

## Pathological gambling disorder: definition, clinical contexts and therapeutic approaches

### Review article

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### Abstract

Starting from the categorical definition of “pathological gambling disorder”, we proceeded to list the individual characteristics, with particular attention to the statistical, clinical, neurobiological and therapeutic profiles, concluding the analysis of the possible strategies to be used to finalize the resolutions to the problems, arising from the disturbance in question.

### Definition and clinical context of pathological gambling disorder

Pathological gambling is a behavioral disorder, therefore a behavioral dependence, which is part of the diagnostic category of impulse control disorders. Like a drug addiction, the pathological gambler shows a growing loss of control over gambling, increasing the frequency of bets, the time spent playing, the amount squandered in the apparent attempt to recover the losses by investing more of their economic possibilities and neglecting the commitments that life requires of them [1-2].

Gambling therefore means a form of entertainment in which the player bets a certain amount of money or valuable goods on the outcome of an event with an uncertain outcome in order to win a greater amount of money or to win the items at stake. Although it is commonly perceived as a recreational activity, if played excessively, gambling can have negative consequences up to becoming a real pathology. In the latest edition of the Diagnostic and Statistical Manual of Mental Disorders, the “Gambling Disorder” was included among the “Substance-

free Disorders” within of the new diagnostic category of “Dependency disorders and substance-related disorders”. For the first time, therefore, this pathology is recognized as a dependency since, although there are no substances, the three basic components are considered to be the common component of all addictions, namely obsessiveness, impulsivity and compulsion. In its clinical definition of persistent, recurrent and maladaptive behavior behavioral indicators (such as increasing the frequency of play to try to recover losses), emotional and psychological correlates (such as being excessively absorbed by the game) and social problems are considered cheap (like having jeopardized or having lost a significant relationship due to gambling).

In addition to the compulsive aspects, pathological gambling is characterized by typical cognitive distortions, such as the illusion of control over the outcome of the plays and the distorted perception of the so-called “quasi-winnings”, that is, game situations in which a combination occurs which it approaches that chosen by the bettor perceived as an approximation of a success and therefore as an incentive to continue with the bets. In the most serious cases this compulsive hypothesis is associated with

dissociations of different degrees, capable of keeping the subject “glued” to the screen even for several consecutive hours without feeling tired. Distorted cognitions appear to be common among pathological gamblers (Joukhador et al, 2003) and some cognitive models consider them a central element of the disorder (as in the case of the Pathways Model of Problem and Pathological Gambling by Blaszczynski and Nower, 2002, one of the most influential cognitive-behavioral matrix reports regarding pathological gambling). Pathological gamblers can easily remember the victories due to a heuristic availability (Tversky and Kahneman, 1974), they may not be able to carefully consider the odds of winning compared to the risk of loss (Fletcher et al., 2011) and can erroneously attribute the winnings to personal skills due to an illusion of control (Langer, 1975). Pathological gamblers often give bizarre explanations of the game they play and why they play. Often their knowledge is situational and individual players can simultaneously support beliefs that are not logically consistent (MacLaren et al., 2011). For example, a gambler could continue to bet after a series of losing results and accept the “gambler’s fallacy”, that is the belief that a winning result should be imminent, considering it unlikely that the previous series of losses could continue, even if the results are independent of each other (Tversky and Kahneman, 1974). As for the illusion of control, EGMs can be attractive as they can convey to the player the feeling of having some control over the results and that the risk of loss can be minimized (Haw, 2009). This is because players can adjust the size and number of simultaneous bets per spin and this indirectly changes the average amplitude and frequency of winnings [3-4].

The data in the scientific literature indicate that in minors the problems of gambling are placed between 3.2% and 8.4% and above, and that an early approach to gambling experiences expose the risk of developing over time a Gambling Disorder. Furthermore, participation in non-active and non-strategic games such as scratch cards, lotteries, bingo, is a favoring factor in the development of gambling problems (Rahman et al., 2012); however, the data is really fragmented and partial, linked to studies of an academic nature with rather small and in any case not statistically significant populations, since it is not possible in fact to have the certainty of the extension of the psychopathological condition in the world population and find the suitable sample for a cross-sectional study, especially among younger and older populations. For this

reason, we rely on national champions to have greater control over the hypotheses put forward and the possible relevance of statistical errors.

