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Neural Correlates of Cognitive Control in Gambling Disorder: a Systematic Review of fMRI Studies

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Highlights

- Impaired cognitive control over gambling behaviors represents a core feature of Gambling Disorder
- Cognitive control can be conceptualized as the result of different sub-processes (i.e. response inhibition, conflict monitoring, decision-making and cognitive flexibility)
- Impaired activity in prefrontal areas (i.e. DLPFC, ACC, OFC) may account for impaired cognitive control, contributing to GD clinical phenomenology
- Among prefrontal areas, OFC has been hypothesized to modulate affective/motivational aspects of cognitive control
- Pharmacological and brain stimulation treatments may be possible strategies targeting cognitive control in GD

Abstract

Decreased cognitive control over the urge to be involved in gambling activities is a core feature of Gambling Disorder (GD). Cognitive control can be differentiated into several cognitive sub-processes pivotal in GD clinical phenomenology, such as *response inhibition*, *conflict monitoring*, *decision-making*, and *cognitive flexibility*. This article aims to systematically review fMRI studies, which investigated the neural mechanisms underlying diminished cognitive control in GD. We conducted a comprehensive literature search and collected neuropsychological and neuroimaging data investigating cognitive control in GD. We included a total of 14 studies comprising 499 individuals. Our results indicate that impaired activity in prefrontal cortex may account for decreased cognitive control in GD, contributing to the progressive loss of control over gambling urges. Among prefrontal regions, orbital and ventromedial areas seem to be a possible nexus for sensory integration, value-based decision-making and emotional processing, thus contributing to both motivational and affective aspects of cognitive control. Finally, we discussed possible therapeutic approaches aimed at the restoration of cognitive control in GD, including pharmacological and brain stimulation treatments.

Keywords: pathological gambling; prefrontal cortex; response inhibition; value-based decision-making; impulsivity; cognitive flexibility; delay discounting; Iowa Gambling Task; reversal learning; conflict monitoring; orbitofrontal cortex; affective processing; transcranial magnetic stimulation.

1. Introduction: Cognitive Control and Impulsivity in Gambling Disorder

1.1 Cognitive Control Domains

Decreased cognitive control over the urge to be involved in gambling activities is a core feature of Gambling Disorder (GD) (American Psychiatric Association, 2013). Cognitive control does not represent a unitary process, instead it can be conceptualized as the sum of high order cognitive faculties interacting in the achievement of goal-oriented flexible behaviors (Morton et al., 2011) (Koechlin et al., 2003). As such, cognitive control can be differentiated into several cognitive sub-processes, such as *response inhibition*, *conflict monitoring*, *decision-making* and *cognitive flexibility*

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(see **Figure 1**), all of which prove to be pivotal in GD clinical phenomenology (Goudriaan et al., 2014).

Response inhibition, as measured by tasks such as the go/no-go and stop-signal task, indicates the ability to suppress automatic motor response (Aron, 2007). Depending on the circumstances, successful suppression of motor response can involve distinct behavioral processes such as "action restraint" and "action cancellation" (Schachar et al., 2007). Both these processes operate on pre-planned motor actions. On the one hand, "action restraint" describes the inhibition of the motor response before initiation of that response. Action restraint is usually studied with the go/no-go task that focuses on the ability to either respond (by pressing a designated key or lever) or withhold from responding, depending on whether a go stimulus or a no-go stimulus is presented. On the other hand, "action cancellation" refers to the suppression of a motor action during its execution and is studied using the stop-signal task. In this task, each trial starts off as a go-response trial, so no preliminary go or no-go selection is required. In a sub-set of trials, when the "stop" signal occurs, subjects must change their response, suppressing the go response for a preset period of time. The stop signal (which can be either auditory or visual) always implies an inhibitory response, so no decision needs to be made by the subjects. The stop signal task has been specifically conceived to eliminate decision-making from the experimental paradigm (Eagle et al., 2008). In healthy individuals, the activity of a common brain network, including the ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), supplementary motor area (pre-SMA), dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex, is hypothesized to underlie motor inhibition performances in both the stop-signal and go/no-go tasks (Rubia et al., 2001). Furthermore, the pattern of activation of a common brain network has been found to be bilateral for the go/no-go task and predominantly confined to the right hemisphere for the stop-signal task (Aron et al., 2004; Rubia et al., 2001). Deficits in response inhibition seem to be involved in substance use disorders (SUD), the development and perpetuation of GD (Smith et al., 2014) as well as relapse (Adinoff et al., 2007; Goudriaan et al., 2008). Furthermore, impaired response inhibition is significantly associated with increased GD severity (Brevers et al., 2012).

Conflict monitoring, as measured, for example, by the Stroop color-word task (Levin and Tzelgov, 2014), refers to the ability to ignore irrelevant interfering stimuli during information processing (Botvinick et al., 2001). Suppressing response to irrelevant information is critical in achieving goal-oriented behaviors (Nigg, 2000). The Stroop color-word task is a classic cognitive paradigm, which has been frequently adopted in both clinical and research settings. This task requires participants to name the color of the words presented as quickly as possible and not to read the words themselves. The interference of word reading upon color naming (an effect known as Stroop interference), is usually observed if a word is displayed in a color different from the color it actually names. The Stroop effect is frequently estimated in terms of an increased reaction time to color naming when both nouns and displayed colors are incongruent as compared to the condition when they are congruent (Pardo et al., 1990). As the Stroop color-word task involves the suppression of a prepotent response (i.e., word reading) in favor of a less automatic behavior (i.e., color naming), it is considered to be a suitable and valid measure of conflict monitoring (Gruber et al., 2002). A number of cortical areas including DLPFC, ACC, pre-SMA, VLPFC and insula have been found to be activated in healthy individuals during the execution of the Stroop color-word task. ACC may play a further role

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in interference tasks by monitoring behavioral performances and detecting possible errors, by selecting appropriate response and, finally, by conveying decisions to the motor system (Leung et al., 2000). Poor performance on the Stroop task has been associated with significant difficulties in controlling gambling behaviors (Boyer and Dickerson, 2003).

Decision-making is broadly defined as the faculty to favor certain choices by pondering their conceivable punitive or rewarding outcomes. Decision-making also participates in the prefrontal, executive functions that normally facilitate appropriate behaviors or achievement of current goals (Koechlin and Summerfield, 2007; Stuss and Alexander, 2000). The Iowa Gambling Task (IGT) (Bechara et al. 1994) is considered to be an ecologically valid and reliable measure of decision-making, and it has been extensively used in pathologically addicted individuals (Brevers et al., 2013). Optimal performance on this task is attained through making choices that favor long-term gains rather than choices which lead to immediate and more substantial gains but also carry the risk of greater loss. On each trial of the IGT, participants choose a card from one of four card decks. Following each draw, a specified amount of play money is awarded. The goal is to acquire as much money as possible across trials. The four decks differ in their long-term outcomes. Decks A and B consistently deliver high immediate gains, but lead to greater loss over time, making these decks risky or disadvantageous. The other two decks (C and D) are considered safe or advantageous, resulting in smaller immediate gains, but providing greater gains in the long run. Choosing among different options according to their long- and short-term outcomes implies the activity of different prefrontal areas. The orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC), of which the OFC is a part, regulate the affective and motivational aspects of decision-making, while the DLPFC and lateral inferior prefrontal cortex (PFC) are involved in the rational and cognitive evaluation of risk and benefit (Bechara, 2005). Decision-making impairments, as measured by the IGT, have been consistently associated with GD (Wiehler and Peters, 2015). GD subjects, in fact, seem to perform poorly on the IGT, frequently chasing the larger, immediately rewarding gains, which ultimately lead to long-term losses (Brevers et al., 2013).

