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# Pathological gambling in Parkinson's disease: what are the risk factors and what is the role of impulsivity?

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## Abstract

The incidence of pathological gambling in Parkinson's patients is significantly greater than in the general population. A correlation has been observed between dopamine agonist medication and the development of pathological gambling. However, scientists conjecture that the affected patients have underlying risk factors. Studies analysing Parkinson's patients have detected that patients who developed pathological gambling are younger, score higher on novelty-seeking tests, are more impulsive and are more likely to have a personal or family history of alcohol addiction. In addition, some genetic variations have been associated with the susceptibility of developing pathological gambling, which include mutations of DRD3, 5-HTTLPR and GRIN2B. Studies focusing on neurofunctional discrepancies between Parkinson's patients with and without pathological gambling have found increased functional activation and dopamine release in regions associated with the mesolimbic reward system. Furthermore, there is also evidence showing increased processing of reward and decreased activation elicited by punishment, suggesting altered learning processes. Furthermore, the role of deep brain stimulation of the nucleus subthalamicus (STN DBS) is controversial. In most Parkinson's patients, pathological gambling resolved after the initiation of the STN DBS, which might be explained by discontinuation or decrease in dopamine agonist medication. However, it has been also shown that some patients are more impulsive while the STN DBS is activated. These differences may depend on the DBS localization in the more limbic or motor part of the STN and their regulative effects on impulsivity. Further research is needed to clarify susceptibility factors for the development of pathological gambling in Parkinson's patients.

## Introduction

Pathological gambling is defined in the current classification system of the World Health Organization (1992) (ICD-10) as an impulse control disorder (ICD) which causes excessive, uncontrollable gambling despite financial losses and social problems, while the latest version of the *Diagnostic and Statistical Manual* (*DSM-5*) of the American Psychiatric Association (2013) grouped pathological gambling together with substance-related and addictive disorders and renamed it to gambling disorder. Despite this aetiological debate, in Parkinson's patients it has been observed that pathological gambling occurs more frequently (3.4–6.1%) than in the general population (0.25–2%), alongside with ICDs, such as binge eating, so called hypersexuality and compulsive shopping (Cox *et al.*, 2005; Avanzi *et al.*, 2006; Grosset *et al.*, 2006; Voon *et al.*, 2006; Bondolfi *et al.*, 2008; Weintraub *et al.*, 2010; Santangelo *et al.*, 2013). The aetiology of the development of pathological gambling in Parkinson's disease is still unclear, however, research suggests an association with dopamine replacement therapy, specifically with dopamine agonists (Voon *et al.*, 2006; Weintraub *et al.*, 2006; Gallagher *et al.*, 2007). This review summarizes evidence in this field of research attempting to reveal the relationship between Parkinson therapy and pathological gambling, discusses the reasons why some patients react on them differently than others, what the relevant risk factors are and considers how impulsivity may contribute to the development of gambling symptoms.

## Risk factors

Several risk factors have been identified after studying Parkinson patients with pathological gambling. Voon *et al.* (2007) found that these patients are younger, earned a higher score in tests investigating novelty-seeking and impulsive behaviour, and were more likely to have a personal or family history of alcohol abuse. Being male and smoking in the past also seem to be risk factors (Gallagher *et al.*, 2007; Valença *et al.*, 2013). In this respect, pathological gambling with and without Parkinson's disease is rather similar: young age, male sex, impulsivity, novelty-seeking, smoking and alcoholism are also considered risk factors for pathological gambling in the general population (Johansson *et al.*, 2009). Observing the progress of

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their disease, in comparison to other Parkinson's patients, those who later develop pathological gambling tend to have an earlier onset of the illness and also suffer more frequently from manic or hypomanic episodes during the on-period of dopaminergic medication (Voon *et al.*, 2007).

## Association with Parkinson's disease therapy

Even in the first case reports about Parkinson's patients developing pathological gambling, a clear correlation has been observed with the initiation or dose escalation of dopaminergic medication (Molina *et al.*, 2000; Seedat *et al.*, 2000). In further studies comparing the effect of different Parkinson's therapies, dopamine agonists emerged as the medication with the strongest association with the development of pathological gambling (Voon *et al.*, 2006; Weintraub *et al.*, 2006, 2010; Gallagher *et al.*, 2007). Some studies claim that pramipexole could have the largest effect (Dodd *et al.*, 2005). Other studies systematically comparing different dopamine agonists have found no significant difference between each of them (Weintraub *et al.*, 2006; Gallagher *et al.*, 2007). Recent research also shows a strong effect of aripiprazole, prescribed for the treatment of mood disorders and schizophrenia, with stronger gambling-related cognition in comparison to other dopamine agonists (Grall-Bronnec *et al.*, 2016).

