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Review article

Neural correlates of cognitive control in gambling disorder: a systematic review of fMRI studies

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A R T I C L E I N F O

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A B S T R A C T

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.

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* (see Fig. 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.

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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***, as measured by tasks based on **reversal learning** paradigms. ▪ ***Non-Reward-Based***, 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.

Fig. 1. Different sub-processes contributing to cognitive control.

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 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 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 et al., 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