

PATHOLOGICAL GAMBLING IN PD: DISEASE OR DRUG RELATED?

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A group of disorders sharing a failure to resist an impulse to perform a typically pleasurable activity that is finally harmful to the person or to others are known under the common denomination of impulse control disorders (ICDs). Many of these abnormal behaviours are increasingly recognized in patients with Parkinson's disease (PD) and the augmented risk of suffering the devastating social and personal consequences of pathologic gambling has emerged in PD as one of the most prominent concerns related to ICDs. Nevertheless, a recently published key paper (Weintraub et al, Arch Neurol 2010) found that the point prevalence of ICDs was 13.6% and made clear that gambling (5%) and nongambling ICDs such as compulsive sexual behavior (3.5%), or compulsive buying (5.7%) occur at a similar frequency in a big PD sample. These disorders are especially seen in PD patients with young age of onset, higher doses of antiparkinsonian drugs, pre-existent or current depression, pre-existing recreational drug or alcohol use, and high novelty seeking personality traits. Compelling evidence has stressed the relation between dopaminergic replacement and development of ICDs in PD, especially but not exclusively, with dopamine agonist therapy. Nevertheless, the pathophysiology of underlying mechanisms is not fully understood. The question arises as to whether pathologic gambling and the other ICDs has to be considered pure adverse side-effects of dopamine replacement therapy or, as it is the case with hallucinations, it is the disease itself which facilitates ICDs to appear. From a clinical point of view, there may be arguments for both opinions. On one side, pathologic gambling and other ICDs appearing in restless legs patients treated with dopamine agonists (Cornelius et al., Sleep. 2010) demonstrates that dopaminergic medications used in a non-PD population can trigger the same behaviors, further supporting the concept that the medications, rather than the underlying disease process, are predominantly to blame. On the other side, the emergence of pathologic gambling in PD patients following STN-DBS despite a significant reduction or discontinuation of dopamine agonists indicates that STN-DBS *per se* may be a potential initiator of pathologic gambling, further supporting the concept of an underlying malfunctioning of the structures supporting reward and reinforcement. Hence, it well may be that the two arguments are not mutually exclusive being pathologic gambling in PD both disease- and drug-related.

Dopaminergic mesolimbic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, as well as associated frontostriatal circuitry, play a major role in the mechanisms of reward-based learning, motivation, and impulse control. Dopamine has a major role in promoting the allocation of effort (Niv et al., 2007; Salamone et al., 2005), in potentiating responding for conditioned reinforcement (Everitt and Robbins, 2005; Hernandez et al., 2006; Phillips et al., 2003; Schultz, 2006), or setting the gain on incentive salience attribution (Berridge, 2007).

A number of mechanisms have been proposed to explain why persistently elevated dopaminergic stimulation promotes the development and maintenance of addictive behaviors. Chronic non-physiological neuronal stimulation with dopaminergic drugs may alter the role of dopamine in the reinforcement of learning algorithms which allow a comparison of actual and expected outcomes (computation of prediction error) updating subject predictions and influencing subsequent choices. Particularly, dopaminergic overstimulation might increase the rate of learning from gain outcomes distorting estimation of gain cues. Likewise, chronic agonism may increase striatal prediction of error activity, implying a "better than expected" outcome, producing a choice bias towards gains. Chronic stimulation of a particular region of dopamine receptors leading to behavior sensitization may impair reward processing and inhibitory control mechanisms causing a shift from goal-directed behaviors to habit formation in ways that promote pathological repetition of behaviors. Complementary, tonic stimulation of dopamine receptors might specifically desensitize the dopaminergic reward system by preventing decreases in dopaminergic transmission (pauses) that occurs with negative feedback thereby impairing the negative reinforcing effect of losing. Interestingly, a study using functional magnetic resonance imaging found that tonic dopaminergic stimulation with

dopamine agonists in PD patients, specifically diminished reward processing in the lateral orbito-frontal cortex (OFC) by relatively increasing activity during negative errors of reward prediction (van Eimeren T, et al., *Neuropsychopharmacology* 2009).

Abnormality in dopaminergic binding and dopamine release similar to that previously demonstrated in patients with drug addictions, have also been observed in functional neuroimaging studies in PD patients with pathological gambling. A study using SPECT in PD patients with pathological gambling showed a resting state overactivity (enhanced dopamine release) of the mesocorticolimbic network (right OFC, hippocampus, amygdala, insula, and ventral pallidum) (Cilia et al., *Arch Neurol* 2008).

