

# Gambling and Neuroscience

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BIBLIOGRAPHY WITH ABSTRACTS



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## Brain architecture and function

McCarrey, A. C., J. D. Henry, et al. (2012). "Age differences in neural activity during slot machine gambling: an fMRI study." PLoS One 7(11): e49787.

*Abstract:* This study aimed to assess the potential association between age-related prefrontal brain changes and slot machine gambling, an activity that has become increasingly popular among older adults. Functional magnetic resonance imaging was used to assess healthy older and younger adults whilst playing a slot machine. Results revealed that the older group over-recruited several bilateral and contralateral brain structures relative to the younger group. Specifically, older adults exhibited increased neural activation in the superior prefrontal cortex and left orbitofrontal cortex, indicating greater reliance on these structures. These results suggest a compensatory mechanism, by which older adults recruit a greater number of neural networks from both hemispheres to complete the same gambling task as their younger peers. The broader implications of these findings are discussed in relation to theories of neurocognitive and degenerative change that occurs in late adulthood.

Pallanti, S., M. M. Haznedar, et al. (2010). "Basal Ganglia activity in pathological gambling: a fluorodeoxyglucose-positron emission tomography study." Neuropsychobiology 62(2): 132-138.

*Abstract:* BACKGROUND: Pathological gambling (PG) is a disorder classified as an impulse control disorder (DSM-IV) bridging impulsive, compulsive and addictive behaviors. The striatum and thalamus are supposed to be involved in the pathophysiological substrate of these behaviors. An increased relative glucose metabolic rate (rGMR) in patients with a diagnosis of PG had previously been reported in the medial and orbitofrontal cortex. We extended our studies to include functional alterations of the striatum and thalamus in a cohort of patients with PG before and after treatment with lithium. METHODS: Twenty-one patients with PG who met lifetime comorbid bipolar spectrum diagnoses and a comparison group of 21 age- and sex-matched controls underwent a baseline positron emission tomography (PET) scan. Sixteen of these patients entered a randomized double-blind placebo-controlled parallel-group-design trial of lithium and underwent a follow-up PET scan at week 10. Anatomical MRI were obtained and the structures outlined on consecutive axial slices. These individual hand-drawn templates were used to identify structures on the PET scan of each patient, and the rGMR was measured. RESULTS: The PG patients had a decrement of the rGMR in the ventral parts of the striatum and thalamus, and an increment of the rGMR in the dorsal parts as compared with the controls. Lithium treatment increased the ventral caudate rGMR to a trend level in the patients, but had no effect on the metabolism of either the putamen or the thalamus. CONCLUSION: Because of their extensive connectivity to the frontal cortex, striatal and thalamic functional alteration may contribute to faulty decision making processes in PG patients. By increasing the ventral rGMR of the caudate nucleus, lithium treatment may reduce cognitive dysfunction and symptoms in PG patients.

Paris, J. J., C. Franco, et al. (2010). "Gambling pathology is associated with dampened cortisol response among men and women." Physiol Behav 99(2): 230-233.

*Abstract:* Pathological gambling has many similarities to pharmacological addiction. Notably, both pathological gambling and drug addiction are characterized by aberrations in hypothalamic-

pituitary-adrenal (HPA) axis responding. As well, there are indications that gender differences may play a role in these processes. Whether gender and/or HPA response are associated with pathological gambling was of interest. Recreational and pathological gamblers (15 men and 6 women per group) had the HPA factor, cortisol, assessed in saliva before and after watching a video of their preferred mode of gambling (slot machines, horse race betting, scratch-off tickets, blackjack, video poker, craps, sports betting, online casino games, or lottery tickets), and a video of neutral stimuli (a rollercoaster ride). Basal levels of salivary cortisol did not significantly differ among recreational and pathological gamblers. However, recreational gamblers demonstrated significantly increased salivary cortisol levels after the gambling and rollercoaster videos, whereas pathological gamblers demonstrated no salivary cortisol increase in response to either video stimulus. There was also a non-significant trend for women to have a greater cortisol response to video stimuli compared to men. These data suggest that pathological gambling is associated with hypoactive HPA response to gambling stimuli, similar to chronic drug exposure, and gender may contribute to this effect.

Potenza, M. N. (2013). "Neurobiology of gambling behaviors." *Curr Opin Neurobiol* 23(4): 660-667.

*Abstract:* For many, gambling is a recreational activity that is performed periodically without ill effects, but for some, gambling may interfere with life functioning. A diagnostic entity, pathological gambling (PG), is currently used to define a condition marked by excessive and problematic gambling. In this review, the current status of understanding of the neurobiologies of gambling and PG is described. Multiple neurotransmitter systems (norepinephrine, serotonin, dopamine, opioid and glutamate) and brain regions (ventral striatum, ventromedial prefrontal cortex, insula, among others) have been implicated in gambling and PG. Considerations for future directions in gambling research, with a view towards translating neurobiological advances into more effective prevention and treatment strategies, are discussed.

Potenza, M. N., M. A. Steinberg, et al. (2003). "Gambling urges in pathological gambling: a functional magnetic resonance imaging study." *Arch Gen Psychiatry* 60(8): 828-836.

*Abstract:* BACKGROUND: Gambling urges in pathological gambling (PG) often immediately precede engagement in self-destructive gambling behavior. An improved understanding of the neural correlates of gambling urges in PG would advance our understanding of the brain mechanisms underlying PG and would help direct research into effective treatments. METHODS: Echoplanar functional magnetic resonance imaging was used to assess brain function during viewing of videotaped scenarios with gambling, happy, or sad content. Participants rated the quality and magnitude of their emotional and motivational responses. RESULTS: Men with PG (n = 10) reported mean +/- SD greater gambling urges after viewing gambling scenarios vs control subjects (n = 11) (5.20 +/- 3.43 vs 0.32 +/- 0.60;  $\chi^2_{21,19} = 21.71$ ;  $P < .001$ ). The groups did not differ significantly in their subjective responses to the happy ( $P = .56$ ) or sad ( $P = .81$ ) videotapes. The most pronounced between-group differences in neural activities were observed during the initial period of viewing of the gambling scenarios: PG subjects displayed relatively decreased activity in frontal and orbitofrontal cortex, caudate/basal ganglia, and thalamus compared with controls. Distinct patterns of regional brain activity were observed in specific temporal epochs of videotape viewing. For example, differences localized to the ventral anterior cingulate during the final period of gambling videotape viewing, corresponding to the presentation of the most provocative gambling stimuli. Although group

differences in brain activity were observed during viewing of the sad and happy scenarios, they were distinct from those corresponding to the gambling scenarios. CONCLUSIONS: In men with PG, gambling cue presentation elicits gambling urges and leads to a temporally dynamic pattern of brain activity changes in frontal, paralimbic, and limbic brain structures. When viewing gambling cues, PG subjects demonstrate relatively decreased activity in brain regions implicated in impulse regulation compared with controls.

Roy, A., B. Adinoff, et al. (1988). "Pathological gambling. A psychobiological study." Arch Gen Psychiatry 45(4): 369-373.

*Abstract:* We investigated psychobiological substrates of pathological gambling by measuring levels of norepinephrine, monoamine metabolites, and peptides in cerebrospinal fluid, plasma, and urine. Pathological gamblers had a significantly higher centrally produced fraction of cerebrospinal fluid levels of 3-methoxy-4-hydroxyphenylglycol as well as significantly greater urinary outputs of norepinephrine than controls. These results suggest that pathological gamblers may have a functional disturbance of the noradrenergic system. This system has been postulated to underlie sensation-seeking behaviors, aspects of which are thought to be abnormal among pathological gamblers.

Santangelo, G., P. Barone, et al. (2013). "Pathological gambling in Parkinson's disease. A comprehensive review." Parkinsonism Relat Disord 19(7): 645-653.