Cognitive flexibility normally refers to the capacity to flexibly switch from one learned strategy to another when faced with new environmental contingencies. As some authors claim, GD individuals may suffer from a specific, reward-based cognitive inflexibility, preventing them from recognizing variations in stimulus-reward contingencies and, therefore, prohibiting optimal choices (Boog et al., 2014; Cavedini et al., 2002). Within this conceptual framework, reward-based cognitive inflexibility is intimately associated with both the idea of impaired decision-making under conflicting contingencies (Goudriaan et al., 2008) and that of reward sensitivity (Boog et al., 2013). The principles of *reversal learning* are generally used in the evaluation of reward-based cognitive inflexibility (Vanes et al., 2014). Reversal learning normally implies the adjustment of a previously reinforced behavior according to changes in stimulus-reward contingencies. Reversal learning is typically epitomized by visual discrimination tasks, where subjects are asked to respond to a specific stimulus-reward pairing and then reverse their preference once the task contingency is changed (Cools et al., 2002). Task contingency can be either deterministic or probabilistic. In probabilistic reversal learning tasks, the choice of the appropriate stimulus is rewarded in a high, but not total, percentage of trials, and negative feedback can be occasionally given to a correct response. Thus, the difficulty in performing this task is due to its probabilistic nature and, subsequently, the need to continuously

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integrate feedback over a number of trials (Waltz and Gold, 2007). However, several studies indicate that GD individuals may display a broader, non-reward-based cognitive inflexibility, as measured by tasks such as the Wisconsin card-sorting task (WCST), and thus persist in non-optimal strategies during problem-solving challenges (Goudriaan et al., 2006; Odlaug, 2011). In humans, the OFC and other ventral prefrontal areas have been frequently implicated in reversal learning, whereas deficits in lateral prefrontal areas (such as the DLPFC) seem to be more involved in non-reward-based cognitive inflexibility (Klanker et al., 2013). High degrees of cognitive inflexibilities have been positively associated with several parameters of gambling severity, such as gambling frequency, amount of money lost, and gambling urge intensity (Leppink et al., 2016).

1.2 Impulsivity

Impulsivity is generally defined as the tendency to act rapidly, without premeditation or conscious judgment (Moeller et al., 2001). Moreover, it is often considered an expression of diminished cognitive control (Bari and Robbins, 2013), as well as a hallmark of endogenous vulnerability in the development of addictive behaviors (Koob, 2015). From a neurocognitive perspective, impulsivity is often incorporated with the concept of "disinhibition," which is considered as a transient alteration of frontal, top-down control mechanisms. These mechanisms are normally implicated in the suppression of automatic or reward-driven responses during the elaboration of appropriate behavioral patterns (Aron, 2007). Impulsivity is a multidimensional construct (Moeller et al., 2001) frequently differentiated into several sub-domains that refer to distinct cognitive and motivational processes (Bari and Robbins, 2013; van Holst et al., 2010; Winstanley et al., 2006).

Among the various behavioral expressions of impulsivity, the concepts of *action impulsivity* and *choice impulsivity* have recently gained consistency in the field of addictive behaviors (Wang et al., 2016) (see **Figure 2**).While *action impulsivity* is broadly represented by the tendency to "act on the spur of the moment" (Patton et al., 1995), reflecting an impaired ability to withhold motor response (e.g., poor response inhibition), *choice impulsivity* is underscored within the paradigm of delay discounting. Delay discounting refers to the individual propensity to seek small immediate rewards rather than those which are larger but delayed, akin to the inability to delay gratification (Reynolds, 2006). Delay discounting tasks typically involve repeated hypothetical choices, across a range of amounts and delays -between smaller, immediately available amounts of money and others which are more substantial but delayed. As some authors argue, hypothetical rewards could be discounted less than potentially real or real rewards, because they lack motivational properties (Kirby, 1997). However, several studies conducted on healthy individuals found no substantial differences in the degree of discounting between real/potentially real rewards and hypothetical rewards (see Odum, 2011 for a review). A growing body of evidence demonstrates that the activity of a specific neural network, which includes VMPFC, ventral striatum (VS) and posterior cingulate cortex, may integrate reward magnitude and delay into a single neural code of subjective value, as opposed to coding them separately (Hare et al., 2009; Peters and Büchel, 2009; Kable and Glincher, 2007). Adverse changes in delay discounting have been associated with a variety of psychiatric disorders including SUD and GD (Petry, 2001; Volkow and Baler, 2015). Moreover, the steepness of reward discounting has also

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been consistently correlated with self-report measures of impulsivity in GD individuals (Wiehler and Peters, 2015).

Over the past few years, several reviews have clearly indicated a lack of cognitive control and high rates of impulsivity in GD through self-report questionnaires and neurocognitive tasks (Conversano et al., 2012; Di Nicola et al., 2014; Goudriaan et al., 2014; van Holst et al., 2010). Conversely, there are only a limited number of neuroimaging studies which investigate the neural mechanisms underlying diminished cognitive control and impulsivity in GD. Therefore, this article aims to systematically review functional magnetic resonance imaging (fMRI) studies that target cognitive control and impulsivity in GD. Possible therapeutic approaches aimed at the restoration of cognitive control will be discussed in the last part of the paper.

2. Methods

A literature search of the databases PubMed/MEDLINE, ISI Web of Science, Psychology and Behavioural Sciences Collection and CINAHL was conducted in order to find appropriate published articles on functional neuroimaging studies in pathological gambling. A search algorithm was employed based on a combination of the terms "functional neuroimaging," "neuroimaging," "magnetic resonance imaging," "functional MRI" and "gambling." The search included all publications prior to and including July 2016; no earliest date limit was applied. To expand the search, reference lists of the retrieved articles were also screened for additional studies.

All functional neuroimaging studies, or subsets of studies, involving adult patients with pathological gambling (PG) or problem gambling (PrG) were eligible for inclusion. Throughout this article we refer to individuals as PG if the diagnosis was made by DSM-IV or ICD-10 assessment, while we refer to individuals as PrG if gambling problems were assessed using questionnaires or if not all participants in the samples fulfilled DSM or ICD PG criteria. We excluded: (i) review articles, editorials, letters, comments and conference proceedings; (ii) case reports; (iii) studies dated before 1990 if the diagnosis system did not use operationalized criteria, but rather only disease names with no diagnostic criteria (i.e., ICD-9); (iv) studies not utilizing fMRI; (v) fMRI studies without any neurocognitive or behavioral task or those with tasks not specifically targeting cognitive control and impulsivity and (vi) studies without a control group.

Two researchers independently reviewed the titles and abstracts of the articles retrieved, applying the above-mentioned inclusion and exclusion criteria. The researchers then independently reviewed the full-text version of the articles to confirm their eligibility for inclusion, or subsequent exclusion.