Psychological characteristics (impulsiveness, search for sensations and / or novelties, poor coping skills, low conformism, less self-discipline, peer group influence) tend to favor various risk behaviors such as drinking alcohol, smoking, using illegal substances , gambling, having relationship difficulties, poor academic performance and episodes of petty crime. The family can also play a dysregulative role through family difficulties, poor attention to children and low parental control, family conflicts, ill-treatment, traumas, inadequate models of behavior towards gambling; that is protective through dialogue, support, intra-family respect, elasticity in the face of changes, tolerance to frustration, correct information and adequate behavior towards gambling.

The presence of at least four of the following symptoms, for at least twelve months, justifies the clinical psychopathological diagnosis: [1]

1. he needs to gamble with increasing amounts of money to reach the desired excitement;
2. is restless or irritable when trying to reduce or interrupt gambling;
3. has repeatedly tried unsuccessfully to check, reduce, or stop gambling;
4. is excessively absorbed by gambling;
5. often gambles when he feels uncomfortable;
6. after losing the game, he often returns another day to make up;
7. mind to hide the extent of one’s involvement in gambling;
8. has endangered or lost a significant relationship, work, or educational or career opportunities due to gambling;
9. relies on others to raise money to alleviate a desperate financial situation caused by gambling.

A particular clinical form is that consumed on the internet: the web allows at any time access to an immensity of games to which the individual is invited to participate via banners that delude the player of being able to earn huge amounts by investing a small amount money. Paradoxically, some studies have shown that the phenomenon is spreading exorbitantly during periods of

economic crisis. Secondly, while the traditional gambler is forced to carry out his activity in specific places, the Internet allows the player to access directly from their home, effectively eliminating any resistance capable of interrupting the pathological activity of the subject. The possibility of playing away from the judging eyes of other people reduces the chances of the player becoming aware of having a problem and setting limits in their actions. Moreover, since it is difficult to verify the age of the player, this phenomenon is likely to also involve minors, despite the current legislative legislation limits gambling to adults. Here too, as in other internet-addictions, the subject remains imprisoned in a vicious circle, to the point of neglecting, in pathological cases, human, social and family relationships.

### **The neural correlates in pathological gambling disorder [5]**

Already in the past various brain imaging studies have been performed (Potenza 2003, Best 2002, New 2002) which, using neuroimaging techniques, have scientifically documented that patients suffering from pathological gambling, subjected to evocative visual stimulation the game of gambling, they had an impulse awakening to play with activation of some brain areas with the coexistence of a decrease in ventro-medial prefrontal cortex activity and consequent deficit of impulse control and decision-making processes.

Given the similarities between pathological gambling and drug addiction, neuroimaging research on pathological gambling has made and used paradigms similar to those used in research on substance use disorders. In particular, the response to reward (gain) and loss, responsiveness to stimuli, impulsiveness and decision-making were investigated.

In a very recent study (Balodis 2012), a reduction in neural activity in the ventral striatum nucleus, in the prefrontal cortex and in the insula has been documented in gamblers vs controls. A reduced activity of the cortico-striatal neurocircuit was also observed during the phases of elaboration of the monetary reward obtained with gambling. This implies, in the gambler with gambling addiction, alterations in the ability to evaluate and predict the loss that aggravate the picture of pathological gambling. A reduction in striatal activity was also observed during the anticipation period in the expectation of gain, with a simultaneous tendency to impulsive behavior.

In this regard, De Ruiter (2009) has documented that in subjects suffering from pathological gambling there is a failure to activate the right ventro-lateral prefrontal cortex, both in terms of monetary gain and loss. This leads to a deficit in behavioral control.

The reactivity to the stimulus deriving from the vision and recall of memory of gambling in problem gamblers was also studied (Goudriaan 2009). In these, a greater activation of the limbic areas (striatum, hippocampus and amygdala) has been observed, strongly correlated with a greater degree of craving in the most problematic players. Less activation of the ventro-lateral area of the prefrontal cortex was found in problem gamblers in various studies that investigated both the reward associated with the game and the loss. In both cases, this lower activation was documented with significant differences compared to the healthy control group. Similar observations have been made by other authors (Reuter 2005; Tanabe 2007) which reported a reduced activation in pathological gamblers in the VMPFC area and in the OCD area (Remijnse, 2006).

