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Does decision-making during gambling involve primary roles for the pre-frontal cortex and anterior cingulate cortex

Victoria Y. M. Suen, Peter H. Silverstone*

Department of Psychiatry, University of Alberta, Edmonton, Canada

Email address:
vsuen@ualberta.ca (V. Y. M. Suen), peter.silverstone@ualberta.ca (P. H. Silverstone)

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Abstract: Functional magnetic resonance imaging (fMRI) studies have implicated multiple brain regions as being involved in the complex process of decision-making, including gambling. While decision-making is a key aspect of everyday life, the consequences of poor decision-making can be greatly magnified during gambling. Thus, it is useful to review current evidence regarding the brain regions involved in gambling. To date, there have been three tasks that have been frequently used to examine the paradigm of decision-making during gambling: the Iowa Gambling Task, the Game of Dice Task, and the Wisconsin Card Sorting Task. There are four brain regions that are most consistently involved, the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), and anterior cingulate cortex. Interestingly, we have recently found that disobedience to an authority figure in a gambling task also involves activation in the amygdala, ventrolateral prefrontal cortex (vlPFC) and anterior insula. Taken together, we propose that decision-making in the context of gambling is primarily determined in the pre-frontal cortex (PFC) and anterior cingulate cortex (ACC). While multiple other brain regions are likely involved, the primacy of the PFC and ACC in decision-making during gambling behaviours should be more fully recognized.

Keywords: fMRI, Gambling, Pre-Frontal Cortex, Anterior Cingulate Cortex

1. Introduction

The overall study of decision-making aims to elucidate our ability to process information and choose a beneficial action. Gambling is an extension of this, except that there is usually a clear financial reward available. Dysfunctional decision-making is frequently found in gamblers [1-4] with increased reward seeking behaviour and decreased sensitivity to loss during behavioural tasks being found in problem gamblers [1,5,6]. Several decision-making and risk-taking tasks are commonly employed to assess risky decision-making, and the most widely used are the Iowa Gambling Task (IGT)[7], the Game of Dice Task (GDT)[8], and the Wisconsin Card Sorting Task (WCST)[9]. Potential underlying brain regions associated with each task have been examined utilizing many techniques, including functional magnetic resonance imaging (fMRI), which has helped clarify similarities and differences between the tasks and the regions most commonly activated while they are being carried out. This review aims to bring together the findings from the abundance of behavioural, neurobiological, and psychological studies, and from this determine if there is there is enough evidence from existing fMRI studies to determine if there are any specific brain regions that appear most critical to decision making during gambling. Any such regional changes are also likely to be critical in other, non-gambling, decisions made in situations of uncertainty. While this information is currently available, there have been no previous reviews to synthesize this information and examine this issue specifically.

2. Decision-Making Tasks

2.1. Iowa Gambling Task (IGT)

The IGT [7] is one of the most validated and widely used measures of decision-making [10]. The task involves asking subjects to select cards, one at a time from any of four decks with the goal to maximize profits. However, the participants

are not told how many turns they will have (typically 100) and that two of the decks are advantageous in the long-term (long-term reward with short-term punishment) while the other two are not (long-term punishment with short-term reward). Thus, this task requires participants to learn that in order to gain long-term reward, they must first endure short-term punishment.

2.1.1. Findings

This task is a sensitive measure of impaired decision-making as several populations have been shown to differ significantly in task performance from healthy controls. Several clinical populations have been shown to display decision-making deficits by favoring short-term goals. These include individuals with orbitofrontal (OFC)/ventromedial prefrontal cortex (vmPFC) lesions [11], substance addiction leading to frontal lobe dysfunction [12], Parkinson's disease [13], Huntington's disease [14], schizophrenia [15], obsessive-compulsive disorder [16], and anorexia nervosa [17]. Following the dual-model process of self regulation [18], it is suggested that the ability to decide advantageously, based on long-term and short-term outcomes, is derived from activation from both an impulsive amygdala-striatum based system and a reflective prefrontal based system. The impulsive network promotes automatic, habitual and salient behaviors, while the reflective network is credited with forecasting the future consequences of decisions and employing the inhibitory control when necessary [18]. This reflective network is also thought to include executive functions, which consist of various cognitive abilities to control thought, emotion and action [19]. Overall, it is believed that task deficits are due to impairments in using feedback from previous trials to aid in current decision-making [19]. This is thought to be mediated by OFC/vmPFC dysfunction as well as dysfunction in the limbic network including the amygdala, previously implicated in emotion processing [20,21].