Levodopa seems to play a less important role as only a few patients developed pathological gambling under levodopa monotherapy (Dodd *et al.*, 2005; Voon *et al.*, 2006; Gallagher *et al.*, 2007), however, studies suggest that additionally prescribed levodopa raises the risk of the development of pathological gambling and ICDs (Dodd *et al.*, 2005; Weintraub *et al.*, 2010). Particularly high doses and long-term use of levodopa and short-acting dopamine agonists are also associated with dopamine dysregulation syndrome and punding, that is, stereotypic behaviour (Gallagher *et al.*, 2007).

Further, subthalamic nucleus deep brain stimulation (STN DBS) has a controversial role in the development of pathological gambling in Parkinson's disease. It has been observed that after the initiation of STN DBS therapy, gambling symptoms resolved (Ardouin *et al.*, 2006; Bandini *et al.*, 2007; Castrioto *et al.*, 2014). These results could be explained by the significant reduction in the dosage of dopamine agonist medications. However, in some individual cases, pathological gambling and/or impulsive behaviour only developed after STN DBS surgery (Funkiewiez *et al.*, 2003; Contarino *et al.*, 2007; Smeding *et al.*, 2007; Hälbig *et al.*, 2009; Demetriades *et al.*, 2011); although in these cases the symptoms resolved spontaneously or after the change in stimulation parameters and further reduction in dopaminergic therapy. This could be associated with the stimulation of the limbic subregion of the STN which has been shown to affect neurotransmission in the limbic basal ganglia-thalamocortical circuitry (Winter *et al.*, 2008). Evidence also shows that patients are more impulsive after activating STN DBS (Frank *et al.*, 2007; Hälbig *et al.*, 2009). As impulsivity is considered as a risk factor for developing pathological gambling in Parkinson patients (Voon *et al.*, 2007), the contentious effects of STN DBS raise questions about the role of impulsivity in the development of gambling behaviour in general (Table 1).

## Genetic predisposition

The fact that not all Parkinson's patients develop medication-associated impulse control disorders or pathological gambling and that most of the patients solely developed pathological gambling under dopaminergic medication suggests an underlying genetic vulnerability mechanism (Voon *et al.*, 2006). To analyse the genetic susceptibility of Parkinson's patients with pathological gambling, several genes have been examined that are relevant for the function of the mesolimbic reward system. The most obvious genes to investigate are the dopamine receptor genes, which could be affected by dopaminergic medications. Some studies suggest that a certain mutation of the DRD2 gene (Taq1A) is more frequent in pathological gamblers than in the general population (Lobo *et al.*, 2010). This variation in the gene may be connected to a lower density of D2-receptors in the striatum (Thompson *et al.*, 1997) and to impulsivity (Eisenberg *et al.*, 2007), while the literature is inconclusive regarding its potential role in alcohol addiction (Heinz *et al.*, 1996; Heinz & Goldman, 2000; Munafò *et al.*, 2007). However, no significant difference was found between the frequency of this mutation between Parkinson's patients with and without pathological gambling (Lee *et al.*, 2009). Interestingly, recent case reports suggest that not only dopamine agonists but also dopamine antagonists acting on the D2 receptors can trigger pathological gambling (Grötsch *et al.*, 2015), which underlines the role of this receptor. On the other hand, the homozygote genotype of a single nucleotide mutation

TABLE 1. Main results of studies on the association of pathological gambling with Parkinson's disease therapy