*Abstract:* Pathological gambling (PG) and other Impulse Control Disorders (ICDs), such as hypersexuality, compulsive eating and buying, are often reported in Parkinson's disease (PD). The prevalence of PG is 2.2%-7% in treated PD patients, which is higher than the background population rate. As other non motor symptoms in PD, PG is frequently under-reported by patients and caregivers and may be under-recognized by the treating physicians. Factors associated with PG include male sex, younger age or younger age at PD onset, personal or family history of substance abuse or ICD, a personality profile characterized by impulsiveness, and treatment with dopamine agonists (DA) more than with levodopa (l-dopa). The DA effect seems to be a class effect and not specific for any DA. Neurofunctional studies suggest that medication-induced downregulation of frontostriatal connections and upregulation of striatum might combine to induce impulsive behavior. A dysfunction of fronto-subcortical circuits in PD patients with PG is also supported by neuropsychological findings of impaired executive control and monitoring abilities. Management of ICDs in PD is complex, and until now only discontinuation and/or tapering of DA treatment seem to be an effective management strategy for ICDs in PD. There is no empirical evidence supporting the use of psychiatric drugs for PG such as antipsychotics and antidepressants. Data regarding the effect of deep brain stimulation (DBS), particularly of subthalamic nucleus, on PG and ICDs in PD are still limited and sometimes conflicting since improvement of PG or new onset of PG after surgery have been reported.

Studer, B., A. M. Apergis-Schoute, et al. (2012). "What are the Odds? The Neural Correlates of Active Choice during Gambling." Front Neurosci 6: 46.

*Abstract:* Gambling is a widespread recreational activity and requires pitting the values of potential wins and losses against their probability of occurrence. Neuropsychological research showed that betting behavior on laboratory gambling tasks is highly sensitive to focal lesions to the ventromedial

prefrontal cortex (vmPFC) and insula. In the current study, we assessed the neural basis of betting choices in healthy participants, using functional magnetic resonance imaging of the Roulette Betting Task. In half of the trials, participants actively chose their bets; in the other half, the computer dictated the bet size. Our results highlight the impact of volitional choice upon gambling-related brain activity: Neural activity in a distributed network - including key structures of the reward circuitry (midbrain, striatum) - was higher during active compared to computer-dictated bet selection. In line with neuropsychological data, the anterior insula and vmPFC were more activated during self-directed bet selection, and responses in these areas were differentially modulated by the odds of winning in the two choice conditions. In addition, responses in the vmPFC and ventral striatum were modulated by the bet size. Convergent with electrophysiological research in macaques, our results further implicate the inferior parietal cortex (IPC) in the processing of the likelihood of potential outcomes: Neural responses in the IPC bilaterally reflected the probability of winning during bet selection. Moreover, the IPC was particularly sensitive to the odds of winning in the active-choice condition, when the processing of this information was required to guide bet selection. Our results indicate an important role of the IPC in human decision-making under risk and help to integrate neuropsychological data of risk-taking following vmPFC and insula damage with models of choice derived from human neuroimaging and monkey electrophysiology.

van Holst, R. J., W. van den Brink, et al. (2010). "Why gamblers fail to win: a review of cognitive and neuroimaging findings in pathological gambling." Neurosci Biobehav Rev 34(1): 87-107.

*Abstract:* The purpose of this review is to gain more insight in the neuropathology of pathological gambling (PG) and problem gambling, and to discuss challenges in this research area. Results from the reviewed PG studies show that PG is more than just an impulse control disorder. PG seems to fit very well with recent theoretical models of addiction, which stress the involvement of the ventral tegmental-orbito frontal cortex. Differentiating types of PG on game preferences (slot machines vs. casino games) seems to be useful because different PG groups show divergent results, suggesting different neurobiological pathways to PG. A framework for future studies is suggested, indicating the need for hypothesis driven pharmacological and functional imaging studies in PG and integration of knowledge from different research areas to further elucidate the neurobiological underpinnings of this disorder.

## Brain injury

Bonatti, E., L. Zamarian, et al. (2008). "Making decisions and advising decisions in traumatic brain injury." Cogn Behav Neurol 21(3): 164-175.

*Abstract:* OBJECTIVE AND BACKGROUND: Decision under ambiguity and decision under risk are fundamental in every-day life. METHODS: We investigated these 2 types of decision in traumatic brain injury (TBI) patients through the Iowa Gambling Task (IGT), the Probability-Associated Gambling (PAG) task, and a counsel version of the PAG task. Although in the IGT rules for gain and losses are implicit and probability information is missing, in the PAG task and the counsel task rules are explicit and probabilities are well-defined. RESULTS: In the IGT, TBI patients selected more disadvantageously than healthy controls and failed to develop an advantageous strategy over time. Patients also made less

advantageous choices than controls in the PAG task and the counsel task. Compared with controls, TBI patients gambled more frequently with low probabilities and less frequently with high probabilities. Overall, participants decided more advantageously in the counsel task, which does not provide feedback, than in the PAG task. Importantly, our results indicate that TBI patients' performance on all decision tasks correlated with executive functions. CONCLUSIONS: Our study shows that TBI patients have difficulties in decision under risk and decision under ambiguity. Difficulties may be attributed to deficient learning from feedback and to reduced risk estimation, but not to impulsive risk taking behavior.

Brand, M., E. Kalbe, et al. (2005). "Decision-making impairments in patients with pathological gambling." Psychiatry Res 133(1): 91-99.

*Abstract:* Pathological gambling (PG) is most likely associated with functional brain changes as well as neuropsychological and personality alterations. Recent research with the Iowa Gambling Task suggests decision-making impairments in PG. These deficits are usually attributed to disturbances in feedback processing and associated functional alterations of the orbitofrontal cortex. However, previous studies with other clinical populations found relations between executive (dorsolateral prefrontal) functions and decision-making using a task with explicit rules for gains and losses, the Game of Dice Task. In the present study, we assessed 25 male PG patients and 25 male healthy controls with the Game of Dice Task. PG patients showed pronounced deficits in the Game of Dice Task, and the frequency of risky decisions was correlated with executive functions and feedback processing. Therefore, risky decisions of PG patients might be influenced by both dorsolateral prefrontal and orbitofrontal cortex dysfunctions.

Guercio, J. M., T. Johnson, et al. (2012). "Behavioral treatment for pathological gambling in persons with acquired brain injury." J Appl Behav Anal 45(3): 485-495.

*Abstract:* The present investigation examined a behavior-analytic clinical treatment package designed to reduce the pathological gambling of 3 individuals with acquired brain injury. A prior history of pathological gambling of each patient was assessed via caregiver report, psychological testing, and direct observation of gambling behavior. Using an 8-week one-on-one client-patient format, a treatment program was developed in which the patient learned about the antecedents, consequences, and motivating operations that controlled the emission of gambling behavior. Data were collected on both self-report of gambling urges and behavior following therapy and during in situ gambling opportunities. The therapy program reduced urges to gamble and actual gambling for all patients. The potential of behavior-analytic therapy for reducing the pathological gambling of patients with and without brain injury is discussed.

Homaifar, B. Y., L. A. Brenner, et al. (2012). "Traumatic brain injury, executive functioning, and suicidal behavior: a brief report." Rehabil Psychol 57(4): 337-341.