For each study selected for inclusion, details regarding the publication were gathered (i.e., author names, year of publication, country of origin); data was collected on the patients and comparison characteristics (i.e., number of PG patients and controls, mean age, gender, SOGS, BDI) as well as on how the PG diagnosis was performed, the neuroimaging method and cognitive task used. All of this information was extracted by one author and subsequently verified, independently, by the other.

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Tissue-air interfaces can result in spurious magnetic field gradients in the periorbital region, with a consequent loss of MR signal and image distortion. This problem, which may affect fMRI studies focusing on the OFC, is more pronounced at high magnetic fields, and for fast Gradient-Echo based sequences, like EPI (Echo-Planar-Imaging), typically used in functional MRI studies. Signal loss depends on acquisition parameters, like the Echo-time, and on slice orientation. Several strategies have been proposed to mitigate this problem (Deichmann et al., 2003; Weiskopf et al., 2007; Domsch et al., 2013). These include judicious orientation of the imaging slice (Deichmann et al., 2003), compensatory gradient pulses (Deichmann et al., 2003), optimization of resolution and echo-time (Weiskopf et al., 2007), slice-dependent echo-times (Domsch et al., 2013). In **Table 1** we indicate the fMRI methods used in the studies hereby reviewed, with specific reference to the strategies used to optimize image quality in the orbitofrontal region, when explicitly described in the articles.

Although OFC and VMPFC functional specialization has been extensively investigated and defined (Wallis, 2011), there is still debate over their anatomical separation. It has been recently proposed that these areas are part of the same functional network, namely Orbitomedial Cortex (Öngür and Price, 2000). In our work we decided to merge results on both areas, referring to the label of OFC/VMPFC.

3. Results

The literature search generated 587 studies. Applying the criteria mentioned above, 548 studies were excluded based on titles and abstracts. 39 full-text articles were retrieved. Of these, two articles were excluded, being duplicate studies (Miedl et al., 2014b; Peters et al., 2013); seven articles were excluded because the studies utilized either structural MRI or diffusion tensor imaging (DTI) or resting-state fMRI (Chamberlain et al., 2016; Grant et al., 2015; Jung et al., 2014; Koehler et al., 2015, 2013; Rahman et al., 2014; Zois et al., 2016); two articles were excluded because the studies were conducted without a control group (Dannon et al., 2011; Miedl et al., 2014a); fourteen articles were excluded because the studies did not employ tasks specifically targeting cognitive control or impulsivity (Balodis et al., 2012a, 2012b; Choi et al., 2012; Crockford et al., 2005; Dixon et al., 2014; Fauth-Bühler et al., 2014; Potenza et al., 2003b; Reuter et al., 2005; Romanczuk-Seiferth et al., 2015; Sescousse et al., 2013, 2016; van Holst et al., 2014; Worhunsky et al., 2014; Yang et al., 2016). Finally, 14 studies comprising 499 individuals were included in the qualitative analysis (see **Figure 3** and **Table 1**).

Depending on which neurocognitive task was employed, the reviewed fMRI studies will be divided into five different sections: *response inhibition, conflict monitoring, decision-making, cognitive flexibility, delay discounting and choice impulsivity*. The last part of the paper will discuss possible therapeutic approaches aimed at the restoration of cognitive control in PG.

3.1 Response Inhibition

Two fMRI studies evaluated response inhibition in GD (de Ruiter et al., 2012; van Holst et al., 2012a, 2012b). de Ruiter et al., (2012) investigated the neural circuits underlying impaired response inhibition in 17 subjects with PrG, 18 heavy smokers (HSM) and 17 healthy controls (HC) performing

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a stop-signal task. In both the PrG and HSM group, though no behavioral differences were found compared to HC, a hyporesponsiveness in dorsomedial prefrontal cortex (DMPFC) was reported during both successful and failed response inhibition trials versus control trials. Specifically, PrG individuals compared to HC, showed hypoactivation of the dorsal ACC during failed inhibition, while a significantly lower activation in a region of right DMPFC bordering on ACC was described in PrG group compared to HC during successful inhibition. The extent of DMPFC hyporesponsiveness during successful inhibition was also found to be associated with the severity of PrG.

To assess the influence of affective stimuli in GD, van Holst et al. (2012a) evaluated 16 PrG and 15 HC individuals, all male, while performing a modified affective go/no-go fMRI paradigm containing gambling-related, neutral, positive or negative affective pictures. During go trials, four affective blocks of pictures containing gambling-related, neutral, positive or negative images were presented (i.e., neutral, positive, negative and gamble go trials). The no-go trials in these blocks included only neutral pictures. Identified behavioral outcomes were given by the percentage of impulsive errors committed during no-go trials along with mean reaction times within the different blocks. Compared to HC, mean reaction times were significantly slower in PrG during the blocks of positive and negative pictures. PrG performances were similar in accuracy to HC during the positive, negative and neutral blocks. However, PrG committed significantly less impulsive errors, compared to HC, while watching gambling-related pictures. Response inhibition (i.e., neutral inhibition) was firstly investigated by contrasting blood-oxygenation-level-dependent (BOLD) response during neutral go trials vs. BOLD response during no-go trials which occurred within the block of neutral pictures (i.e., neutral no-go trials), and greater activation of bilateral DLPFC and right ACC was observed in PrG compared to HC. The effect of affective stimuli on response inhibition was investigated by separately comparing BOLD activity during no-go trials which occurred within the positive, negative and gamble affective blocks of pictures (i.e., positive, negative and gamble no-go trials) with BOLD activity during neutral no-go trials. For the contrast gamble no-go versus neutral no-go, a decreased activation of bilateral DLPFC and right ACC was observed in PrG compared to HC. During positive versus neutral no-go trial, PrG showed a significantly decreased activity of bilateral DLPFC and left VS when compared to HC. Lastly, a decreased activity of right DLPFC and left ACC was observed in PrG, as opposed to HC, when comparing negative and neutral no-go trials.

In a further study, van Holst et al. (2012b) re-analyzed these fMRI data, assessing the influence of affective stimuli over changes in functional connectivity associated with response inhibition. During neutral inhibition, PrG displayed a lower functional connectivity, compared to HC, between the left caudate and occipital cortex. While looking at gambling-related pictures (gamble no-go vs neutral no-go), PrG demonstrated a stronger positive correlation, compared to HC, between response inhibition accuracy and functional connectivity between the left caudate and bilateral medial frontal cortex. During positive inhibition sessions (positive no-go vs neutral no-go), PrG showed a greater functional connectivity, compared to HC, between the left caudate and the occipital cortex. During negative inhibition trials (negative no-go vs neutral no-go trials), PrG displayed an increased functional connectivity, compared to HC, between the left caudate and the right anterior cingulated cortex.

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3.2 Conflict Monitoring

A single fMRI study conducted by Potenza et al. on 13 PG male individuals and 11 HC performing a Stroop color-word task, evaluated conflict monitoring in PG. PG and HC performed similarly on the Stroop color-word task in terms of incorrect response percentage and mean reaction times to incongruent stimuli. PG and HC showed an overlapping pattern of activity in several brain areas including cingulate cortex, VLPFC, insula and thalamus while performing the Stroop color-word task. However, following the presentation of incongruent stimuli, a decreased BOLD responsivity was observed in left middle and superior frontal gyri bordering the superior frontal sulcus laterally and the OFC ventrally among PG subjects compared to HC (Potenza et al., 2003a).

