Chapter 7

Pathological Gambling: PET Studies

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1. Introduction

Pathological gambling(PG) affects 1–3% of the adult population, and has high comorbidity [1].

PG is a persistent or maladaptive gambling behavior characterized by excessive time consumed to gambling or thinking about gambling, needing togamble with increasing amounts of money, chasing one's losses, unsuccessful efforts to stop gambling and financial/social problems due to gambling. Hence, PG can also be considered as a behavioral addiction since the characteristics and diagnostic criteria share many common features with substance addictions [2].

PG can be classified as an impulse control disorder, that can be described as a "chain" of subjective states including arousal, craving and acting, accompanied by a feeling of elation and followed by disphoria, all of which are supposed related to an underpinning neurobiology [3].

It is widely suggested that gambling excitement is central to the disorder, and that it is associated with physiological measures of arousal, that are increased during the gambling [4].

It's become a common opinion among researchers that the use of imaging studies as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) can be a way to learn more about pathophysiology of this disorder.

2. Brain areas involved

Functional imaging studies of the prefrontal and orbitofrontal cortex have implicated dysfunction of these structures both in the pathological gambling.

A recently published functional magnetic resonance imaging (fMRI) study reported that the healthy controls activated their ventromedial and subgenual prefrontal cortex during a 'loss-

chasing game' more then during decisions to quit. The authors suggested that PG patients may have a neural substrate involving these areas, as loss-chasing is one of the cardinal symptoms of the disorder [1]. Compared to controls, patients with PG had greater activation of the prefrontal cortex Brodmann Areas (BA) 9 and 44 while watching gambling-related images [5], lending evidence to the hypothesis that prefrontal cortex areas were also involved in craving aspects of pathological gambling.

Hollander et al. in a previous study [6], in an entirely different cohort of PG patients assessed with FDG-PET, found that monetary-rewarded blackjack was associated with a significantly higher relative metabolic rate in the primary visual cortex (BA 17), the cingulate gyrus (BA 24), the putamen, and prefrontal BA areas 47 and 10 compared to playing blackjack for points only.

An fMRI study of the Iowa Gambling Task (IGT) confirmed medial frontal/cingulated activation during decision-making and greater activation in gamblers than controls in ventral medial frontal areas [7]. This pattern suggests heightened limbic and sensory activation in gambling for monetary reward with increased emotional valence, and confirms the salience of monetary reward in PG.

Other MRI studies on healthy volunteers responding to monetary consequences reported an activation in prefrontal and premotor cortices. This has been interpreted as related to the integration of reward choice salience and preparatory behaviors for obtaining rewards. The basal ganglia and the caudate nucleus in particular are fundamental structures for liking behavior to rewarding and aversive outcome, and they are also involved in modulation decision-making and risk-taking behaviours. These structures have a key role in learning and reasoning processes, and this is reflected in basal ganglia dysfunction.

Some studies have proposed that the salience of monetary reward would be correlated to caudate and nucleus accumbens activation [3]

3. Investigations on neural circuits involved

Over the past 2 decades, National Institute of Mental Health (NIMH) has supported research to understand mental disorders as brain disorders. NIMH has therefore launched the Research Domain Criteria (RDoC) project.

RDoC is an experimental approach to the classification of mental disorders that incorporates multiple dimensions: behavior, thought patterns, neurobiological measures, and genetics. RDoC uses genetics, imaging, and cognitive science for understanding deficits in social behavior. The RDoC project has a primary focus on neural circuits. While genes cut across the current diagnostic labels, neuroimaging often helps us to sub-divide current groups. This is particularly interesting when we consider the PG and signs of behavioral alterations related.

The RDoC framework is a heuristic to facilitate the incorporation of behavioral neuroscience in the study of psychopathology. RDoC first aims to identify reliable and valid psychological and biological mechanisms and their disruptions, with an eventual goal of understanding how anomalies in these mechanisms drive psychiatric symptoms [8].

RDoC classification rests on three assumptions. First, the RDoC framework conceptualizes mental illnesses as brain disorders. In contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits. Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging, and new methods for quantifying connections in vivo. Third, the RDoC framework assumes that data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management.

Examples where clinically relevant models of circuitry-behavior relationships augur future clinical use include fear/extinction, reward, executive function, and impulse control. The practitioner of the future could supplement a clinical evaluation of mental disorders with data from functional or structural imaging, genomic sequencing, and laboratory-based evaluations of fear conditioning and extinction to determine prognosis and appropriate treatment, analogous to what is done routinely today in many other areas of medicine.

