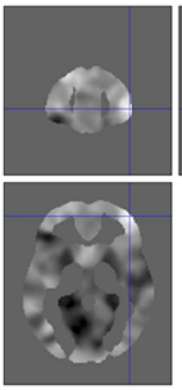

Figure A2.3. T-Map for Negative Urgency- Grey Matter association in PGD

Note: crosshairs point peak cluster coordinates. Abbreviations: PGD, patients with gambling disorder; HC, healthy controls.

Appendix 3: A critical review of voxel-based morphometry studies in gambling disorder

Beyond results' interpretability, it is important to consider the present study in the context of previous studies investigating grey matter (GM) differences between patients with gambling disorder (PGD) and control groups. Discordances across studies, however, must be interpreted under the light of the many methodological and statistical differences between them (especially those regarding sample size and composition, and the control of potentially confounding factors), which make them not directly comparable.

Some studies have failed to detect differences between groups, or have found differences in areas not directly related to the ones identified here. The first published investigation assessing grey matter differences in gambling disorder (GD) was carried out by Joutsa and colleagues (2011), in a relatively small sample of PGD and healthy controls (HC). They found no significant grey matter differences between groups. However, participants from the GD group presented comorbidities. van Holst et al. (2012) investigated structural differences using voxel-based morphometry between PGD, alcohol abusers, and HC. Likewise, no significant differences were found between PGD and HC. In this case, potential confounders (including smoking status, age, and intelligence) were measured and entered the analyses as covariates. Five gamblers, however, did not meet the criteria for GD. More recently, Rahman et al. (2014) found reduced volumes in right hippocampus and right amygdale in a sample of 32 non-treatment seeking PGD. However, a proportion of PGD showed comorbid drug abuse and they did not mention any correction method for multiple comparisons or multiple areas of interest.

Other studies report differences in the opposite direction. For example, Koehler et al. (2015) found increased grey matter volume in ventral striatum and prefrontal cortex of PGD. Nevertheless, differences fell below significance after correction for multiple comparisons. A similar case can be made for Fuentes et al. (2015), who found no clusters of significant regional differences in the whole-brain voxel-wise volume comparison between PGD and HC, and further examined absolute and regional grey matter volumes in 11 selected ROIs, using an uncorrected $p<0.01$ threshold. They observed increased absolute global grey matter volume in PGD, and decreased relative regional grey matter volume in right hippocampus, left putamen, and right thalamus. Therefore, given the methodological limitations from these studies, results should be interpreted cautiously.

A further structural MRI study comparing 16 PGD and 17 HC (Grant et al., 2015) detected reduced cortical thickness in frontal and parietal regions, with samples recruited from the community. The MINI In-

ternational Neuropsychiatric Interview was used to exclude psychiatric comorbidities in PGD, although the PGD group presented significantly higher depressive symptomatology scores. Concerning gambling symptoms, this study used Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling.

Lastly, a recently published study by Zois et al (2017) investigated GM differences using voxel-based morphometry in a sample of PGD without substance use disorder comorbidities, and two groups of PGD with substance abuse comorbidities (alcohol and poly-substance abuse). The HC sample from this study included regular gamblers, and participants diagnosed with specific phobias. Still, this study is probably the one most directly comparable to the present one. The threshold for significance was defined at $p<0.01$ AlphaSim corrected, and, in the contrast between HC and PGD without comorbidities, a reduction of grey matter volume was observed in the medial part of the superior frontal gyrus. That is, results for the key group comparison were overlapped with our findings.

4. Causal learning in gambling disorder: beyond the illusion of control

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4.1 Abstract

Causal learning is the ability to progressively incorporate raw information about dependencies between events, or between one's behavior and its outcomes, into beliefs of the causal structure of the world. In spite of the fact that some cognitive biases in gambling disorder can be described as alterations of causal learning involving gambling-relevant cues, behaviors and outcomes, general causal learning mechanisms in gamblers have not been systematically investigated.

In the present study, we compared gambling disorder patients against controls in an instrumental causal learning task. Evidence of illusion of control, namely, overestimation of the relationship between one's behavior and an uncorrelated outcome, showed up only in gamblers with strong current symptoms. Interestingly, this effect belonged of a more complex pattern, in which gambling disorder patients manifested a poorer ability to discriminate between null and positive contingencies. Additionally, anomalies were related to gambling severity and current gambling disorder symptoms.

Gambling-related biases, as measured by a standard psychometric tool (GRCS), correlated with performance in the causal learning task, but not in the expected direction. Indeed, performance of gamblers with stronger biases tended to resemble the one of controls, which could imply that anomalies of causal learning processes play a role in gambling disorder, but do not seem to underlie gambling-specific biases, at least in a simple, direct way.

4.2 Introduction

In order to successfully navigate through our lives, humans and other animals need to make sense of our world, detecting regularities, distinguishing true causal links from spurious correlations, and accurately estimating the strength of those links. Indeed, human learning literature has stressed the adaptive value of incorporating information on environmental regularities into causal beliefs (i.e. causal learning; see Perales & Shanks, 2007, for a review), and the potential contribution of its maladjustment to some mental conditions (e.g., psychosis, Janssen et al., 2006; anxiety problems, Mathews & McLeod, 1994; Remmerswaal et al., 2014; and depression, Moore & Fresco, 2012; Blanco et al., 2009, 2012).

Although experimental protocols diverge, most causal learning tasks present a common structure, resembling conditioning tasks. In the prototypical scenario, people are exposed to a series of trials, in each of which a candidate cause and a candidate effect can be present or absent. In instrumental causal learning tasks,

the presence of the cause in each trial is determined by the participant, or the cause is the participant's response itself (see Perales & Catena, 2006). The degree of contingency between instrumental response and outcome is measured as ΔP, the difference between outcome's probability in presence of the response, , and in its absence, , both of which are programmed by the experimenter. In general, judgments of the causal relationship tend to mirror contingency between cause (response) and outcome. However, judgments also depart from contingency in a wide range of situations (Hattori & Oaksford, 2007; White, 2011). Of particular interest here is the illusion of control, namely, learners' tendency to judge null response-outcome contingency as portraying evidence of causal connection, particularly in scenarios in which either the instrumental response or the outcome are frequent (Yarritu, Matute, & Vadillo, 2014).

Cognitive distortions are an important ingredient of gambling disorder. Among them, the tendencies to perceive patterns in series of random events (e.g. Jessup & O'Doherty, 2011), to establish superstitious causal connections between environmental cues and gambling outcomes (e.g. Joukhador et al., 2004), and to overestimate the degree of personal control over gambling outcomes (e.g. Coventry & Norman, 1998), can be described as alterations of causal induction. In this context, a number of studies have investigated how gambling disorder patients (GDPs) learn reward contingencies in non-gambling contexts (see, for example, Vanes et al., 2014). However, to our knowledge, and in spite of the importance of causal learning tasks in helping to model dynamic aspects of causal induction, these tasks have only been used once in GDPs (Orgaz et al., 20013). In that study, programmed contingency between learners' response and outcome was null, = =.80 (ΔP=0), and GDPs judged the null relationship as more positive than healthy controls (HCs) (i.e. they presented a stronger illusion of control). However, gambling-related traits were not directly assessed, so it was not possible to examine the potential relation between bias as detected in the task and biases outside the task (and other clinical features of gambling disorder). More importantly, non-null response-outcome contingencies were not included in the study, so it was not possible to test whether putative anomalies in judging non-contingency generalize to situations in which participants do have some actual control over outcomes.

This gap precludes the possibility of confirming and characterizing the existence of general causal learning distortions in gamblers. Hence, in the present study, we used a standard instrumental causal learning task to corroborate the existence of performance differences between GDPs and sociodemographically similar HCs. Moreover, we intend to determine the potential relation of learning indices with self-report gambling-related biases and gambling severity. Here, we used two versions of the instrumental causal learning task,

the first one arranged with null contingency and the second one with positive contingency. We hypothesize (1) deviations from contingency to be larger in GDPs that than in HCs, particularly in the null contingency condition. We also expect such deviations (2) to predict gambling status/severity and (3) causal attribution biases, as measured by psychometric tools, in the GDPs group.

4.3 Participants and ethical considerations

Thirty-five treatment-seeking gambling disorder patients (GDP group), recruited from AGRAJER, APLIJER, and ALUJER treatment centers in Granada, Linares, and Jaén (Spain), and 32 healthy controls (HC group) participated in this study. All of them signed an informed consent form, and were paid 10€/h for their participation. The study was approved by the Ethics Committee of the University of Granada and was in accordance with the Helsinki Declaration.

	Group					
	HC		GDP			
n	32		35			
Females/Males	2/30		1/34			
	Mean	SE	Mean	SE	F	p
Months in treatment			5.994	.931		
Age	34.719	1.683	36.829	1.976	.649	.423
Education years	13.281	.543	13.029	.788	.067	.796
Estimated IQ	103.047	1.785	100.221	2.085	1.048	.310
Depression (BDI-II)	4.031	.763	11.057	.969	16.142	<.001
Alcohol misuse (MC)	1.063	.205	.800	.178	.942	.335
Drugs misuse (MC)	.813	.198	.286	.151	4.567	.036

Four leftmost columns stand for mean and standard errors for continuous variables, and frequency counts for discrete ones. Continuous variables were submitted to a one-factor ANOVA to check for matching across groups. Statistics corresponding to such ANOVAs (F and p) are presented in the two rightmost columns of the lower panel.

BDI Beck depression inventory, MC MultiCAGE CAD-4, HC healthy controls, GDP gambling disorder patients, IQ intelligence quotient (as computed from the matrices and vocabulary indices of the Weschler Adult Intelligence Scale).

Inclusion criteria for GDPs, apart from the GD diagnosis, were abstinence from gambling for at least 15 days, and estimated IQ above 80. The IQ criterion also held for HC group. Participants with psychiatric diagnosis (including addictive disorders other that nicotine dependence and gambling disorder), as informed by the therapist, or any history of neurological disease or brain trauma, as informed by the participant, were excluded from the study. Table 1 presents descriptive statistics and differences across groups in potential confounders. The two groups were matched in most variables. GDPs showed —as expected— a higher disphoric mood score (below the clinical significance threshold), and less current potentially problematic use of illegal drugs (attributable to recommended abstinence from all drugs during treatment).

4.4 Methods

Instruments and variables

Instrumental causal learning task

Materials were presented, and responses collected, by using a PC laptop computer. The task was programmed using Visual Basic 6. Participants were seated approximately 60 cm away from the screen.

The task was divided into three 32-trial blocks. Each trial commenced with a button on the centre of the screen with the prompt "Click or not?" (instrumental response). The button remained on screen for 2500 ms or until the participant mouse-clicked on it. 750 ms later, the outcome (a schematic drawing) was presented or not. The occurrence of the outcome was accompanied by the message "You win 5 points", whereas its non-occurrence was accompanied by the message "You lose 5 points". The drawing (or its absence) and the message remained on screen for 500 ms. A 750 ms-long fixation "+" separated the offset of the outcome/message from the onset of the following trial. In each block, the participant was allowed to click on the button up to 24 times, and a counter on the top of the screen showed how many "clicks" the participant had left in the ongoing block. When they ran out of clicks, the response button was disabled and remained so until the beginning of the next 32-trial block.

After every 32-trial block, the participant was asked to judge the degree to which she/he thought clicking on the button caused or prevented the occurrence of the outcome, in a scale ranged from -100 (clicking maximally prevents the outcome) to 100 (clicking maximally causes the outcome). The 0-point of the scale indicated that clicking neither caused nor prevented the outcome. The judgment was made using a visual scale with a slide bar. The two dependent variables from the task were block-by-block causal judgments, and number

of clicks (instrumental responses) per block.

Gambling severity

To estimate gambling severity we used the Spanish version of the South Oaks Gambling Screen (SOGS; Lesieur & Blume, 1987). This is the only validated instrument to assess gambling severity in Spanish, and has good psychometric properties (Echeburúa et al., 1994).

Estimated Intelligence Quotient (IQ)

We used vocabulary and matrices subtests of the WAIS-IV test (Weschler Adult Intelligence Scale; Weschler, 2008). The two raw scores were translated into verbal/non-verbal IQ scores, and averaged to obtain an IQ-estimate.

Dysphoric mood

The revised version of the Beck Depression Inventory (BDI–II; Beck et al., 1996) was used to check for differences between groups in depressive symptoms. This test has been validated in Spanish, and has good psychometric properties (Sanz et al., 2003).

Gambling-related cognitive biases

In order to assess gambling-specific biases, we used the Gambling Related Cognitions Scale (GRCS; Raylu & Oei, 2004). This questionnaire has been validated in a separate study (Del Petre et al., in preparation) with 500 regular gamblers. This validation study has yielded good levels of reliability and a well-fitting factorial structure.

GRCS questionnaire assesses five gambling-related cognitions. Inability to stop and gambling expectations, refer to personal beliefs of lacking the ability to control gambling impulses, and overvaluing the joy or reward that can be obtained from gambling, respectively, and are not directly related to causal learning. Illusion of control (IC; overestimation of personal control over gambling outcomes), predictive control (PC; perceived ability to predict future outcomes), and interpretative biases (IB; the tendency to attribute past losses to bad luck or other external removable factors, and wins to ability) have to do with how gamblers connect gambling outcomes between them or with environmental cues. For the present study, we averaged these three dimensions in a single score.

Drug/alcohol misuse and gambling status

The MultiCAGE CAD-4 questionnaire is a screening tool designed to detect risky or problematic al-

cohol and drug use, gambling, internet surfing, videogaming, sexual behavior, money spending/shopping, and eating. Each subscale is composed of four yes/no items to report craving, others' complaints about the behavior, guilt or shame feelings/lack of acknowledgment, and self-reported compensatory behaviors. The scales used in the present work (gambling, alcohol, and illegal drug use) have shown good psychometric properties and criterion validity (Pedrero-Pérez et al., 2007).

Procedure and design

The instruments described here are part of a larger protocol including physiological and psychological measures, not directly relevant to the aims of the present study. The paper-and-pencil tools were randomized and presented together, either before or after causal learning tasks.

Participants performed the causal learning task twice, so that response-outcome contingency was manipulated across tasks, in a balanced order. In each trial of the null-contingency condition, the outcome was delivered with a .66 probability, independently of participant's behavior. In the positive contingency condition, outcome was delivered with a .75 probability when the participant clicked on the button and with a .25 probability when she/he did not. Participants were instructed to regard the two tasks as completely independent of each other.

In order to ensure generalizability, two stimuli sets were used as outcomes. For 19 participants in the GDP group, and 16 participants in the HC group, the drawings used as outcomes in the two tasks were a clover and a diamond. For the remaining 16 participants in the GDP group, and the remaining 16 in the HC group, the outcomes were two simple geometric shapes (a circle and a square). The two stimuli from each set were randomly assigned to the NC and PC conditions.

Dependent variables were block-by-block causal judgments, and the number of clicks (instrumental responses) per block. In a first analysis stage, both judgments and clicks were submitted to a three-factor (Group: GDP, HC, between-participants; Contingency: Positive vs null, within-participants, Block: 1–3, within-participants) repeated measures analysis of variance (ANOVA). In a second analysis stage, we restricted the analyses to participants in the GDP group. Judgments and number of clicks per block were submitted to several analyses of covariance (ANCOVA) with block and contingency as within-participant factors, and relevant scores from gambling-related psychometric tools as covariates.

For all analyses, the significance threshold was set at $p<.050$. Violation of the sphericity assumption

was managed by using the Greenhouse–Geisser method for adjustment of degrees of freedom (Geisser & Greenhouse, 1958; Greenhouse & Geisser, 1959).

4.5 Results

Causal judgments

Figure 1 displays mean causal judgments for each group and contingency, across blocks. The contingency x group x block ANOVA yielded significant effects for contingency, $F(1, 65)=70.267$, $MSE=2104.091$, $p<.001$, $\eta_p^2=.519$, block, $F(2, 130)=10.626$, $MSE=921.522$, $p<.001$, η p2=.141, contingency x block, $F(2, 130)=3.610$, $MSE=1026.197$, $p<.030$, $\eta_p^2=.053$, and, most importantly, contingency x block x group, $F(2, 130)=3.676$, $MSE=1026.197$, $p=.028$, $\eta_p^2=.054$. If stimuli set was included as an extra between-participant factor in this analysis, it had no significant effect, did not interact with any other factor, and did not affect any of the results regarding the other factors, so it was not further considered (see supplementary materials S1).

A polynomial decomposition analysis in the significant three-way interaction only yielded a significant linear component ($p=.008$; $p=.921$ for the quadratic component). That component reflects the fact that the difference between the two contingency conditions in block effect slopes varies across groups. Namely, the HC group ($p<.001$), but not the GDP group ($p=.976$), discriminated better between the two contingencies as a function of task length. Extra analyses to ensure that these effects are not contaminated by differences between programmed and actual contingencies are described in supplementary materials (S1).

