

Neurobiology of Pathological Gambling: A Literature Review

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Abstract

Pathological gambling is an impulse-control disorder associated with difficulty managing urges to gamble even at the cost of oneself. This review seeks to investigate existing research on the neurobiological bases of pathological gambling, including abnormal function of brain regions and neurotransmitter systems. Existing research indicates that decreased activity in the prefrontal cortex and ventral striatum is associated with pathological gambling behaviors. Additionally, abnormal production and function of dopamine and serotonin is implicated to be affiliated with pathological gambling. However, the exact abnormalities in these systems are not clearly defined, and further research is required to determine if hyper- or hypo- states are related to pathological gambling. Pharmacological treatments can be investigated based on these neurobiological bases, such as glutamate-related agents and selective serotonin reuptake inhibitors.

Introduction

“Gambling addiction” exists on a spectrum of severity, and existing research mainly focuses on three types of problematic gambling behaviors. First, pathological gambling (PG) is defined in the DSM-IV as an impulse-control disorder consisting of “persistent and maladaptive gambling behavior” (APA, 1994). It is indicated by five diagnostic criteria, including a) a preoccupation with gambling, b) a need to gamble with increasing amounts of money to achieve excitement, c) repeated failure to cut down or stop gambling behaviors that is associated with irritability or restlessness, d) gambling as a coping mechanism, and e) gambling despite negative financial, legal, or social outcome. In comparison, problem gambling is the common term used for patients who are caused distress by their gambling habits but do not display five of the criteria described in the DSM-IV as defining gambling addiction. Lastly, the DSM-V has replaced the definition of pathological gambling with that of gambling disorder (GD), a substance-related and addictive disorder defined as “persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress” indicated by similar signs over a 12-month period (APA, 2013). In this paper, I will present research surrounding pathological gambling.

Pathological gambling is a prevalent behavior observed in societies such as the United States. In 2008, lifetime gambling (participation in gambling activity at any point in one’s lifetime) was reported by 78.4% of U.S. respondents; lifetime problem gambling (experiencing problem gambling at any point in one’s lifetime) was reported by 2.3% of respondents, and 0.6% of respondents reported struggling with lifetime PG (Kessler et. al, 2008). While these results demonstrate that most U.S. respondents did not struggle with problem gambling or PG, the facilitation of gambling activities in recent years by video game loot box (items that can be spent inside video games for randomized rewards) systems and monetized gaming activities, is to be noted. Engagement in such activities has been indicated to positively correlate with symptoms of PG (King & Delfabbro, 2020). Additionally, these types of gambling activities are easily accessible by adolescents.

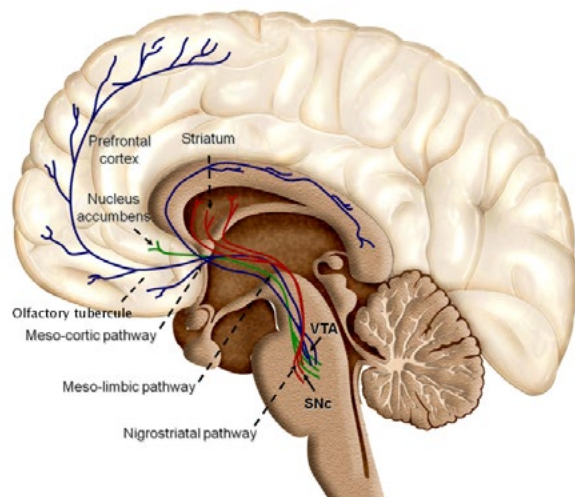
Problem gambling and PG are also associated with financial and social loss. The largest annual gambling losses for respondents averaged \$4,800 USD according to the U.S. National Comorbidity Survey Replication in 2008 (Kessler et. al, 2008). Furthermore, pathological gamblers have reported suffering in their interpersonal relationships. A 2021 study specifically investigated the romantic relationships between PG patients and their partners. The study found that PG was associated with a worse perception of the quality of romantic relationships, as well as an association between PG and insecure attachment (Ponti et. al, 2021). While this study was limited by self-report data and a small sample size, it is clear that PG is associated with negative financial and social consequences and should be treated as the social issue it is. By improving current understanding of PG’s neurobiological bases, PG’s negative social costs can be more effectively avoided.