3.3 Decision-Making

Six different fMRI studies evaluated decision-making in PG. Three of these studies used an IGT paradigm (Brevers et al., 2016; Power et al., 2012; Tanabe et al., 2007); the remaining studies assessed decision-making within a quasi-realistic blackjack scenario (Miedl et al., 2010), a card-deck paradigm (Brevers et al., 2015) and a probabilistic gambling task (Gelskov et al., 2016).

Tanabe et al. (2007) evaluated neural correlates of 16 HC, 20 SUD individuals and 20 SUD subjects with comorbid PrG (SUD-PrG) performing a modified version of the IGT in which cards were selected by a computer, allowing subjects only to accept or pass them. Moreover, unlike the original IGT, subjects could only receive a single monetary "gain" or "loss" during trials in which cards were accepted, rather than obtaining constant rewards and occasional punishment. No statistically significant behavioral differences were observed among groups on IGT performances. Relative to controls, SUD and SUD-PrG groups showed blunted activity in OFC/VMPFC and infragenual ACC when a card was accepted, as compared to when a card was passed. Furthermore, an increased activity in these same regions was described in SUD-PrG group, compared to HC group, when deciding to play risky as opposed to safe decks. However, no differences in brain activity were observed, among the three groups, when trials of gains were compared with those of losses and vice versa.

Power et al. (2012) used fMRI to assess the brain activity of 13 PG subjects and 13 matched HC performing a computerized version of the IGT. As expected, PG individuals performed worse on the IGT than HC, favoring high-risk choices, especially after they had experienced gains or losses. During high-risk deck selections, as opposed to safe deck selections, PG individuals compared to HC, displayed an increased activation in the right caudate, OFC/VMPFC, superior frontal gyrus, amygdala and hippocampus.

In Brevers et al. (2016), 15 PrG and 15 HC subjects underwent an fMRI scan while performing the IGT. Based on the South Oaks Gambling Screen (SOGS) scores, PrG individuals were divided into non-problem gambling (n = 4), low-problem gambling (n = 6) and high-problem gambling (n = 5). No significant behavioral differences were found between the groups. Compared to HC, PrG showed increased activity in the right VS as well as decreased activity in the right OFC/VMPFC and DLPFC during deck selection, as opposed to baseline. Moreover, a significant positive correlation between SOGS scores and VS activity was observed in the PrG group. During deck selection, as opposed to

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baseline, functional connectivity analyses revealed, in PrG, relative to HC, an increased VS connectivity in regions including occipital fusiform gyrus, posterior cingulate cortex, superior and middle temporal gyrus. Connectivity, between the VS seed and the occipital fusiform and the middle temporal gyrus, was also positively correlated with SOGS scores.

Miedl et al. (2010) assessed, using fMRI, neural correlates of 12 PrG and 12 HC male individuals within a quasi-realistic blackjack scenario where participants had to choose whether or not to draw a card in high-risk and low-risk gaming situations. No behavioral differences were found between the groups. In fact, both PrG and HC showed a significantly lower percentage of high-risk compared with low-risk-hit trials. During low-risk gaming situations, as compared with high-risk trials, PrG showed, relative to HC, a significantly increased activation pattern in regions including right superior temporal gyrus, right VLPFC and right thalamus. Furthermore, when contrasting brain activation patterns during gains versus losses, an increased BOLD signal was detected, in PrG as opposed to HC, within areas including right superior frontal, left inferior parietal and left superior parietal cortices.

Gelskov et al. (2016) evaluated brain activity of 14 PG and 15 HC individuals while performing a gambling task in which they were asked to accept or pass mixed gain-loss bet proposition with a fifty-fifty probability of winning or losing. Despite similar behavioral performances, a U-shaped pattern of neural activity towards bets with the most appealing or aversive gain-loss ratios was observed in regions including caudate and DLFPC among PG subjects, as compared to HC. Furthermore, a positive correlation between gambling severity, as measured by the SOGS scores, and activity in the precuneus, was observed during the individual assessment of these ratios.

Using an adapted version of the card-deck paradigm, Brevers et al. (2015) evaluated the neural activity of 10 PG and 10 matched HC subjects who were asked to choose between sure payoffs and bet options which offered larger but uncertain rewards. Bet propositions could be selected in either risky situations, where the probability of reward was known by participants (i.e., decision-making under risk) or ambiguous situations, where the participants were unaware of the probability of reward (i.e., decision-making under ambiguity). Compared to HC, PG individuals took more bet options, but did not bet differently in risky or ambiguous situations; furthermore, in these situations, PG showed no differential brain activation. Between-group analysis revealed in PG, but not in HC, a decreased activity within the right globus pallidus during decision-making under risk, as opposed to decision-making under ambiguity. Conversely, as compared to HC, PG individuals showed increased activation in the right putamen before choosing to bet as opposed to the sure payoff.

3.4 Cognitive Flexibility

Two fMRI studies evaluated cognitive flexibility in PG (de Ruiter et al., 2009; Verdejo-Garcia et al., 2015). Verdejo-Garcia et al. (2015) adopted a probabilistic reversal learning task to assess cognitive flexibility in a sample of 18 PG individuals, 18 cocaine users and 18 HC. Compared to PG and HC, cocaine users committed more perseverative errors (e.g., errors resulting from the continued response to a previously reinforced stimulus, in spite of the task rules having changed). Compared to HC, PG individuals and cocaine users displayed a significantly decreased activation in the right VLPFC during reversal shifting, as opposed to perseveration, although no significant correlation with

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behavioral measures was found. Relative to PG individuals, cocaine users further showed increased dorsomedial PFC activation during perseveration.

de Ruiter et al. (2009) assessed response perseveration and reward/punishment sensitivity of 19 PrG individuals, 19 nicotine dependent (ND) subjects and 19 HC performing a probabilistic reversal-learning task where participants could either win or lose money by choosing between two simultaneously presented stimuli. A planning task (the Tower of London) was further administered to measure executive functions. Between-group analysis showed significant differences with respect to the total amount of money won, with PrG individuals earning less money compared to ND and HC. fMRI results of both monetary gain and loss events were separately contrasted with the baseline condition when between-group analyses were performed. Compared to HC, monetary loss was associated with a significantly decreased activation of right stick with VLPFC in PrG and ND, while monetary gain was associated with significant decreased activation of the same area in PrG only. Monetary loss followed by behavioral shifting, as opposed to monetary loss resulting in no behavioral shift, was associated in PrG, compared to HC, with a significantly decreased activation in the left cerebellum. No behavioral differences were observed among groups during the planning task performance. However, PrG individuals, as compared to HC, showed less posterior parietal activation during successful performance of increasingly difficult task planning, as computed with a parametric contrast for increasing task difficulty which did not take into account the baseline trials.

3.5 Delay Discounting and Choice Impulsivity

Three fMRI studies evaluated choice impulsivity and delay discounting in GD (Hinvest et al., 2011; Miedl et al., 2015, 2012).