| Study | Sample | Main results |
|---|---|---|
| Ardouin *et al.* (2006) | 7 PD patients with PG | After STN DBS PG resolved, possibly due to reduction in dopaminergic medication |
| Bandini *et al.* (2007) | 2 PD patients with PG | After STN DBS and reduction in dopaminergic medication PG resolved |
| Castrioto *et al.* (2014) | 20 PD patients after STN DBS | IGT score significantly improved after STN DBS and reduction in dopaminergic medication |
| Contarino *et al.* (2007) | 11 PD patients after STN DBS | Transient ICD after STN DBS surgery |
| Dodd *et al.* (2005) | 11 PD patients with PG | Strong association with DA, PG did not develop under L-dopa monotherapy, but L-dopa might be contributory |
| Funkiewiez *et al.* (2003) | 50 PD patients after STN DBS | Transient ICDs after STN DBS surgery |
| Frank *et al.* (2007) | 32 PD patients | Higher impulsivity on STN DBS |
| Gallagher *et al.* (2007) | 177 PD patients with PG | Strongest association with DA; no clear difference between each DA; L-dopa the most frequently co-prescribed medication |
| Hälbig *et al.* (2009) | 53 PD patients | Higher BIS scores in PD patients with STN DBS; ICD more frequent in patients after STN DBS |
| Voon *et al.* (2006) | 297 patients with PD | PG more frequent in patients with DA monotherapy and DA + L-dopa then L-dopa monotherapy; no association to dose |
| Weintraub *et al.* (2006) | 272 patients with PD | No difference between each DA; higher LEDD associated with ICDs |
| Weintraub *et al.* (2010) | 3090 patients with PD | Highest ICD frequency in patients under combined DA and L-dopa therapy; strong association with DA; no difference between DA medications |

BIS, Barratt Impulsivity Scale; DA, dopamine agonists; ICD, impulse control disorder; IGT, Iowa gambling task; LEDD, L-dopa equivalent daily dose; PD, Parkinson's disease; PG, pathological gambling; STN DBS, subthalamic nucleus deep brain stimulation.

(p.S9G) of the DRD3 gene has been shown to have a higher frequency in pathological gamblers with Parkinson's disease (Lee *et al.*, 2009). This mutation is not associated with increased risk for pathological gambling in the general population (Lobo *et al.*, 2010). However, the heterozygote genotype of this mutation has been reported to be linked to impulsivity (Retz *et al.*, 2003; Limosin *et al.*, 2005). This mutation was also associated with decreased response rate to pramipexole in Parkinson's patients (Liu *et al.*, 2009), which could result in higher prescribed dosage. According to our current knowledge, there has not been any study performed yet to assess the relationship between DRD4 mutations and pathological gambling in Parkinson's patients. However, the number of tandem repeats of a 48-bp region in the DRD4 gene is associated with pathological gambling, substance abuse and impulsivity, with discordant results of what number of repeats is relevant (de Castro *et al.*, 1997; Comings *et al.*, 1999; Eisenberg *et al.*, 2007). Healthy subjects with this genotype also presented an increased gambling behaviour after receiving L-DOPA (Eisenegger *et al.*, 2010).

Another neurotransmitter system that has been shown to be affected in patients with pathological gambling is the serotoninergic system. de Castro *et al.* (1999) have observed a significantly higher frequency of the short (S) allele of the promoter region of the serotonin transporter gene, 5-HTTLPR, in male pathological gamblers compared to the general population. The S allele of 5-HTTLPR has also been associated with increased risk of developing depression under stress (Karg *et al.*, 2011), some aspects of impulsivity (Sakado *et al.*, 2003), impulsive aggression and increased activity in the amygdala after negative affective visual stimuli (Heinz *et al.*, 2011). An association between this mutation and pathological gambling has indeed been observed in patients with Parkinson's disease (Lee *et al.*, 2009).

Another mutation that may be associated with pathological gambling in Parkinson's patients is the mutation of GRIN2B (Lee *et al.*, 2009). GRIN2B is a gene from the 2B subunit of the NMDA receptor, which is mainly expressed in the hippocampus, the striatum and also the cortex (Loftis & Janowsky, 2003). The variation found to be more frequent in Parkinson's patients with pathological gambling is a single nucleotide polymorphism. Its specific role in the development of pathological gambling in Parkinson's disease is unclear, as this variation does not cause an amino acid change (c.366C>G). Furthermore, it was also found to be associated with schizophrenia (Li & He, 2007), as a different polymorphism of GRIN2B has been associated with obsessive compulsive disorder (Arnold *et al.*, 2004). Nevertheless, Ness *et al.* (2011) found a different single nucleotide polymorphism of the GRIN2B gene to be related with risky decision-making, which might be considered as impulsive behaviour and therefore explain a link to PG in Parkinson's disease.

These research findings suggest that an underlying genetic susceptibility might facilitate the development of pathological gambling in Parkinson's patients. However, some studies are inconsistent and there are some differences between pathological gamblers with and without Parkinson's disease. Altogether, these results and the observed connection to dopaminergic medication described above suggest that the vulnerability of Parkinson patients towards pathological gambling may be triggered by dopamine agonists.