*Abstract:* OBJECTIVE: The aim of this pilot study was to explore the relationship between executive dysfunction and suicidal behavior in two groups of participants: (Group 1, n = 18) veterans with traumatic brain injury (TBI) and a history of at least one suicide attempt (SA), and (Group 2, n = 29) veterans with TBI and no history of SA. Controlling for the severity of TBI, it was hypothesized that

participants in Group 1 would perform more poorly than those in Group 2 on measures of executive functioning. DESIGN: The primary outcome variable was decision making as assessed by performance on the Iowa Gambling Task (IGT). Secondary outcome variables included laboratory-measured impulsivity as measured by the Immediate and Delayed Memory Test (IMT/DMT), abstract reasoning as measured by the Wisconsin Card Sorting Test (WCST), and aggression as measured by the Lifetime History of Aggression (LHA) scale. RESULTS: Among those in Group 1, time between TBI and first suicide attempt postinjury varied widely (months to nearly 30 years). Only the WCST perseverative errors score differed significantly between individuals with and without histories of one or more suicide attempts (SAs). CONCLUSION: Suggestions for future study of SA among those with TBI are provided. When working with individuals with TBI, clinicians are encouraged to incorporate suicide risk assessment into their practice. Augmenting this process with a measure of perseveration may be beneficial.

Levine, B., S. E. Black, et al. (2005). "Gambling task performance in traumatic brain injury: relationships to injury severity, atrophy, lesion location, and cognitive and psychosocial outcome." Cogn Behav Neurol 18(1): 45-54.

*Abstract:* OBJECTIVE: To determine the sensitivity of the Gambling Test (GT) to the neurocognitive effects of traumatic brain injury (TBI) and to examine the cognitive, neural, and psychosocial correlates of impaired GT performance in patients with TBI. BACKGROUND: The GT is sensitive to behavioral deficits in patients with prefrontal brain damage, especially in ventral regions. Patients with TBI and behavioral deficits often have focal ventral prefrontal damage as well as diffuse damage. Analysis of the correlates of the GT in this population has implications for interpretation of the GT in other groups. METHOD: Seventy-one TBI patients were administered the GT, neuropsychological tests, and psychosocial outcome questionnaires. Patients also had high-resolution structural magnetic resonance imaging analyzed for both lesion location and tissue compartment volumes. RESULTS: The GT was sensitive to TBI in general, but not to TBI severity or quantified chronic phase atrophy. Marked impairment was observed in (but not limited to) patients with large frontal lesions. There were modest correlations between the GT and tests of working memory and executive functioning as well as between self- and other-rated real-life memory, executive, and emotional problems. CONCLUSIONS: The GT can be a useful adjunct to assessment of patients with TBI. Interpretation of GT performance in patients with complex neuropsychological deficits such as TBI should consider the influence of domain-general resources in addition to specific ventral prefrontal function.

Njomboro, P., S. Deb, et al. (2012). "Apathy symptoms modulate motivational decision making on the Iowa gambling task." Behav Brain Funct 8: 63.

*Abstract:* BACKGROUND: The present study represents an initial attempt to assess the role of apathy in motivated decision making on the Iowa Gambling Task. Clinical descriptions of patients with apathy highlight deficits in the cognitive, emotional and behavioural aspects of goal directed activity, yet standard neurocognitive tests of these measures fail to demonstrate reliable sensitivity to the disorder. Available research suggests the Iowa Gambling Task is a robust test of complex emotional socio-executive processes involved in motivational decision making, which can analogue real-world goal-directed behaviour. METHODS: We ask whether performance on the Iowa Gambling Task can distinguish brain damaged patients with apathy symptoms from 1) brain damaged patients without apathy and 2) neurologically intact controls. Overall, 22 healthy adults and 29 brain damaged

patients took part in this study. RESULTS: Brain damaged patients with apathy were distinctively impaired on the Iowa Gambling Task compared to both non-apathetic brain damaged patients and neurologically intact healthy controls. On the other hand, standard measures for the cognitive control of behaviour failed to show this sensitivity. CONCLUSIONS: Our results demonstrated that the Iowa Gambling Task is sensitive to the presence of apathy symptoms. We discuss these findings in terms of neurocognition deficits in apathy and the related implications for rehabilitation and clinical intervention.

Regard, M., D. Knoch, et al. (2003). "Brain damage and addictive behavior: a neuropsychological and electroencephalogram investigation with pathologic gamblers." *Cogn Behav Neurol* 16(1): 47-53.

*Abstract:* BACKGROUND: Gambling is a form of nonsubstance addiction classified as an impulse control disorder. Pathologic gamblers are considered healthy with respect to their cognitive status. Lesions of the frontolimbic systems, mostly of the right hemisphere, are associated with addictive behavior. Because gamblers are not regarded as "brain-lesioned" and gambling is nontoxic, gambling is a model to test whether addicted "healthy" people are relatively impaired in frontolimbic neuropsychological functions. METHODS: Twenty-one nonsubstance dependent gamblers and nineteen healthy subjects underwent a behavioral neurologic interview centered on incidence, origin, and symptoms of possible brain damage, a neuropsychological examination, and an electroencephalogram. RESULTS: Seventeen gamblers (81%) had a positive medical history for brain damage (mainly traumatic head injury, pre- or perinatal complications). The gamblers, compared with the controls, were significantly more impaired in concentration, memory, and executive functions, and evidenced a higher prevalence of non-right-handedness (43%) and, non-left-hemisphere language dominance (52%). Electroencephalogram (EEG) revealed dysfunctional activity in 65% of the gamblers, compared with 26% of controls. CONCLUSIONS: This study shows that the "healthy" gamblers are indeed brain-damaged. Compared with a matched control population, pathologic gamblers evidenced more brain injuries, more fronto-temporo-limbic neuropsychological dysfunctions and more EEG abnormalities. The authors thus conjecture that addictive gambling may be a consequence of brain damage, especially of the frontolimbic systems, a finding that may well have medicolegal consequences.

Sigurdardottir, S., T. Jerstad, et al. (2010). "Olfactory dysfunction, gambling task performance and intracranial lesions after traumatic brain injury." *Neuropsychology* 24(4): 504-513.

*Abstract:* OBJECTIVE: To estimate the incidence of olfactory dysfunction across traumatic brain injury (TBI) severity and decision-making deficits with regard to intracranial lesions' location and laterality. METHOD: A 1-year prospective study including 115 participants (16-55 years) with mild, moderate, and severe TBI. The Brief Smell Identification Test was used 3 months postinjury with a follow-up testing of olfactory dysfunction at 1 year. The Iowa Gambling Task (IGT) and 3 tasks of the Delis-Kaplan Executive Function System were administered 3-months postinjury. MRI was performed 1-year postinjury and TBI severity groups were then divided with respect to frontal, fronto-temporal, diffuse, and no lesions. RESULTS: The incidence of olfactory dysfunction was estimated to be 22.3% at 3 months and 13.5% at 1 year. No significant differences were found on olfactory dysfunction across TBI severity at either check. Anosmia was identified in 10% with severe TBI and 3% with mild TBI. Olfactory

dysfunction was associated with verbal fluency tasks. Repeated-measures analysis of variance revealed no significant effect over blocks on IGT, and no main group or interaction effects regarding TBI severity, lesions' location, or laterality. IGT performance at 3-months postinjury was deficient in 83% of persons with intracranial lesions and 71% of those without lesions. CONCLUSIONS: Olfactory dysfunction is independent of TBI severity, showing improvements in one third of cases from 3- to 12-months postinjury. However, anosmia was related to TBI severity. There is evidence for marked decision-making deficits after TBI, all subgroups performed similarly and failed to develop an advantageous strategy over time.

## Decision-making

Bolla, K. I., D. A. Eldreth, et al. (2004). "Sex-related differences in a gambling task and its neurological correlates." Cereb Cortex 14(11): 1226-1232.