The RDoC focuses on neural circuitry, with levels of analysis progressing in one of two directions: upwards from measures of circuitry function to clinically relevant variation, or downwards to the genetic and molecular/cellular factors that ultimately influence such function. [9] Fear circuitry and executive functioning are examples of two functional domains where the relevant circuitry and behaviors seem relatively clear, and these have been selected as the initial areas to be developed; other examples might include reward circuitry and frontostriatal circuits. So, we could begin to create neurobiological circuit maps of behavioral and cognitive functioning and explicate the ways in which activity in these circuits becomes dysregulated in mental disorders.

Patient subjects with relevant presenting psychopathology might be grouped on the basis of a genetic polymorphism or a particular response to a neuroimaging task rather than a DSM/ICD diagnosis; in this manner, investigators can query relevant mechanisms as they cut across traditional categories. [10]

The rationale for the RDoC approach is to facilitate translation of modern molecular biology, neuroscience, and behavioral approaches toward explicating the pathophysiology of disorders. By targeting circuit functioning and relevant behaviors, one particular goal is that this process will direct the search for treatment targets in various domains. [11]

RDoC's integrative approach includes cognition along with social processes, arousal/regulatory systems, and negative and positive valence systems as the major domains, because these neurobehavioral systems have all evolved to serve the motivational and adaptive needs of the organism. With its focus on neural circuits informed by the growing evidence of the neurodevelopmental nature of many disorders and its capacity to capture the patterns of co-occurrence of behaviors and symptoms, the RDoC approach holds promise to advance our understanding of the nature of mental disorders. [12]

Based on RDoC approach, we could identify some neural circuits supposed involved in PG: Nucleos Accumbes (NA) - Orbital Frontal Cortex (OFC) relatively to craving; OFC - Caudates Nucleus (NC) respect to inhibition failure; Limbic system – OFC concerning to affective

instability; Anterior Cingulate Cortex (ACC) – OFC about economic decision making. These networks represent hypotheses to be studied to understand the mechanisms underpinning the PG, a disorder regarding addiction and decision making.

In this respect, PET could become a key tool in this evolving diagnostic and therapeutic process.

4. The role of dopamine

Brain dopamine neurons code rewarding environmental stimuli by releasing endogenous dopamine (DA), a transmission signal that is important for reinforcement learning. Human reward-seeking gambling behavior, and especially PG, has been presumed to be modulated by brain DA [13].

Several neurotransmitters, and especially DA, have been implicated in the neurobiology of PG [4]. Its release is associated with change in subjective experience and reinforcement of behavior.

Linnet et al. [4] in their study proposed that DA release would be associated with increased excitement levels in PG compared with healthy controls. The study showed that PG with decreased binding potentials in the ventral striatum had significantly higher excitement levels than healthy controls. DA is a neurotransmitter associated with addictive behaviours through a heightened sensitivity to certain types of "reward" such as foods high in sugar or fat content and substances such as cocaine or metamphetamine.

Even if systemic pharmacological interventions such as cocaine and amphetamine lead to release of DA in the whole dorsal and ventral striatum, it appears that more specific types of stimulation leads to regionally restricted dopamine release. And this is supported by the segregation of cortical and and sub-cortical imputs to the striatum.

The relation between DA release and bahavioural reward suggests that the DA system is associated with maladaptative behavior in PG [14].

The salience of monetary reward was reported as correlated to caudate and nucleus accumbens activation. It has been supposed that a dopaminergic neuron activity in these regions may be involved in the acquisition of the associations between salient contextual stimuli and rewarding events [3].

The role of DA in PG is further supported by reports of associations between dopaminergic medications and impulse control disorders in patients with Parkinson's disease (PD) [15]. There are only a few reported functional imaging studies in pathological gamblers with contradicting support for the concept of reward deficiency.

In pathological gamblers, DA release correlated positively with gambling symptom severity. The gamblers who have the most severe symptoms release the most DA. Correlation analyses showed that the most severely addicted gamblers released more DA during high reward gambling than less addicted gamblers. A Positron Emission Tomography (PET) study investigating PD patients with and without PG, showed increased DA release during gambling

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in patients with PG [16]. Personality traits commonly associated with PD, such as impulsivity and antisociality, are also associated with increased, and not decreased, mesolimbic DA responses [17,18, 19].