Much like frontal lesion patients, substance abuse individuals have also demonstrated the disadvantageous preference for the "short-term gain/long-term loss" decks, otherwise termed delay discounting, when presented with the IGT [22,23]. This pattern, of poorer performance in the IGT has been consistently repeated in pathological gamblers, as pathological gamblers appear to display a strong preference for the harmful decks in the IGT [1,2]. However, there have been some studies that have not found this significant difference between the two populations [24,25]. This lack of consistent support may be due to small sample sizes as well the heterogeneity of gamblers as a group (strategic vs. non-strategic game preference/psychological profiles) [19]. For instance, both pathological gamblers and controls who score highly on sensation seeking displayed significantly increased activity in the ventral striatum during the IGT [26], an area previously linked to anticipation of monetary rewards [27].

Researchers have also found increased delayed discounting in pathological gamblers in an fMRI study [28] . The authors found a negative correlation between gambling severity and valuation signals in the ventral striatum, vmPFC and ventral tegmental area for delayed rewards [28]. Importantly, they found reward representation differences in gamblers depending on condition – neural value correlations increase in delayed discounting and decreased in probability discounting throughout the reward system [28]. In an fMRI study employing the IGT, pathological gamblers exhibited increased OFC, caudate, hippocampus and amygdala activation during high-risk deck selection [29] which is consistent with previous studies with the addition that previous studies have also implicated the amygdala, OFC as well as the ACC [30-32]. As these regions also make up the dopamine reward pathways, these results provide support for the popular hypothesis that an increased salience of immediate potential rewards relative to future losses may be one of the mechanisms by which gambling behavior is maintained.

2.2. Game of Dice Task (GDT)

The GDT [8] is a gambling task in which - unlike in the IGT - the rules for both gains and losses are explicit, as are the winning probabilities throughout the entire task. This explicit knowledge of the probabilities allows individuals to plan a long-term strategy in order to increase their outcome. In this task, participants are asked to guess what number on which they think a single die will land in order to maximize their funds. There are four types of guesses: a single number, combination of two possible numbers, combination of three possible numbers or a combination of four possible numbers. Each type of choice is associated with a gain/loss amount should the die match/not match the chosen option. The smaller probability that the choice will be correct the greater the reward/loss. Thus, if a participant chose a single number then the probability of winning would be 1:6 and this option would yield the highest amount of reward/loss. If a participant chose a combination of four numbers the probability of having the correct number increases to 4:6; however, this would yield a smaller reward than any of the other options. All of this is presented visually so that the probabilities can be easily discerned. After the participant makes his selection the die is rolled and the winning number revealed. Participants receive both visual and auditory feedback and their monetary total is adjusted accordingly. This is repeated for a total of 18 rounds. The three and four number combination choices are considered advantageous choices, as their winning probabilities are greater than 50% and are associated with lower gains but also lower penalties. Disadvantageous choices are the single or two number combination choices, as their winning probabilities are less than 50% and are associated with higher gains but also higher penalties. Thus, the GDT assesses decision-making under risk and uncertainty [8].

2.2.1. Findings

Alcoholic Korsakoff patients (patients whose former alcohol abuse led to frontal lobe dysfunction and brain damage) were shown to have impaired performance in this

task where healthy controls displayed risk-avoidant decision-making [8]. Women with binge eating disorder [33], individuals diagnosed with bulimia nervosa [34], and Parkinson's patients [35] have also shown deficits in this task. Choosing disadvantageous options in the GDT was correlated with poor performance in the modified WCST in executive functions such as categorization, set-shifting and cognitive flexibility [8].