## Neurofunctional alterations

Several studies have compared neuronal activation patterns of Parkinson's patients with and without pathological gambling. Summarizing the results, differences have been found in the activity of regions associated with the mesolimbic reward system, mainly in the orbitofrontal cortex (OFC) and the ventral striatum (Cilia *et al.*, 2008; Steeves *et al.*, 2009; Voon *et al.*, 2010). For example, Cilia *et al.* (2008) compared the blood perfusion of different brain regions in Parkinson's patients with pathological gambling with patients who only have Parkinson's disease and a control group in a SPECT imaging study in a resting condition. They have observed a generally increased blood flow in the OFC, hippocampus, parahippocampal gyrus, amygdala, ventral striatum and cuneus on the right hemisphere and in the insulae on both sides in Parkinson's patients with pathological gambling compared to both other groups.

Rosa *et al.* (2013) studied the function of the subthalamic nucleus by capturing local field potentials (LFP) in Parkinson's patients with and without pathological gambling on medication during an economic task. The LFPs were recorded with the aid of STN DBS electrodes that were implanted 4 days prior to the experiment. The economic task included non-conflict and conflict decisions with stimuli pairs with the same probability vs. stimuli pairs with different probabilities of winning money. In conflict situations, risky choices could result in a higher reward, however, the task was overall designed to reward more non-risky choices. The results showed that during the economic decision-making task, low-frequency oscillations synchronize in the subthalamic nucleus. This synchronization was stronger during high-conflict situations in comparison to low-conflict situations in patients with pathological gambling. Patients without pathological gambling showed no differences in the synchronization of low-frequency oscillations during conflict or non-conflict situations. The results of this experiment underline the role of the subthalamic nucleus in decision-making and might also explain why symptoms of pathological gambling resolve in some Parkinson patients after STN DBS surgery. However, the results do not explain why patients usually only improve after months of STN DBS therapy.

Some studies focused more on the dopaminergic system and several differences were found between pathological gamblers with Parkinson's disease and Parkinson's patients without gambling. The turnover of monoamines, including dopamine, in the OFC was found to be higher (Joutsa *et al.*, 2012), further the dopamine release during gambling tasks was found to be significantly increased in pathological gamblers (Steeves *et al.*, 2009). These results suggest that the vulnerability to gambling problems is partly mediated by increased dopaminergic neurotransmisson the OFC and the ventral striatum. Pathological gambling in these patients may be caused by dopamine agonists in the mesolimbic dopaminergic system, particularly in the ventral striatum, which is less affected by the disease than the dorsal striatum.

As dopamine agonist therapy seems to have a very strong association with the development of pathological gambling (Voon *et al.*, 2006; Gallagher *et al.*, 2007; Weintraub *et al.*, 2010), imaging studies have been conducted to further understand the effect of this medication. Dopamine agonists have been shown to effect reward processing; patients on this medication have a diminished reaction in the OFC after negative prediction errors compared to patients on levodopa therapy or off medication (Van Eimeren *et al.*, 2009), suggesting a decreased learning effect after punishment. Voon *et al.* (2010) also found evidence supporting this theory – Parkinson's patients with and without pathological gambling or compulsive shopping were compared in a prediction learning task on or off dopamine agonists. Patients with pathological gambling were faster and better at learning and had a higher activity in the ventral striatum and the OFC during reward-related learning while on medication. On the contrary, while learning through loss, the activity of these areas was lower in this group of patients than in the group

with Parkinson's disease only under the same circumstances. Ray *et al.* (2012) suggest that these patients have an impaired activation of D2- and D3-autoreceptors caused by tonic stimulation through dopamine agonists. Through the absence of negative feedback, the dopamine concentration is more constant than in patients not suffering from pathological gambling. These findings could be used to propose that dopamine agonists cause a higher vulnerability to pathological gambling due to impaired learning processes. As a consequence of the impaired negative feedback, the dopamine concentration would not decrease to the previous level after a reward-related dopamine release. The high level of dopamine could also blunt the drop of dopamine concentration after punishment. This might result in a reward-based learning with a decreased learning effect from punishment.

Imaging studies with non-Parkinson patients with pathological gambling also showed differences in the activation of the mesolimbic rewards system, however, the results are not consistent. Some studies showed a reduced activation of the prefrontal cortex and ventral striatum during loss and gain anticipation as well (Balodis *et al.*, 2012; Choi *et al.*, 2012), others showed higher activity in the striatum during gain anticipation (Romanczuk-Seiferth *et al.*, 2015). The activity of the prefrontal cortex and the ventral striatum also seems to be diminished after successful loss avoidance compared to healthy control subjects (Romanczuk-Seiferth *et al.*, 2015). Neuronal activity during loss and gain anticipation and loss avoidance have not been researched yet in Parkinson's patients with pathological gambling.