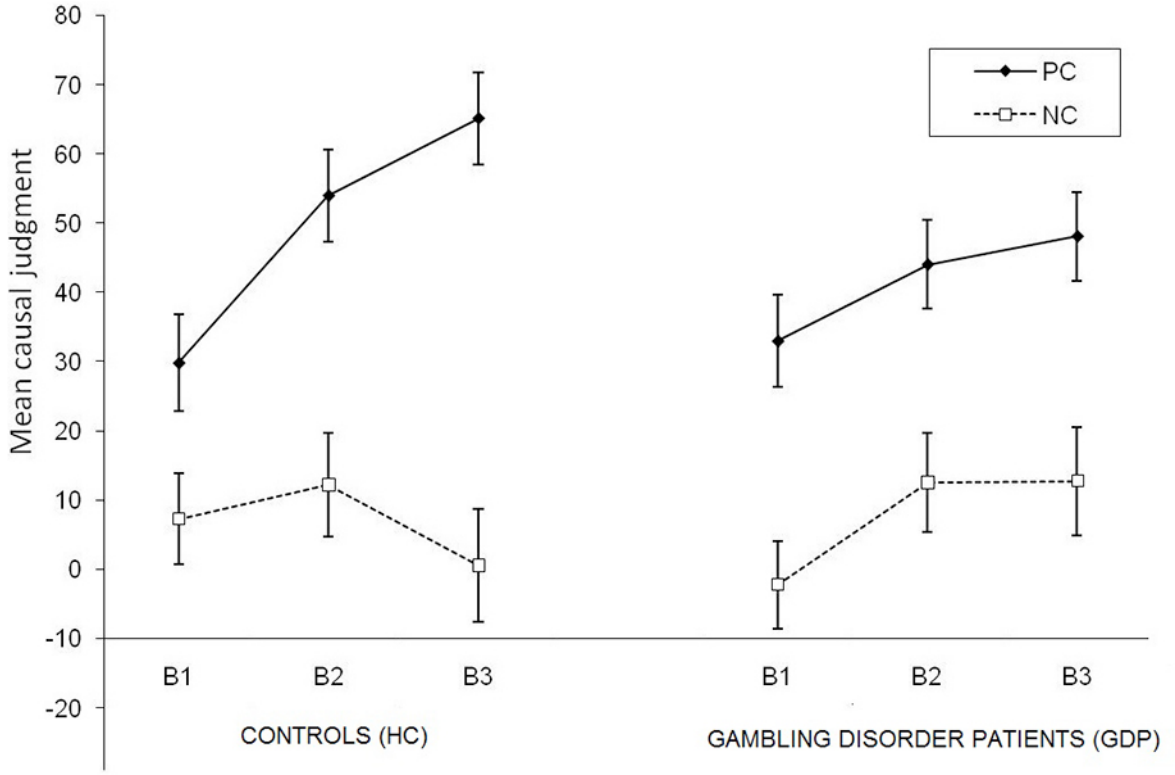

Figure 1. Mean action-outcome causal judgments across blocks (B1-B3), groups (GDP: gambling disorder patients, HC: healthy controls), and contingency conditions (PC: positive contingency, NC: null contingency).

Relationship between causal judgments and gambling-related behavior

In the GDP group, first, we ran an ANCOVA with contingency and block as within-participant factors, and self-reported gambling-related bias score as covariate. This analysis yielded a significant bias effect, $F(1, 33)=4.149$, $MSE=5043.768$, $p=.050$, $\eta_p^2 =.112$, and a bias x contingency interaction, $F(1, 33)=5.733$, $MSE=2196.812$, $p=.022$, $\eta_p^2 =.148$. All other effects remained far from significance (min. $p=.123$). In order to visualize these effects, we segregated between gamblers with strong and weak self-reported bias (median-split). In the positive contingency condition, mean (SE) judgments were 28.370 (8.101) and 56.176 (8.330) for the weak bias and strong bias participants, respectively. In the null contingency condition, the corresponding mean (SE) judgments were 11.963 (8.657) and 3.922 (8.908). That is, somewhat surprisingly, gamblers with a stronger self-reported bias were better at discriminating between the two contingencies.

Secondly, we ran a similar analysis, with contingency and block as within-participant factors, and SOGS gambling severity score as the only continuous covariate. This analysis did not yield any significant effect (min. $p=.148$). However, when MultiCAGE gambling sub-score was used as covariate, the analysis yielded

significant effects for contingency, F(1, 33)=8.568, MSE=2440.534, p=.006, η_p^2=.206, contingency x block, F(2, 66)=3.436, MSE=1153.225, p=.039, η_p^2=.094, and MultiCAGE gambling subscore x contingency x block, F(2, 66)=3.858, MSE=1153.225, p=.027, η_p^2=.105. As displayed in Figure 2, the MultiCAGE score–causal judgment link tended to grow as the task advanced in the no-contingency condition, and reached significance for the last block.

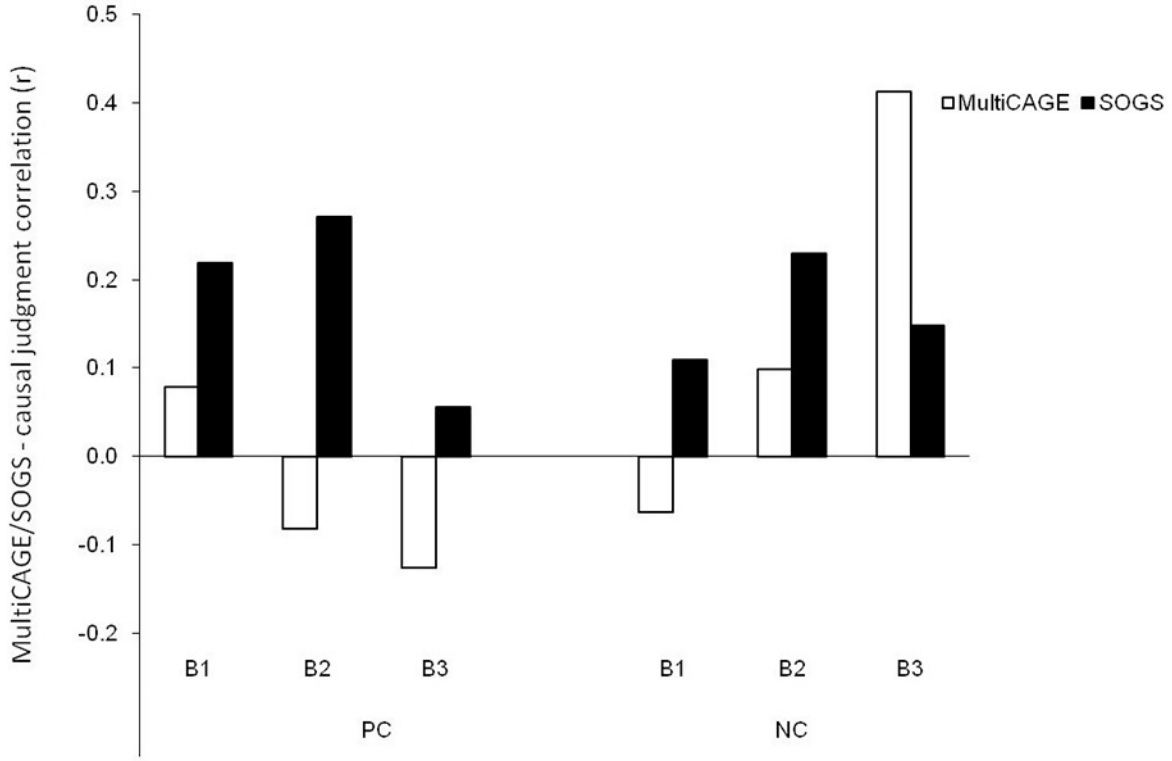

Figure 2. r coefficients for correlations between block-by-block causal judgments and multiCAGE gambling scores (shallow bars) / SOGS severity scores (black bars).

Instrumental responses

Instrumental responses (number of clicks) across block, contingency and group conditions (Figure 3) mostly paralleled the effects found with causal judgments. The block x contingency x group ANOVA yielded significant effects for contingency, F(1, 65)=32.070, MSE=17.119, p<.001, η_p^2=.330, and for the contingency x block x group interaction, F(2, 130)=3.139, MSE=11.592, p=.049, η_p^2= .046. The effect of block was close to significance (p=.060), and all other effects remained far from significance (min. p=.335). Again, if stimuli set was included as an extra between-participant factor in this analysis, it had no significant effect, did not interact with any other factor (min. p=.131), and did not affect any of the results regarding the other factors, so it was not further considered.

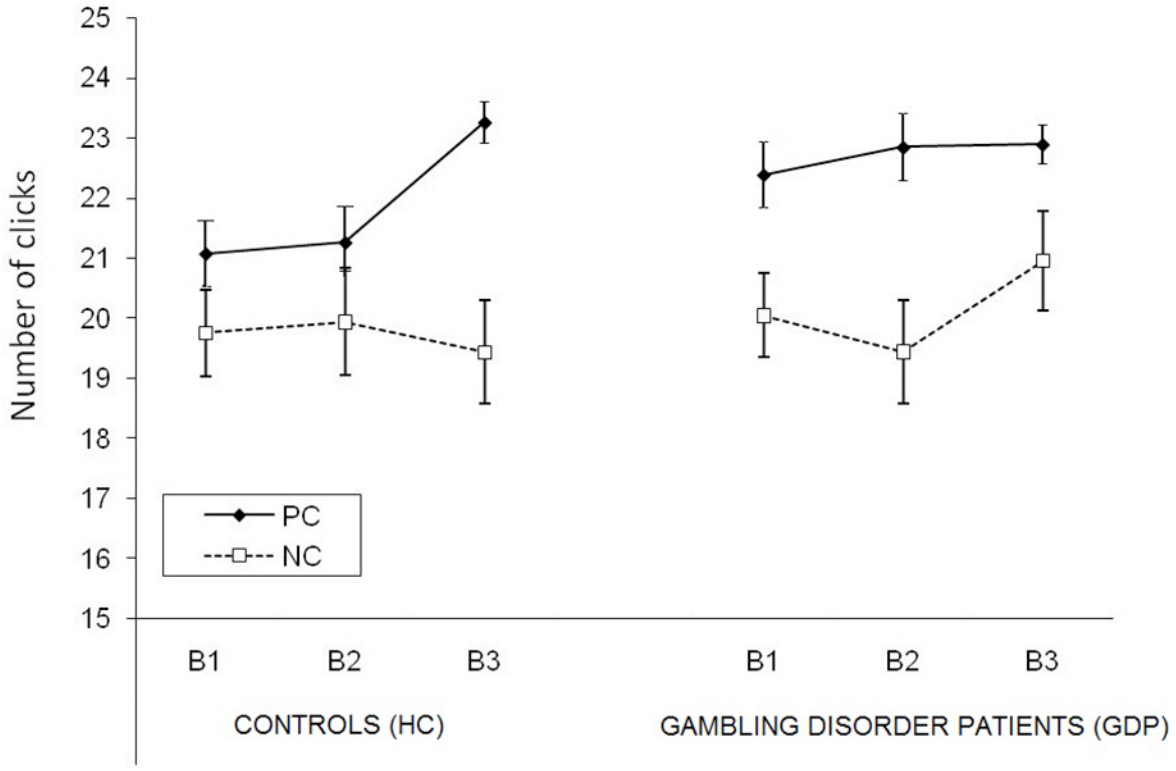

Figure 3. Number of instrumental responses (button clicks) across blocks (B1-B3), groups (GDP: gambling disorder patients, HC: healthy controls), and contingency conditions (PC: positive contingency, NC: null contingency).

Polynomial analysis of the contingency x block x group interaction showed that the lineal component was close to significance (p=.065; whereas p=.098 for the quadratic component). The analysis of the block x contingency interaction in the HC group revealed a significant linear component (p=.021) that was absent in the GDP group (p=.714) . In other words, as it happened with causal judgments, HCs, but not GDPs, discriminated better between the two contingencies as a function of task length.

Relationship between instrumental responses and gambling-related behavior

The contingency x block ANCOVA, with gambling-related bias score as covariate, did not yield any significant effect (min. p=.272). However, when SOGS severity score was used as covariate, the analysis yielded significant effects for contingency, $F(1, 33)=9.308$, $MSE=16.161$, $p=.004$, $\eta_p^2=.220$, and, most importantly, severity, $F(1, 33)=7.455$, $MSE=24.428$, $p=.010$, $\eta_p^2=.184$. The contingency x severity interaction was close to significance (p=.065). All other effects remained non-significant (min. p=.228). Correlation coefficients between SOGS scores and block-by-block number of instrumental responses are displayed in Figure 4. In contrast with what happened with causal judgments, MultiCAGE gambling sub-score did not predict block-by-block in-

strumental responses. In the corresponding ANCOVA, there was only a significant effect of contingency, $F(1, 33)=7.709$, $MSE=16.960$, $p<.001$, $\eta p2=.189$ (for the remaining effects, min. $p=.176$).

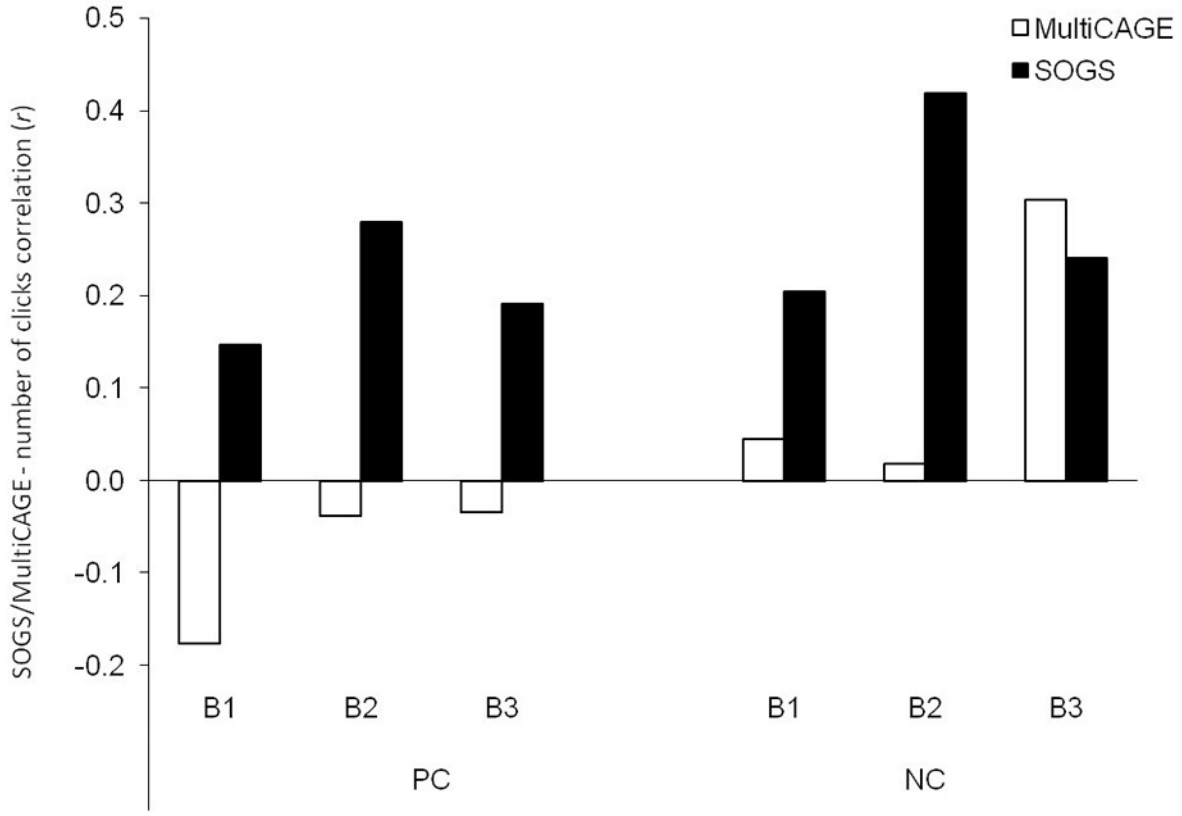

Figure 4. *r* coefficients for correlations between block-by-block number of instrumental responses (clicks) and multiCAGE gambling scores (shallow bars) / SOGS severity scores (black bars).

4.5 Discussion

These results only partially corroborate our starting hypotheses. First, participants did not show a neat control illusion bias in any of the two groups. By the end of the null contingency task, controls almost perfectly judged the action–outcome relationship as non-contingent. Gamblers' judgments were slightly less accurate, but the absolute difference between the two groups was non-significant.