*Abstract:* We investigated sex-related differences in task performance and brain activity in the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) during performance of a decision-making task (the Iowa Gambling Task). When men and women were examined separately, men activated extensive regions of the right lateral OFC and right DLPFC, as well as the left lateral OFC. In contrast, women activated the left medial OFC. Examining sex differences directly, men showed better task performance and greater lateralized brain activity to the right hemisphere than women. This was exemplified by greater activation in a large area of the right lateral OFC of men during their performance of the Iowa Gambling Task. In contrast, women had greater activation in the left DLPFC, left medial frontal gyrus and temporal lobe during this task. Thus, brain mechanisms engaged by men and women when solving the same decision-making task are different. These observations indicate that sex-related differences contribute to the heterogeneity observed in both normal and abnormal brain functioning. These results also provide further evidence of sexual dimorphism in neurocognitive performance and brain function.

Bubier, J. L. and D. A. Drabick (2008). "Affective decision-making and externalizing behaviors: the role of autonomic activity." J Abnorm Child Psychol 36(6): 941-953.

*Abstract:* We tested a conceptual model involving the inter-relations among affective decision-making (indexed by a gambling task), autonomic nervous system (ANS) activity, and attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms in a largely impoverished, inner city sample of first through third grade children (N=63, 54% male). The present study hypothesized that impaired affective decision-making and decreased sympathetic and parasympathetic activation would be associated with higher levels of ADHD and ODD symptoms, and that low sympathetic and parasympathetic activation during an emotion-inducing task would mediate the relation between affective decision-making and child externalizing symptoms. In support of our model, disadvantageous decision-making on a gambling task was associated with ADHD hyperactivity/impulsivity symptoms among boys, and attenuated sympathetic activation during an emotion-inducing task mediated this relation. Support for the model was not found among girls.

Labudda, K., O. T. Wolf, et al. (2007). "Decision-making and neuroendocrine responses in pathological gamblers." Psychiatry Res 153(3): 233-243.

*Abstract:* Recent neuropsychological research indicates that patients with pathological gambling (PG) exhibit deficits in laboratory tasks of decision-making which are suggested to be associated with neurochemical alterations within the prefrontal cortex. Some studies also revealed that hypothalamic-pituitary-adrenal axis activity in gamblers is altered. To date, very little is known about the relationship between decision-making and neuroendocrine parameters. Therefore, we examined patients with PG (n = 22) and healthy comparison subjects (n = 19) with a laboratory task of decision-making (Game of Dice Task) and sampled salivary cortisol and alpha-amylase (sAA) concentrations before and in the course of task performance. Results showed that the PG patients' neuroendocrine responses were comparable to those of the healthy subjects, even though the patients had severe decision-making deficits. Within both groups, there were no changes in cortisol and sAA responses. However, correlations and a subgroup analysis for sAA revealed that only those patients who showed less disadvantageous decision-making patterns had an increase of sAA during the task. Accordingly, the increase of sAA--as an indirect marker of sympathetic nervous system activity--in those patients with less severe decision-making deficits could reflect the use of somatic markers biasing the decision-making process.

Rivalan, M., E. Coutureau, et al. (2011). "Inter-individual decision-making differences in the effects of cingulate, orbitofrontal, and prelimbic cortex lesions in a rat gambling task." Front Behav Neurosci 5: 22.

*Abstract:* Deficits in decision-making is a hallmark of several neuropsychiatric pathologies but is also observed in some healthy individuals that could be at risk to develop these pathologies. Poor decision-making can be revealed experimentally in humans using the Iowa gambling task, through the inability to select options that ensure long term gains over larger immediate gratification. We devised an analogous task in the rat, based on uncertainty and conflicting choices, the rat gambling task (RGT). It similarly reveals good and poor performers within a single session. Using this task, we investigated the role of three prefrontal cortical areas, the orbitofrontal, prelimbic, and cingulate cortices on decision-making, taking into account inter-individual variability in behavioral performances. Here, we show that these three distinct subregions are differentially engaged to solve the RGT. Cingulate cortex lesion mainly delayed good decision-making whereas prelimbic and orbitofrontal cortices induced different patterns of inadapted behaviors in the task, indicating varying degree of functional specialization of these three areas. Their contribution largely depended on the level of adaptability demonstrated by each individual to the constraint of the task. The inter-individual differences in the effect of prefrontal cortex area lesions on decision-making revealed in this study open new perspectives in the search for vulnerability markers to develop disorders related to executive dysfunctioning.

van den Bos, R., J. Homberg, et al. (2013). "A critical review of sex differences in decision-making tasks: focus on the Iowa Gambling Task." Behav Brain Res 238: 95-108.

*Abstract:* It has been observed that men and women show performance differences in the Iowa Gambling Task (IGT), a task of decision-making in which subjects through exploration learn to differentiate long-term advantageous from long-term disadvantageous decks of cards: men choose more cards from the long-term advantageous decks than women within the standard number of 100 trials. Here, we aim at discussing psychological mechanisms and neurobiological substrates underlying

sex differences in IGT-like decision-making. Our review suggests that women focus on both win-loss frequencies and long-term pay-off of decks, while men focus on long-term pay-off. Furthermore, women may be more sensitive to occasional losses in the long-term advantageous decks than men. As a consequence hereof, women need 40-60 trials in addition before they reach the same level of performance as men. These performance differences are related to differences in activity in the orbitofrontal cortex and dorsolateral prefrontal cortex as well as in serotonergic activity and left-right hemispheric activity. Sex differences in orbitofrontal cortex activity may be due to organisational effects of gonadal hormones early in life. The behavioural and neurobiological differences in the IGT between men and women are an expression of more general sex differences in the regulation of emotions. We discuss these findings in the context of sex differences in information processing related to evolutionary processes. Furthermore we discuss the relationship between these findings and real world decision-making.

Wang, S., I. Krajbich, et al. (2012). "The role of risk aversion in non-conscious decision making." Front Psychol 3: 50.

*Abstract:* To what extent can people choose advantageously without knowing why they are making those choices? This hotly debated question has capitalized on the Iowa Gambling Task (IGT), in which people often learn to choose advantageously without appearing to know why. However, because the IGT is unconstrained in many respects, this finding remains debated and other interpretations are possible (e.g., risk aversion, ambiguity aversion, limits of working memory, or insensitivity to reward/punishment can explain the finding of the IGT). Here we devised an improved variant of the IGT in which the deck-payoff contingency switches after subjects repeatedly choose from a good deck, offering the statistical power of repeated within-subject measures based on learning the reward contingencies associated with each deck. We found that participants exhibited low confidence in their choices, as probed with post-decision wagering, despite high accuracy in selecting advantageous decks in the task, which is putative evidence for non-conscious decision making. However, such a behavioral dissociation could also be explained by risk aversion, a tendency to avoid risky decisions under uncertainty. By explicitly measuring risk aversion for each individual, we predicted subjects' post-decision wagering using Bayesian modeling. We found that risk aversion indeed does play a role, but that it did not explain the entire effect. Moreover, independently measured risk aversion was uncorrelated with risk aversion exhibited during our version of the IGT, raising the possibility that the latter risk aversion may be non-conscious. Our findings support the idea that people can make optimal choices without being fully aware of the basis of their decision. We suggest that non-conscious decision making may be mediated by emotional feelings of risk that are based on mechanisms distinct from those that support cognitive assessment of risk.

Xue, G., Q. He, et al. (2012). "The gambler's fallacy is associated with weak affective decision making but strong cognitive ability." PLoS One 7(10): e47019.

*Abstract:* Humans demonstrate an inherent bias towards making maladaptive decisions, as shown by a phenomenon known as the gambler's fallacy (GF). The GF has been traditionally considered as a heuristic bias supported by the fast and automatic intuition system, which can be overcome by the reasoning system. The present study examined an intriguing hypothesis, based on emerging evidence from neuroscience research, that the GF might be attributed to a weak affective but strong cognitive

decision making mechanism. With data from a large sample of college students, we found that individuals' use of the GF strategy was positively correlated with their general intelligence and executive function, such as working memory and conflict resolution, but negatively correlated with their affective decision making capacities, as measured by the Iowa Gambling Task. Our result provides a novel insight into the mechanisms underlying the GF, which highlights the significant role of affective mechanisms in adaptive decision-making.