## The role of impulsivity

As described above, impulsive behaviour is considered to be a general risk factor for developing pathological gambling in patients with Parkinson's disease (Voon *et al.*, 2007; Johansson *et al.*, 2009). However, there are studies that indicate a more specific connection: Frank *et al.* (2007) compared two groups of patients with Parkinson's disease with a control group, assessing their learning ability in a probabilistic prediction task and their performance in a conflict-based decision task. One of the groups of Parkinson's patients was treated with dopaminergic medication, the other group with STN DBS and low-dose dopaminergic therapy. The first group's performance was compared on and off medication, the second group's performance on and off STN DBS without changing the dosage of their medication. The results in the prediction task in the group taking dopaminergic medication only were similar to the findings of Voon *et al.* (2010) described above, that is, the learning ability of patients from negative outcome was impaired on medication. The activation of deep brain stimulation showed no effect on the learning ability of the patients, neither after reward nor after punishment. On the other hand, in the conflict-based decision task, patients with activated STN DBS responded faster in high- rather than in low-conflict conditions, while off deep brain stimulation, their response was slower during high-conflict situations. Dopaminergic medication did not affect the difference in decision-making speed in high- vs. low-conflict conditions. These results suggest that deep brain stimulation promotes higher impulsivity. This result is supported by other experiments assessing patients with STN DBS clinically with the Barratt Impulsiveness Scale (Hälbig *et al.*, 2009) and the Simon task (Wylie *et al.*, 2010).

If high impulsivity can promote pathological gambling, as suggested by the results of Frank *et al.* (2007), there should be a higher risk for Parkinson's patients treated with STN DBS. However, there are only individual cases of patients developing pathological gambling after initiation of deep brain stimulation (Smeding *et al.*, 2007), with no clear way of interpretation, because dopaminergic medication had also been changed post-operatively. For example, Hälbig *et al.* (2009) found a higher frequency of impulse control disorders (ICDs) in Parkinson's patients treated with STN DBS. However, the difference in prevalence of ICDs to the patient group only receiving drug therapy was not significant and it was not described when these patients developed ICDs and how long they had already received DBS therapy. This information is relevant, as the recovery from ICDs after the initiation of DBS therapy can take up to 4 years and in some cases the symptoms initially worsen after the therapy (Ardouin *et al.*, 2006). The effects on impulsive and compulsive behaviour of STN DBS can also depend on the localization of the electrodes. The stimulation of the limbic subregion of the STN or the stimulation of adjacent structures can change the neurotransmission in limbic brain regions (Winter *et al.*, 2008). These findings question the causal relationship between high impulsivity and pathological gambling in Parkinson's patients. Altogether, more research is needed for clarification of the effects of STN DBS. On the other hand, the results of those studies comparing the effect of STN DBS and dopamine agonist medication support the theory that Parkinson's patients with pathological gambling show impaired learning mechanisms modulated by dopamine agonists. Therefore, alterations of reward and punishment processing seem to play a prominent role in the development of pathological gambling in Parkinson's patients.

## Conclusions

Several genetic and neurofunctional findings suggest that individual differences in dopaminergic neurotransmission in the ventral striatum and associated brain areas contribute to pathological gambling in Parkinson's disease, and indicate complex interactions between such risk factors. Taken together, altered learning processes in Parkinson's patients with pathological gambling appear to include increased baseline blood perfusion of mesolimbic brain areas, increased activation by reward and reduced activation by punishment in those brain areas, which are implicated in reinforcement learning (Schultz, 2002), impulsivity (Horn *et al.*, 2003), addiction (Kalivas & Volkow, 2005) and pathological gambling (Romanczuk-Seiferth *et al.*, 2015).

However, most of the studies performed in Parkinson's patients with pathological gambling are retrospective or cross-sectional research, which makes the analysis of potentially causal factors more difficult. For example, in cross-sectional studies, impulsivity seems to be an important risk factor (Voon *et al.*, 2007); however, these findings are not fully consistent with the results of experimental studies on the effects of DBS of the STN. Prospective or longitudinal studies could broaden the perspective on the role of potential risk factors, that is, impulsivity or impaired learning. Despite the obstacles in conducting such studies, the results of this research can play a crucial role in understanding the development of pathological gambling and ICDs not only in Parkinson's patients but also in the general population.

## Conflict of interests

No conflicts declared.

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