With fMRI, Goudriaan and collaborators (2010) compared the reactivity to stimuli in 17 non-smoking pathological gamblers (GAPs), 18 people who smoke heavily tobacco, not gamblers, and 17 healthy control subjects. Participants saw images related to gambling, smoke-related images and neutral images during functional magnetic resonance imaging. When images related to the game were seen, compared to the neutral ones, a greater activation was found in the occipito-temporal areas, in the posterior cingulate cortex, in the paraippocampal gyrus and in the amygdala in gamblers compared to the control subjects and to the smoking. Furthermore, a positive correlation was found between subjective craving and BOLD signal activation in the ventro-lateral prefrontal cortex and in the left anterior insula. Comparing the control group with the other two groups, no significant differences were found in brain activity induced by smoking-related stimuli. Brain areas with greater response to gambling-related images in pathological gamblers are regions involved in motivation and visual processing, similar to the neural mechanisms underlying the reactivity to drug-related stimuli in drug addiction.

As already mentioned above, from the neuropsychological evaluation it emerged that the neuropsychological functioning of pathological players is similar to that of subjects with neurological damage

of the frontal lobe and with drug use disorders. These latest studies suggest that gamblers are compromised in decision-making processes, which leads them to neglect or ignore the negative consequences of immediate rewards (obtained through gambling), and even irrational beliefs, which lead them to overestimate the real chances of winning (Conversano 2012). Through fMRI studies conducted on gamblers while watching gambling movies, abnormalities in the activation of the frontal lobes and subcortical-cortical neural circuits that project to the frontal cortex, along with decreased activation of the orbit cortex, have often been observed -frontal and ventromedial prefrontal cortex (Conversano 2012). These data indicate an important additional information, namely that the “near misses” reinforce the desire to gamble through an anomalous involvement of the reward circuit, despite the objective lack of monetary reinforcement in such trials (Clark 2009). The fMRI showed that the areas involved in these processes are: the ventral putamen, the anterior insula, the midbrain and the rostral anterior cingulate cortex. Subsequent studies (Billieux J et al., 2012) have also shown that in gamblers the reactions of brain areas where learning takes place at a victory or near-win on slot machines are almost the same. This means that the quasi-win, that is when the reel stops with just one click away from winning, produces in pathological gamblers the same activity on the gratification system that produces an effective win. In these cases, the players report that since the near-win was not particularly gratifying, they feel a desire to continue playing again. The next figure shows that quasi-winning activates the insula which is significantly involved in craving.

In the fMRI study by De Ruiter and colleagues (2009), it has been shown that gamblers show severe behavioral perseveration as a response to the play stimulus, associated with reduced activation in the right ventrolateral prefrontal cortex in response to both loss and monetary gain. Pathological gambling, therefore, is linked to behavioral perseverance with stimulus (compulsion) and decreased sensitivity to rewards and punishments, as indicated by hypoactivation of the ventrolateral prefrontal cortex when money is lost or gained. Furthermore, the integrated planning capacity and normal dorsal frontostriatal reactivity indicate that this deficit is not due to reduced executive functioning. Perseverance in response and ventral prefrontal hyporesponsiveness

to monetary loss could be markers for maladaptive behaviors observed in both substance and behavioral addictions without substance. These results are in line with those addiction theories that postulate that decreased dopaminergic transmission precedes the development of addictive behaviors and that the repeated use of drugs, or pathological gambling, results in a further reduction in transmission of dopamine, associated with a decrease in sensitivity to rewarding stimuli.

A recent study by Dannon et al. (2011) investigated the relationship between the functioning of the frontal cortex and the seriousness of gambling in pathological gamblers with neuroimaging (score at the South Oaks Gambling Screen). Functional magnetic resonance imaging was used to assess the brain activity of ten male gamblers not in drug treatment during the execution of a computerized alternation learning task, adapted for fMRI. It has been shown that the performance for performing tasks in connection with gambling depends on the functioning of the regions of the fronto-lateral and medial cortex. Even these preliminary data suggest that pathological gambling may be characterized by specific neurocognitive changes linked to the frontal cortex.