Nevertheless, the analysis of judgment dynamics across blocks and contingency conditions reveals some important between-group differences. In general, the longer the task, the better controls discriminated between contingencies. That was not the case for gamblers, for whom there was a tendency to make slightly higher judgments as the task progressed, with the difference between tasks remaining constant.

Instrumental responses closely paralleled judgments: HCs tended to click more often as the task pro-

gressed in the positive contingency task, but not in the null contingency task, a pattern that was absent in GDPs. Thus, again, controls ended up discriminating better than gamblers between conditions in which reward was contingent on instrumental responses, and conditions in which it was not.

These results are partially at odds with Orgaz et al.'s (2013) study, in which both a neat control illusion and a difference between groups were reported. Some obvious procedural differences could account for the discordant results, although, at this point, any explanation remains tentative. First, non-mediated action-outcome instrumental tasks as the one used in the present study are less likely to elicit judgment biases than mediated ones (in Orgaz et al. study, participants were asked to administer or not a drug to a series of fictitious patients, and then judge whether the drug was effective or not). Second, adding payoffs to outcomes can strengthen the effect of corrective feedback on non-rational responses, when provided in a consistent manner (see Shanks et al., 2002). Third, in the present study, we limited the number of instrumental responses to a maximum of 24 in each block, which ensures some degree of exposure to the probability of the outcome when an instrumental response has not been made. And fourth, our procedure ensured a closer matching between GDPs and HCs samples, which may have removed confounding factors.

Most other studies on reward-based contingency learning in GDPs have focused on anomalies of reversal learning, and simply ensured, for the sake of control, that GDPs and HCs had reached the acquisition learning asymptote before measuring reversal learning differences (see, Janssen et al., 2015; for a recent example; van Holst et al., 2010; for a review). In Vanes et al.'s (2014), however, acquisition of reward contingencies was specifically investigated, independently of reversal and extinction learning. In this case, the task used was a trial-by-trial pattern discrimination task in which participants were asked to react to some, but not to all patterns by pressing the space bar, and the goal of the task was to find out which patterns required a response and which did not. This study found reversal and extinction differences between patients and controls, but not acquisition differences. Nevertheless, the procedure was very different to ours: first, only instrumental responses, but not judgments, were collected. Second, reinforcement was deterministic instead of probabilistic. And third, contingently and non-contingently reinforced responses were intertwined in the same task, instead of separated in different tasks, which makes the discrimination between contingencies overtly easier.

Most interestingly, in accordance with our second hypothesis, our results on the relationship between causal learning indices and gambling-related traits in the GDP group suggest that the subtlety of main group effects, and, potentially, divergences across studies, could be related to individual differences among GDPs.

Higher SOGS scores were associated to worse contingency discrimination as measured by instrumental responses, whereas MultiCAGE gambling score correlated with more distorted judgments as the task progressed.

In general, SOGS correlates only moderately with MultiCAGE-gambling score ($r = .315$, unilaterally significant at $p = .032$, for GDPs in the present study; $r = .857$, unilaterally significant at $p<.001$ for HCs and GDPs pooled together). SOGS items are worded to refer to the individual's past, whereas MultiCAGE-gambling contains 2 (out of 4) items questioning about the current existence of gambling cravings, and problem acceptance/acknowledging. In other words, the differential pattern of correlations for MultiCAGE and SOGS scores could be attributable to the fact that the two instruments measure quite different constructs, the first more related to current persistence of gambling disorder symptoms, the second more related to severity of gambling before the decision to initiate treatment was made (see Michalczuk et al., 2011; Raylu & Oei, 2004; Young & Whol, 2009; Xian et al., 2008, for studies reporting moderate correlations of cognitive distortions with gambling severity and with urgency/craving). Still, our results are inconclusive with regard to a possible dissociation between different indices of causal learning with regard to their relationships with past vs current gambling disorder symptoms.

Finally, in relation to our last hypothesis, we found some connection between causal learning indices and gambling-related biases (as measured by the GRCS questionnaire), but this was in the direction opposite to the one expected. Actually, in face of a content analysis of the items belonging to each of the three GRCS subscales under scrutiny (illusion of control, predictive control and interpretative biases), a rather simple pattern of connections between them and causal learning tasks was expected. In accordance with Orgaz et al. (2013), we hypothesized causal learning anomalies to underlie –and thus directly correlate with– gambling-specific biases. Unexpectedly, gambling-specific biases made participants in the GDP group make higher judgments (particularly in the positive contingency condition), which made their performance resemble the one of controls.

Preliminary results (Ruiz de Lara et al., 2016) suggest that this inverse relation between causal learning anomalies and gambling-related biases as measured by psychometric tools also emerge in differential patterns of both variables with functional connectivity of the insular cortex. A promising, although still tentative account of this unexpected dissociation could be based on the fact that gambling-related cognitive distortions –particularly the illusion of control– are significantly more intense in gamblers preferring skill-based games than in those preferring chance games. Myrseth et al. (2010) found gamblers with predilection for skill-based games to be more prone to gambling-related cognitive distortions. A possibility exists that some gamblers

are more skillful and dexterous at managing general reward contingencies (and thus more accurate in judging such contingencies in causal learning tasks), and such perceived competence plays a role at maintaining false beliefs about gambling abilities. This idea is supported by studies suggesting that some GDP are very accurate at capturing statistical information from games and gambling devices, a type of information mostly useless to avoid losses, but directly contributing to a false sense of mastery (King et al., 2010).

4.6 Limitations and strengths

Conclusions from the present study are affected by several limitations. First, cross-sectional methodology precludes strong inferences about the directionality of the relation between causal learning and gambling-related traits. And second, sample size is limited by the availability of patients in the treatment centers where they are recruited. Underpowering due to small sample sizes could have rendered some real effects non-significant.

On the other hand, the present study is the most careful attempt to date to explore causal learning in gambling disorder. The task has been tested many times, and is considered a well designed, precise instrument to study the mapping of basic statistical information onto causal beliefs. Additionally, the two samples were well matched in a number of confounders, so that potential extraneous factors that could have generated differences between them have been removed. Moreover, the analysis of relationships between causal learning indices and gambling-related traits in the GDP group represents an advance in accounting for previous weak or inconsistent results. And finally, for the sake of transparency, both significant and non-significant results, consistent or not with our previous hypothesis, are reported.

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Compliance with Ethical Standards

Conflict of Interests

The authors declare no financial interests or potential conflicts of interest.

Ethical Approval

All participants were informed about the procedure followed in the studie and signed informed consent. All protocols

performed in the studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the University of Granada and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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4.8 Supplementary material

Actual contingencies as delivered to participants and their potential effect on causal judgments and instrumental responses

Actual contingencies

As noted above, truly probabilistic instrumental tasks do not ensure that the probabilities of the outcome in the presence and absence of the instrumental response match programmed ones, so that the contingency levels participants are actually exposed to present some interindividual random variability, which could also account for some variability in judgments and other learning indices.

In order to rule that possibility out, we carried out a block x group x stimuli set ANOVA on contingencies as experienced by the participants. Programmed contingencies were ΔP=.00 for the NC condition and ΔP=.50 for the PC one. One participant did not make any instrumental response in two blocks of the NC condition, and another one did the same in one block of the same condition; actual contingencies are not computable in the absence of the candidate cause, so data were missing in those three points. As expected, there was a strong main effect of contingency, $F(1, 61)=1129.784$, MSE=.026, $p<.001$, $\eta 2=.949$, so that mean actual contingency (standard error) was .517 (.011) for the PC condition, and -.013 (.012) for the NC one. There was also an unpredicted significant block x contingency interaction, $F(2, 122)=7.045$, MSE=.023, $p=.001$, $\eta 2=.104$. Mean actual contingencies (SE) across blocks were .540 (.014), .498 (.020), and .575 (.015), for the PC condition, and .025 (.021), -.008 (.023), and -.056 (.022), for the NC one. No other effects resulted to be significant (min. p=.199). In other words, despite the significant block x contingency interaction, mean actual contingencies closely matched the programmed ones and did not differ across groups.

Potential effects on causal judgments

In order to further ensure that results reported in the Causal judgments subsection of the main manuscript were not contaminated by actual contingencies, we ran a complementary analysis. First, for each block and contingency condition, causal judgments were regressed over actual contingencies (as delivered to participants, see details above), and non-standardized residuals were kept for further analysis. These residuals (interpretable as causal judgments in which the influence of objective contingency has been removed away) were subsequently submitted to an analysis of covariance (ANCOVA) with block, contingency condition, group, and stimuli set as independent factors, and BDI score as a continuous covariate. In this analysis, the

contingency x block x group interaction fell below the significance threshold, $F(2, 120)=2.584$, $MSE=826.263$, $p<.080$. The BDI score was very far from having any marginal or interactive effect on residuals by itself (min. $p=.225$). When the BDI was removed from the analysis, the contingency x block x group contingency regained significance, $F(2, 122)=4.252$, $MSE=814.853$, $p=.016$, $\eta^2=.065$. All other effects in the design remained far from significance (min. $p=.175$).

Potential effects on instrumental responses

A similar analysis with residuals resulting from regressing block–by–block instrumental responses over actual block–by–block contingencies, and including the BDI score in the contingency x block x group x stimuli set ANCOVA also yielded a contingency x block x group significant interaction, $F(2, 120) = 3.270$, $MSE = 7.552$, $p = .041$, $\eta^2 = 0.052$. The main effect of group, and the third-order interaction involving the four factors were close to significance ($p = .080$, and $p = .067$, respectively). All other effects remained far from significance (min. $p = 0.341$).

5. The paradoxical relationship between emotion regulation and gambling-related cognitive biases

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5.1 Abstract

Background

Gambling behavior presents substantial individual variability regarding its severity, manifestations, and psychological correlates. Specifically, differences in emotion regulation, impulsivity, and cognitive distortions have been identified as crucial to describe individual profiles with implications for the prevention, prognosis, and treatment of gambling disorder (GD).

Aims and method

The aim of the present study was to investigate the associations of gambling-related cognitions (measured according to the GRCS model) with impulsivity (UPPS-P model) and emotion regulation (CERQ model), in a sample of 246 gamblers with different levels of gambling involvement, using mixed-effects modelling to isolate theoretically relevant associations while controlling for the potentially confounding effects of sociodemographic and clinical covariates.

Results

Affective/motivational dimensions of UPPS-P impulsivity positive urgency and sensation seeking, on the one hand, and CERQ emotion regulation strategies reappraisal, rumination and blaming others, on the other, independently and significantly predicted distorted gambling-related cognitions.

Conclusions

These results (a) reinforce the ones of previous studies stressing the relevance of emotional and motivational processes in the emergence of gambling-related cognitive distortions; and (b) replicate the seemingly paradoxical finding that gamblers use emotion regulation strategies customarily considered as adaptive (i.e. reappraisal) to strengthen and justify their biased beliefs about gambling outcomes and controllability.

5.2 Introduction

Gambling disorder (GD) is a behavioral addiction [1] characterized by preoccupation and loss of control over gambling behavior, and persistent gambling engagement despite adverse consequences [2], with a worldwide estimated lifetime prevalence ranging between 0.7 and 6.5% [3]. GD is associated with a wide repertoire of negative consequences [4], and is also frequently comorbid with mood and anxiety disorders [5,6], substance-use disorders [7,8], and general health problems [9].

Over the last years, there has been a significant increase in GD research, and important advances have been made at elucidating its etiology and vulnerability markers [10,11]. Accordingly, GD must be regarded as a multifaceted phenomenon [12], influenced by a variety of risk factors, including genetic dispositions [13,14], sociodemographic and exposure variables [15,16], personality factors [17,18], family antecedents of GD or substance-use disorders [19,20], and adverse events during childhood [21,22].

With regard to more proximal causes, converging evidence shows the relevance of a number of individual processes and predispositions regarding gambling course and development [23,24]. Specifically, a large body of research has identified emotion regulation deficits [12,25,26], impulsivity [17,27,28], and gambling-related cognitive distortions [29,30], among the most critical variables contributing to GD.

More specifically, and in direct relation with the aims of the present study, emotion regulation refers to conscious and unconscious actions, either overt or covert, involved in monitoring, evaluating, and modulating emotional reactions [31,32], and converging evidence emphasizes its central role in GD [12,33]. On the one hand, individuals with GD (IGD) tend to use gambling itself as an emotion regulation strategy [34,35]. The successful attenuation of negative emotions through gambling engagement can operate as a source of negative reinforcement, predisposing individuals to maintain gambling [36,37]. Accordingly, studies have found that the use of gambling to cope with negative emotions is associated with worse gambling outcomes, higher severity, and the number of gambling activities practiced [34,37,38]. On the other hand, IGD also present anomalies in covert emotion regulation, namely conscious or unconscious mental processes used to attenuate negative emotions or enhance positive ones [25,39,40]. Specifically, IGD are more prone to use maladaptive emotion regulation strategies, such as emotional suppression [41,42], and less prone to use adaptive ones, as reappraisal [26].

Relatedly, GD is associated with impulsivity, and particularly with its emotional aspects [17,43,44]. Available evidence also shows that emotion-driven impulsivity and emotion dysregulation are tightly linked [45–48], and that problem gambling can be motivated both by the impulsive desire to avoid negative mood states and by the impulsive desire to maintain and enhance positive mood states [49].

Theoretical models of the role of emotion regulation in problematic gambling

Current etiological models attribute a key role to emotion regulation in the vulnerability, course, and prognosis of GD. In the seminal Pathways Model [12], conditioned gamblers are those whose gambling has

become problematic as a consequence of the reinforcement schedules and other contingencies present in gambling setting and devices, but do not present further complications. The emotionally vulnerable gambler subtype is however described as more prone to suffer from depression and anxiety, and also to use gambling as a strategy to cope with negative affect, whereas the impulsivist/antisocial subtype presents more impulsivity and a heightened risk of comorbid externalizing problems. Extensive evidence shows that comorbidity between addictions and other externalizing problems is driven by a common transdiagnostic factor that largely overlaps with negative urgency, and has been described as a form of emotion dysregulation [50, 51].

The recently proposed Gambling Space Model (GSM, [52]) reformulates the Pathways Model from a dimensional perspective. The model proposes the existence of four dimensions that would be relevant for the characterization of risky gambling and GD. The first two of them comprise the gambler's sensitivity to the positively and negatively reinforcing properties of gambling (with emotionally vulnerable gamblers scoring high in their sensitivity to negatively reinforcing gambling properties, namely using gambling to cope). The third one, general emotion dysregulation, mostly coincides with the tendency to lose control in negative emotional circumstances, so gamblers in the high end of this dimension would largely overlap with impulsivist/antisocial ones. Finally, the fourth dimension, self-deceptive reasoning, captures the tendency to use elaborated reasoning strategies to justify heavy gambling and disguise its negative consequences. This fourth dimension allows the characterization of a new phenotype, sociodemographically characterized by younger age and higher education, and psychologically characterized by particularly strong gambling-related cognitive distortions, and heightened sensitivity to the rewarding features of gambling activities [53,54]. This subtype is becoming progressively more prevalent [55–57], and seems difficult to accommodate into the Pathways Model, but would be easily described in the GSM as the combination of high scores in the dimensions for self-deceptive reasoning and the sensitivity to gambling rewarding properties.

The interplay between emotion regulation and gambling cognitions

Gambling-related cognitions are among the most reliable indices of risky/disordered gambling, and some of them can be defined as cognitive biases regarding one's ability to predict and influence gambling outcomes [58,59]. Nevertheless, despite being defined as cognitions, these beliefs have been consistently linked to non-strictly-cognitive constructs. According to Michalczuk and colleagues [44], for example, impulsivity in IGD is associated with gambling biases because impulsive behavior in decision making contexts can predispose gamblers to accept distorted beliefs without questioning. However, this interpretation fails to account for

the finding that cognitive biases correlate more robustly and systematically with emotional and motivational aspects of impulsivity (sensation seeking, positive urgency and negative urgency) than with its purely cognitive facets (lack of perseverance and premeditation) [60].

Alternatively, the GSM conceptualizes distorted gambling cognitions as a manifestation of self-deceptive reasoning, namely the proneness to distort reality in a self-serving way, and generates two new predictions. First, as far as gambling cognitions are motivated, emotional and motivational dimensions of impulsivity (positive and negative urgency, and sensation seeking) are expected to be more strongly connected to them than purely cognitive facets (lack of perseverance, and lack of premeditation). This prediction arises from the assumption that cognitive biases are fueled by the same emotions and motives that trigger affect-driven impulsivity.