Many research studies have been conducted to investigate the relationships between neurobiological attributes and PG. By understanding these relationships, clinical interventions can be developed to treat PG and problem gambling to increase the quality of life for patients. Peer reviewed research has revealed that pathological gambling is associated with impaired activation in the prefrontal cortex and mesolimbic system, as well as abnormalities in the production and function of neurotransmitters. It is important to understand the underlying neurological mechanism of pathological gambling, so that more resources can be allocated to the development of clinical and medical interventions to treat pathological gambling.

Brain Regions linked to Pathological Gambling

The main brain areas demonstrated to be linked to PG are the prefrontal cortex and ventral striatum. Both areas are associated with regulating functions associated with gambling behavior, such as impulse inhibition, reward seeking, and reward anticipation. Hypoactivity of both areas is proposed to be affiliated with PG across several studies.

Figure 1
Reward Structures in the Human Brain



Note. This figure provides an overview of the anatomy of reward structures in the brain. Dopaminergic neurons are located in the substantia nigra (SNc) and ventral tegmental area (VTA) of the midbrain. Their axons project to other parts of the brain including the striatum and PFC. Modified from Overview of reward structures in the human brain, by Arias-Carrión et. al, 2010 (https://intarchmed.biomedcentral.com/articles/10.1186/1755-7682-3-24/figures/1_91). CC BY 3.0.

The prefrontal cortex

The prefrontal cortex (PFC) is the area of the cerebral cortex covering the frontal lobe. Dopamine in the PFC serves to regulate cognitive control and is responsible in part for attention, impulse inhibition, prospective memory, and cognitive flexibility functions (Pizzorno & Murray, 2020). In relation to PG, the PFC's role in impulse control is especially of note, as PG patients often struggle to properly manage gambling impulses. Additionally, increased activity in response to reward reception, such as that in gambling behaviors, has been demonstrated in the PFC (Choi et. al, 2012).

Brain imaging studies have been widely used to investigate the relationship between the PFC and PG. Certain cognitive tasks are known to typically trigger cerebral blood flow and metabolic responses in prefrontal cortical areas; however, in PG patients, this activity fails to occur or is diminished, indicating

diminished PFC function (Elman et. al, 2013). For example, decreased ventromedial PFC activity has been demonstrated in response to gambling cue presentation and incongruent stimulus presentation (Stroop task) in PG patients (Potenza et. al, 2003). Potenza et. al selected 13 PG patients and 11 healthy subjects (both groups were similar in age and all were high school graduates). Event-related fMRI imaging was used to analyze ventromedial PFC activity while subjects performed the Stroop task. While both PG and healthy subjects demonstrated activity changes in similar parts of the brain (which includes the right insula, right thalamus, and dorsal anterior cingulate), they differed mainly in activation of the left ventromedial PFC. PG patients demonstrated decreased activity in this region “with a lesser contribution from increased activity in healthy subjects” (Potenza et. al, 2003). The findings of this study indicate PFC hypoactivity may be characteristic of PG.

Gambling addicts have been demonstrated by fMRI scans to experience decreased ventromedial prefrontal activation (associated with impulse control) during inhibition tasks, indicating a lack of inhibition as well as altered reward response (Potenza et. al, 2003). fMRI studies, alongside other imaging and behavioral studies on PG patients, indicate impaired ventromedial PFC activity, executive function, and decision-making – overall, this points to “an alteration in the functional organization of the PFC” (Koehler et. al, 2013).

Fluid intelligence has not been demonstrated to differ between PG patients and controls (Koehler et. al, 2013). This indicates that although activation of the PFC in response to cognitive tasks has been shown to be diminished in PG patients, overall cognitive capacity does not appear to be affected by PG.

Ventral striatum

The ventral striatum (VS) is part of the basal ganglia of the forebrain. The VS itself consists of the nucleus accumbens and the olfactory tubercle. The VS is part of the reward system, and is thus associated with reward-seeking behavior such as that engaged in by gamblers. VS function has also been associated with reward responsiveness and motivational drives, and has been implicated to be associated with habit formations and compulsions (Leeman & Potenza, 2012).

Anticipation of reward is a function highly associated with the ventral striatum. In PG patients, decreased activation in the VS has been demonstrated during reward anticipation (Choi et. al, 2012). Choi et. al selected 15 male PG patients, 15 healthy controls, and 13 OCD patients (group-matched for age, sex, and gender) and analyzed brain activation using fMRI imaging during a monetary incentive task (Choi et. al, 2012). The team chose to focus on regions of interest within the anterior insula and ventromedial caudate nucleus, which is part of the ventral striatum, and found that PG subjects demonstrated decreased neural activity in the ventromedial caudate nucleus compared to OCD and healthy patients. These results indicate that VS hypoactivity may be a feature associated with PG.