## Dopamine/reward systems

Baarendse, P. J., C. A. Winstanley, et al. (2013). "Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task." Psychopharmacology (Berl) 225(3): 719-731.

*Abstract:* RATIONALE: The inability to make profitable long-term decisions has been implicated in several psychiatric disorders. There is emerging evidence to support a role for dopamine (DA) in decision making, but our understanding of the role of noradrenaline (NA) and serotonin (5-HT) in decision making, and of possible interactions between the three monoamines, is limited. Moreover, impulsivity has been associated with aberrant decision making, but the underlying mechanisms are incompletely understood. OBJECTIVE: The purpose of this study is to improve our understanding of the neuropharmacological mechanisms of decision making and impulse control. METHODS: We investigated the effects of amphetamine (0.25-1.0 mg/kg) and selective reuptake inhibitors of DA (GBR12909; 2.5-10 mg/kg), NA (atomoxetine; 0.3-3.0 mg/kg), and 5-HT (citalopram; 0.3-3.0 mg/kg) in a rat gambling task (rGT). Since the rGT allows for detection of impulsive action, i.e., premature responding, we also assessed the relationship between decision making and impulsivity. RESULTS: In the rGT, rats developed an optimal choice strategy from the first session onwards. Elevation of endogenous DA or NA levels increased and decreased impulsivity, respectively, but did not alter decision making. However, simultaneous blockade of DA and NA disrupted decision making, reflected by a relative decrease in choice for the advantageous choice options. Increasing 5-HT neurotransmission did not affect decision making or impulsivity. CONCLUSIONS: These data suggest important but complementary or redundant roles of DA and NA neurotransmission in decision-making processes based on reward probability and punishment. Moreover, impulse control and decision making in the rGT rely on dissociable mechanisms.

Bubier, J. L. and D. A. Drabick (2008). "Affective decision-making and externalizing behaviors: the role of autonomic activity." J Abnorm Child Psychol 36(6): 941-953.

*Abstract:* We tested a conceptual model involving the inter-relations among affective decision-making (indexed by a gambling task), autonomic nervous system (ANS) activity, and attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms in a largely impoverished, inner city sample of first through third grade children (N=63, 54% male). The present study hypothesized that impaired affective decision-making and decreased sympathetic and parasympathetic activation would be associated with higher levels of ADHD and ODD symptoms, and that low sympathetic and parasympathetic activation during an emotion-inducing task would mediate the relation between affective decision-making and child externalizing symptoms. In support

of our model, disadvantageous decision-making on a gambling task was associated with ADHD hyperactivity/impulsivity symptoms among boys, and attenuated sympathetic activation during an emotion-inducing task mediated this relation. Support for the model was not found among girls.

Campbell-Meiklejohn, D., J. Wakeley, et al. (2011). "Serotonin and dopamine play complementary roles in gambling to recover losses." Neuropsychopharmacology 36(2): 402-410.

*Abstract:* Continued gambling to recover losses--'loss chasing'--is a prominent feature of social and pathological gambling. However, little is known about the neuromodulators that influence this behavior. In three separate experiments, we investigated the role of serotonin activity, D(2)/D(3) receptor activity, and beta-adrenoceptor activity on the loss chasing of age and IQ-matched healthy adults randomized to treatment or an appropriate control/placebo. In Experiment 1, participants consumed amino-acid drinks that did or did not contain the serotonin precursor, tryptophan. In Experiment 2, participants received a single 176 mug dose of the D(2)/D(3) receptor agonist, pramipexole, or placebo. In Experiment 3, participants received a single 80 mg dose of the beta-adrenoceptor blocker, propranolol, or placebo. Following treatment, participants completed a computerized loss-chasing game. Mood and heart rate were measured at baseline and following treatment. Tryptophan depletion significantly reduced the number of decisions made to chase losses, and the number of consecutive decisions to chase, in the absence of marked changes in mood. By contrast, pramipexole significantly increased the value of losses chased and diminished the value of losses surrendered. Propranolol markedly reduced heart rate, but produced no significant changes in loss-chasing behavior. Loss chasing can be thought of as an aversively motivated escape behavior controlled, in part, by the marginal value of continued gambling relative to the value of already accumulated losses. Serotonin and dopamine appear to play dissociable roles in the tendency of individuals to gamble to recover, or to seek to 'escape' from, previous losses. Serotonergic activity seems to promote the availability of loss chasing as a behavioral option, whereas D(2)/D(3) receptor activity produces complex changes in the value of losses judged worth chasing. Sympathetic arousal, at least as mediated by beta-adrenoceptors, does not play a major role in laboratory-based loss-chasing choices.

Djamshidian, A., F. Cardoso, et al. (2011). "Pathological gambling in Parkinson's disease--a review of the literature." Mov Disord 26(11): 1976-1984.

*Abstract:* The prevalence of pathological gambling is 3.4% to 6% in treated Parkinson's disease, which is higher than the background population rate. In this review we discuss current evidence to indicate that dopamine agonists are much more likely to trigger this behavior than either L-dopa or selective monoamine oxidase B inhibitor monotherapy. New insights from recent behavioral and functional imaging studies and possible treatment approaches are also covered. A PubMed literature search using the terms "gambling" and "Parkinson's disease," "impulse control disorder," "impulsive compulsive behaviour," "dopamine agonist," of individual dopamine agonists, and of ongoing drug trials, using <http://www.clinicaltrials.gov>, was carried out for the period up to January 2011.

Jones, H. B. and S. George (2011). "'You never told me I would turn into a gambler': a first person account of dopamine agonist--induced gambling addiction in a patient with restless legs syndrome." BMJ Case Rep 2011.

*Abstract:* Dopaminergic agents are commonly used and effective treatments for restless legs syndrome (RLS), a disabling sensorimotor disorder. Less known are some of the potentially disabling side effects of these treatments, particularly iatrogenic gambling addiction, as is described here. Here the authors present a 62-year-old man, with a 20-year history of RLS, who developed gambling addiction while on dopaminergic treatment. He was not forewarned of this side effect, nor was he ever screened for gambling behaviours prior to or during treatment. Eight months after discontinuation of dopaminergic treatment and after 10 sessions of cognitive-behavioural therapy for gambling addiction, his gambling behaviours have partially resolved. To our knowledge, this is the first ever first person account of this condition. To prevent the devastating consequences of gambling addiction or to minimise its impact by early intervention, the authors call for clinicians involved in treatment of RLS to follow these simple measures: screen patients for gambling behaviours prior to the onset and during dopaminergic treatment; forewarn patients of this potential side effect; and if patients screen positive, refer them to specialist gambling treatment services, in addition to making necessary changes to their medication regime.

Joutsa, J., J. Johansson, et al. (2012). "Mesolimbic dopamine release is linked to symptom severity in pathological gambling." *Neuroimage* 60(4): 1992-1999.