Pathological gamblers are characterized by growing concern about gambling, which leads them to neglect stimuli, interests and behaviors that were once of great personal importance. To explore the association between this and the fact that neurobiological dysfunctions in the reward circuit are the basis of the pathological game, De Greck and colleagues (2010) carried out a study with 16 pathological gamblers without drug therapy and 12 control subjects healthy. In conclusion, in pathological players a diminished deactivation was found during monetary loss events in some of the important areas involved in the reward: the left accumbens nucleus and the left putamen. Moreover, while the players were subjected to the vision of stimuli of great personal relevance, the researchers found a diminished neural activity in all the important areas in the reward, compared to the control subjects. This study demonstrated for the first time an altered neuronal activity in the reward circuit while watching stimuli with personal relevance in pathological gamblers.

Miedl and colleagues (2010) studied the neuronal correlates of risk assessment and reward processing in 12 occasional gamblers (males, range 25-49 years) and

12 problem gamblers (males, range 29-) with fMRI. 57 years) during a semi-realistic blackjack game. Subjects had to decide whether or not to choose a card in high or low risk blackjack situations. Although both groups did not differ in behavioral data, the BOLD signal in problematic and occasional players was significantly different in thalamic, frontal-inferior and temporal-upper areas. While pathological players showed a consistent increase in signal during very risky situations and a decrease in low-risk situations, casual players presented an opposite pattern. Both groups showed increased activity in the ventral striatum and posterior cingulate during reward processing. Furthermore, problem gamblers have shown a distinct pattern of fronto-parietal activation that is thought to reflect a memory network of stimulus-induced addiction, which was triggered by gambling-related stimuli.

Van Holst and collaborators (2012) investigated the neural response for the first time during expectations of reward or loss in pathological gamblers. In summary, according to this study, compared to the control subjects, pathological players show more activity in the reward system during the latter's expectation, while no differences were observed between the two groups in the loss value system. This study also provides evidence that the players problematic are characterized by an anomalous increase in the coding of the expectation of reward, which can make them too optimistic about the results of the game.

Although not always consistent, studies with fMRI on pathological players have highlighted the presence of dysfunctions in different brain areas that can influence three distinct areas of behavior (Conversano 2012):

1. the expectations, which reflect both the expected reward based on the observed probabilities and the reinforcement associated with a stimulus;
2. the compulsion, which implies the repetitive application of a behavioral strategy despite the lack of the reward association with the stimulus;
3. the decision-making process, which requires balancing expectations against stimulus-associated rewards or reinforcing probabilities.

Therefore, various studies have shown the correlation between different brain areas and structures affecting the behavior and expression of pathological gambling.

## Clinical strategies for the management of the disorder [6]

Although the potential efficacy of various pharmacological classes has been confirmed and demonstrated, it has been investigated in a fair number of double-blind placebo studies, and despite an accurate meta-analysis that included published randomized trials between 2000 and 2006 confirmed a general efficacy of the pharmacological treatment with timoleptics, timoregolatori, antagonists of opioids and glutamatergic agents, to date no drug has received specific indication in the treatment of pathological gambling.

Given the still empirical character of gambling treatment, the setting of the therapy can be positively affected by an under-typing of the disorder in: 1) obsessive-compulsive subtype; 2) impulsive subtype; 3) additive subtype. Specific studies aimed at investigating the outcome of pharmacological treatment have been conducted mostly on numerically limited series, consisting of case-reports, open-label studies and single and double-blind studies, often not very homogeneous as regards the evaluation of the objectives (reduction of symptomatology vs. cessation of playful behavior) [7].

The alteration of serotonergic control is an important element in the genesis of the disorder [8]. This is supported by the observation of reduced levels of 5-hydroxyindolacetic acid, the main serotonin metabolite at the cerebrospinal level of male subjects suffering from pathological gambling [9], or of the platelet serotonin transporter in a group of players of both sexes [10], and from the clinical evidence of efficacy of treatment with non-selective serotonin reuptake inhibitors such as clomipramine [11] and with selective serotonin reuptake inhibitors (SSRIs) in the short-term reduction of symptoms and compulsive behaviors, regardless of the presence of depressive symptoms [12,13].