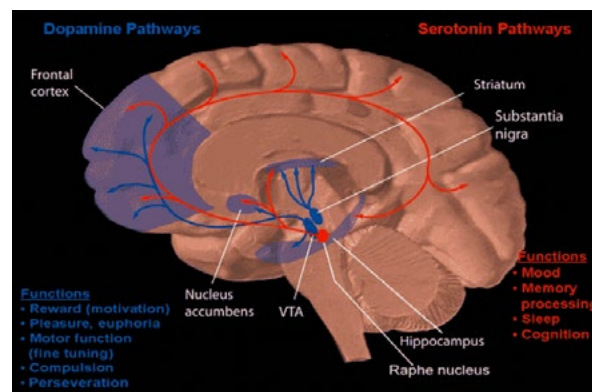
Other fMRI research corroborates the findings of Choi et. al (Reuter et. al, 2005). This same research indicated that reduced ventral striatal activity, along with ventromedial prefrontal activation, was negatively correlated with gambling severity. During simulated gambling tasks, PG patients showed diminished VS activation during anticipation of reward (Reuter et. al, 2005). The hypoactive state of the VS associated with PG indicates “decreased reward sensitivity, suggestive of high risk for addictive behavior” (Choi et. al, 2012). Other fMRI research found no correlation between participants’ scores on the Gambling Symptom Assessment Scale or the Kurzfragebogen zum Glücksspielverhalten questionnaire, which measures DSM-IV diagnosis criteria for PG, and functional connectivity between the PFC and VS (Koaehler et. al, 2013). This poses a contradictory conclusion that the interaction between the PFC and VS affects the probability of developing behaviors rather than the severity of PG symptoms. Thus, no clear conclusion can be drawn regarding whether ventral striatal activity is affiliated with severity of symptoms or merely the presence of symptoms.

Neurotransmitters linked to Pathological Gambling

Dysfunction of neurotransmitter systems is also evident in patients affected by PG. While links to several neurotransmitters such as norepinephrine have been suggested, dopamine and serotonin are the main two neurotransmitters implicated in PG. Excessive dopamine has been generally asserted to be associated

with PG, while diminished serotonin levels have been proposed in association with PG.

Figure 2
Dopamine and Serotonin Pathways



Note. From Dopamine and serotonin pathways, by National Institutes of Health, 2009 (<https://www.drugabuse.gov/pubs/teaching/largegifs/slide-2.gif>). In the public domain.

Dopamine

Dopamine (DA) is a neurotransmitter associated with executive function, motivation, arousal, reward, and reinforcement. These cognitive functions are highly associated with PG, which is characterized by reward-seeking behavior through the pursuit of monetary gain, as well as difficulty controlling gambling behaviors. Increased DA function and activity has been proposed to be associated with PG (Boileau et. al, 2014).

Ventral striatal DA synthesis capacity has been demonstrated to “correlate with inter-individual variation in disinhibitory personality traits” (Larence & Brooks, 2014), especially fiscal irresponsibility. The fact that ventral striatal DA synthesis capacity increases with tendencies of fiscal irresponsibility is consistent with the fact that these traits are present and associated with PG.

Additionally, dopaminergic response to oral amphetamines has been demonstrated by PET scan to be greater in PG subjects over control subjects (Bouileau et. al, 2014). This again supports the idea that dopaminergic function, being related to the reward-seeking nature of gambling, is altered in

patients with PG.

Increased DA activity has been demonstrated to promote risky gambling behavior such as that seen in PG patients. Researchers who studied loss-chasing – gambling intended to recover losses – administered pramipexole (PPX) to healthy adult subjects in order to test the relationship between DA and loss-chasing behavior. PPX is a dopamine D3/2 agonist; administering it replicates the effect of DA binding to receptors. Administration of PPX in the study “[increased] the value of losses that participants were willing to chase and, at the same time, [reduced the value of losses that participants were willing to surrender when quitting (Campbell-Meiklejohn et. al, 2010).” While overall, PPX did not increase the proportion of loss-chasing or consecutive loss-chasing decisions, the results of the study indicated that increased DA activity promoted riskier gambling behaviors.