And second, the GSM hypothesizes a substantial overlap between biased gambling-related cognitions and elaborated emotion regulation strategies. In other words, it counterintuitively predicts that putatively adaptive emotion regulation strategies used by healthy individuals to deal with negative emotions (e.g. different forms of reappraisal, re-attribution, or refocusing, generally associated with positive outcomes) can be used by IGD and risky gamblers to deal with negative events (e.g. losses) and enhance positive emotions that help them justify their excessive gambling. In line with this prediction, two recent studies by Navas and colleagues [25], and Jara-Rizzo et al. [61] have shown that treatment-seeking IGD and community gamblers with stronger cognitive distortions are more prone to use putatively adaptive emotion regulation strategies (i.e. putting into perspective, from the Cognitive Emotion Regulation Questionnaire, CERQ [62], and reappraisal form the Emotion Regulation Questionnaire, ERQ [63]) than healthy controls. In other words, elaborated emotion regulation strategies, including those customarily regarded as adaptive, can contribute to cognitive distortions and gambling maintenance.

Study aims

The present study is aimed at corroborating the two abovementioned predictions regarding the relationship between emotion regulation and gambling related cognitions. First, the closer relationship of gambling cognitions with emotional/motivational aspects of impulsivity than with its cognitive components. And second, the (seemingly counterintuitive) direct relationship between gambling cognitions and emotion regulation strategies that could reflect gamblers' attempts to distort reality in a self-serving way.

The present study thus attempts a conceptual replication of the pattern of results reported by Navas et al. [25], and Jara-Rizzo et al. [61], specifically regarding the relationships between emotion regulation and gambling cognitions. Beyond the face value of conceptual replications, in the present study we used an emotion regulation questionnaire (CERQ) assessing a collection of strategies that allows to identify those that can be potentially used for self-deception (e.g. different types of reappraisal or blaming others). Although this is the same instrument used in Navas et al. [25], here we use a much larger sample, and the methodology is improved in a number of ways. Additionally, the existence of previous results allows a research strategy that is more confirmatory than exploratory (and thus restricts the number of models to consider).

The hypotheses were tested in a heterogeneous sample of recreational gamblers and IGD from Spanish communities. As output variables, gambling severity was measured using the South Oaks Gambling Screen (SOGS, Spanish version [64]), and gambling-related cognitive distortions were assessed with the Gambling Related Cognitions Scale (GRCS [65]). Relevant predictors were impulsivity dimensions included in the UPPS-P model (negative urgency, positive urgency, sensation seeking, lack of premeditation, and lack of perseverance [66]), and dispositional use of emotion regulation strategies included in the CERQ [62], both dysfunctional (i.e. catastrophizing, rumination, blaming oneself, and blaming others) and putatively adaptive or functional (i.e. positive refocusing, refocusing on planning, positive reappraisal, acceptance, and putting in perspective). In line with the premises outlined above, we expect (a) emotional and motivational dimensions of impulsivity (urgencies and sensation seeking), to be more strongly associated with cognitive distortions than cognitive impulsivity (lack of perseverance and premeditation); and (b) dispositional use of ego-protecting cognitive strategies of emotion regulation (particularly putting into perspective and reappraisal, according to previous studies) to be positively associated with gambling-related cognitive distortions.

5.3 Methods

Participants and procedure

The study sample comprised 246 gamblers, including 30 treatment-seeking patients with DSM-5-based GD diagnosis, 20 community gamblers who potentially met GD criteria (as assessed by SOGS) but were not in treatment, and 196 community gamblers that did not meet GD diagnostic criteria.

Patients were recruited from a behavioral addictions rehabilitation center in Granada, Spain (AGRAJER, Grenadian Association of Rehabilitated Gamblers). Community gamblers were initially recruited via so-

cial media and advertisements, and researchers also visited university schools and administered a brief screening battery to identify individuals who participate in gambling activities. Recruitment was intended to cover the whole range of gambling involvement, from occasional to heavy gamblers. Potential participants from any source who had gambled at least once were invited to complete the research protocol.

Inclusion criteria for the whole sample were: being at least 18 years old, speaking fluent Spanish, and life-time involvement in any gambling activity, regardless of the money wagered. Although no specific time period was established to define lifetime gambling involvement, only one participant from the whole sample reported not having gambled during the previous year.

The sociodemographic and relevant clinical information collected is depicted in Table 1 (upper panel). Sociodemographic information included age, gender, years of education, and monthly income (according to 6 categories, see Table note). Relevant clinical information included gambling severity and preferred gambling modality. The rightmost column in Table 1 shows the Bayes Factors for the comparisons, in all variables, between IGDs and recreational gamblers. BFs were computed using a Bayesian Mann-Whitney U tests (except for gender, for which a Bayesian contingency table test was performed), with the default priors and specifications in JASP statistical software. In general, BF > 3 is to be interpreted as substantially supportive of the alternative hypothesis of a difference between the groups in the corresponding variable, whereas BF < 1/3 supports the null (no difference between the groups). 1/3 < BF < 3 provides only anecdotal evidence.

Complementarily, among IGDs, 8% gambled at least once a month but less than once a week, 38% gambled at least once a week but less than once a day, and 54% gambled daily, in at least one of the games in the list. Among recreational gamblers, 1 participant (0.5%) had not gambled in the last year, 37.2% had gambled at least once in the last year, but less than once a month, 26.5% had gambled at least once a month, but less than once a week, 33.2% had gambled at least once a week, but less than once a day, and only 2.6% gambled daily, in at least one of the games in the list.

114 participants were assessed face-to-face by one of the researchers, using paper-and-pencil instruments, 92 participants were provided with assessment materials to complete at home, and 40 participants completed the questionnaires using a protocol created in LimeSurvey Pro 2.50 (LimeSurvey GmbH, Carsten Schmitz, HRB 137625).

Participants were informed about the aims and instructions, either face-to-face or by email, and were

required to sign the informed consent prior to participation. Before giving permission to access the questionnaires' platform, online participants were asked to read and understand the aims and instructions, and to give explicit consent to participate in the study. Assessment were performed by psychologists, and supervised by a researcher with seven years of experience in psychological assessment.

The assessment protocol consisted of various self-report measures, some of which are beyond the scope of the present study, and have been previously reported [34] (with an overlap of 76,42% between samples), or will be reported elsewhere. In addition, 21 of the 30 IGD in treatment were proposed to participate in a larger assessment protocol (programmed on a different session). This protocol included neuropsychological tasks and an fMRI session, and will be presented in future reports. Data were collected between October 2015 and December 2017.

The procedure was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee of the University of Granada, as part of the PSI2013-45055-P and PSI2017-85488-P research projects (last author is the principal researcher).

Instruments

The Gambling-Related Cognitions Scale (GRCS [65]) was used to assess gambling cognitions. The GRCS is based on a hierarchical model with five intercorrelated dimensions included in a higher order factor [65]. The first three cognitions are based on early research on pathological gambling-related cognitive biases [66,67], namely predictive control, illusion of control and interpretative bias. The other two cognitions are not strictly considered biases, but pervasive beliefs, adopted from substance-use disorders research [68], and include gambling expectancies and inability to stop gambling. Recent evidence shows that GRCS score is a robust gambling disorder predictor [69,70], and accounts for a significant amount of gambling disorder variance [30,71,72].

We used UPPS-P questionnaire [73] to assess impulsivity. According to this model, impulsivity comprises five dimensions: positive urgency, negative urgency, lack of premeditation, lack of perseverance and sensation seeking [73]. This model has been widely used in GD research with promising results [74]. A large body of research confirms significantly higher impulsivity scores in IGD, compared to controls [44,47,75]. Moreover, this approach has been included in recent theoretical models of GD [52] in an attempt to characterize different GD profiles.

Emotion regulation strategies were assessed using the Cognitive Emotion Regulation Questionnaire (CERQ [62], Spanish version [76]). This tool comprises nine different strategies of emotional regulation triggered by negative valence events. These strategies have been divided into two different clusters depending on whether they contribute to emotional well-being and adaptive behaviors or, on the contrary, they are associated with distress and psychopathological disturbances. Among the former are included: (i) putting into perspective, (ii) positive refocusing, (iii) positive reappraisal, (iv) acceptance, and (v) refocus on planning. The later encompass: (i) self-blame, (ii) other-blame, (iii) rumination, and (iv) catastrophizing.

The South Oaks Gambling Screen (SOGS [77], Spanish version [64]) was used to evaluate gambling severity. This is a 20-item self-report questionnaire that assesses key symptoms and common gambling-related problems. The total score ranges from 0 to 20, and can be used to determine gambling clinical status. Scores between 0 and 2 correspond to non-problem gamblers, scores between 3 and 4 are indicative of risky or problematic gambling and scores between 5 and 20 define the participant as probable pathological gambler [77]. The Spanish version of the questionnaire has shown adequate reliability and validity in general population as well as in pathological gamblers (test-retest reliability, 0.98; internal consistency, 0.94; and convergent validity, 0.92 [64]). In general, correlation between SOGS scores, DSM diagnostic criteria and gambling frequency and severity indices range from moderate to high [78].

Statistical Analysis

In order to investigate the associations between input and output variables involved in central hypotheses, hierarchical linear mixed-effects (LME) modelling, as implemented in the nlme R package (R Core Team, 2018 [79]) was used. Mixed-models methodology is preferable over simple regression for its less restrictive data requirements, higher flexibility, and capacity to handle missing data [80].

Given that sample size was based on availability, no a priori power analysis was feasible. However, given the large number of observations per relevant construct, the large sample size, and the limited number of predictors per model, statistical power is not expected to be a problem.

An initial model was built with participant as a random effect, and SOGS severity was included by default as fixed effect (this was done to verify that associations between input and output variables are not exclusively accounted for gambling severity). The different subscales of the GRCS questionnaire (output variables) were considered as levels of a fixed within-participant factor, and the SOGS x GRCS subscale interaction

was also included in the model. Covariates (age, monthly income, education years, and gender) were included in the initial model but remained for further analyses only if they yielded significant effects (as tested using a t-test for the corresponding effect, with a relatively lenient $p \leq 0.10$), and the same was done with covariate x GRCS subscale interactions. To facilitate the interpretation of effect estimates, and avoid convergence problems, all continuous variables were scaled and zero-centered prior to analyses. The final H0 model thus contained participant in the random part, and SOGS severity, GRCS subscale, SOGS x GRCS subscale, and all the covariates and their interactions with GRCS subscale with significant ($p<=0.10$) contributions to the initial model (please note that the lenient threshold is used only for covariate inclusion in the model, that is, to make sure no relevant covariates are left out).

A first H1 model tested the associations between impulsivity dimensions and gambling-related cognitions. Upon the H0 model, each UPPS-P dimension was included if (a) its inclusion contributed to model fit (forward test), and (b) its exclusion from a saturated model with all UPPS-P dimensions substantially hampered model fit (backward test). After considering marginal effects of UPPS-P dimensions, the same procedure was followed by UPPS-P dimension x GRCS subscale interactions (i.e. differential effects of UPPS-P dimensions for each of the cognitions in the GRCS). Substantial UPPS-P dimension x GRCS subscale interactions were followed with GRCS subscale by subscale regressions. Model fit decisions were made on the basis of two criteria: the Akaike Information Criterion (AIC [81]) and the Likelihood-Ratio test. A second H1 model was built, using the same procedure, to test associations of CERQ emotion regulation scores with GRCS cognitions. This procedure ensures robustness of predictor effects across the presence and absence of other potential predictors.

5.4 Results

Descriptive data for GRCS, UPPS-P and CERQ are shown in Table 1 (lower panel).

	Total sample (n= 246)		**IGDa [105] (n=50)**		**Recreational gamblers (n=196)**		
	Mean (SD)		*Mean (SD)*		*Mean (SD)*		*BF10*
Age	33.14 (13.88)		33.78 (11.46)		32.97 (14.47)		0.187
Gender	82 females		1 female		81 femalesvt		2.270 x 107
Years of education	15.23 (3.96)		13.82 (3.91)		15.60 (3.90)		8.523
Monthly income*	4.13 (1.58)		4.22 (1.61)		4.11 (1.58)		0.161
Gambling severity (SOGS)	2.55 (3.95)		9.54 (3.12)		0.73 (1.00)		5.972 x 108
Preferred gambling modality** [83]	Type I	Type II	Type I	Type II	Type I	Type II	
	n=77	n=128	n=20	n=23	n=57	n=105	
Gambling cognitions (GRCS)b							
Predictive control	2.48 (1.51)		3.93 (1.68)		2.10 (1.22)		64413.72
Illusion of control	1.78 (1.20)		2.69 (1.57)		1.55 (0.96)		210.39
Interpretative bias	2.53 (1.73)		4.19 (1.88)		2.09 (1.40)		6615.03
Gambling expectancies	2.39 (1.51)		3.94 (1.90)		1.99 (1.08)		8803.14
Inability to stop gambling	1.78 (1.38)		3.89 (1.55)		1.24 (0.60)		64484.83
Impulsivity (UPPS-P)b							
Positive urgency	2.53 (0.65)		2.79 (0.59)		2.46 (0.65)		81.80
Negative urgency	2.52 (0.77)		2.94 (0.71)		2.40 (0.74)		107.37
Sensation seeking	2.39 (0.80)		2.58 (0.84)		2.34 (0.78)		0.62
Lack of premeditation	1.84 (0.61)		2.12 (0.66)		1.76 (0.58)		7.27
Lack of perseverance	1.71 (0.62)		2.01 (0.65)		1.63 (0.59)		28.35
Emotion regulation strategies (CERQ)b							
Putting into perspective	3.36 (1.01)		3.34 (1.03)		3.36 (1.00)		0.19
Positive refocusing	2.53 (1.06)		2.77 (1.11)		2.47 (1.04)		0.74
Positive reappraisal	3.39 (1.11)		3.31 (1.19)		3.41 (1.09)		0.18
Acceptance	3.56 (1.04)		3.96 (0.95)		3.46 (1.04)		21.62
Refocus on planning	3.76 (1.00)		3.92 (0.94)		3.72 (1.02)		0.66
Self-blame	2.52 (1.06)		3.31 (1.23)		2.31 (0.91)		640.93
Other-blame	1.91 (0.80)		2.02 (1.08)		1.88 (0.71)		0.18
Rumination	3.17 (1.05)		3.50 (1.10)		3.08 (1.01)		29.11
Catastrophizing	2.17 (0.90)		2.85 (1.01)		1.98 (0.77)		180841.02

Note: a Community gamblers with SOGS severity score ≥ 5 [105] and treatment seeking gamblers. b GRCS range [1-7]; UPPS-P range [1-4]; CERQ range [1-5]; * Monthly income in Euros, 1: ≤ 600; 2: 601 - 1000; 3: 1001 - 1500; 4: 1501 - 2000; 5: 2001 - 2500¸; 6 ≥ 2500. ** Preferred gambling modality was classified according to Navas et al.'s criteria [83]. Type I: Cards, casino games, skills and sports bets; Type II: Lotteries, pools, bingo, and slot machines. Missing data [Individuals with gambling disorder/Recreational gamblers]: Age = 0/7; gender = 0/5; years of education = 1/7; Socio-economic status = 0/5; Preferred gambling modality = 7/34; GRCS = 0/1; UPPS-P = 0/6; CERQ = 0/7.

A first model was built with GRCS scores (in the five GRCS subscales) as the output variable, participant as random-effects factor, and age, gender, education years, monthly income, SOGS, and GRCS subscale as fixed-effects factors. [Please note that each participant had 5 GRCS scores (1 per GRCS subscale), but GRCS score was treated as a single dependent variable, with GRCS subscale treated as a within-participant factor]. Additionally, age, gender, education years, monthly income, and SOGS interactions with GRCS subscale (representing potentially differential effects of covariates across different GRCS cognitions) also entered the model as fixed-effects factors. Fitting was performed with the restricted maximum likelihood (REML) estimation approach. Running this model yielded significant ($p < 0.10$; see statistical analyses for a justification of this threshold) effects for age ($t = -4.05$, $p < 0.001$), education years ($t = -1.72$, $p = 0.087$), income ($t = -1.93$, $p = 0.055$), and SOGS ($t = 9.046$, $p < 0.001$). GRCS subscale interacted with age (maximum $t = 5.07$, minimum $p < 0.001$, across interaction contrasts), and SOGS (maximum $t = 4.82$, minimum $p < 0.001$). In other words, the final H0 model included age, education, income, SOGS, GRCS subscale, age x GRCS subscale, and SOGS x GRCS subscale in the fixed part, and participant in the random part. This model was used for further comparisons involving theoretically relevant factors.