It is important to note that the IGT has also been used to examine decisions under conditions of ambiguity, as well as the risks involved as the task progresses [36]. In the beginning phases of the IGT, probabilities and outcomes are ambiguous; however, as the task progresses participants acquire some knowledge about each of the decks and the decision-making switches from being under conditions of ambiguity to conditions of risk, much like the GDT [36]. Some authors suggest that executive functions are taxed differently based on whether the decision-making is occurring under conditions of ambiguity or risk [34]. They hypothesize that ambiguity does not call upon executive functions but risky decisions more heavily draw on the executive functions system. This may indicate how some of the differences in findings between the GDT and IGT may be explained. However, it is well accepted that the OFC and amygdala appear to have important roles in decision-making under conditions of ambiguity [37]. In an fMRI study comparing ambiguous and risky decision-making, activation in the OFC and amygdala corresponded with ambiguous decisions, while activation in the dorsal striatum (caudate nucleus) was found to correlate negatively with ambiguity but positively with expected rewards [37]. The authors suggest that the OFC and amygdala respond to the degree of uncertainty/ambiguity, much like a vigilance evaluation system. Behavioral tests with OFC lesion patients also revealed an inability to distinguish between ambiguity and risk conditions [37].

Pathological gamblers were also found to be impaired in decision-making using the Game of Dice task (GDT) [38]. Importantly, in Brand et al. (2005), the gamblers were also assessed with a neuropsychological battery and, as a group, scored within normal ranges. The frequency of disadvantageous decisions was correlated with specific executive functions (categorization, set-shifting, cognitive flexibility and interference susceptibility) but not with personality traits [38]. Pathological gamblers appear to display a failure to use negative feedback after a disadvantageous choice to improve decision-making on following rounds compared to controls [38]. Additionally, one group tested the neuroendocrine responses (salivary cortisol and alpha-amylase concentration; sAA) before and during task performance [3]. Post-hoc analysis revealed that heightened sAA during the task was found in patients who demonstrated *less* disadvantageous decision-making compared to other patients [3]. It was proposed that, as a marker of sympathetic nervous system activity, the increase of sAA in patients with less severe decision-making deficits may be indicative of a somatic marker affecting the decision-making process [3].

2.3. Wisconsin Card Sorting Task (WCST)

The WCST [9] tests executive functions in humans. Participants are asked to sort a deck of cards according to some predetermined rule, but are not explicitly told what the rule is, and are given feedback to let the participant know if they have used the correct rule. The three possible rules used to sort the cards are (1) to sort them by the color of the items, (2) to sort by the number of items, or (3) to sort by the shape of the items on the card. The rule by which the cards are to be sorted changes throughout the task and the participants must adapt with the change in feedback. Participants are scored based on the number of different categories they were able to achieve as well as the number of perseveration errors that occurred (i.e. how frequently they continued to sort by an old rule once a new one has been established).

2.3.1. Findings

Previous research has found impairments in patients with lesions in the prefrontal cortex [39] and fMRI studies have supported these findings, linking the prefrontal cortex to set shifting [40,41]. There has been some speculation that the basal ganglia is also involved in the WCST since impairments have also been seen in Parkinson's disease patients [42]. Others have reported a dissociation in activity between the mid-ventrolateral prefrontal cortex (vlPFC) and mid-dorsolateral prefrontal cortex (dlPFC) during the WCST [43]. While both areas were activated during set shifting, the mid-dlPFC also exhibited an increase in activation during set maintenance. The same authors also found that both the caudate and putamen were involved with performance on the WCST, activating during negative feedback trials [43].

Two other groups administered the Wisconsin Card Sorting Task (WCST) to gamblers and controls and found that gamblers performed significantly worse than the controls [4,44]. In one of these studies subjects were administered two other measures of cognitive flexibility, the Controlled Oral Work Association Test and the Trail Making Task A and B, and gamblers performed poorly on both compared to controls [4]. A further study found supporting evidence for the WCST results, since it was the only task (administered alongside a verbal fluency test and the Wechsler memory scale) to show group differences, with pathological gamblers demonstrating greater difficulty on the task than healthy controls [45].