However, conflicting research posits that DA production and function decreases with PG rather than increases. As discussed earlier, VS hypoactivity in PG patients indicates “decreased reward sensitivity, suggestive of high risk for addictive behavior (Choi et. al, 2012).” Choi et. al links VS hypoactivity to a hypodopaminergic state and decreased reward sensitivity. Additionally, a hypodopaminergic state has been previously attributed to substance abuse disorders including cocaine, methamphetamine, heroin, and alcohol dependencies (Boileau et. al, 2014). However, because of the inherent clinical and behavioral differences between substance abuse disorders and PG, it is not clear if these findings are generalizable to PG.

While increased DA production and function has been proposed to be associated with PG, there also exists evidence that contradicts this conclusion. The existence of a relationship between PG and abnormal DA levels is clear, but further research is necessary to define the nature of this relationship.

Serotonin

Serotonin is a neurotransmitter associated with, among others, the functions of behavioral initiation, inhibition, and aggression. Like dopamine, these functions are highly associated with the act of gambling. Studies surrounding the relationship

between serotonin and PG are less numerous than those surrounding the relationship between DA and PG. However, serotonergic dysfunction has still been demonstrated on multiple occasions to be associated with PG. Existing evidence has suggested both hyposerotonergic and hyperserotonergic states as being associated with PG.

Research into serotonin presence in PG patients has indicated a potential link between a hyposerotonergic state and PG. In male PG patients, hallmarks of a reduced serotonergic function have been demonstrated, namely diminished cerebrospinal fluid levels of 5-hydroxyindoleacetic acid and diminished platelet levels of monoamine oxidase activity (Iancu et. al, 2008). Additionally, research into the serotonin transporter (SERT) protein found decreased maximum binding capacity in PG patients (Marazziti et. al, 2008b). All of these factors indicate that decreased serotonergic production or function are associated with PG.

However, increased serotonin activity has also been proposed to be affiliated with PG behaviors. Research into loss chasing suggested a relationship between loss chasing and serotonin (Campbell-Meiklejohn et. al, 2010). Serotonin is made from the amino acid tryptophan, and the study made use of tryptophan depletion to test the effects of serotonin on loss-chasing behaviors. 34 healthy adult patients of mixed gender were selected by the research team to participate and followed a low-protein diet (<2g) the day before the study and faster overnight. During the study, the team administered drinks containing tryptophan to 17 subjects and administered drinks lacking tryptophan to 17 others before asking subjects to participate in a computerized loss-chasing game. To eliminate confounding variables, subjects were not informed of the probabilities of good or bad outcomes or how much play money they had accumulated during the game, and were told that they could not achieve the best outcome by either exclusively playing or quitting. Prior research referenced by the study indicated that tryptophan depletion, which would reduce serotonin activity, would be “expected to increase gambling to recover losses in [the study’s] healthy adult participants (Campbell-Meiklejohn et. al, 2010).” However, the opposite occurred, and tryptophan depletion actually resulted in a reduced proportion of loss chasing decisions in the study’s subjects. This would indicate that serotonin may play a role in loss

chasing, a noted PG behavior.

Compared to DA, serotonin's role in PG is less clearly defined. While it is clear that serotonin is affiliated with PG, evidence has surfaced that supports both increased and decreased serotonin activity/production in PG patients. More research is needed to define how abnormal serotonin activity contributes to PG and PG behaviors.

Pharmacological Treatment of Pathological Gambling

By understanding the previously demonstrated neurobiological bases of PG, treatment plans and interventions can be developed to address it in patients. By understanding how PG affects and is affected by the brain, particularly in relation to neurotransmitter systems, drug treatments can be developed to target PG. This section will review existing research on pharmacological interventions and their effectiveness in treating PG patients. However, instead of covering all existing research, this section focuses on interventions that have a firm foundation in existing literature.

Glutamate

The glutamatergic system is especially notable in how it has been investigated as being potentially of benefit in pharmacological treatment of PG. Glutamate is a principal excitatory neurotransmitter, and it has been proposed that addictions rise out of an impaired ability to inhibit drug seeking behaviors (Pettorruso et. al, 2014). Whether this conclusion is generalizable to PG is unclear, but based on this idea, the glutamatergic system has been proposed to be of use in the exploration of clinical treatments of PG. Furthermore, the nucleus accumbens, which makes up a vital part of the ventral striatum, is associated with reward-seeking behavior. Improving glutamatergic tone in the nucleus accumbens "has been implicated in reducing the reward-seeking behaviour in substance addictions (Grant et. al, 2012)."