Applying a computational model, Miedl et al. (2012) correlated subjective reward value to brain activity during delayed and probabilistic discounting in a sample of 16 PG and 16 HC individuals. As expected, PG displayed higher discounting rates of delayed rewards compared to HC. Conversely, a trend towards lower discounted rates of probabilistic reward was observed in PG. Compared to HC, a significantly increased correlation between OFC/VMPFC, ACC, VS activity and subjective value representation was found in the PG group for delayed rewards, while the opposite pattern (with a significantly diminished correlation between OFC/VMPFC, VS, ACC activity and subjective values) was observed in PG individuals, relative to HC, for risky rewards during the probabilistic discounting task. Furthermore, the degree of the correlation between subjective value representation and OFC/VMPFC, VS activity during delay discounting was also found to be negatively associated with gambling severity.

Miedl et al. (2015) investigated event-related fMRI activity of 15 PG and 15 HC subjects who were asked to choose either a smaller, but immediately available monetary reward (SIR) or a larger, delayed reward (LDR). As expected, PG showed higher discounting degrees compared to HC. A widespread activation, including the bilateral inferior parietal lobule extending to the postcentral gyrus, thalamus, superior/medial frontal gyrus and cingulate gyrus, was observed in PG during the comparison of LDR and SIR, whereas HC only displayed focal activity in the left sensorimotor cortex. In the PG group, indifferent decisions (i.e., choices where the individual value of the immediately

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available and delayed reward yields were almost the same), compared to sure decisions (i.e., choices characterized by a clear preference for either the immediate or delayed reward), were associated with increased activity in the bilateral fronto-parietal cortex, insula, anterior cingulate gyrus, and striatum, whereas HC only showed activity in bilateral frontal cortex and insula. Conversely, sure decisions relative to indifferent decisions, were associated with striatal, ACC, insula, and medial frontal activity exclusively in HC, while PG showed inferior parietal and superior temporal activity.

Hinvest et al. (2011) used fMRI to investigate the neural correlates of self-rated impulsivity and venturesomeness in a sample of 15 PrG individuals, 10 recreational drug users and 9 HC during tasks involving delayed and risky choice. Half of the trials of the task consisted in forced choices between two identical alternatives with the same hypothetical amount of money and delay. Conversely, the remaining trials allowed participants to choose between two different options which differed from each other in reward magnitude and delay. Gamblers and recreational drug users scored significantly higher on impulsivity than HC. When selecting between delayed rewards, as opposed to forced choices, activity within the pregenual ACC and VLPFC correlated positively with impulsivity scores across the three groups.

4. Discussion

Although definitive conclusions cannot be drawn, taken together, the results indicate that impaired activity in prefrontal areas, including DLPFC, ACC and OFC/VMPFC (see **Table 2**), may account for impaired cognitive control, contributing to some aspects of PG and PrG clinical phenomenology, such as those related to the progressive loss of control over gambling behaviors. On the one hand, an imbalanced activity in ventromedial prefrontal areas, including the medial part of OFC as well as the more ventral sectors of the medial prefrontal cortex and ACC, has been observed in most of the fMRI studies which have assessed decision making (Brevers et al., 2016; Brevers et al., 2015; Power et al., 2012; Tanabe et al., 2007) and choice impulsivity (Miedl et al., 2015, 2012). On the other hand, an abnormal pattern of activity within dorsal and ventrolateral prefrontal regions including DLPFC, DMPFC, dorsal ACC and VLPFC has been described in those studies which have adopted response inhibition (de Ruiter et al., 2012; van Holst et al., 2012a, 2012b;) and reversal learning tasks, respectively (de Ruiter et al., 2009; Verdejo-Garcia et al., 2015). PFC is widely recognized to play a crucial role in cognitive control coordinating individual's perceptions, internal states and motivation in context-appropriate behaviors (Miller, 2000). Lesions of PFC may, in fact, weaken cognitive control resulting in impaired decision-making and response inhibition, cognitive inflexibility and higher degrees of impulsivity (Ridderinkhof et al., 2004).

However, the way in which cognitive control may interact with affective and motivational processes in GD is still matter of investigation (Goschke and Bolte, 2014; Potenza, 2014). Among prefrontal areas, VMPFC is part of a wider network including regions of the ventral PFC, hypothalamus, amygdala, insula and dopaminergic midbrain, as well as areas in the basal ganglia, such as the ventral and dorsal striatum (Schoenbaum et al., 2006). Along with other mesocorticolimbic areas, VMPFC plays a key role in salience attribution, enhancing dopamine transmission in mesolimbic networks

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when gambling-related cues are present (Rømer Thomsen et al., 2014). Dopaminergic firing modulates prefrontal cortex activity by enhancing corticostriatal-thalamic connectivity and thus facilitating the continuation of goal-oriented behaviors (Leyton and Vezina, 2014; Rigoli et al., 2016; Robbins and Arnsten, 2009). There is some evidence showing how gambling-related cues can improve cognitive control in PG individuals by enhancing cortico-striatal connectivity (van Holst et al., 2012a, 2012b). However, greater striatal dopamine release has been associated both with higher clinical severity scores in PG individuals performing gambling tasks (Joutsa et al., 2012) as well as with poorer performance scores on the IGT (Linnet et al., 2011, 2010).

Thanks to its reciprocal connections with other cortical and subcortical structures, VMPFC has been recently indicated as a possible nexus for sensory integration, cognitive control and emotional processing (Kringelbach, 2005). Moreover, VMPFC, in particular in its medial OFC component, has been proposed to be involved both in the affective representation of reinforcers as well as the subjective hedonic experience of rewards, thus contributing to some motivational and affective aspects of cognitive control (Bechara et al., 2000; Bryden and Roesch, 2015). A few seminal preclinical studies published over the last few years have pointed to the OFC/VMPFC as a pivotal region in decision-making under risk. The first example of direct evidence indicating that neurons in the OFC encode economic value in non-human primates was presented in Padoa-Schioppa and Assad (2006), where electrophysiological recordings demonstrated the existence of populations of neurons in the OFC whose activity was related to economic choices. Importantly, subsequent studies have shown that these populations of neurons reflect subjective risk attitude, and encode the risk associated with specific options (Raghuraman and Padoa-Schioppa, 2014).These studies provide a neurobiological basis for the role of the OFC/VMPFC in risk encoding and processing, and corroborate many observations in humans that point to this region as critically important in risk-taking and impulsive behaviors within different populations, including adolescents (Galvan et al., 2006) drug addicts (Goldstein and Volkow, 2011), high-compulsivity (Evans et al., 2004) and mood disorder subjects (Schmaal et al., 2016)

Factors such as mood, stress and negative affective states might therefore modulate cognitive control in PG, or at least influence the motivational drive to engage in gambling behaviors (Di Nicola et al., 2010). Mood-related impulsivity, for example, has been found to be particularly relevant in PG individuals (Michalczuk et al., 2011), whose impulsive acts and decreased cognitive control have been hypothesized to arise through an interaction with current emotional states (Billieux et al., 2010). As suggested by some authors, the urge to engage in gambling behaviors may arise from the inability to regulate emotional states (Ricketts & Macaskill, 2009). Deficits in emotional regulation may contribute to the use of maladaptive coping strategies in GD, resulting in failures of self-regulation and impulse control (Williams et al., 2012).