*Abstract:* BACKGROUND: Brain dopamine neurons code rewarding environmental stimuli by releasing endogenous dopamine, a transmission signal that is important for reinforcement learning. Human reward-seeking gambling behavior, and especially pathological gambling, has been presumed to be modulated by brain dopamine. METHODS: Striatal dopamine release was studied with [(11)C]raclopride positron emission tomography (PET) during gambling with an ecologically valid slot machine gambling task. Twenty-four males with and without pathological gambling (DSM-IV) were scanned three times, and the effects of different gambling outcomes (high-reward and low-reward vs. control task) on dopamine release were evaluated. RESULTS: Striatal dopamine was released in both groups during high-reward but also low-reward tasks. The dopamine release during the low-reward task was located in the associative part of the caudate nucleus. During the high-reward task, the effect was also seen in the ventral striatum and the magnitude of dopamine release was associated with parallel gambling "high". Furthermore, there was a positive correlation between dopamine release during the low-reward and the high-reward task. There was no general difference in the magnitude of dopamine release between pathological gamblers and controls. However, in pathological gamblers, dopamine release correlated positively with gambling symptom severity. CONCLUSIONS: Striatal dopamine is released during gambling irrespective of gambling outcome suggesting that the mere expectation/prediction of reward is sufficient to induce dopaminergic changes. Although dopamine release during slot machine gambling is comparable between healthy controls and pathological gamblers, greater gambling symptom severity is associated with greater dopaminergic responses. Thus, as the dopamine reward deficiency theory predicts blunted mesolimbic dopamine responses to gambling in addicted individuals, our results question the validity of the reward deficiency hypothesis in pathological gambling.

Lim, S., J. Ha, et al. (2012). "Association study on pathological gambling and polymorphisms of dopamine D1, D2, D3, and D4 receptor genes in a Korean population." *J Gambl Stud* 28(3): 481-491.

*Abstract:* Several studies have reported that some dopaminergic receptor polymorphisms are associated with pathological gambling (PG). Considering that there are major race and ethnic group difference in dopaminergic polymorphisms, the result of genetic association studies should be confirmed in more homogeneous population to avoid problems of population stratification. The present study aimed to investigate whether selected polymorphisms in the dopamine receptors genes (DRD1, DRD2, DRD3, and DRD4) are associated with PG in Korean population which is consisted of only Korean ancestry. Subjects were 104 men with a diagnosis of PG and 114 unrelated age-matched normal control men. Genotyping was performed for the DRD1 gene -48 A/G, DRD2 gene TaqI A, DRD3 gene Ser9Gly, and DRD4 gene exon III variable number tandem repeat polymorphisms. The method of multifactor dimensionality reduction (MDR) was used to analyze gene-gene interactions. There were no differences in the frequencies of any studied polymorphisms between patients with PG and normal controls. MDR analysis did not show a significant effect of the 4 dopamine receptor gene polymorphisms on susceptibility to PG ( $P > 0.05$ ). The present study suggests that the analyzed polymorphisms of the dopamine receptor genes might not be associated with PG in a Korean population.

Martinez-Castrillo, J. C., L. Vela, et al. (2011). "Nonmotor disorders and their correlation with dopamine: can they be treated by currently available methods?" *Neurologist* 17(6 Suppl 1): S9-17.

*Abstract:* Many of the nonmotor symptoms in Parkinson disease have a dopaminergic basis, whether the result of dopaminergic degeneration or as a result of dopaminergic treatment. In the latter case, the symptoms may be genuine side effects of drugs (hypotension, pathologic gambling, etc.) or they may be secondary either to the pathoplastic effect they have on the natural course of the disease (nonmotor fluctuations) or to the lack of dopamine (apathy, depression, dopamine withdrawal syndrome, etc.). In all these cases, dopaminergic treatment can be helpful. However, many other nonmotor (and motor) symptoms will have no correlation with dopamine; therefore, they require different treatments, very often with little efficacy, as in apathy or cognitive decline.

Oberg, S. A., G. J. Christie, et al. (2011). "Problem gamblers exhibit reward hypersensitivity in medial frontal cortex during gambling." *Neuropsychologia* 49(13): 3768-3775.

*Abstract:* Problem gambling (PG) is increasingly conceptualized as an addiction akin to substance abuse, rather than an impulse control disorder, however the mechanism of addiction remains unclear. Neuroimaging investigations have supported a "reward deficiency" hypothesis for PG by suggesting a blunted response to gambling, particularly in the striatum. Here we describe electrophysiological evidence of a hypersensitive response to gambling feedback in problem gamblers. Previous research in healthy participants has shown that feedback during gambling tasks triggers stereotypical neural responses including the Feedback-Related Mediofrontal Negativity (FRN), the feedback-related P300, and an increase in induced theta-band (4-8 Hz) power. We tested the theory that abnormal feedback processing characterizes brain activity in problem gamblers while gambling. EEG was recorded from non-gamblers and self-identified gamblers as they engaged in a computerized version of the Iowa Gambling Task. Feedback about valence (win vs. loss) triggered a FRN in both groups, but in gamblers this was preceded by an early-latency hypersensitive fronto-central difference to feedback. This early FRN was correlated with gambling severity and was localized to medial frontal cortex using distributed source imaging (CLARA). Gamblers also differed in responses to risk, showing a

blunted P300 component and less EEG power in the theta band. Here we suggest that a more nuanced interpretation of reward deficiency is called for with respect to PG. For certain aspects of brain function, gamblers may exhibit hypersensitivity to reward feedback more akin to drug sensitization than reward deficiency. Our results also suggest that the neurologically normal brain employs dissociable systems in the processing of feedback from tasks involving risky decision making.

Sescousse, G., G. Barbalat, et al. (2013). "Imbalance in the sensitivity to different types of rewards in pathological gambling." Brain 136(Pt 8): 2527-2538.

*Abstract:* Pathological gambling is an addictive disorder characterized by a persistent and compulsive desire to engage in gambling activities. This maladaptive behaviour has been suggested to result from a decreased sensitivity to experienced rewards, regardless of reward type. Alternatively, pathological gambling might reflect an imbalance in the sensitivity to monetary versus non-monetary incentives. To directly test these two hypotheses, we examined how the brain reward circuit of pathological gamblers responds to different types of rewards. Using functional magnetic resonance imaging, we compared the brain responses of 18 pathological gamblers and 20 healthy control subjects while they engaged in a simple incentive task manipulating both monetary and visual erotic rewards. During reward anticipation, the ventral striatum of pathological gamblers showed a differential response to monetary versus erotic cues, essentially driven by a blunted reactivity to cues predicting erotic stimuli. This differential response correlated with the severity of gambling symptoms and was paralleled by a reduced behavioural motivation for erotic rewards. During reward outcome, a posterior orbitofrontal cortex region, responding to erotic rewards in both groups, was further recruited by monetary gains in pathological gamblers but not in control subjects. Moreover, while ventral striatal activity correlated with subjective ratings assigned to monetary and erotic rewards in control subjects, it only correlated with erotic ratings in gamblers. Our results point to a differential sensitivity to monetary versus non-monetary rewards in pathological gambling, both at the motivational and hedonic levels. Such an imbalance might create a bias towards monetary rewards, potentially promoting addictive gambling behaviour.

Stojanov, W., F. Karayanidis, et al. (2003). "Disrupted sensory gating in pathological gambling." Biol Psychiatry 54(4): 474-484.

*Abstract:* BACKGROUND: Some neurochemical evidence as well as recent studies on molecular genetics suggest that pathologic gambling may be related to dysregulated dopamine neurotransmission. METHODS: The current study examined sensory (motor) gating in pathologic gamblers as a putative measure of endogenous brain dopamine activity with prepulse inhibition of the acoustic startle eye-blink response and the auditory P300 event-related potential. Seventeen pathologic gamblers and 21 age- and gender-matched healthy control subjects were assessed. Both prepulse inhibition measures were recorded under passive listening and two-tone prepulse discrimination conditions. RESULTS: Compared to the control group, pathologic gamblers exhibited disrupted sensory (motor) gating on all measures of prepulse inhibition. Sensory motor gating deficits of eye-blink responses were most profound at 120-millisecond prepulse lead intervals in the passive listening task and at 240-millisecond prepulse lead intervals in the two-tone prepulse discrimination task. Sensory gating of P300 was also impaired in pathologic gamblers, particularly at 500-millisecond lead intervals, when performing the discrimination task on the prepulse. CONCLUSIONS: In the context

of preclinical studies on the disruptive effects of dopamine agonists on prepulse inhibition, our findings suggest increased endogenous brain dopamine activity in pathologic gambling in line with previous neurobiological findings.