Administration of agents associated with glutamate have yielded promising results. The administration of N-acetyl cysteine (NAC), which

modulates glutamate, to 27 PG patients over an 8-week period resulted in 59% of subjects experiencing significant reductions in PG symptoms during the open-label phase (Grant et. al, 2012). After another 6-week double-blind phase, 83% of subjects who received NAC experienced significant reductions compared to 28.6% of subjects who received the placebo. These results indicate that NAC may be of potential benefit as a pharmacological treatment for PG. Other research indicated that memantine, which reduces glutamate excitability, could be of potential benefit to PG patients by reducing cognitive and compulsive symptoms in PG patients (Pettorruso et, al, 2014). In a 10-week open-label trial, 29 PG patients experienced significant decreases in PG-YBOCS (Yale-Brown Obsessive Compulsive Scale modified for PG) scores as well as time spent gambling.

Considering glutamate's relationship to PG behaviors as well as existing clinical research on glutamate-related agents, investigating the glutamatergic system as a means of treating PG holds promise for future research. Glutamate-related agents such as NAC and memantine have already been shown to aid in relief of PG symptoms; further research may also prove successful and more significant if performed on a larger scale.

SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are medications which function through the inhibition of serotonergic reuptake, increasing serotonin activity (Chu & Wadhwa, 2022). They are commonly used as a treatment for depression and have a limited effect on the function and production of other neurotransmitters like DA. Considering the earlier discussed link between serotonin and PG, SSRIs have been proposed as being of benefit to PG patients.

Paroxetine is one such SSRI that has been investigated as a treatment for PG. Following a 1-week placebo phase, 45 PG patients either received a placebo or paroxetine over 8 weeks (Kim et. al, 2002). Patients who received paroxetine may also have received increasing doses. Statistically significant reductions in scores on the Gambling Symptom Assessment Scale and Clinical Global Impressions were observed in the paroxetine group over the placebo group, indicating that paroxetine may be

beneficial in treating PG.

Fluvoxamine is another SSRI that has been investigated as a treatment for PG. However, research into fluvoxamine has yielded mixed results in double-blind studies. One 16-week crossover study supported its efficacy with an average dose of 207 mg/day, but a longer 6-month parallel-arm study found no significant difference between fluvoxamine recipients and placebo recipients (Grant et. al, 2012). It is important to recognize that the latter study had high drop-out rates. Still, the mixed results mean that fluvoxamine cannot yet be reliably suggested as a treatment for PG symptoms.

Investigation into other SSRIs yielded no significant results at all. Investigation into sertraline, another SSRI, demonstrated no significant difference in improvement between placebo and active-recipient PG subjects over 6 months (Grant et. al, 2012). SSRIs theoretically hold promise as potential treatments for PG symptoms due to the relationship between serotonin and PG. However, just like research into the serotonergic system's role in PG, clinical research into SSRIs have resulted in very mixed results. SSRI treatments as a group are worth investigating, but studies should be conducted on individual treatments to indicate clinical significance.

Conclusion

Research into the neurobiological bases of PG is best characterized as mixed evidence. While hypoactivity in brain regions such as the prefrontal cortex and ventral striatum has been strongly indicated by existing research, neurotransmitter systems of dopamine and serotonin are less clearly defined. For both of the neurotransmitter systems discussed in this review, findings support both hyperactivity and hypoactivity as being potentially associated with PG, although DA is more strongly implicated to be associated with increased production and function than serotonin is with either increased or decreased levels. Similarly, studies done on pharmacological treatments for PG have not all yielded clear results. While some treatments such as NAC, memantine, and paroxetine have been indicated by clinical research to hold significant promise as treatments for PG symptoms, other treatments such as fluvoxamine and sertraline did not appear to be as strongly supported. While

glutamate-related agents and SSRIs hold promise, it appears that individual treatments should be investigated and these groups of treatments cannot be generalized as beneficial or not.

Overall, existing research is promising in determining the neurobiological bases of PG as well as potential treatments for its symptoms. In the case of particular brain regions, hypoactivity of the PFC and VS are strongly supported by existing research. However, more research is necessary to indicate the exact relationships between neurotransmitter systems and PG as well as determining future pharmacological treatments for PG symptoms.

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