2.4. Comparisons between the Tasks

It can be seen that each of the three tasks has different strengths and weaknesses, but it is interesting to note how often they affect similar regions of the brain, particularly the pre-frontal cortex (PFC) and the anterior cingulate cortex (ACC). These tasks include a mix of both ambiguous (IGT and WCST) and explicit (GDT) rules of risk, and help illustrate the complexity involved in decision-making. As decision-making can occur under a myriad of situations, it is

important to have a variety of tasks in order to fully understand how decision-making occurs. Variations of the Go/No-Go tasks, a task in which participants are asked to attend and respond to certain stimuli (a Go trial) while ignoring others (a No-Go trial), are also often used in decision-making studies. Interestingly, studies using this task have found that problem gamblers displayed greater activation in the dorsolateral prefrontal cortex, ACC and ventral striatum van [46]. This occurred when viewing gambling pictures in a Go/No-Go task that featured gambling and non-gambling images, where gamblers performed more slowly on No-Go trials that were paired with neutral images. This was linked to greater activation in the dorsolateral prefrontal cortex and ACC [46]. Aside from the decision-making process, reward and learning may shift during decision-making and forms another focus in decision-making research.

3. Reward Prediction Error

At its most simplistic form, reward prediction error refers to the degree to which a reward is surprising to a subject [47]. In this pioneering research [47], behavioral experimental results were combined with measures of physiological response of dopaminergic neurons in primates during a basic reinforcement-based learning task. In summary, midbrain dopamine firing was recorded when there was an unpredicted occurrence of juice (the unconditioned stimulus; UCS) prior to learning. Post learning, the conditioned stimulus (CS) predicts the delivery of a reward (the UCS) and thus when the reward arrives according to prediction there is no error in the prediction of the reward, and the dopamine neurons fail to activate to the delivery of the reward. Rather, the neurons fire in response to the CS, the reward-predicting stimulus. Should the CS be presented but no reward follows, dopamine neuron activity is depressed at precisely the time when the reward ought to have occurred [47]. The authors concluded that dopamine neurons appeared to be predictors of how well actual events fit to previously learned predictions about those events [47]: an increase in dopamine firing was exhibited if the event was better than expected, no signal was measurable if the event occurred as expected, and a depressed signal or rate of firing was exhibited if the event was worse than expected. This was termed the Reward Prediction Error hypothesis [47]. More specifically, this hypothesis states that dopamine encodes the difference between the experienced and predicted reward of an event. This technique has been increasingly paired with fMRI studies, and researchers have adopted fMRI to study reward prediction error more closely.

3.1. Functional Magnetic Resonance Imaging and Reward Learning

Utilizing neuroimaging techniques, areas of interest identified as being relevant include the midbrain, ventral striatum, nucleus accumbens (NAcc), amygdala, OFC and medial prefrontal cortex, areas that are all innervated by mesolimbic dopamine pathways [48]. Specifically, fMRI studies have shown that the ventral striatum is activated preferentially during reward anticipation while the medial prefrontal cortex is preferentially activated during reward outcome [49,50]. It also appears that reward may manifest itself differently in the brain depending on the timing of the reward and learning. It has been found that during a task in which subjects learned to choose options that lead to monetary gains versus losses, activation in the striatum and lateral OFC correlated with immediate reward prediction while longer-term future reward (small immediate losses leading to long term benefit) correlated with dlPFC and inferior parietal cortex activation [51]. Others have reported that the caudate exhibited greater activation in the early learning stages, for example where participants learn cues that predicted a juice reward with either active choice or passive association in an fMRI study [52,53]. These authors found that while reward prediction error correlated with activity in the ventral striatum for both tasks, the caudate was recruited only during the active choice task. Taken together, these studies suggest that both the ventral striatum and caudate have an important role in what appears to be reward learning.

3.2. Incentive Salience vs. Reward Prediction Error

In a recent review the importance of differentiating between reward prediction error and incentive salience is emphasized [54]. Incentive salience refers to a form of Pavlovian-related “wanting” or motivation for rewards, and is mediated by the mesocorticolimbic brain systems [55,56]. In contrast, while “wanting” typically occurs in conjunction with “liking” this is not always the case, and manipulations involving dopamine can dissociate the two [56-58].

While previously it was believed that dopamine release was responsible for causing pleasure [59], it has since been shown that dopamine is not required for normal ‘liking’ reactions [57]. This has been supported by evidence that patients with dopamine depletion (Parkinson’s) report normal ratings of pleasure [60], and elevating dopamine levels does not appear to enhance pleasure [58]. It has been proposed that while dopamine appears to code for reward learning, closer examination of the evidence reveals that it does not actually cause learning in terms of reward, but rather causes incentive salience for both learned and unlearned rewards [54].