Voon, V., J. Gao, et al. (2011). "Dopamine agonists and risk: impulse control disorders in Parkinson's disease." *Brain* 134(Pt 5): 1438-1446.

*Abstract:* Impulse control disorders are common in Parkinson's disease, occurring in 13.6% of patients. Using a pharmacological manipulation and a novel risk taking task while performing functional magnetic resonance imaging, we investigated the relationship between dopamine agonists and risk taking in patients with Parkinson's disease with and without impulse control disorders. During functional magnetic resonance imaging, subjects chose between two choices of equal expected value: a 'Sure' choice and a 'Gamble' choice of moderate risk. To commence each trial, in the 'Gain' condition, individuals started at \$0 and in the 'Loss' condition individuals started at -\$50 below the 'Sure' amount. The difference between the maximum and minimum outcomes from each gamble (i.e. range) was used as an index of risk ('Gamble Risk'). Sixteen healthy volunteers were behaviourally tested. Fourteen impulse control disorder (problem gambling or compulsive shopping) and 14 matched Parkinson's disease controls were tested ON and OFF dopamine agonists. Patients with impulse control disorder made more risky choices in the 'Gain' relative to the 'Loss' condition along with decreased orbitofrontal cortex and anterior cingulate activity, with the opposite observed in Parkinson's disease controls. In patients with impulse control disorder, dopamine agonists were associated with enhanced sensitivity to risk along with decreased ventral striatal activity again with the opposite in Parkinson's disease controls. Patients with impulse control disorder appear to have a bias towards risky choices independent of the effect of loss aversion. Dopamine agonists enhance sensitivity to risk in patients with impulse control disorder possibly by impairing risk evaluation in the striatum. Our results provide a potential explanation of why dopamine agonists may lead to an unconscious bias towards risk in susceptible individuals.

## Executive function

Betancourt, L. M., N. L. Brodsky, et al. (2012). "Is executive cognitive function associated with youth gambling?" *J Gamb Stud* 28(2): 225-238.

*Abstract:* Our objectives for this report were to identify trajectories of youth gambling behavior, and to examine their relation to executive cognitive function (ECF) and associated problem behaviors. Philadelphia school children, enrolled at ages 10-12 years ( $n = 387$ ; 49% male), completed three annual assessments of risk behaviors, ECF, impulsivity, problem behaviors and demographics. Across ages 10-15 years, using methods from Nagin et al., two groups were identified: Early Gamblers ( $n = 111$ ) initiated early and continued in later assessments, and Later Gamblers ( $n = 276$ ) initiated at later ages and gambled less. Betting money on cards and sports were the most frequently reported gambling behaviors. Using gambling group as outcome, final backward selection logistic regression model showed Early Gamblers are more likely male ( $P = 0.001$ ), report more active coping ( $P = 0.042$ ), impulsive behaviors ( $P \leq 0.008$ ), and have friends who gamble ( $P = 0.001$ ). Groups were similar in ECF, parental monitoring, marital status, SES, and race. Early Gamblers had higher incidence of

problem behaviors and drug use (all  $P \leq 0.006$ ). Two gambling groups were identified in early adolescence with Early Gamblers showing higher levels of impulsivity and comorbid problems but similar levels of ECF compared to Late Gamblers. As more gambling groups are identified through later adolescence, ECF may emerge as a relevant precursor of problem gambling at this later time.

Gansler, D. A., M. W. Jerram, et al. (2011). "Does the iowa gambling task measure executive function?" *Arch Clin Neuropsychol* 26(8): 706-717.

*Abstract:* The Iowa Gambling Task (IGT) is assumed to measure executive functioning, but this has not been empirically tested by means of both convergent and discriminant validity. We used structural equation modeling (SEM) to test whether the IGT is an executive function (EF) task (convergent validity) and whether it is not related to other neuropsychological domains (discriminant validity). Healthy community-dwelling participants ( $N = 214$ ) completed a comprehensive neuropsychological battery. We analyzed the conventional IGT metric and three alternative metrics based on the overall difference of advantageous minus disadvantageous choices made during the last 60 IGT responses and advantageous minus disadvantageous choices based on two specific decks of cards (D minus A). An a priori six-factor hierarchical model of neuropsychological functioning was confirmed with SEM. Attention and processing speed were grouped as "non-associative" factors. Fluency, executive functioning, visual learning/memory, and verbal learning/memory were grouped as higher-level "associative" factors. Of the non-associative factors, attention, but not speed, predicted IGT performance. When each associative factor was entered along with attention, only EF improved the model fit and that was only for metrics based on trials 41-100. SEM indicates metrics based on trials 1-100 are influenced by attention, and metrics based on trials 41-100 are influenced by attention and EF. Its associative strength with attention is twice that of EF. Conceptually, the IGT is a multi-trait task involving novel problem-solving and attentional domains to a greater extent, and executive functioning to a lesser extent.

Kerr, A. and P. D. Zelazo (2004). "Development of "hot" executive function: the children's gambling task." *Brain Cogn* 55(1): 148-157.

*Abstract:* Development of affective decision-making was studied in 48 children at two ages (3 and 4 years) using a simplified version of the Iowa Gambling Task (IGT). On each of 50 trials, children chose from 1 of 2 decks of cards that, when turned, displayed happy and sad faces, corresponding to rewards (candies) won and lost, respectively. Cards in 1 deck offered more rewards per trial, but were disadvantageous across trials due to occasional large losses; cards in the other deck offered fewer rewards per trial, but were advantageous overall. On later trials, 4-year-olds made more advantageous choices than 3-year-olds, and 4-year-olds made more advantageous choices than would be expected by chance, whereas 3-year-olds made more disadvantageous choices than would be expected by chance. These findings, which were especially pronounced for girls, indicate that affective decision-making develops rapidly during the preschool period, possibly reflecting the growth of neural systems involving orbitofrontal cortex.

Ledgerwood, D. M., E. S. Orr, et al. (2012). "Executive function in pathological gamblers and healthy controls." *J Gambl Stud* 28(1): 89-103.

*Abstract:* Executive function (EF) deficits may underlie some of the impulse control problems seen in pathological gambling. Pathological gamblers (PGs, n = 45) and controls (n = 45) were compared on several measures of EF (including measures of response inhibition, working memory, cognitive flexibility and perseveration, planning and decision-making), as well as memory and intelligence tests to examine whether PGs evidence EF dysfunction. Compared with controls, PGs exhibited specific deficits on measures of planning and decision-making. PGs also exhibited relative deficits on a measure of perseveration, but this deficit was no longer significant after controlling for group differences in intelligence. These results suggest that PGs may experience deficits on specific components of EF.

Lehto, J. E. and E. Elorinne (2003). "Gambling as an executive function task." Appl Neuropsychol 10(4): 234-238.

*Abstract:* The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) was investigated in relation to fluid intelligence and two conventional executive function tasks: letter fluency and the Wisconsin Card Sorting Test. Fifty-one children aged 8-10 years and a heterogeneous group of 40 adults served as participants. Adults outperformed children on all measures except one; this was the number of good cards selected in the IGT. Intercorrelations among executive function tasks were low. The number of good cards in the IGT appeared to be lower than in previous studies. Reasons for poor performance are discussed. The IGT may possess some shortcomings, which should be investigated in future studies. In clinical usage, the IGT may best serve as a complementary tool to the executive functions test battery.

Marazziti, D., M. Catena Dell'osso, et al. (2008). "Executive function abnormalities in pathological gamblers." Clin Pract Epidemiol Ment Health 4: 7.