When UPPS-P scores in its different dimensions were used as predictors (upon the H0 model), only positive urgency and sensation seeking passed the forward and backward tests ($\Delta AIC = -10.768$, L.Ratio = 10.768, $p < 0.001$; $\Delta AIC = -17.185$, L.Ratio = 19.185, $p < 0.001$; $\Delta AIC = -2.418$, L.Ratio = 4.418 $p = 0.036$; and $\Delta AIC = -8.215$, L.Ratio = 10.215, $p = 0.001$, for the positive urgency and sensation seeking forward tests, and the corresponding backward tests, respectively). Among UPPS x GRCS subscale interactions, only the sensation seeking x GRCS subscale interaction passed both the backward and forward tests [$\Delta AIC = -22.306$, L.Ratio = 30.306, $p < 0.001$; and $\Delta AIC = -17.434$, L.Ratio = 25.435, $p < 0.001$; all comparisons were performed fitting models with with the maximum likelihood (ML) estimation approach]. In other words, the best-fitting model included the same effects as the H0 model, plus positive urgency, sensation-seeking, and the sensation seeking x GRCS subscale interaction. Predicted GRCS values from the best-fitting model are depicted in Fig 1. The five panels in the Figure represent the effects of positive urgency (different lines), and

sensation seeking (horizontal axis), for the five GRCS subscales (gambling expectancy, inability to stop gambling, control illusion, predictive control, and interpretative bias), respectively.

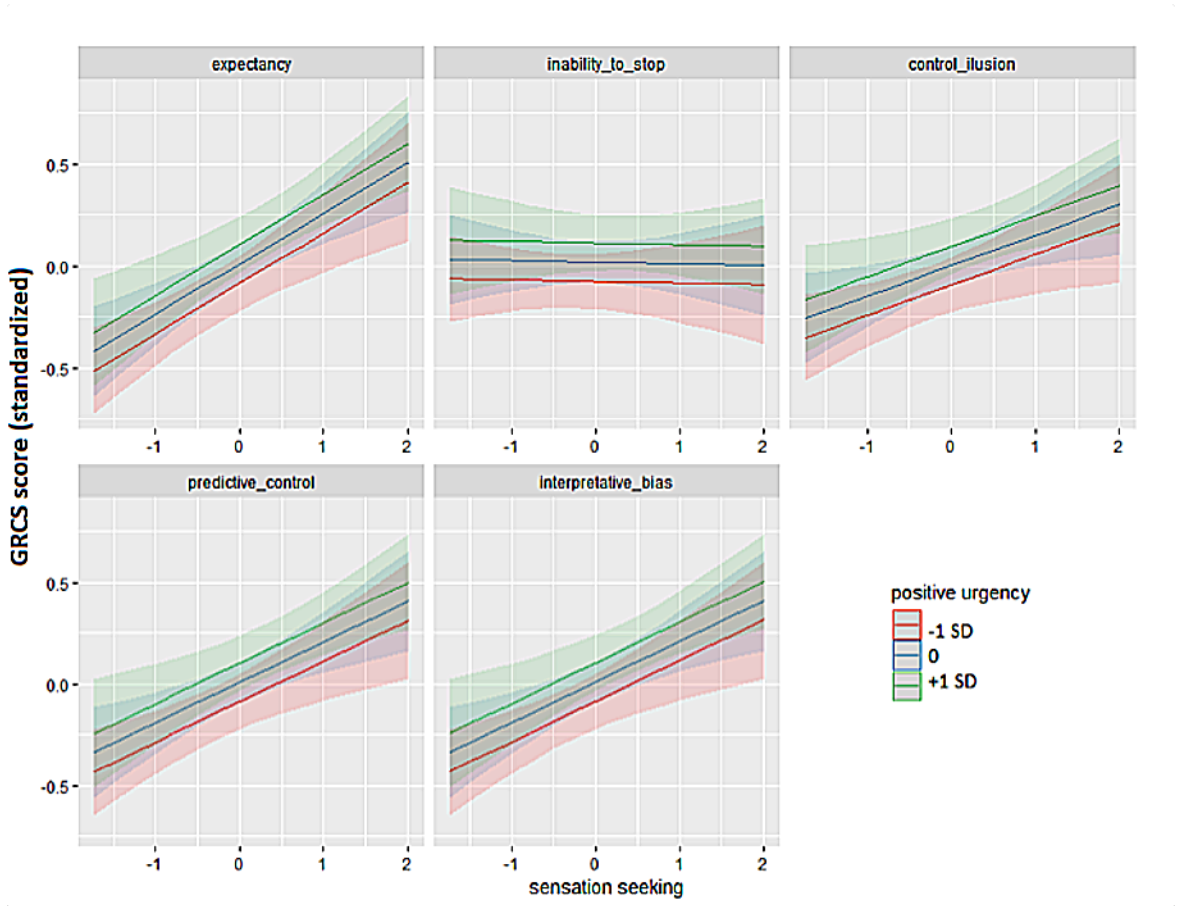

Fig 1. Associations of UPPS-P positive urgency and sensation seeking with scores across GRCS subscales (as predicted by the best-fitting UPPS-P + covariates model)

The effects of positive urgency and the sensation seeking x GRCS subscale interaction were followed by regression analyses for each GRCS subscale separately (using positive urgency and sensation seeking as main predictors, and age, education years, income, and SOGS scores as potential confounders). These analyses yielded significant effects of positive urgency on control illusion [B = 0.147, SE = 0.067, t = 2.210, p = 0.028, R2nsj = 0.022, CI (0.001; 0.074)], and predictive control [B = 0.146, SE = 0.058, t = 2.469, p = 0.014, R2nsj = 0.027, CI (0.001; 0.083)]. Sensation seeking significantly influenced predictive control [B = 0.173, SE = 0.060, t = 2.908, p = 0.004, R2nsj = 0.037, CI (0.004; 0.099)], interpretative bias [B = 0.210576, SE = 0.061, t = 3.452, p < 0.001, R2nsj = 0.051, CI (0.010; 0.12)], and gambling expectancies [B = 0.266, SE = 0.060, t = 4.457, p < 0.001, R2nsj = 0.082, CI (0.027; 0.16)].

An identical analysis rationale was followed to estimate the relationships between CERQ emotion reg-

ulation strategies and GRCS cognitions. Against the H0 Model, only the strategies reappraisal and blaming others passed both the forward and the backward tests (ΔAIC = -4.616, L.Ratio = 6.616, p = 0.010; ΔAIC = -10.624, L.Ratio = 12.624, p < 0.001; ΔAIC = - 7.500, L.Ratio = 9.500 p = 0.002; and ΔAIC = -9.349, L.Ratio = 11.349, p < 0.001). Additionally, among CERQ scores x GRCS subscale interactions, both the reappraisal x GRCS subscale, and the rumination x GRCS subscale passed the forward and backward tests (ΔAIC = -8.571, L.Ratio = 16.571, p = 0.002; ΔAIC = -2.243, L.Ratio = 10.243, p < 0.037; ΔAIC = - 4.300, L.Ratio = 12.300 p = 0.015; and ΔAIC = -2.113, L.Ratio = 10.113, p = 0.039; see Fig 2). The five panels in the Figure represent the effects of reappraisal (different lines), and rumination (horizontal axis), for the five GRCS subscales (gambling expectancy, inability to stop gambling, control illusion, predictive control, and interpretative bias), respectively.

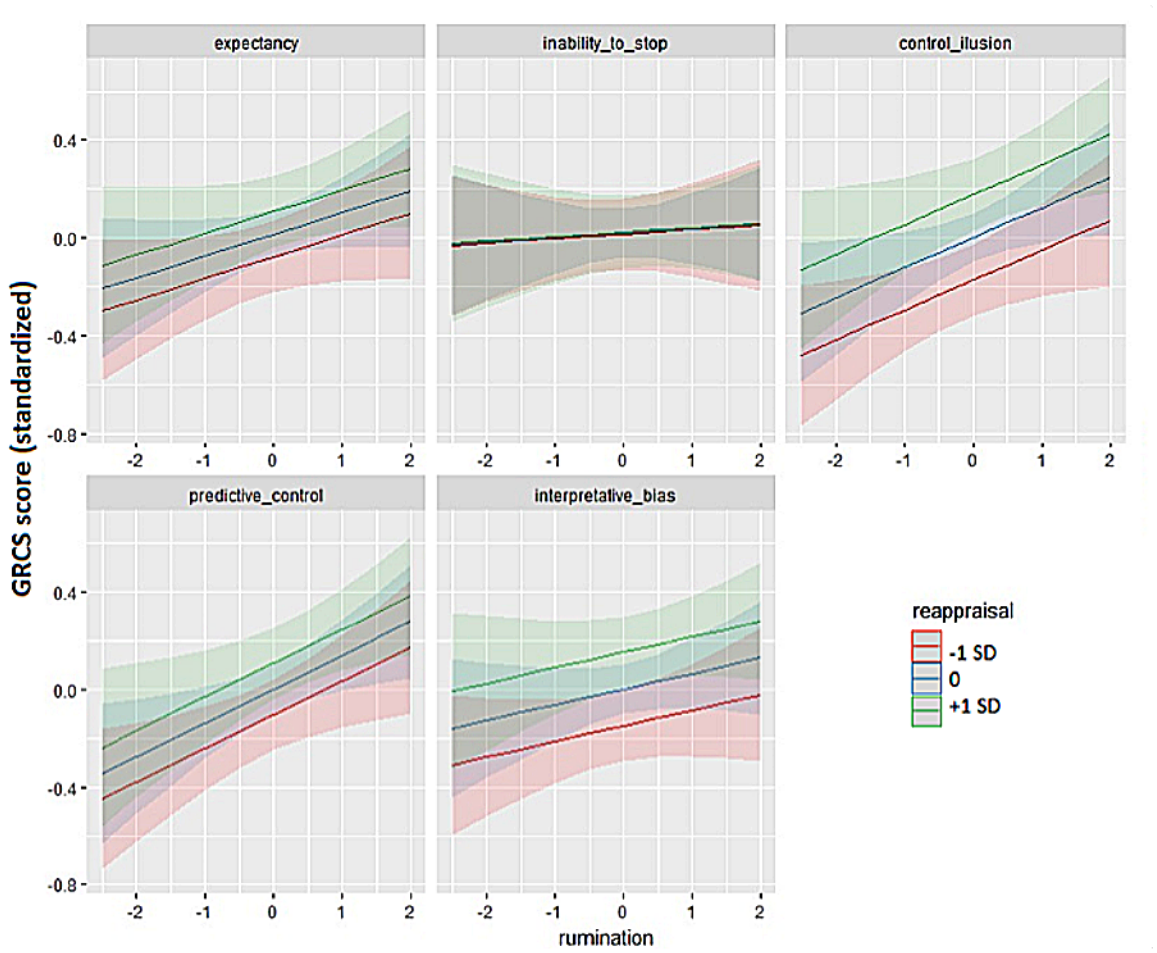

Fig 2. Associations of CERQ reappraisal and rumination with scores across GRCS subscales (as predicted by the best CERQ + covariates model). **Note:** The effect of blaming others was not found to interact with bias type, and is not shown in the figure. Effect sizes of the associations between blaming others and GRCS scores are reported in the text.

Similarly to impulsivity measures, associations between CERQ dimensions and GRCS cognitions were

followed up using GRCS measure-by-measure regression analyses. In all of them, reappraisal, blaming others, and rumination scores were used as predictors, along with age, education years, income, and SOGS scores. Reappraisal use significantly predicted the strength of control illusion [B = 0.173, SE = 0.062, t = 2.795, p = 0.006, R2nsj = 0.034, CI (0.003; 0.095)], predictive control [B = 0.112, SE = 0.055, t = 2.032, p = 0.043, R2nsj = 0.018, CI (~0; 0.069)], and interpretative bias [B = 0.147, SE = 0.057, t = 2.596, p = 0.010, R2nsj = 0.030, CI (0.002; 0.088)]. In accordance with its non-interactive effect, the use of blaming others significantly predicted the strength of all GRCS cognitions: inability to stop gambling [B = 0.121, SE = 0.044, t = 2.764, p = 0.006, R2nsj = 0.030, CI (0.003; 0.094)], control illusion [B = 0.189, SE = 0.059, t = 3.200, p = 0.002, R2nsj = 0.044, CI (0.007; 0.110)], predictive control [B = 0.155, SE = 0.053, t = 2.994, p = 0.004, R2nsj = 0.038, CI (0.004; 0.100)], interpretative bias [B = 0.127, SE = 0.054, t = 2.328, p = 0.021, R2nsj = 0.024, CI (0.001; 0.079)], and gambling expectancies [B = 0.160, SE = 0.054, t = 2.969, p = 0.003, R2nsj = 0.039, CI (0.005; 0.102)]. Finally, rumination significantly predicted predictive control [B = 0.139, SE = 0.055, t = 2.537, p = 0.012, R2nsj = 0.028, CI (0.002; 0.086)].

5.5 Discussion

This study investigated emotion regulation predictors of gambling-related cognitions in individuals with different levels of gambling involvement. Using mixed-effects analysis to adjust for the effects of potential confounders and gambling severity, and in accordance with previous research [44,52,60], results showed that positive urgency, and sensation seeking (from the UPPS-P impulsivity scale), and reappraisal, rumination and blaming others (from the CERQ emotion regulation questionnaire) were associated with gambling cognitions (as measured by GRCS).

The association between gambling-related cognitions and impulsivity dimensions was specific for the emotional/motivational facets of impulsivity, positive urgency and sensation seeking. Negative urgency, however, was not significantly associated with gambling cognitions. Although previous studies have reported this association [44,60], it has also been shown to vanish when impulsivity dimensions are controlled for one another, and for gambling severity (see supplementary materials in Del Prete et al. [60]). Thus, despite the documented importance of negative urgency in GD severity and complications [17,44,82], it seems to hold no independent predictive value over gambling beliefs.

More importantly, the fact that negative urgency was not independently associated with gambling

cognitions (in contrast with positive urgency and sensation seeking) is congruent with recent reports that gambling-related cognitions are stronger, and cognitive biases more prevalent, in gamblers who are highly sensitive to appetitive stimuli and motives [83,84]. Although it was hypothesized that, as long as cognitive biases are affect-driven and motivated, they should be linked to affect-driven impulsivity dimensions, it has been consistently shown that negative urgency is specifically linked to complications in the form of generalized externalizing problems beyond gambling [85,86]. Our results suggest that this complication pathway (probably underlying the impulsivist/antisocial cluster from the Pathways Model [12]), is mostly independent from cognitive symptomatology. Indeed, the combination of sensitivity to appetitive motives, strong cognitive distortions, and preference for certain game modalities, seems to be characteristic of an emerging cluster of problematic gamblers, as shown by recent reports [52].

In relation to the emotion regulation strategies from the CERQ model, results are closely coincident with Jara-Rizzo et al. [61], and mostly compatible with Navas et al.´s [83] findings. In the former, an association was found between reappraisal (as measured by the ERQ questionnaire) and cognitive biases. In the latter, the association between CERQ emotion regulation and gambling-related cognitive biases was restricted to the strategy putting into perspective (the potential association between reappraisal and cognitive biases vanished when emotion regulation strategies were tested against each other). Taken together, however, results confirm our hypothesis that gamblers can display relatively sophisticated emotion regulation strategies, including putatively adaptive ones in conjunction with strong cognitive distortions. Although blaming others is certainly not an adaptive strategy, it can also be effective at reframing gambling outcomes in a way that helps the gambler to maintain gambling behavior despite its negative consequences. In other words, blaming others would help gamblers to reinterpret positive outcomes as caused by personal abilities, and negative outcomes as a result of external influence.

This pattern of results bears important theoretical and clinical implications. In general terms, findings from the present study are consistent with the Gambling Space Model (GSM [52]). Although the DSM-5 establishes a unidimensional classification for GD severity based on the number of diagnostic criteria met by the patient, the GSM, in accordance with recent studies [10,87], and contemporary proposals turning towards dimensionality and transdiagnosis (Research Domain Criteria, RDoC [88,89]), highlights the relevance of variables that contribute to individual differences in GD, as predictors of decisive clinically-relevant indicators. The GSM was developed as an attempt to integrate these variables, and explain their implications for the

behavioral and clinical manifestations of the disorder.

The two main findings in the present study regarding the GSM are: (a) the specificity of impulsivity-cognitions associations for emotion and motivation-driven dimensions of impulsivity (and the lack of predictive value of cognitive dimensions of impulsivity), and (b) the association of self-serving emotion regulation strategies with the tendency to hold biased gambling-related beliefs. Both findings reinforce the existence of a self-deceptive cognitive style where affect and its regulation play a central role.