It is also important to recognize differences between animal and human studies. While animal studies can employ stringent physiological conditions during both training and testing, under which a CS–triggered incentive salience will appear to track learning [54] , in humans, life is not that constant and physiological states can vary. Studies that manipulate physiological state to new levels, and those never before experienced, have shown that rather than a reward prediction error, dopamine levels may be more linked to incentive salience, or ‘wanting’ [54]. Thus, dopamine release appears more closely related to “wanting

things" than to actually obtaining them [54]. These results support dopamine's role in incentive salience rather than simply reward prediction error.

4. vmPFC/OFC Role in Reward Decision-Making

The vmPFC/OFC is involved in the processing of the reward value of stimuli, a key function to decision-making [61]. It has recently been suggested as the area in which rewards of all types are valued on a common scale by which comparisons are measured and decisions subsequently made [62]. Many studies focused on monetary rewards have implicated the medial prefrontal cortex, ventral striatum, posterior cingulate cortex, amygdala and insula in reward magnitude [63-65]; however, studies including more than one type of reward have also been conducted to determine how these areas are recruited, if at all, when the decisions are based on non-monetary rewards. The first of such studies was conducted by FitzGerald et al. [66], who used both money and consumer goods. The researchers found that ventro-medial prefrontal cortex and orbitofrontal cortex (vmPFC/OFC) activation was correlated with subjective values for both reward types both in terms of gains and losses. Three reward types, money, food, and consumer goods, were then used to explore this further and for all three types of reward subjective values were represented in the vmPFC/OFC [67]. Interestingly, other studies have also found evidence for ventral striatum involvement [68]. Furthermore, studies have found that equal behavioral value does in fact reveal equal BOLD signal in the vmPFC/OFC, providing evidence that these different types of reward are all represented as a single common currency of equal value in these areas [68,69].

Research with non-human primates has suggested the OFC's involvement in motivation, affect, and reward processing [70,71]. The OFC is particularly important to the rapid adjustments in behavior in response to changes in the environment [61]. OFC lesions have been shown to cause deficits in reversal learning, where animals will perseverate on stimuli that had at one time been rewarded but no longer are [72,73]. Additionally, animals with damage to the OFC show deficits in Go/No-Go tasks, choosing to respond in no-go trials [74]. This pattern of Go/No-Go task deficit has also been shown in patients with frontal-lobe damage [75]. Therefore, it is likely that the OFC plays an important role in the dysfunctional decision-making often seen in gamblers.

5. Dorso-Lateral Pre-Frontal Cortex Role in Decision-Making

The dorso-lateral pre-frontal cortex (dlPFC) is one of the key areas responsible for keeping and influencing information being used in working memory [76,77]. Decision-making requires working memory to maintain a focus on goal hierarchies and monitor competing options [61]. There is also evidence suggesting that the dlPFC is involved in the processing of relational information and the integration of information [78]. The importance of the prefrontal cortex in integrating information was found in patients with frontal lobe damage, who performed poorly on tasks that required the integration of information from two or more sources compared to temporal lobe patients and healthy controls [78]. Coupled with findings that the task used elicited activation in the dlPFC in an fMRI study [79], and that significant activation was also found in the dlPFC in a study of transitive inference [80], it is believed that the dlPFC plays a key role in mediating relational processing [61]. Others have assessed decision-making under ambiguous contexts that do not have clearly correct choices, otherwise termed adaptive decision making [81,82]. In this task, participants are shown a target picture of a shape and asked to choose one of two shapes that varied in similarity to the target shape. In one condition, participants were asked to select the shape that they "liked best" while in another condition they were asked to select the shape that was either most similar or most different. While healthy controls made their choices in the first condition based on a balance of similarity and dissimilarity, patients with damage to the left dlPFC chose shapes that were more dissimilar to the target [82]. In the other two conditions, there were no significant differences between the groups thus showing that frontal lobe damage did not affect directed decision-making but caused dysfunction in undirected decision-making. These results suggest that decision-making with a specified goal is linked to the dlPFC. Another study comparing decision-making under either an explicit rule condition or a no-rule condition found that the right dlPFC was activated during the no-rule condition while the rule conditioned elicited bilateral activity [83]. The authors suggested that the right hemisphere might be more involved in the resolution of ambiguity in the absence of explicit rules. An interesting case study reported on the impact of right frontal lobe ablation, documenting that when presented with a task to redesign a laboratory (the subject had previously worked as an architect) the subject spent more time planning how to complete the project but showed marked deficits in his ability to execute the plans he had previously made [84]. These observations support the hypothesis that the right dlPFC plays an important role in accessing and processing based on previous knowledge.