A study using [(11)C] raclopride positron emission tomography (PET) compared dopaminergic function during gambling in PD patients, with and without pathological gambling, following dopamine agonists. Patients with pathological gambling demonstrated greater decreases in binding potential in the ventral striatum during gambling (13.9%) than control patients (8.1%), likely reflecting greater dopaminergic release. Notably, ventral striatal bindings at baseline during control task were also lower in patients with pathological gambling. (Steeves TD, et al., *Brain* 2009). Similar results of reduced tracer binding in the ventral striatum of PD patients with PG compared to PD controls, was found in a recent SPECT study (Cilia R, et al, *Neurobiol Dis* 2010). These latter results were interpreted as possibly reflecting either a reduction of mesolimbic projections or, alternatively, a lower membrane DAT expression on presynaptic terminals (Cilia R, et al, *Neurobiol Dis* 2010).

Nevertheless, unphysiologic chronic dopaminergic exposure does not explain different susceptibility in developing pathologic gambling or other ICDs in patients being exposed to similar doses and duration of dopaminergic replacement. Besides overfunctioning and sensitization/desensitization effects due to overexposure to dopaminergic drugs, pathological changes in the same structures critical for reward processing and negative feed-back learning may also contribute to bias decision making processes predisposing PD patients to the different behavioral manifestations of ICDs. Differences in striatal denervation patterns of dopamine neuronal cell loss (Damier P, et al, *Brain* 1999), early pathological involvement of the amigdala (Braak H, et al., *Neurology* 2005) and the orbitofrontal cortex (OFC) might also be implicated. Notably, stereotyped behaviors, compulsions, impulsivity, hypersexuality, and even pathological gambling have been described in the frontal lobe variant of fronto-temporal dementia (Lo Coco and Nacci, *J Neuropsychiatry Clin Neurosci* 2004; Passant et al., *Alzheimer Dis Assoc Disord* 2005) in patients not exposed to dopaminergic drugs. Nondemented patients with mild PD studied with high resolution RM show significant cortical thinning in the temporal, inferior parietal, rostral frontal, and orbitofrontal cortical areas with a topographical distribution similar to that of the neocortical Lewy bodies (Lyo CH, et al., *Mov Disord* 2010). Moreover, impairment in decision-making and recognition of facial emotions can be observed at the early stages of PD accompanied by degeneration of OFC and amygdala (Ibarretxe-Bilbao N, et al., *Eur J Neurosci*. 2009). Thus, intrinsic dysfunction of these structures implicated in impulse control and feed-back learning might also contribute to the emergence and persistence of pathological gambling in PD by distorting the capacity to appropriately guide behaviour when facing negative consequences.

Accordingly, unmedicated PD patients demonstrate an impaired mesolimbic reward prediction response and diminished functional connectivity of the ventral striatum with other regions of the limbic cortex, suggesting a neural substrate that may predispose to the development of ICDs.

The hypothesis of a contribution of the intrinsic PD pathology to render patients predisposed to behave as pathological gamblers or to suffer other ICDs may also be approached in non-ICD PD patients by examining their sensitivity to reward and punishment and the relationship of these behaviours to their cognitive status.

We used the Iowa Gambling Task (IGT) and a comprehensive neuropsychological battery to further characterize the relationship between limbic and cognitive dysfunction in a representative sample of nondemented PD patients without antecedents of ICD. PD patients performed significantly worse on the IGT by making disadvantageous choices characterized by immediate large rewards and delayed larger punishments confirming subclinical dysfunction of the limbic system. No clear relationship with demographic variables including dopaminergic treatment and motor response to levodopa (stable or fluctuating) emerged. As it was observed in other studies, performance on the IGT was not related to executive function. In contrast, an inverse relationship was found between the IGT and memory and global cognitive performance, with patients with the better global cognitive score and memory scores performing significantly worse on the IGT. Although impaired decision-making appeared unrelated to executive

dysfunction, notably patients with the better cognitive status appeared more prone to assume risky behaviors. (Pagonabarraga J et al., Mov Disord 2007). In contrast to that observed in non ICDs samples, a recent study showed that PD patients with ICD had poorer working memory performance than either controls or PD patients without ICD. PD plus ICD patients also showed decreased learning from negative feedback and increased learning from positive feedback in off compared with on dopaminergic medication. (Djamshidian A, et al., Mov Disord 2010).

Conclusions: The emergence of pathological gambling and other ICDs in a number of PD patients may require the interaction of dopaminergic therapy, premorbid personality and progression of disease. More data on the interaction between dopaminergic overstimulation and relatively subtle changes produced by the disease itself in the brain structures mediating reward and decision making may help to explain why some patients in spite of not having an addictive profile or addictive drug behaviour makes the bad decision of continuing gambling in the face of adverse consequences.