Within this conceptual framework, gambling urge intensity, as subjectively reported by PG individuals exposed to gambling-related stimuli, has been found to correlate with increased activity in temporal areas, which are involved in the retrieval and processing of personal, relevant emotional memories, and with decreased activity in medial PFC, a brain region associated with cognitive top-down emotional processing (Balodis et al., 2012b). As some authors point out, consistent with a negative reinforcement model of addiction, craving may be thought of as the individual's memory of

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addictive rewarding experiences superimposed on a negative affective state (Koob and Le Moal, 2008).

In conclusion, given the scarce number of neuroimaging studies and their methodological heterogeneity, no definitive conclusion can be drawn on which is the underlying neural mechanism of cognitive control in PG. Most of the studies have, in fact, adopted neurocognitive tasks which evaluate more than one neurocognitive domain, while still only a few have evaluated cognitive control in ecologically valid contexts (e.g., within gambling scenarios or during trials involving gambling-related cues). Future studies could benefit from pharmacological challenges combined with neuroimaging techniques in order to elucidate some neurobiological aspects of cognitive control in PG individuals along with the possibility to restore prefrontal functioning in these subjects. Lastly, a more detailed comprehension of how motivational/affective processes interact with cognitive control could surely provide interesting insights into the study of GD pathophysiology and treatment.

5. Potential Therapeutic Approaches Targeting Cognitive Control in GD

5.1 Pharmacological Interventions

Impaired OFC/VMPFC functioning, as revealed by neuroimaging studies, is not an exclusive feature of GD, but rather it has been linked to the vast majority of psychiatric conditions (Russo and Nestler, 2013). VMPFC and OFC potentially play a key role in salience attribution and value-based decision making. The latter may be defined as the choice-selection process, which is based on a subjective assessment of affective value, possible consequences and the risk-benefit ratio of all possible choices (Rangel et al., 2008). Value-based decision-making guides one's behavior, at every moment, toward the most advantageous choice for the individual. Through its downstream connections to the nucleus accumbens (NAcc), amygdala and hippocampus, VMPFC provides cortical control over behavioral outcomes (Schoenbaum et al., 1998; Volkow and Baler, 2015; Wallis, 2011). When the strength of these connections is dampened, the activity of subcortical areas may become relatively free from VMPFC control, leading to maladaptive, automatic reward-driven behaviors. As a result, decision-making is impaired and control over impulsive behavior is weakened.
The restoration of proper VMPFC functioning, which in turn may lead to an improved cognitive control over gambling behaviors, can therefore represent a desirable outcome of pharmacological treatments. Some of the medications currently used in GD treatment exert their clinical efficacy partly through the modulation of prefrontal circuits activity.

Antidepressants, particularly those primarily affecting the serotonergic system, are currently widely used in the treatment of GD (Grant et al., 2016; Lupi et al., 2014). It has been demonstrated that serotonergic transmission strongly supports cognitive control through the activation of different classes of 5HT receptors on OFC pyramidal cells and interneurons (Robbins and Arnsten, 2009). Serotonergic transmission allows cortical inhibitory control over emotional responses following exposure to aversive cues (Jasinska et al., 2012). Serotonin depletion in OFC has been also associated with reward-based cognitive inflexibility in non-human primate models (Clarke et al., 2007, 2004). Among antidepressant medications, those belonging to the SSRI (Selective Serotonin Re-uptake

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Inhibitors) class have been hypothesized to positively modulate cognitive control networks during response inhibition trials (Drueke et al., 2013; Macoveanu et al., 2013), although current evidence is still not definitive and remains difficult to interpret.

Although alterations within dopamine activity have long been implicated in addictive behaviors (Potenza, 2013), the precise role of dopaminergic system in GD pathophysiology remains still unclear. A balanced dopaminergic transmission within PFC has been proposed to be pivotal in sustaining cognitive control (Fattore and Diana, 2016). However, both compounds which block D2-like receptors function (Fong et al., 2008; McElroy et al., 2008) and those showing pro-dopaminergic activity (Smith et al., 2011; Zack and Poulos, 2004) have failed to improve GD symptomatology.

Possible current pharmacological approaches in the treatment of GD can consist of an indirect modulation of dopamine activity through the use of opiate receptor antagonists, such as naltrexone and nalmefene (Piquet-Pessôa and Fontenelle, 2016). These drugs demonstrate the ability to reduce dopamine release within the mesolimbic system through the disinhibition of GABAergic interneurons that negatively modulate dopaminergic neurons in the ventral tegmental area (Grant and Kim, 2006). Moreover, κ-opioid receptors antagonism may also show beneficial effects on both affective and cognitive domains in GD, improving mood-related impulsivity as well as negative affective states (Fattore and Diana, 2016).

Some studies suggest that antiepileptic drugs, particularly those used as mood stabilizers, may directly modulate prefrontal circuit function, which could, in turn, alleviate GD symptoms (Bullock and Potenza, 2012; Di Nicola et al., 2014; Pettorruso et al., 2014a). This prospective is further supported by the fact that these drugs (though administered in an off-label regimen) have proven to be highly effective in SUD treatment (Pettinati et al., 2013). Among mood stabilizers, lithium has demonstrated to reduce both impulsive choice and impulsive action in animal models (Halcomb et al., 2013; Ohmura et al., 2012). By increasing glucose metabolism rate within OFC, DLPFC, ACC and VS, lithium has further been hypothesized to improve gambling behaviors and affective instability in GD subjects (Hollander et al., 2008; Pallanti et al., 2010). According to available data, mood stabilizers may be thus effective medications with regards to the modulation of executive functions (van Amelsvoort and Hernaus, 2016). This activity may be attributed to their capacity to affect circuit dynamics, mainly through the inhibition of voltage-dependent sodium currents and increase in GABAergic transmission. Regardless, it is essential to bear in mind that their effect does not simply *turns on* or *off* circuit function and supporting GABAergic transmission does not necessarily imply an inhibition of excitatory discharges. For example, GABAergic interneurons play a pivotal role in synchronizing cortical pyramidal cell oscillations, which support cognitive control (Bartos et al., 2007).

5.2 Brain Stimulation Therapies

Brain stimulation methods have been proposed as a possible therapeutic intervention to target cognitive dysfunctions in addictive disorders, as well as in GD. The majority of studies in the field of pathological addiction have investigated the use of repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive tool that stimulates nerve cells in superficial areas of the brain. rTMS induces a magnetic field that is able to produce a substantial electrical field in the brain, causing the

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depolarization of nerve cells. This, in turn, results in the stimulation or disruption of local brain activity.

In view of GD being a type of risk-taking behavior, direct current stimulation and rTMS, which have been shown to affect decision-making processes, have been proposed as possible therapeutic options. Both methods have been used in left and right DLPFC with positive preliminary results in the improvement of inhibitory control and risk taking behaviors (Fecteau et al., 2007; Knoch et al., 2006). Considering that PFC is activated by gambling-related stimuli in cue exposure paradigms (van Holst et al., 2010), a preliminary study has been conducted applying low frequency deep-TMS to the left PFC in five PG patients (Rosenberg et al., 2013). In this study, no difference in gambling behaviors was observed, thus demonstrating the inefficacy of the inhibition of left PFC in the treatment of PG. Several studies using TMS have suggested a significant reduction in drug-craving associated with left DLPFC stimulation (Gorelick et al., 2014), while a meta-analysis found no difference in the reduction of craving among studies targeting the left or right hemispheres (Jansen et al., 2013). Recently, a randomized sham-controlled study (Gay et al., 2016) reported a moderate decrease in cue-induced craving following a single session of high frequency rTMS applied over the left DLPFC in a GD sample, though no significant difference in gambling behavior was observed at one week follow-up. These results are consistent with a substantial inter-individual variability in the neuroanatomy of PFC. Future studies using fMRI in the individual targeting of brain regions could improve efficacy of rTMS for the treatment of GD.