Striatal DA is released during gambling irrespective of gambling outcome suggesting that the mere expectation/prediction of reward is sufficient to induce dopaminergic changes. Greater gambling symptom severity is associated with greater dopaminergic responses. The dopaminergic response to reward-predicting stimulus and the linkage between addiction severity and DA release in pathological gamblers may play roles in the development and the symptomatology of the maladaptive gambling behavior [20].

Individuals suffering from substance abuse and dependence have cognitive and behavioural decision-making impairments similar to PG, that could be associated with dopaminergic dysregulations. Recent researches suggest that the dopamine system and ventral striatum play a central role in PG as well as substance dependence. In healthy controls DA appears to be associated with, instead in PG dopamine might be also associated with monetary losses. This suggest a dopaminergic base of susceptibility to immediate reward seeking in PG [21].

In PG the DA system may be associated with dysfunctional learning (reward prediction error), that is associated with increased activation of midbrain DA neurons, which stimulate synaptic DA release in the striatum and through the brain.

Impulse control disorders such as PG are a serious and common adverse effect of DA replacement medication in PD. Patients with PG have increased impulsivity and abnormalities in striatal DA, in common with behavioural and substance addictions in the non-PD population. Symptomatic relief of motor symptoms in PD is achieved by increasing endogenous dopamine levels using levodopa, or by synthetic activation of DA receptors using DA agonists. DA agonists in particular may contribute to the development of impulse control disorders (ICDs) in about 13% of PD patients [22, 23]. PD patients with PG have dysfunctional activation of DA autoreceptors in the midbrain and low DA tone in the anterior cingulated cortex. Thus, altered striatal and cortical DA homeostasis may incur vulnerability for the development of PG in PD, linked with the impulsive personality trait. Natural variation in DA homeostasis in the midbrain and cortex can impact an individuals' propensity for impulsivity and, as such, modulate risk for ICDs in PD. DA agonists may exaggerate these dopaminergic influences over behaviour, turning a previous tendency to engage in rewarding activities into a pathological inability to abstain from them [24].

More recently, Linnet et al. [25] investigated the dopaminergic coding of reward and uncertainty in PG sufferers and healthy controls. They used PET with the tracer [(11)C]raclopride to measure DA release, and they used performance on the Iowa Gambling Task (IGT) to determine overall reward and uncertainty. The data supported an inverse relation between striatal DA release and IGT performance if the PG group, but not in the healthy control group. These findings are consistent with the hypothesis of dopaminergic sensitivity toward uncertainty, and show as dopaminergic sensitivity to uncertainty is pronounced in PG, but not among non-gambling healthy controls. So it’s reasonable to assume that, in PG patients, decisions with maximum uncertainty and variance are associated with the highest dopami-

nergic activation. Morevover, dopaminergic coding of variance in IGT performance in PG was strongest in the combined striatum and in the ROI(Return On Investment) analysis, only the putamen reached significance level. This may suggest a strong role of the putamen in relation to uncertainty, which may exceed that of the ventral striatum by a factor of 2 to 3.

5. PET specific studies

Hollander et al. [26] therefore hypothesized that lithium effects would decrease relative metabolic rate in at least some portions of the cingulate and orbitofrontal systems. Since they have recently reported elevated relative white matter metabolic rates in frontal regions in patients with schizophrenia [20], and since the statistical parametric mapping analysis in fMRI gambling studies showed group difference clusters partially encompassing white matter underlying cortical areas [7], they assessed white matter metabolic rates underlying each BA on an exploratory basis. In another previous treatment study, lithium was effective in reducing both gambling behavior and affective instability [27].

Although mood stabilizers and serotonin reuptake inhibitors have shown some efficacy in the treatment of this condition, there is little known about how these pharmacological interventions work. In patients with PG, relative glucose metabolic rates (rGMR) in the orbitofrontal cortex and medial frontal cortex were significantly increased at baseline compared to normal controls. Lithium administration was associated with widespread effects in the prefrontal cortex and cingulate gyrus. Lithium increased rGMR further in the orbitofrontal cortex, heightening normal/patient differences, but it also increased the rGMR of the posterior cingulate and the dorsolateral frontal cortex normalizing the metabolic rate in these regions.

Cortical areas implicated in impulse control disorders show increased rGMR in PG at baseline. Lithium treatment, while alleviating the symptoms, further increases rGMR in these areas [18].