Nonetheless, the absence of any independent link between negative urgency and cognitive distortions requires some further detailing of the model. As noted earlier, negative emotions do not seem to be particularly intrusive in self-deceptive gamblers. It could be that these gamblers are highly effective at regulating them, or alternatively, that they are not particularly prone to experience negative emotions and moods. Whatever the case is, a new prediction emerges: the low impact of negative affect in combination with strong cognitive biases should translate into high levels of problem denial and treatment reluctance or ambivalence (see [34] and [90] for similar arguments). On the other hand, this lack of relationship between negative urgency and cognitive biases reinforces the model in its conceptualization of negative urgency as a proxy for a different complication pathway in GD, namely, the malfunctioning of automatic, model-free emotion regulation mechanisms that are hypothesized to give rise to the externalizing problems that frequently co-occur with GD and other addictions [17,91].

Beyond the GSM, and the specific hypothesis of the present study, our results also have some other implications, both within and outside the gambling arena. First, the finding that gambling-related cognitions are more tightly linked to appetitive emotions and motives than to aversive ones also resonates with previous reports that gambling craving is inversely associated with positive affect, whereas alcohol craving directly correlates with negative affect [92]. In other words, at least in some cases, gambling seems to be easily triggered by a lack of positive experiences (rather than by the presence of negative ones). In view of the central importance of craving in the very definition of addictive processes, any similarities and differences between craving elicitation across addictive disorders deserves closer attention.

And second, the evidence presented here regarding the involvement of positive urgency and sensation seeking in gambling-related cognitions, along with related work showing the clinical importance of negative urgency in GD [17,44,75], is fully consistent with previous reports that the emotional and motivational

aspects of impulsivity play specific and central etiological roles in the transition from risky behaviors to GD and other addictions [49,93]. Additionally, the differential involvement of positive and negative urgency in different gambling pathways (the former more related to sensitivity to rewarding properties of gambling and fueling cognitive distortions, and the latter involved in externalizing complications of gambling) adds upon the available evidence that these two aspects of emotion-driven impulsivity are theoretically distinct and have different clinical implications [60,94,95].

Indeed, the present study also bears clinical relevance. Cognitive distortions are among the main factors underlying gambling involvement, clinical status and gambling severity [96–98]. Our results show that people who are more prone to impulsive behavior under the influence of positive emotions (scoring high in positive urgency), and more strongly motivated by novel and exciting experiences (sensation seekers) are also more prone to develop gambling-related cognitive biases. Moreover, the association between sensation seeking and gambling expectancies suggests that there is a cluster of gamblers particularly motivated by gambling-triggered arousal and thrill. A number of studies [90,99] suggest that IGD with these characteristics are, in general, less aware of their gambling problems, present a weaker motivation to quit or reduce their gambling, are more likely to drop out from therapy, and are also less compliant with treatment assignments. The chances of intervention success with CBT and cognitive restructuration techniques alone may be thus thinner in these cases, and motivational intervention becomes recommendable [100,101].

The fact that the dispositional use of elaborated emotion regulation strategies also denotes vulnerability to cognitive biases offers a solution to the apparent paradox that general cognitive skills and numerical abilities do not protect gamblers from cognitive distortions [25,102,103], which is important for GD prevention. First, gambling distortions do not seem to be primarily rooted in the lack of probability, mathematical, or reasoning skills, but in motivational factors. And second, cognitive emotion regulation strategies probably require some preservation of the same executive functions that underlie such skills [104].

Finally, although in this study we were not particularly interested in sociodemographics by themselves (but only as control variables), it is worth to mention that age also emerged as a strong predictor of the strength of gambling cognitions, with older participants holding less distorted beliefs that younger ones. Once again, evidence suggests that self-deception seems to be particularly severe in an emerging cluster of gamblers, characterized by younger age, prevalence of positive and excitement-related motives, and preference for skill-based, high-arousal games. Some recent results seem to indicate that this subtype is growing in importance, but

probably underrepresented in clinical and prevalence studies.

Limitations and strengths

The present study, using a large sample intending to cover the whole range of gambling involvement, provides novel contributions to the understanding of the complex interplay between individual traits that depict different gambling profiles. The inclusion of both community and disordered gamblers allows better generalizability of the results. We used validated and reliable measures to assess gambling traits (UPPS-P, GRCS, CERQ) and appropriate mixed-effects analysis. Linear mixed-effects models are less restrictive with regard to data requirements and allow higher flexibility in the models' specifications [80]. The method employed for a predictor to be considered significant was stringent, to ensure the soundness of the findings. Additionally, we also evaluate the potential confounding effects of a wide range of sociodemographic and clinically-relevant variables.

Findings from the present investigation should also be considered in light of several limitations. First, the cross-sectional nature of the statistical design precludes any inference regarding causal directionality. Second, the use of self-reported questionnaires to assess the constructs included in the models, and absence of objective measures of performance, may not entirely represent the cognitive and emotional processes involved. It may also influence results due to recall bias and social desirability. Third, and in relation to the previous caveat, effects sizes are mostly small ($R2 > 0.01$), or medium ($R2 > 0.06$) but not trivial ($R2 < 0.01$), according to customary conventions. These values are fully consistent with the ones reported in related work [90]. This is partially attributable to the measurement error of the scales used, but also, as mentioned earlier, to the fact that some of them were used as proxies to the construct of interest. Further research is indeed underway to find more direct ways to measure such constructs. Complementarily, small effect sizes are also attributable to the fact that, in all analyses, gambling severity was controlled for: as correlations between constructs in the current sample are strongly driven by severity, any estimates of effect sizes beyond severity are likely to be conservative. Fourth, for the sake of parsimony, we restricted the selection of variables of interest and confounders based on a priori hypotheses. A number of alternative models could have also been built. And fifth, the sample size was not large enough to compare between different subsets of gamblers, for instance, based on their preferred gambling modality or their motives for gambling.

Conclusion

Overall, our results delve into the understanding of individual differences and diverse gambling profiles among IGD, and cast light on apparent paradoxes regarding the relationships between gambling-related beliefs and emotional processes. More specifically, they suggest that gambling-related cognitive biases are tightly entangled with emotional and motivational processes, and, probably, cannot be effectively treated if these processes are neglected. Future research should confirm their generalizability to different samples and addictive disorders, and consider additional factors that could further delineate specific gamblers' profiles.

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Competing interests
JCP is an academic editor of Plos One, this does not alter our adherence to PLOS ONE policies on sharing data and materials. CMRL and JFN have no conflicts of interest to declare.

Data Availability
The open database and code files for these analyses are available without restriction at the Open Science Framework website (https://osf.io/seuzt/).

Footnotes
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6. General discussion

6.1 Summary of results

Study 1. Psychobiology of gambling-related cognitions in gambling disorder.

1. Evidence on reward processing mechanisms in GD patients is heterogeneous, showing a mixed pattern of hyper- and hypo-responsivity in mesocorticolimbic regions, including striatum, medial prefrontal cortex and insula. Research on the brain responses to near-misses in GD patients yielded more consistent results, showing an augmented response in ventral striatum and insula associated with an increased motivation to gamble.

2. GD research on gambling craving applying the cue-reactivity paradigm showed a consistent pattern of increased responses to gambling-related stimulus in the insula, anterior and posterior cingulate cortex, dorsomedial prefrontal cortex, parahippocampal gyrus and amygdala. These studies also reported an association between gambling cue-reactivity and craving measures.

3. The finding that cognitive bias cannot be explained by inadequate statistic or numerical abilities, together with results showing that gamblers with high cognitive bias demonstrated a better performance on general-domain cognitive functions and associations between gambling bias and intentional emotion regulation strategies, suggest that these altered cognitive processes can be motivated by the desire to continue gambling or attempts to cope with negative gambling outcomes.

Study 2. Regional grey matter volume correlates of gambling disorder, gambling-related cognitive distortions, and emotion-driven impulsivity.

With regard to structural measures, dmPFC regional GMV was reduced in GD patients, compared to HC. Additionally, in GD patients, IB and NU scores were associated with reduced volumes in dACC and right vlPFC, respectively.

1. GD patients showed diminished dorsomedial prefrontal cortex grey matter volume, relative to HC.

2. GD patients dorsal anterior cingulate cortex grey matter volume showed a negative relationship with interpretative bias scores.

3. GD patients right ventrolateral prefrontal cortex (vlPFC) regional volume was negatively associated with negative urgency measures.

4. Post-hoc analysis showed that GD patients with high negative urgency scores demonstrated a significant reduction in vlPFC regional volume, compared with GD patients with low negative urgency and healthy

controls.

Study 3. Causal Learning in Gambling Disorder: Beyond the Illusion of Control.

1. Participants did not manifest a pure illusion of control bias. Gamblers contingency judgements on the null-contingency condition were less accurate that controls, but differences were not significant.

2. Gamblers judgments and responses were not sensitive to differences in contingency conditions, demonstrating a less accurate contingency discrimination. Gamblers differences in judgements and instrumental responses remained constant between contingency conditions.

3. GD severity measures showed a negative association with indices of contingency discrimination, both with instrumental responses and judgements. Thus, higher gambling problems were associated with more inaccurate responses and distorted judgements.

4. Gamblers with high cognitive bias made more accurate in judgements in the positive contingency condition, showing a similar performance to controls.

Study 4. The paradoxical relationship between emotion regulation and gambling-related cognitive biases.

The two main findings from the present study are:

1. A specific relationship of gambling cognitions with emotional and motivational dimensions of impulsivity (positive urgency and sensation seeking).

2. An association between deliberate emotion regulation strategies (reappraisal and blaming others) and gambling-related cognitions.

6.2 Discussion

In the current thesis, we have analyzed different aspects of the inner architecture and relationships of gambling-related cognitive biases in GD patients and non-clinical community gamblers. The studies included in this thesis employ a number of different methods and approaches – from bibliographic review to experimental methods and MRI techniques – to examine gambling cognitions at distinct levels of analysis. In essence, the studies encompassing this work highlight the central relevance of gambling cognitions in problematic gambling, and illustrate how gambling cognitions interact with neurocognitive processes and individual traits to define specific gambling subtypes and pathways to gambling disorder (GD) vulnerability and clinical man-

ifestations. In this chapter, the results of these studies will be summarized and integrated in a comprehensive discussion that attempt to depict the role of gambling cognitions in the etiology and variability of GD.

Basic neurocognitive processes underlying gambling cognitions

The initial review chapter this thesis analyzes gambling cognitions in terms of underlying neurocognitive processes. Our starting point was that the altered processing of utility, uncertainty and risk that underlies exaggerated or distorted cognitions relies on neurocognitive components can be assessed using validated research paradigms and brain imaging techniques.

First, dysfunctional reward processing mechanisms are assumed to influence how the individual experiences the reinforcing properties of gambling, and can promote exaggerated expectancies about these rewards. In particular, considering rewards beyond objective wins and jackpots, and broadening the concept to include a wide variety of motives that gamblers allude as their essential reasons to gamble, that are intrinsically rewarding by themselves. These dysfunctional reward processes manifest as altered neural responses to different types of rewards. However, GD literature on does not provide an unequivocal pattern of findings, and inconsistencies can be partially explained by the use of diverse procedural variations, differences in gambling samples, and methodological shortcomings (Cox et al., 2017; Kessler et al., 2017).

Initial reports using different procedures (monetary incentive delay, card guessing and probabilistic reversal learning tasks) to study reward processing mechanisms in GD patients suggested a hyporesponsivity of striatal, medial prefrontal and insular regions (Balodis et al., 2012a; Choi et al., 2012; de Ruiter et al., 2009; Reuter et al., 2005). Nevertheless, essential distinctions between these tasks, as the differential involvement of learning processes, prevent any simple conclusion. In addition, contrasts-of-interest diverge between studies (reward anticipation vs. delivery, gain vs. loses).

Even if we focus on a single research paradigm to study neural activity associated with reward and punishment processing, (i.e. the monetary incentive delay task, MIDT; Knutson et al., 2000), differences between studies can be found (Balodis et al., 2012a; Choi et al., 2012; Romanczuk-Seiferth et al., 2015; Sescousse et al., 2013; Tsurumi et a., 2014). A recent meta-analysis attempted to disentangle these discrepancies on brain reward processing, drawing a distinction between reward anticipation and outcome delivery phases (Luijten et al., 2017). This study analyzed investigations in GD and found a pattern of diminished striatal activity during both reward anticipation and delivery in GD patients. Conversely, studies using ecologically-valid settings, as

computerized gambling games, have reported increased activity in striatal regions during anticipation of monetary rewards (van Holst et al., 2012a; Worhunsky et al., 2014). In other words, hypo/hyper-reactivity could also depend on whether rewards are gambling-specific or unrelated to gambling activities.

A more consistent pattern of results arises in relation to near-misses. Near-misses are a prototypical example on how specific features of gambling games' design can influence gambling expectancies and motivation. Near-miss events are loss instances that fall close to a win, and because of their perceptual similarities can be interpreted by gamblers as informative on skill acquisition (Clark et al., 2014), and thus promote illusory control and perceived winning expectancies. Neural responses to near-misses in gamblers are indeed associated with a consistent pattern of increased ventral striatal and insular activation that mirror win-related responses and enhance gambling motivation (Clark et al., 2009; Sescousse et al., 2016).

A second set of findings involves the pervasive belief of inability to stop gambling. This belief is proposed to emerge from recurrent unsuccessful attempts to regulate gambling craving. In turn, craving arises from learned associations between external cues and the reinforcing effects of addictive agents (Robinson & Berridge, 2008), inducing neuroadaptations in different brain networks and endowing gambling cues with incentive salience (Limbrick-Oldfield et al., 2017; van Holst et al., 2014). The process of incentive salience can be assessed using the cue-reactivity paradigm, a widely used neurocognitive approach to study brain responses to craving-inducing cues (Drummond, 2000).

The most replicated finding of cue-reactivity studies in GD is an augmented response of mesocorticolimbic regions, including insula, dorsomedial prefrontal cortex, anterior and posterior cingulate cortex, amygdala and parahippocampal gyrus (Crockford et al., 2005; Goudriaan et al., 2010; Kober et al., 2016; Limbrick-Oldfield et al., 2017). Notably, two studies found a relationship between cue-related brain activity in the insula and craving rates (Goudriaan et al., 2010; Limbrick-Oldfield et al., 2017), which suggest a possible function for insular cue-reactivity in signaling gambling craving and inability to stop gambling.

The imperative motivational impulse towards gambling developed by the process of incentive sensitization marks the initiation of craving in response to gambling cues. Thereafter, repeated ineffective attempts to regulate this imperative urge to gamble derive in a perceived inability to stop gambling behavior. In this phase of the addiction cycle, gambling becomes compulsive and detached from initial hedonic properties, and ushers in ostensible negative consequences associated to gambling.

Finally, a third set of findings comprise cognitive biases, i.e. control illusion, predictive control, and interpretative bias. As noted earlier, near-misses not only promote exaggerated expectancies, but also enhance feelings of control through illusory beliefs of mastery. However, recent evidence suggests this would be a piece of the cognitive bias puzzle in GD, but not representative of the whole picture. As it will be discussed in more detail later, in relation to the findings of the fourth study of this thesis, the relationships of cognitive bias with emotional aspects of impulsivity highlight their motivational nature. In addition, the complex interplay of cognitive bias and deliberate emotion regulation strategies provides a new understanding of such altered cognitive processes, and defines a unique cognitive profile, the self-deceptive gambler. Accordingly, this interaction is harnessed by the self-deceptive gambler to regulate the impact of negative consequences derived from gambling and justify the loss of control over gambling behavior.

Structural correlates of individual differences in gd patients

Dorsomedial PFC and Gambling Disorder

In the second study from this thesis, we compared volumetric measures between GD patients and matched controls, and explored brain structural signatures of individual differences in the GD group, including those regarding gambling-related cognitive biases (i.e. interpretative bias).

Thereby, we uncovered a diminished dorsomedial prefrontal cortex (dmPFC) grey matter volume in GD patients, relative to healthy controls, replicating previous findings by Zois et al. (2017). However, early volumetric studies in GD reported an inconsistent pattern of results, with some studies failing to find between-group differences (Joutsa et al., 2011; van Holst et al., 2012c), and others finding increases (Koehler et al., 2015) and decreases (Rahman et al., 2014; Grant et al., 2015; Fuentes et al., 2015), in a collection of different areas, including the striatum, hippocampus, amygdala, thalamus and frontal and parietal cortex. Heterogeneity between studies can be attributed to sample characteristics (size, community samples and comorbidities), and methodological shortcomings (whole-brain vs. region-of-interest analysis, and multiple comparisons correction vs. uncorrected results). In view of this limitations, our investigation was particularly careful in several methodological aspects, and especially at selecting a pure GD group without psychiatric and addiction comorbidities. Therefore, once studies apply rigorous methodological approaches and remove potential confounders from GD samples, there seems to emerge a pattern of medial prefrontal grey matter alterations associated with gambling behavior.