The precise mechanisms involved in the therapeutic use of rTMS in the treatment of addiction are not well established. It has been postulated that rTMS modulates dopaminergic and glutamatergic transmission, both involved in the pathophysiology of GD (Pettorruso et al., 2014b). High frequency rTMS studies in rats have proven effective in reducing addiction-related behaviors, correlating with changes in glutamate receptor distribution (Levy et al., 2007). In addition, the use of high frequency rTMS on the left DLPFC has been proposed as a possible intervention to reduce cigarette craving and nicotine dependence (Lefaucheur et al., 2014). Future studies exploring the therapeutic use of high frequency rTMS will shed further light on its potential benefits in the treatment of GD.

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Figure 1. Different sub-processes contributing to cognitive control

Response Inhibition ⟶ *The ability to suppress automatic actions. The* ***go/no-go*** *task and the* ***stop signal*** *task both evaluate response inhibition.*

Conflict Monitoring ⟶ *The ability to ignore irrelevant, interfering stimuli during information processing. The* ***Stroop color-word*** *task evaluates conflict monitoring responses.*

Cognitive Flexibility ⟶ *The capacity to switch flexibly from one learned strategy to another in front of new environmental contingencies. Cognitive flexibility can be divided into:*

- ***Reward-Based Cognitive Flexibility****, as measured by tasks based on* ***reversal learning*** *paradigms.*
- ***Non-Reward-Based Cognitive Flexibility****, as measured by tasks such as the* ***Wisconsin card sorting task****, testing cognitive flexibility during problem solving challenges.*

Decision-Making ⟶ *Broadly defined as the faculty to favor certain decisions by pondering their conceivable punitive or rewarding consequences. The* ***Iowa Gambling Task*** *(IGT) has been widely adopted to assess decision-making in addicted individuals.*

Figure 2. Different expressions of impulsivity

Action Impulsivity *(i.e.,* ***Motor Impulsivity****)* ⟹ *The inability to suppress inappropriate motor responses to prepotent stimuli. High degrees of action impulsivity reflect poor response inhibition.*

Choice Impulsivity ⟹ *The propensity to seek small immediate rewards rather than those which are larger and delayed, akin to the inability to delay gratification. Choice impulsivity is underscored within the paradigm of* ***delay discounting.***