Buckholtz et al. [17, 18], using the PET ligand [18F] Fallypride, found that trait impulsivity was negatively associated with binding to DA D2/3 receptors in the midbrain. DA receptors in this region are dominated by autoreceptors [28], which function to limit striatal DA release following reward. This suggests that midbrain autoreceptors influence individuals' propensity for impulsivity, and opens the possibility that excessive striatal DA release following gambling rewards in PD patients with PG, shown in Steeves et al. [29], stems from reduced control overstriatal DA by midbrain autoreceptors.

Ray et al. [19] reported the results of their PET and [11C] FLB-457 study, a radiotracer with high affinity for DA D2/3 receptors, and therefore sensitivity to extrastriatal, showing midbrain and prefrontal cortex dopaminergic differences in PD patients with and without PG. They suggested that impaired DA homeostasis in the midbrain, resulting in increased striatal DA release during reward, may be responsible for increased impulsivity and therefore vulnerability for addiction in these patients.

Recently, Boileau et al. [30] used PET to test whether PG is associated with abnormalities in D2 and D3 receptor levels, as observed in substance use disorder (SUD). They used Two PET

scans, one with the D3 receptor preferring agonist [11C]-(+)-propyl-hexahydro-naphthooxazin (PHNO) and the other with [11C]raclopride, to assess D2/3 DA receptor availability, and behavioural measures (self-report questionnaires and slot-machine game) to assess subjective effects and relationships to PET measures. The key findings of this study are two: first, in contrast to SUD, PG subjects'binding profile for both D2 and D3 receptor subtypes did not differ significantly from those of healthy controls, suggesting different neurobiological signatures between PG and SUD. Secondly, the study provides novel information regarding the D3 receptor in PG, showing a relationship between D3 levels across PG subjects and symptom severity and impulsiveness. So, D3 may be a viable marker for vulnerability across addictions and a potential target for intervention. The apparent ability of DA agonists in general, and D3-preferring agonists, in particular, to induce impulse control disorders in some patients, suggested an important role for this receptor in PG: its distribution on brain structures receiving afferent ventral striatal projections suggests that its activity can modify limbic output, and thus motivation for reward.

Savitz et al. [31] have tested the effect of a functional missense mutation in the dopamine 3 receptor (DRD3) gene (Ser9Gly, rs6280) on reward-associated DA release in the Striatum. They used two PET scans with [^{11}C]raclopride using the bolus plus constant infusion method. On one occasion subjects completed a sensorimotor task (control condition) and on another occasion subjects completed a gambling task (reward condition). Since PET- [11C]raclopride technique allows exploration of the effects of genetic variation on the amount of DA released under conditions associated with increased phasic release of DA, such as during receipt of unpredicted reward, during receipt of unpredictable monetary reward the glycine allele was associated with a greater reduction in D2/3 receptor binding in the middle caudate and the ventral striatum. Moreover they showed as the glycine allele yields D3 autoreceptors have a higher affinity for DA and display more robust intracellular signaling.

As discussed in Joutsa et al. [13], the binding of [^{11}C]raclopride is sensitive to changes in striatal DA concentration during receipt of non-pharmacological rewards such as a video game, large monetary wins versus large monetary losses and the monetary incentive delay task. Notably, in this study of pathological gamblers and healthy controls who completed 3 PET scans with [^{11}C]raclopride while gambling with a slot machine, the severity of addiction to gambling was positively associated with the degree of DA release in the basal ganglia during gambling.

Consistent with these results, highly impulsive individuals, who are thought to be vulnerable to developing addiction disorders, were shown to have diminished availability of striatal D2/3 autoreceptors, potentially predisposing them to a greater phasic DA response [18].

6. Conclusions

The PET imaging data are potentially important because genetically & not genetically-driven differences in DA receptor function may influence the changes in dopaminergic signaling that modulate emotional, motivational and stress responses.

Although large sample sizes are uncommon in PET studies because of cost and radiation exposure, PET has an advantage over MRI because it allows a particular molecular target to be assayed directly. Thus it is likely that true signals can be detected with relatively small sample sizes. Nevertheless, it would be interesting to examine large samples.

A number of studies have successfully applied multi-modal imaging in order to examine the relationship between serotonergic function or dopamine storage capacity and the hemodynamic response to affective stimuli in regions such as the amygdala. A gambling task could be implemented in a cohort of subjects who complete both [11C]raclopride PET and fMRI. So, it's therefore desirable that future multi-modal imaging studies can combine fMRI and PET data.

These studies would also be compatible with the new way of approaching to mental disorders proposed by NIMH.

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