The area identified by our and Zois' studies (dmPFC) has been hypothesized to operate as an integration hub combining different types of information from different brain regions (Bechara & Damasio, 2005). This brain area is integrated in a network involved in reward-based decision making (Gläscher et al., 2012), and anticipatory dmPFC activity is associated with reward-related dopamine release in the nucleus accumbens (Weiland et al., 2014). Specifically, in decision making contexts, dmPFC is recruited in response to uncertainty, as compared to risk (Hsu et al., 2005). The suggested role of dmPFC in reward-processing under uncertainty has been corroborated in GD research (Balodis et al., 2012a; Worhunsky et al., 2014). A study in GD patients used a computerized slot-machine task to analyze contextually-relevant differences during the anticipation and delivery phases of potential rewards (Worhunsky et al., 2014). GD patients showed alterations of anticipatory signals, displaying heightened reward-related anticipatory activity in a network including dmPFC, striatum and insula (Worhunsky et al., 2014). The dysfunctional anticipatory activity in these areas may reflect altered motivational processes and increased incentive salience related to the experience of gambling urges. Accordingly, studies exploring reactivity to gambling stimulus have also reported increased activity in dmPFC in response to gambling cues (Limbrick-Oldfield et al., 2017; Kober et al., 2016; Balodis et al., 2012b). A recent investigation revealed amplified anterior cingulate, insula and dmPFC responses in GD patients, compared to controls, in response to gambling cues (Limbrick-Oldfield et al., 2017). In addition, a study comparing GD, cocaine-dependent patients and healthy controls showed that dmPFC/dACC responded in a stimulus-specific manner, that is, there was a significant increase in dmPFC activity in GD patients in response to gambling cues, and in cocaine-dependent patients in response to cocaine cues (Kober et al., 2016). Complementarily, cognitive down-regulation of cue-induced craving by two appetitive stimuli (cigarettes and food) in a sample of cigarette smokers was associated with increased activity in a brain network including dorsomedial, dorsolateral and ventrolateral prefrontal cortices, and decreased activity in ventral striatum, subgenual ACC and amygdala (Kober et al., 2010). Therefore, this heighted responsivity of dmPFC in the anticipation of gambling rewards and processing of gambling-related stimuli suggest a potential function in signaling gambling motivation and cue-salience, acquired through a process of associative learning. Tentatively, the diminished dmPFC grey matter volume could be a vulnerability marker associated with a dysfunctional reward-processing and cue-reactivity.

Ventrolateral PFC and Negative Urgency

Beyond case-control structural differences in GD, we were specifically interested in the potential co-

variation between brain morphometric measures and clinical variables that have revealed central in GD symptomatology (Del Prete et al., 2016; Navas et al., 2016; MacLaren et al., 2011; Navas et al., 2019).

Our findings on the associations between impulsivity and brain regional volume in gamblers is consistent with previous literature linking impulsivity, cognitive control and addictive disorders (Dalley et al., 2011; Robbins et al., 2012). In our sample of GD patients, higher levels of negative urgency, the tendency to act rashly in response to negative emotions, were associated with reduced grey matter volume in ventrolateral prefrontal cortex (vlPFC). Then, we further explored the dynamics of this relationship by differentiating between high and low negative urgency GD patients, and contrasting with HC grey matter volume. Post hoc analysis revealed that high NU GD patients showed reduced vlPFC grey matter volume, compared to both low NU gamblers and controls.

The vlPFC activity is associated with the execution of inhibitory control functions in different experimental paradigms (Aron et al., 2004; Rubia et al., 2001). In addition, this region belongs to a brain network implicated in the intentional application of cognitive strategies to down-regulate negative emotions, through its connections with subcortical regions, including amygdala and nucleus accumbens (Ochsner et al., 2004; Wager et al., 2008).

Inhibitory control is an essential ability to optimize adaptive decision making and effectively adjust actions to variations in environmental circumstances. In this vein, negative urgency has been associated with impaired response inhibition (Billieux et al., 2010). Moreover, in gamblers, problems on response inhibition are related with higher severity of gambling (Brevers et al., 2012). In addition, cognitive flexibility is a cognitive control function that addresses the ability to switch between strategies to adapt to changing contextual contingencies. Using a probabilistic reversal learning task, de Ruiter and collaborators (2009) showed that severe response perseveration in GD patients was associated with diminished activity of right vlPFC in response to monetary gains and losses.

The impaired capacity to control emotions due to malfunctioning of cognitive control areas may be relevant to understand key clinical hallmarks of GD, as the loss of control over gambling behavior (Hodgins et al., 2011; O'Connor & Dickerson, 2003). Within this framework, impaired cognitive regulation of emotions elicited by gambling cues is associated with craving responses and compulsive gambling behavior. Nevertheless, the role of this emotional dimension of impulsivity is not restricted to GD. Impulsivity is a psychobiological

trait common to a variety of psychiatric conditions (Bøen et al., 2015; Dawe & Loxton, 2004; MacLaren et al., 2011; Verdejo-García et al., 2008). Specifically, the tendency to impulsive behavior in response to emotional states is considered as a contributing factor of a transdiagnostic endophenotype (Johnson et al., 2013). Consistent with this assertion, in GD, negative urgency is associated with higher gambling severity, clinical complications and poor prognosis (MacLaren et al., 2011; Steward et al., 2017). In the present study, associations of negative urgency with depressive mood and current, treatment resistant GD symptoms support the proposed role in signaling more severe complications.

Dorsal ACC and Interpretative Bias

In the GD sample, dorsal anterior cingulate cortex (dACC) grey matter volume showed a negative association with interpretative bias, a gambling cognition that assesses maladaptive attributional processes of gambling outcomes (Raylu & Oei, 2004).

In addition, we implemented post-hoc analysis to further characterize dACC grey matter volume dynamics between groups, drawing a distinction between high and low interpretative bias gamblers. Results from this analysis only yielded significant differences in the expected contrast: between gamblers with high and low interpretative bias. Notably, the comparison between low-bias gamblers and healthy controls was marginally significant. Consequently, the dACC grey matter volume of gamblers with high interpretative bias was comparable to controls' grey mater volume. This finding might seem contradictory at first glance; however, parallel evidence suggests that cognitive distortions may not arise from a general deficit in neurocognitive functions, and their origins can be grounded in less obvious processes (see Chapter 5). Moreover, they also corroborate the assumption that cognitive distortions cannot be attributed to differences in academic attainment, or insufficient statistical or numerical abilities (Lambos & Delfabbro, 2007), and support the idea that cognitive bias may define a subgroup of gamblers with preserved executive functioning (Navas et al., 2017).

dACC holds a central position in a brain network involved in domain-general cognitive-control functions (Shenhav et al., 2013), and is thus implicated in cognitive flexibility and goal-directed behavior (Botvinick & Cohen, 2014). In addition, converging evidence shows the relevance of dACC in motivated behavior and reward-based decision making (Kolling et al., 2016). Notably, integrative approaches have attempted to combine these functions in a theoretical model that proposes a dACC role in evaluating the motivational value of control behavior to maximize reward benefits (Shenhav et al., 2016). Accordingly, dACC grey matter vol-

ume predicted individual differences in effortful control in a large representative community sample of young adults (Wei et al., 2019). Therefore, dACC integrates different types of information to coordinate decisions about cognitive-control implementation, considering the balance between estimated reward outcome and effort cost. Interestingly, a large-scale meta-analysis including almost 200 studies identified a diminished dACC grey matter volume as a common neurobiological substrate for different mental disorders (schizophrenia, bipolar disorder, addiction, obsessive-compulsive disorder and anxiety disorders; Goodkind et al., 2015). in direct relation to our study, although the negative association between GMV in the dACC and the gambling-related interpretative bias seems to suggest the involvement of the alteration of this area in this gambling bias, the fact that grey matter volume in controls was more similar to high bias than to low-bias patients complicates the interpretation. Most likely, increased GMV in the dACC signals some neuroadaptation characteristic of low-bias patients (e.g. massive practice with pure-chance games). This issue will be discussed again in relation to the results of studies 3 and 4. A clear interpretation of this result, however, definitely requires further research.

General-domain causal learning and cognitive distortions

The third study of this thesis used a computerized version of a standard probabilistic instrumental learning task to analyze performance deficits in GD patients, compared to healthy controls paired in relevant sociodemographic variables. This task was conceived as a mean of modeling, outside the gambling context, one of the most studied cognitive distortions consistently associated with distorted gambling behavior, the illusion of control (Gaboury & Ladouceur, 1989; Goodie, 2005; Ladouceur & Sévigny, 2005). Thereby, we intended to verify if cognitive distortions as measured by psychometric instruments translate into general-domain deficits on associative learning processes. Moreover, a generalization of the dysfunctional cognitions measured by the Gambling-Related Cognitions Scale (GRCS; Raylu & Oei, 2004) to an alteration of causal learning processes would help to understand the etiology of gambling cognitions. An association of gambling biases and causal learning deficits would suggest that distorted cognitions in gambling contexts are grounded on a dysfunction of more general learning functions. Further, we also aimed to examine response and judgment dynamics in both groups, drawing a distinction between contingency levels, and explore the potential predictive value of gambling severity and cognitive distortions measures on performance and judgments.

Contrary to initial hypothesis, however, our findings indicate that GD patients did not demonstrate a pure illusion of control. Gamblers' judgments on the null contingency condition, although less accurate than judgments from control subjects, did not significantly differ from them. Nevertheless, relevant case-control

differences emerged as the task progressed. A closer examination of judgment dynamics revealed that, contrary to controls, GD patients' judgments did not differ between contingency conditions, suggesting a less accurate contingency discrimination. Similarly, healthy controls instrumental responses pattern mirrored changes in contingency conditions, with more frequent responses in the positive contingency condition. Therefore, our findings suggest that, although gamblers did not manifest an unequivocal control illusion bias, they showed insensitivity to differences in contingency conditions, reflected in both instrumental responses during the task and judgments about contingency.

Our findings did not closely replicate results from Orgaz et al., (2013), the first attempt to apply a causal learning task in gamblers to study potential differences in contingencies estimation. In this study, gamblers judged a null contingency between responses and outcome as more positive than healthy controls, as evidence of illusory of control in gamblers. However, discrepancies between research protocols could account for the incongruent findings, as the use of a non-mediated instrumental task, the addition of outcome payoffs, restrictions on the number of instrumental responses, and a careful matching on relevant confounders between groups in our study.

As previously mentioned, besides neat case-control differences, the research approach from this thesis relies more on the examination of how individual differences in clinically relevant measures interact with altered neurocognitive processes to establish distinct gamblers subtypes with unique symptom profiles. This approach would also help to identify how individual differences between gamblers could explain inconsistent findings and the absence of differences in case-control studies. In our study, two different measures of gambling severity (SOGS and MultiCAGE gambling section) were associated with dysfunctional contingency discrimination and distorted judgments in GD patients, respectively.

In direct relation with the aims of the current thesis, we initially hypothesized that cognitive biases would be grounded on a dysfunction of general-domain causal learning processes. Thereby, considering that the GRCS scales included in the analysis were instances of distorted causal learning (illusion of control, predictive control and interpretative bias), we expected a positive association between gambling distortions and indices of causal learning deviation. Unexpectedly, we found a seemingly paradoxical pattern of relationships, where GD patients with higher cognitive distortions more accurately judged the positive contingency between action and outcome. Therefore, in our GD sample, cognitive distortions characterize a group of gamblers more sensitive to detect genuine cause-effect associations. The current findings thus suggest that these cognitive

distortions do not stem from a lack of statistical abilities or problems on probability estimation, since gamblers with more intense gambling cognitions did not exhibit general alterations of associative learning functions.

In the second investigation included in this thesis (see Chapter 3), we uncovered a negative association between interpretative bias, a cognitive bias identified by previous research as predictive of GD severity and clinical status (Del Prete et al., 2016; Navas et al., 2016) and dACC regional grey matter volume, a region associated with domain-general cognitive-control functions (Shenhav et al., 2013) and reward-based decision making (Kolling et al., 2016). However, findings from the present study suggest that the potential domain-general deficits highlighted by a reduced dACC grey matter volume in gamblers with high cognitive bias do not translate into more general malfunctioning of causal learning processes. Moreover, post-hoc analysis comparing dACC grey matter volume between high-bias gamblers, low-bias gamblers and healthy control subjects revealed that dACC regional volume of gamblers with higher cognitive bias was more similar to controls than dACC volume of low-bias gamblers. However, this result is in disagreement with the proposal of reduced dACC grey matter volume as a transdiagnostic neural signature for different psychiatric disorders, and is associated with poor executive functioning in healthy participants (Goodkind et al., 2015).

The interpretation of this piece of evidence in isolation may seem challenging at first, however, if we analyze these results in light of complementary evidence on the relationships between gambling cognitions, emotion regulation strategies and impulsivity, and consider how these different psychobiological traits interact to define unique gambler profiles, a new possibility arises. The interaction of gambling cognitions with specific gambling characteristics can guide individual gambling preferences. The examination of gambling profiles associated with distinct gambling games preferences may help in the understanding of the reported dissociation. Accordingly, compelling preliminary evidence suggests that gamblers preference for skill games is associated with specific clinical, sociodemographic and personality characteristics (Goudriaan et al., 2009; Griffiths et al., 2009; Moragas et al., 2015; Myrseth et al., 2010; Navas et al., 2017). The profile of the strategic gambler is characterized by younger age, earlier disorder onset, higher academic achievement, more intense cognitive distortions, higher reward sensitivity and novelty-seeking, and excitement and mood-enhancement motives to gamble (Barrada et al., 2019; Francis et al., 2015; Griffiths et al., 2009; Ledgerwood & Petry 2010; Moragas et al., 2015; Myrseth et al., 2010; Navas et al., 2017).

The prominence of cognitive distortions in strategic gamblers may help to explain why in our sample of GD patients, gambling bias predicted more accurate judgments in the casual learning task. The perceived

element of skill from these gambling modalities can shape an overconfidence on personal abilities and an erroneous sense of mastery, that in turn promotes illusory control and unrealistic expectations of winning (Myrseth et al., 2010; Navas et al., 2019). Nevertheless, evidence indicates that these perceptions may be unrealistic, since experienced players of skill games failed to predict results above the chance level (Cantinotti et al., 2004; Ladouceur et al., 1998). In addition, sociodemographic attributes as younger age and higher academic achievements would suggest preserved cognitive abilities in this subgroup of gamblers, which is also consistent with their proficiency in the detection and estimation of reward contingencies. Therefore, according to the postulates of the Gambling Space Model, in this group of gamblers, the expression of specific cognitive distortion dimensions would represent a manifestation of the inadequate implementation of cognitive control mechanisms, more than a general cognitive dysfunction (Navas et al., 2019). Additional evidence showing that the profile of gamblers with higher cognitive distortions is not accompanied by cognitive impulsivity or lack of conscientiousness symptoms (see Chapter 5) further supports the idea of the absence of a generalized executive dysfunction in this subgroup of gamblers.

Motivational foundations of cognitive distortions in gd patients

The fourth study of this work examined potential emotion regulation and impulsivity predictors of gambling cognitions, in a heterogeneous sample of gamblers with different levels of gambling involvement. In this section, we will analyze individual findings and attempt to integrate them with results from the studies exposed in previous sections in a coherent framework to understand how heterogeneity of individual gambling traits interact with specific neurocognitive deficits to delineate distinct gamblers profiles.

One of the most significant findings to emerge from this study is the specific relationship between emotional and motivational aspects of impulsivity, including positive urgency and sensation seeking, and gambling-related cognitions. In contrast, despite accumulating evidence showing associations between negative urgency and GD severity and complications (MacLaren et al., 2011; Michalczuk et al., 2011), this impulsivity facet had no independent predictive value in the manifestation of cognitive bias in our group of gamblers.

Recent findings suggest that coping motives mediate the relationship between negative urgency and gambling severity (Kim et al., 2019). Alternatively, as previously noted, cognitive biases are signatures of a specific group of gamblers defined by higher reward sensitivity and novelty-seeking, together with excitement and mood-enhancement motives to gamble (Barrada et al., 2019; Francis et al., 2015; Jiménez-Murcia et al.,

2019; Ledgerwood & Petry 2010). Our findings on the association between cognitive bias and positive urgency and sensation seeking are consistent with evidence linking gambling distortions, emotional dimensions of impulsivity and enhancement motives (Barrada et al., 2019; Canale et al., 2015; Del Prete et al., 2016; Devos et al., 2017; Mathieu et al., 2018).

Therefore, the present study contributes to previous knowledge on the definition of different GD profiles (Blaszczynski & Nower, 2002; Sharpe, 2002; Navas et al., 2019). Specifically, it provides novel insights that help to refine the gambler profile characterized by severe cognitive distortions, including emotional and motivational dimensions of impulsivity. The combination of intense cognitive distortions, positive urgency, sensation seeking, higher reward sensitivity, excitement and mood-enhancement motives and a preference for gambling games with a perceived element of skill delineate this specific cluster of gamblers.