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Figure 3. Prisma flow chart

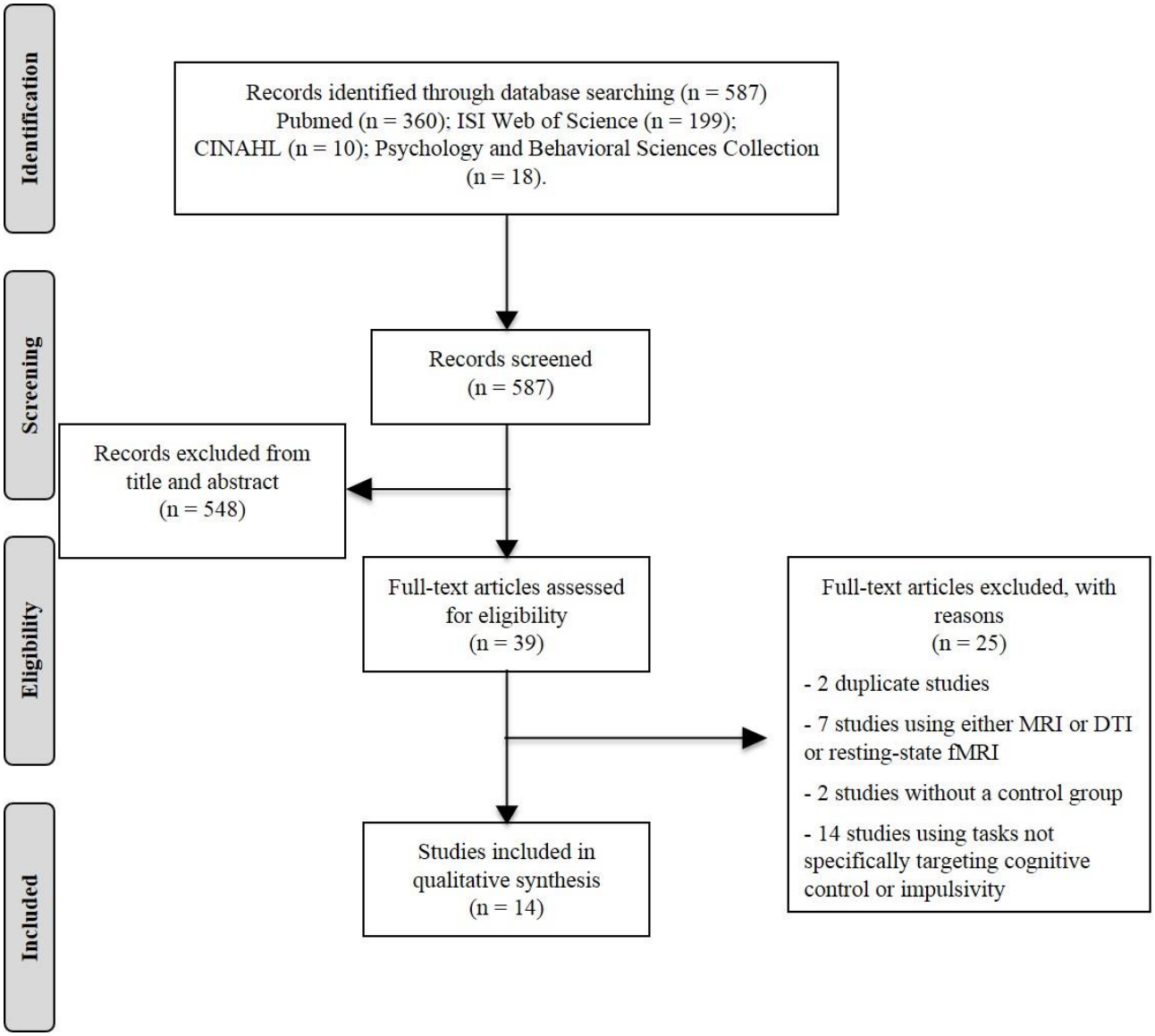

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Table 1. Included studies

Study	Country	Population	Gender *male%*	Age	SOGS	Depression BDI	Diagnosis	fMRI methods	OFC optimization	Cognitive task
Brevers et al., 2015	Belgium	10 PG 10 HC	80%	36.2 (12.95) 34 (8.53)	8.53 (3.48) 0.0	5.5 (4.62) 3.8 (3.76)	DSM IV TR	1.5 T, single shot EPI, TR/TE: 3000/41ms, 33 interleaved slices	NA	Card-Deck paradigm
Brevers et al., 2016	USA	15 PrG 15 HC	40%	24.67 (5.32) 22.07 (1.67)	3.6 (3.48) 0.0	NA	SOGS	3 T, z-shim gradient echo EPI with Prospective Acquisition Correction, TR/TE 2000/25ms	31 slices tilted 30° clockwise along the AC-PC plane	Iowa gambling task
de Ruiter et al., 2009	Netherlands	19 PrG 19 smokers 19 HC	100%	34.3 (9.4) 34.8 (9.8) 34.1 (9.3)	NR	12.1 (12.1) 4.5 (4.0) 3.7 (4.1)	DIS-T SOGS	3 T, EPI TR/TE 2500/30ms, 35 slices	NA	Probabilistic reversal-learning task
de Ruiter et al. 2012	Netherlands	17 PrG 18 smokers 17 HC	100%	35.3 (9.4) 33.8 (9.1) 34.7 (9.7)	9.6 (2.6) - -	11.1 (12.0) 4.4 (4.2) 3.8 (4.4)	DIS-T SOGS	3 T, EPI TR/TE 2500/30ms, 35 slices	NA	Stop signal task
Gelskov et al., 2016	Denmark	14 PG 15 HC	100%	29.43 (6.05) 29.87 (6.06)	11.36 (3.97) 0.33 (0.9)	17 (10.57) 3.47 (2.95)	SCID SOGS	3T, EPI TR/TE 2430/30ms, 41 slices	slice orientation and compensatory gradient pulses	Probabilistic gambling task
Hinvest et al., 2011	UK	15 PrG 10 SUD 9 HC	55.8%	Tot. 23.8 (6.6)	NA	NA	DSM IV	1.5T, single shot EPI TR/TE 3142/40ms, 40 slices	tilted 30°	Temporal discounting task
Miedl et al., 2010	Germany	12 PrG 12 HC	100%	39.5 (9.3) 33.4 (8.0)	10.7 (3.8) 0.7 (0.7)	NA	DSM IV SOGS KFG	3T, EPI TR/TE 2500/30 ms, 44 axial slices	NA	Quasi-realistic Black Jack scenario
Miedl et al., 2012	Germany	16 PG 16 HC	93.7%	35 (2) 38 (2)	10 (1) 0.18 (0.1)	12.2 (2.6) 4.3 (0.7)	SOGS KFG	3 T, EPI TR/TE 2380/25ms, 40 slices with AP alignment	NA	Temporal discounting task
Miedl et al., 2015	Germany	15 PG 15 HC	100%	36.7 (5.8) 36.8 (5.6)	10.9 (2.8) 0.8 (1.3)	NA	DSM IV SOGS	3 T, single shot EPI TR/TE 2000/30ms, 34 slices with AP-PC orientation	NA	Temporal discounting task
Potenza et al. 2003	USA	13 PG 11 HC	100%	35.1 (7.9) 29 (7.1)	12.6 (3.9) -	NA	SCID SOGS	1.5 T, single shot EPI, TR/TE 1650/60ms	variable skip between slices	Stroop task
Power et al., 2012	Canada	13 PG 13 HC	100%	42.4 (10.8) 41.0 (11.0)	13 (4) 0.4 (0.7)	NA	SCID SOGS	3 T, EPI TR/TE 1500/30ms	tilted slice orientation, angle unspecified	Iowa gambling task

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Tanabe et al., 2007	USA	20 PrG + SUD 20 SUD 16 HC	66.6% 100% 45.4%	35 (7) 35 (7) 37 (9)	10.7 (4.4) 0.2 (0.4) 0.1 (0.3)	NA	SOGS	3 T, single shot EPI TR/TE 2000/35ms, slices in standard AP-PC orientation	NA	Iowa gambling task modified
van Holst et al., 2012 a & b	Netherlands	16 PrG 15 HC	100%	34.3 (11.1) 36.2 (10.6)	11.5 (3) 0.07 (0.2)	NA	DSM IV TR SOGS	3 T, EPI TR/TE 2300/30ms, 35 axial slices	NA	Go/no-go while watching blocks of affective (positive, negative, neutral) or
Verdejo-Garcia et al., 2015	Spain	18 PG 18 SUD 18 HC	95%	33.56 (7.97) 34.27 (6.87) 31.17 (4.74)	NA	NA	DSM IV TR	3 T, EPI TR/TE 2000/35ms, 21 axial slices	NA	Probabilistic reversal-learning task

Notes: BDI: Beck Depression Inventory; DIS-T: Diagnostic Interview Schedule, section T; fMRI: Functional magnetic resonance imaging; HC: Healthy control; KFG: Kurzfragebogen zum Glücksspielverhalten, german gambling questionnaire; NA: Not assessed; NR: Not reported; PG: Pathological gambling; PrG: Problem Gamblers; SCID: Structured Clinical Interview for DSM-IV; SOGS: South Oaks Gambling Scren; SUD: Substance use disorder; EPI: Echo-Planar-Imaging; TE: Echo Time; TR Repetition Time.

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Table 2. Differential fMRI activation patterns in cognitive control tasks in PG subjects vs healthy controls.

Cognitive task	Prefrontal Cortex							Striatum		PC	TC	Comments	Reference
	OFC/VMPFC	SFG	MFG	DMPFC	VLPFC	DLPFC	ACC	VS	DS				
Response inhibition				↓								*during successful response inhibition*	de Ruiter et al., 2012
							↓					*during failed response inhibition*	
						↑	↑ *right*					*neutral go vs neutral no-go trials*	Van Holst et al., 2012a
						↓		↓ *left*				*positive no-go vs neutral no-go trials*	
						↓ *right*	↓ *left*					*negative no-go vs neutral no-go trials*	
						↓	↓ *right*					*gamble no-go vs neutral no-go trials*	
Conflict monitoring		↓ *left*	↓ *left*									*following presentation of incongruent stimuli*	Potenza et al., 2003
Decision making	↓						↓					*during decision making*	Tanabe et al., 2007
	↑						↑					*during risky vs safe decks selection*	
	↑ *right*	↑ *right*							↑ *right*			*during risky vs safe decks selection*	Power et al., 2012
	↓ *right*					↓ *right*		↑ *right*				*during deck selection*	Brevers et al., 2016
					↑ *right*						↑	*during low vs high-risk trials in a quasi-realistic*	Miedl et al., 2010

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												black jack scenario	
										↑ *left*		*during gains vs losses*	
						~			~				Gelskov et al., 2016
									↓			*during decision making under risk vs decision making under ambiguity*	Brevers et al., 2015
									↑			*during bet vs sure pay off options*	
Cognitive flexibility					↓ *right*							*during reversal shifting vs perseveration*	Verdejo-Garcia et al., 2015
					↓ *right*							*during monetary loss and win*	de Ruiter et al., 2009
Delay discounting	~						~	~				*as correlated with subjective value representation of risky and delayed rewards*	Miedl et al., 2012
						↑	↑			↑		*during the comparison of LDR and SIR*	Miedl et al., 2015
					~		~					*positively correlated with impulsivity scores*	Hinvest et al., 2011

Notes: ↑: increased activation; ↓: decreased activation; ~: increased or diminished correlation between fMRI activity of the selected areas and task response.
OFC: orbitofrontal cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; DMPFC: dorsomedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; ACC: anterior cingulated cortex; VS: ventral striatum; DS: dorsal striatum; PC: parietal cortex; TC: temporal cortex.