Three studies conducted (in single and double-blind) on samples of modest entities constituted by subjects suffering from pathological gambling, without a significant co-morbidity for other psychiatric disorders, have investigated the efficacy of the treatment with fluvoxamine (100-250 mg / day) [14,15]. The efficacy of paroxetine treatment (10-60 mg / day) was evaluated in two double-blind controlled studies vs. placebo; in the first the drug proved to be effective, in the second the improvement was

not confirmed, although a positive modification of the scores at the Clinical Global Impression Scale (CGI) was highlighted.

Two open-label studies have evaluated the efficacy of citalopram [16] and escitalopram [17]. Citalopram has been used in a sample of 15 subjects and it has been shown that the drug caused a decrease both in gaming behaviors (assessed on the basis of the reduction in the number of days dedicated to the game, the amount of money used and the ideation and the desire to play) in parallel with an improvement in the quality of life. The second trial was conducted in a sample of 16 subjects, 14 of which showed a significant reduction in scores both at the appropriately modified Yale-Brown Obsessive-Compulsive Scale (YBOCS-PG 16), used as a primary efficacy measure, which in the other scales used for the evaluation of secondary outcomes. Similarly to what has been observed both in controlled studies and in clinical practice in the treatment of obsessive-compulsive disorder, SSRIs seem to be able to play a role in the treatment of pathological gambling, but at higher doses than those used in the treatment of depressive disorders.

Among the other monoaminergic reuptake inhibitors it is interesting to use bupropion, which appears to be particularly useful in the treatment of gambling in the presence of comorbidities for ADHD [18], and of nefazodone [19]. There are few studies regarding the efficacy of mood stabilizers (mainly lithium salts, carbamazepine, valproate, topiramate, gabapentin). The rationale for the use of these drugs can be identified in the commonness of poorly controlled and impulsive behaviors between gambling and mixed phases, hypomanic or manic of bipolar disorder [20].

A randomized single-blind study demonstrated the efficacy of treatment with lithium salts or valproic acid in non-bipolar ludopathic patients [21]; topiramate monotherapy also showed good efficacy [22]. Naltrexone (an opioid m receptor antagonist, effective in modulating dopaminergic transmission at the mesolimbic level), commonly used in the treatment of alcohol and opioid dependence, has shown efficacy (average dose of 188 mg / day) in the treatment of play pathological hazard and efficacy was greater in subjects characterized by more pronounced impulsive tracts [23]. Its use is limited by the non-negligible risk of liver toxicity. From this perspective,

the role of the new opioid antagonist nalmefene could be more promising [24].

Since the improvement in glutamatergic tone at the accumbens level was related to a reduction in reward-seeking behavior in drug addiction, N-acetylcysteine, a glutamatergic modulator, was tested showing an action on craving for gambling [25]. Along the same lines, the use of other GABAergic modulators such as acamprosate, d-cycloserine, gabapentin, pregabalin, lamotrigine seems to be promising [26]. There are few data on the efficacy of atypical antipsychotics, sometimes successfully used in strengthening the treatment of resistant obsessive-compulsive disorder; in particular the efficacy of olanzapine versus placebo in the treatment of subjects with video-poker dependence was evaluated [27]. The treatment with modafinil, an atypical stimulant, was also tested in a group of impulsive gamblers [28].

While a reduction in game search was observed in subjects with high levels of impulsivity, subjects with low levels showed the opposite behavior. This data indicates potential future directions of research, which will have to examine the possible modifications of the effects of a given treatment based on the different clinical characteristics and comorbidity of the individual subject. Regarding non-pharmacological treatments, the most tested therapeutic strategies include cognitive-behavioral psychotherapy, bifocal intersocial psychotherapy, group meetings on the model of 'Alcoholics Anonymous', reorganization of the existential schema in specific units related to time dedicated to family, social activities, work, rest and leisure.

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