Moreover, the absence of an association between negative urgency and cognitive bias emphasizes the potential role of this psychobiological trait as a hallmark of an alternative pathway to GD vulnerability, where cognitive distortions do not have a central role (Navas et al., 2019). Specifically, converging evidence suggests negative urgency as a transdiagnostic endophenotype characterized by externalizing complications common to different pathologies (Carlson et al., 2013; Cyders et al., 2016; Settles et al., 2012).

The second major finding from the fourth investigation included in this thesis is the identification of reappraisal and blaming others as reliable predictors of the intensity of gambling-related distortions. Results from the present study corroborate previous findings on the association between deliberate emotion regulation strategies and gambling-related distortions (Jara-Rizzo et al., 2019; Navas et al., 2017). These studies demonstrated the predictive potential of the emotion regulation strategies reappraisal and putting into perspective over gambling cognitions. Overall, these findings indicate that gamblers can implement elaborated emotion regulation mechanisms, including strategies considered as adaptive, as an additional element that contribute to maintain and strengthen cognitive distortions.

The present results thus provide further support and refine the conceptualization of the self-deceptive gambler, where the use of intentional emotion regulation strategies interacts with cognitive distortions to define a specific cognitive style that helps the gambler to mitigate the impact of negative emotions derived from gambling outcomes or to justify their gambling behavior (Navas et al., 2016). In addition, findings from the previous study (see Chapter 5) showed that this subgroup of gamblers is dexterous in the detection of reward

contingencies, which denotes their preserved cognitive abilities.

Hence, it can be conceivably hypothesized that, in self-deceptive gamblers, cognitive distortions reflect patients' attempts to regulate negative emotions derived from gambling, and enhance the positive feelings that helps them to justify excessive gambling involvement despite accumulating losses. Complementarily, although blaming others is not an adaptive strategy, it can also be helpful to attenuate the negative impact of gambling outcomes, and promote gambling involvement despite losses.

The present study thus confirms previous findings and provides additional evidence on the relevance of analyzing individual differences of GD patients and implications for delimitating distinct gambler profiles (Blaszczynski & Nower, 2002; Griffiths, 2005; Sharpe, 2002; Navas et al., 2019). In general, studies included in the current thesis corroborate the postulates of the Gambling Space Model, a coherent theoretical framework that attempt to integrate key vulnerability factors associated with GD etiology, and explain their contributions for the behavioral and clinical profiles associated with the disorder (Navas et al., 2019). The DSM-5 diagnosis of GD is built on a unidimensional classification of GD severity based on the number of diagnostic criteria met by the subject (American Psychiatric Association, 2013). However, recent large-scale, integrative investigations are emphasizing that, more than a unique risk factor that confers vulnerability to GD, there are different neurocognitive alterations that combine with specific personality traits to define distinct pathways to GD vulnerability, and develop in particular gamblers' profiles (Blanco et al., 2015; Chamberlain et al., 2017; Dussault et al., 2011; Ledgerwood & Petry, 2010; Milosevic & Ledgerwood, 2010; Navas et al., 2019; Shaffer & Martin, 2011; Sharpe, 2002). Accordingly, the investigations from this thesis contribute to the understanding of the different gambling profiles by providing novel insights on the interactions of neurocognitive functions with psychobiological traits to explain the transition from recreational to compulsive gambling. In the self-deceptive gambler, cognitive distortions are not associated with a dysfunction in general-domain cognitive functions. Instead, the interaction of certain dimensions of emotional impulsivity and deliberate emotion regulation strategies with cognitive distortions determines the subtype of patients with high reward sensitivity, novelty-seeking, and mood-enhancement motives, as previously described. Preliminary evidence also presented in this thesis suggests that reduced dACC regional volume might also be a neural signature of this cluster of patients.

Separately, negative urgency would be the hallmark of a distinct vulnerability pathway, characterized by externalizing problems and complications, comorbidity with substance addictions, and the use of gambling

to cope with negative emotions (MacLaren et al., 2011; Navas et al., 2019). Our findings indicate that this gambling profile may be associated with a diminished right vlPFC grey matter.

The findings from this work may help us to understand the ongoing paradox of cognitive bias: intact cognitive functions and numerical and statistical knowledge do not protect gamblers from experiencing cognitive distortions (Cunningham et al., 2014; Lambos & Delfabbro; 2007; Navas et al., 2016). In addition, GD research has not revealed an unequivocal relationship between GD and executive dysfunction (Goudriaan et al., 2004; 2014). The findings from the studies included in this thesis suggest that cognitive distortions may be grounded in emotional and motivational factors, more than in the absence of statistical or mathematical aptitudes or inefficient reasoning abilities. Actually, the effective implementation of elaborated emotion regulation strategies with a self-centered motivation may require preserved cognitive functions.

Another important idea supported by this work is the distinction between unique factors contributing to GD vulnerability, and common transdiagnostic constructs shared by different pathologies. In this realm, gambling-related distortions can be considered as specific GD vulnerability factors, that however interact with transdiagnostic neural signatures to define a particular GD profile. Additionally, negative urgency has been identified by previous research as a common endophenotype for pathologies characterized by externalizing symptoms (Cyders et al., 2016; Settles et al., 2012), and in GD delineate a distinct vulnerability pathway, associated with comorbidities, the use of gambling to manage negative affect and diminished vlPFC grey matter volume.

The framework that guided this work, combining different methodological approaches to examine specific neurocognitive processes and psychobiological traits associated with GD vulnerability, is illustrated by contemporary initiatives, as the Research Domain Criteria (RDoC; Brooks et al., 2017; Insel et al., 2010; Shankman & Gorka, 2015). Recent changes in DSM-5 diagnosis of addictive disorders reflected this transition towards a dimensional and transdiagnostic disorder definition. Accordingly, substance use replaced the previous distinction between substance abuse and dependence, and the new category of substance-related and addictive disorders included GD as the first behavioral addiction. The RDoC emphasizes current limitations of categorical, symptom-based diagnosis and proposes a novel conceptualization of psychopathology incorporating neurocognitive evidence (Shankman & Gorka, 2015). The RDoC defines different domains that reflect common neurocognitive processes and can be assessed in terms of specific 'units of analysis' (Insel et al., 2010), that can contribute to better characterize individual differences within disorder categories and promote effec-

tive and individualized intervention approaches.

6.3 Conclusion: theoretical contribution and practical implications

Overall, in the present thesis we have implemented an integrative approach and applied a wide range of methodologies to investigate the neurocognitive bases of gambling cognitions and biases. The overarching finding is that gambling cognitions and biases are not grounded on general-domain cognitive deficits, but they arise from the learning history of interactions of the individual with gambling games, promoted by gambling games structural features. Still, our results reinforce the idea that gambling cognitions are putative hallmarks of maladaptive gambling behavior, as revealed by their relationships with relevant clinical variables and associations with gambling problems and severity.

If gambling cognitions and biases do not simply arise from pre-existing general-domain biases (Study 3), and they are not clearly grounded on alterations of the control network, as shown by their examination at the neural level (Study 2) and the psychometric level (Study 4), which mechanism sustains these altered cognitive processes? The response seems to come, at least for a subgroup of gamblers, from the interplay with emotion regulation mechanisms.

The studies included in this thesis, and particularly Study 4, highlight that interventions targeting gambling cognitions and biases should consider significant associations with emotion regulation strategies that seem to contribute to their maintenance and exacerbation, especially in self-deceptive gamblers. In this vein, our results provide novel insights into the characterization of distinct GD profiles, defined by unique characteristics and associated with specific pathways to GD vulnerability.

Thus, this work is consistent with contemporary approaches in the analysis of neurocognitive evidence and individual heterogeneity to delineate specific pathways to distinct GD profiles in order to implement individually tailored interventions. This approach is still in its incipient stages, and the integration of different methodological and theoretical frameworks is fundamental to articulate a reliable body of work to incorporate translational research into clinical practice. In this context, our work has been guided by a dimensional perspective, analyzing the alterations in the gamblers' cognitive system and exploring their foundations in relation with different elements of the system, including cognitive control and general-domain cognitive functions. In addition, we revealed significant relationships with components of different systems, as reward-based learning (positive valence system) and regulation of aversive affective states derived from gambling involvement (nega-

tive valence system). This research framework is epitomized by the Research Domain Criteria, that integrates information from different levels to examine individual dimensions common to different pathologies, while assuming interactions between distinct domains (Insel et al., 2010).

In clinical terms, the findings from the current thesis suggest that the first approach for a treatment design plan would be to capitalize on an individualized functional analysis to identify relevant reinforcement sources for the specific subject. Accordingly, the recognition of specific motives considered as more relevant for the subject would be useful to guide process-oriented individual psychological interventions (Perales et al., 2020). Thereby, these different motivational profiles would be associated with unique high-risk situations for relapse (i.e. positive versus negative emotional states), and interventions addressing the development of specific coping abilities to manage these situations would be effective for gambling control.

Moreover, once imbalanced incentive motivational processes have been established through the reinforcement learning history of associations with the reward properties of the addictive agent, and imperative motivational urge responses emerge with exposure to gambling cues, treatment should attempt to address correlates of compulsive behavior (Perales et al., 2020). For instance, intervention approaches as controlled exposure (Park et al., 2015) or craving management abilities (Naqvi et al., 2015), and behavioral approaches as stimulus control and relapse prevention (Rash and Petry, 2014) would be effective at these advance stages of the addictive cycle. Specifically, selection of exposure treatment should be done with caution, due to evidence highlighting the potential relapse risk elicited by these interventions (Giroux et al., 2013; Smith et al., 2015).

According to evidence suggesting the cue-triggered origin of craving (Robinson & Berridge, 2008), prevention strategies should address regulation and control mechanisms applicable to the ubiquitous gambling advertising. In addition, findings also indicate that certain gambling games features artificially promote a motivational shift toward addictive goals, foster gambling bias and increase the addictive potential of such games (Parke et al., 2016). Thus, the implementation of restrictions on structural characteristics of games design, as frequency of near-miss events (Clark et al., 2009; 2012; Côté et al., 2003; Kassinove & Schare, 2001), multiline devices, 'stop' and 'hold' buttons (Harrigan et al., 2014; Parke & Griffiths, 2007), and random ratio reinforcement schedules (Haw, 2008; James et al., 2016) is warranted. Moreover, direct regulations as the implementation of limitations in maximum wagering amounts and restrictions in the use of credit cards instead of real money, both factors that have been shown to increase gambling behavior maintenance and money expenditure, would also be justified.

The findings from the present thesis advocate for an individualized analysis of relevant GD vulnerability factors, and how these factors interact to define specific gambler profiles addressing unique dysfunctional processes and variables. Then, gamblers experiencing problems in emotion regulation processes would presumably be frustrated with exposure interventions, and would not be recommended for these cases due to increased treatment dropout risk. For this combination of symptoms, substance addiction research has shown promising results of interventions based on mindfulness practice (Hoppes, 2006).

Alternatively, in gamblers where elaborated emotion regulation strategies combine with intense cognitive distortions to delineate the self-deceptive cognitive style, strengthen their metacognitive abilities would probably be more helpful (Lindberg, Fernie, & Spada, 2011). With this training, self-deceptive gamblers would realize about the implicit association between their pervasive beliefs and motivations to gamble, and the role they play in gambling behavior maintenance.

Likewise, the integrative and dimensional framework to study GD based on neurocognitive components that guided this work can also help to delineate prevention programs attempting to identify high-risk profiles. In this vein, the study of vulnerability profiles based on neurocognitive evidence has advanced in delimitating common substrates of externalizing problems in different pathologies, including substance use disorders (Castellanos-Ryan et al, 2014). This shared externalizing factor is epitomized by high impulsivity and delay discounting, along with altered brain responses in response inhibition processes. Moreover, in GD, findings from prospective investigations have identified infant undercontrolled temperament and childhood and adolescent impulsive behavior as etiological predictors of adulthood disordered gambling (Shenassa et al., 2012; Slutske et al., 2005; 2012). Therefore, development of mechanisms devoted to detect these high-risk profiles and implementation of educational and prevention strategies specifically centered in correcting such vulnerabilities warrants dedication of more economic resources.

6.4 Limitations

The findings from the present work should also be interpreted with caution in light of several limitations.

The cross-sectional nature of studies precludes drawing sound conclusions about the causal direction of results. Thus, substantial efforts should be made to allocate more resources to enable the implementation of longitudinal, and theoretically-informed experimental studies, with large sample sizes and sufficient statistical

power. That would allow to describe disorder development through different phases, to assess if alterations persist after symptom recovery, and determine if deficits precede disorder onset.

Moreover, in Studies 2 and 3 we included samples from three different gambling rehabilitation centers from Andalusia region, nevertheless, all these centers belong to a common regional federation, and share recruitment methods and treatments approaches. Therefore, patients recruited by these centers may have a specific gambler profile with shared characteristics, which may compromise generalization of results to different disordered gambling populations. In addition, the low proportion of female participants in samples from studies 2 and 3 limits its potential generalization to female gamblers, which have been shown to present some specific characteristics (González-Ortega et al., 2015; McCormack et al., 2014; Nower & Blaszczynski, 2006). Further, community gamblers and healthy controls samples were recruited through personal networks of GD patients and researchers involved in the studies; thus, they may not be completely independent and hold some particularities.

Also, the studies from this thesis belong to a research project that extended through 5 years, and samples were recruited consecutively. Thus, GD patients' samples were related and partially overlapping between studies, which arises the limitation of drawing general conclusions from a limited number of observations. Then, replication of results in independent samples is warranted.

In this realm, it is important to note the idiosyncratic characteristics from rehabilitation centers where samples were recruited. Instead of treatment units from the public healthcare system, they are non-governmental organizations with limited professionals and economic resources, and they apply a specific treatment approach, so recruitment capacity from these institutions is limited. Moreover, we implemented relatively strict inclusion criteria for patients' selection, specifically, to remove potential confounders, as substance addiction comorbidities. Thus, rigorous inclusion criteria also contribute to sample size restrictions.

Furthermore, the studies featured in this thesis do not fully adhere to recommendations from open science practices, which are increasingly considered essential for ensuring results reproducibility. We made a substantial effort to select and adapt methodological approaches to address each individual research question, based on strictly a priori hypothesis, however, we did not preregister study aims, hypothesis, and methodologies, although datasets, when possible, have been made available in public repositories (Study 4). We acknowledge science as a whole would benefit from following these practices, in terms of quality, transparency and

reproducibility, and we are currently working towards this direction for future projects.

6.5 Future studies

The studies presented in this thesis leaves a number of unresolved questions, that warrants further investigation in future studies.

It would be of interest to investigate whether gambling cognitions precede the onset of gambling disorder symptoms. Accordingly, preliminary longitudinal evidence in GD suggests a potential etiological role of gambling cognitions predicting later gambling problems (Leonard & Williams, 2016; Nicholson et al., 2016). The analysis of potential vulnerability factors would require a prospective monitoring of large samples and evaluations at various time points, but would be helpful to identify additional variables that predict GD appearance. It would also help to corroborate results from the scarce longitudinal studies in GD (Shenassa et al., 2012; Slutske et al., 2012). These large-scale prospective studies can also be useful to delineate the developmental course of individual differences in the definition of distinct gambling profiles.

The evidence reviewed in the first study from this thesis suggest a potential role of gambling games structural characteristics in promoting gambling cognitions, through specific reinforcement learning mechanisms and exploiting the effect of uncertainty on reward system (Fiorillo et al., 2003; Preuschoff et al., 2006; Linnet et al., 2012). It would be useful to analyze the unique effects of different gambling games features on the intensity of gambling cognitions and other clinically-relevant variables. Moreover, to implement experimental protocols using MRI techniques would also allow to delimitate the effects of structural features on the neural processing of gambling rewards.

As we already mentioned in the previous sections of this work, the particular characteristics of the GD rehabilitation centers where our samples were recruited, imposed a series of limitations in the use of gambling games or money as a reward. Thus, it would be informative to replicate our findings using simulated gambling scenarios, to validate the predictions from our work in ecological settings.

In the initial review chapter from this thesis, we described the inconsistent findings of reward processing research in GD. Moreover, and in line with the framework that define this work, it would be useful to examine if heterogeneity of results might be related with individual differences associated with different gambling profiles. The analysis of reward processing mechanisms using MRI techniques, during reward anticipation and outcome delivery phases, drawing a distinction between GD profiles with high and low gambling

cognitions would help to disentangle if these hallmarks of GD can explain the inconsistent results arising from previous research.

In view of the interplay of gambling cognitions with deliberate emotion regulation strategies and emotional and motivational dimensions of impulsivity, it would be useful to explore the mechanisms that explain such relationships.

6.6 Discussion section references

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