In an fMRI study of gambling urges participants were asked to view a video designed to evoke emotional and motivational cues to gambling [85]. The pathological gambling group exhibited less activation in the cingulate gyrus, OFC, caudate, basal ganglia and thalamic areas compared to healthy controls [85]. Others found, with a similar gambling movie paradigm, an increased BOLD signal in the right dlPFC, right inferior frontal gyrus, medial frontal gyrus, left parahippocampal region and left occipital cortex when pathological gamblers were presented with gambling-related cues [86]. It was suggested that pathological gamblers recruit regions that comprise parts of

the dlPFC network and are associated with attention, reward expectancy, and behavioral planning for attaining rewards compared to healthy controls [86].

6. Anterior Cingulate Cortex (ACC) Role in Decision-Making

The ACC has been implicated in decision-making that is highly ambiguous, and it is believed to contribute to the processing of conflicting options with a high likelihood of making an error [61]. Thus, increased ACC activation has been elicited when participants made errors in a task of matching a cue letter (A) to a target letter (X) and this activation was greater when the errors were made under high competition (A presented with a Y, or B presented before an X; [87]). The role of the ACC in conflict monitoring has also been suggested [88,89] as trials in which incompatible stimuli were presented elicited ACC activity. Additionally, when an incompatible trial was preceded by a compatible trial, thus when the conflict was the most salient, ACC activation was greater than if the incompatible trial had been preceded by another incompatible trial [88]. The ACC has also been implicated in outcome anticipation [90] where, as outcome uncertainty increased so did activity in the ACC and OFC. In this study, the authors also found that higher arousal level (as measured by galvanic skin response) was associated with activation in the ACC, dlPFC and parietal cortex during the delay period between decision-making and outcome notification [90]. This suggests that any decision-making in which an outcome is not guaranteed is linked to activation in the ACC. This region is thus crucial when examining decision-making while gambling.

7. Conclusion and Hypothesis

It can be seen that the evidence to date suggests that there are several considerations to be aware of when considering the current research evidence on decision-making, particularly when it involves conditions of rewards and uncertainty, as is the case with gambling.

While the current evidence suggests that multiple brain regions have been shown to be involved at some level, there is consistency that both the pre-frontal cortex (PFC) and anterior cingulate cortex (ACC) are critically involved when gambling decisions are made. There appears to be strong evidence that the ventro-medial prefrontal cortex/orbitofrontal cortex (vmPFC/OFC) is strongly implicated in dysfunctional decision-making behavior [28,91]. This area also appears to be involved in planning and motivation, both of which are very obviously linked to decision-making in gambling behavior. Decision-making also requires access to past memories, and this involves the dorsolateral prefrontal cortex (dlPFC) [18,86]. Finally, the anterior cingulate cortex (ACC) has emerged as a particular region of interest in risky and ambiguous decision-making [61] and we have found changes in the ACC when disobeying "expert" advice in a gambling paradigm [92].

Taken together we therefore hypothesize that these two regions are integral to gambling behavior. This would imply that treatments specifically designed to modulate activation within these regions, in response to gambling cues, might be a promising area for future research. This is not to minimize the multiple, and complex, neuronal interactions that occur during gambling and which lead to a specific decision nor the certain involvement of many other brain regions. Nonetheless, we hope by clarifying the critical nature of these two regions in particular in decision making during gambling decisions, specific therapeutic tasks, interactions, or therapies, may be designed that could be more successful in stopping pathological gambling behavior than current treatment modalities.

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