*Abstract:* BACKGROUND: Pathological gambling (PG) is an impulse control disorder characterized by persistent and maladaptive gambling behaviors with disruptive consequences for familial, occupational and social functions. The pathophysiology of PG is still unclear, but it is hypothesized that it might include environmental factors coupled with a genetic vulnerability and dysfunctions of different neurotransmitters and selected brain areas. Our study aimed to evaluate a group of patients suffering from PG by means of some neuropsychological tests in order to explore the brain areas related to the disorder. METHODS: Twenty outpatients (15 men, 5 women), with a diagnosis of PG according to DSM-IV criteria, were included in the study and evaluated with a battery of neuropsychological tests: the Wisconsin Card Sorting Test (WCST), the Wechsler Memory Scale revised (WMS-R) and the Verbal Associative Fluency Test (FAS). The results obtained in the patients were compared with normative values of matched healthy control subjects. RESULTS: The PG patients showed alterations at the WCST only, in particular they had a great difficulty in finding alternative methods of problem-solving and showed a decrease, rather than an increase, in efficiency, as they progressed through the consecutive phases of the test. The mean scores of the other tests were within the normal range. CONCLUSION: Our findings showed that patients affected by PG, in spite of normal intellectual, linguistic and visual-spatial abilities, had abnormalities emerging from the WCST, in particular they could not learn from their mistakes and look for alternative solutions. Our results would seem to confirm an altered functioning of the prefrontal areas which might provoke a sort of cognitive

"rigidity" that might predispose to the development of impulsive and/or compulsive behaviors, such as those typical of PG.

Reid, R. C., H. L. McKittrick, et al. (2012). "Self-reported differences on measures of executive function in a patient sample of pathological gamblers." Int J Neurosci 122(9): 500-505.

*Abstract:* Patients seeking help for pathological gambling often exhibit features of impulsivity, cognitive rigidity, poor judgment, deficits in emotion regulation, and excessive preoccupation with gambling. Some of these characteristics are also common among patients presenting with neurological pathology associated with executive deficits. Evidence of executive deficits have been confirmed in pathological gamblers using objective neurocognitive tests, however, it remains to be seen if such findings will emerge in self-report measures of executive control. These observations led to the current investigation of differences between a group of pathological gamblers (n = 62) and a comparison group (n = 64) using the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A). Significant differences between the groups emerged over all nine subscales of executive functioning with the most dramatic differences on BRIEF-A subscales Inhibit, Plan/Organize, Shift, Emotion Control, Self-Monitor, and Initiate among the pathological gamblers. These results provide evidence that support findings among pathological gamblers using objective neuropsychological measures and suggest that the BRIEF-A may be an appropriate instrument to assess possible problems with executive control in this population.

Roca, M., T. Torralva, et al. (2008). "Executive functions in pathologic gamblers selected in an ecologic setting." Cogn Behav Neurol 21(1): 1-4.

*Abstract:* BACKGROUND: Recent studies have reported deficits in measures of decision making in pathologic gamblers (PGs) suggesting an involvement of the prefrontal cortex in the pathophysiology of this disorder. As only 7% to 12% of PGs are thought to seek treatment, most of the studies have relied on few specifically selected groups of PGs recruited from psychiatric units who were undergoing or seeking treatment and therefore their results are poorly representative of the general PG population. METHODS: The present study compared decision making and executive functions among 11 PGs who were selected from an ecologic setting and 11 healthy controls. RESULTS: The PG group selected fewer advantageous cards on a decision-making task, the Iowa Gambling Task, and made more commission errors on the Go-No Go task, a test of inhibitory control, compared with controls. CONCLUSIONS: The impairments in decision making are similar to those previously reported in individuals with prefrontal lesions and treatment-seeking PGs. PGs also presented impairment in tasks of inhibitory control suggesting an involvement of the prefrontal cortex in the pathophysiology of pathologic gambling (PG). The deficits in decision making and inhibition of irrelevant information observed in this study may have distinct but additive effects upon the development of PG behavior.

Schiebener, J., L. Zamarian, et al. (2011). "Executive functions, categorization of probabilities, and learning from feedback: what does really matter for decision making under explicit risk conditions?" J Clin Exp Neuropsychol 33(9): 1025-1039.

*Abstract:* In two experiments with healthy subjects, we used the Game of Dice Task (GDT), the Probability-Associated Gambling (PAG) task, the Iowa Gambling Task (IGT), and executive-function

and logical thinking tasks to shed light on the underlying processes of decision making under risk. Results indicate that handling probabilities, as in the PAG task, is an important ingredient of GDT performance. Executive functions and logical thinking also play major roles in deciding in the GDT. Implicit feedback learning, as measured by the IGT, has little impact. Results suggest that good probability handling may compensate for the effects of weak executive functions in decisions under risk.

Toplak, M. E., G. B. Sorge, et al. (2010). "Decision-making and cognitive abilities: A review of associations between Iowa Gambling Task performance, executive functions, and intelligence." Clin Psychol Rev 30(5): 562-581.

*Abstract:* The Iowa Gambling Task (IGT) has been used to study decision-making differences in many different clinical and developmental samples. It has been suggested that IGT performance captures abilities that are separable from cognitive abilities, including executive functions and intelligence. The purpose of the current review was to examine studies that have explicitly examined the relationship between IGT performance and these cognitive abilities. We included 43 studies that reported correlational analyses with IGT performance, including measures of inhibition, working memory, and set-shifting as indices of executive functions, as well as measures of verbal, nonverbal, and full-scale IQ as indices of intelligence. Overall, only a small proportion of the studies reported a statistically significant relationship between IGT performance and these cognitive abilities. The majority of studies reported a non-significant relationship. Of the minority of studies that reported statistically significant effects, effect sizes were, at best, small to modest, and confidence intervals were large, indicating that considerable variability in performance on the IGT is not captured by current measures of executive function and intelligence. These findings highlight the separability between decision-making on the IGT and cognitive abilities, which is consistent with recent conceptualizations that differentiate rationality from intelligence.

von Hippel, W., L. Ng, et al. (2009). "Executive functioning and gambling: performance on the trail making test is associated with gambling problems in older adult gamblers." Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 16(6): 654-670.

*Abstract:* Rates of gambling problems in older adults have risen with increased accessibility of gambling venues. One possible contributor to problem gambling among older adults is decreased self-control brought about by diminished executive functioning. Consistent with this possibility, Study 1 revealed that older adults recruited from gambling venues reported greater gambling problems if they also experienced deficits in executive functioning, measured via the Trail Making Test. Study 2 replicated this finding and demonstrated that problem gambling is associated with increased depression among older adults, mediated by increased financial distress. These studies provide support for the hypothesis that older adult gamblers who have executive functioning problems are also likely to have gambling problems.

## Genetics

Agrawal, A., K. J. Verweij, et al. (2012). "The genetics of addiction-a translational perspective." Transl Psychiatry 2: e140.

*Abstract:* Addictions are serious and common psychiatric disorders, and are among the leading contributors to preventable death. This selective review outlines and highlights the need for a multi-method translational approach to genetic studies of these important conditions, including both licit (alcohol, nicotine) and illicit (cannabis, cocaine, opiates) drug addictions and the behavioral addiction of disordered gambling. First, we review existing knowledge from twin studies that indicates both the substantial heritability of substance-specific addictions and the genetic overlap across addiction to different substances. Next, we discuss the limited number of candidate genes which have shown consistent replication, and the implications of emerging genomewide association findings for the genetic architecture of addictions. Finally, we review the utility of extensions to existing methods such as novel phenotyping, including the use of endophenotypes, biomarkers and neuroimaging outcomes; emerging methods for identifying alternative sources of genetic variation and accompanying statistical methodologies to interpret them; the role of gene-environment interplay; and importantly, the potential role of genetic variation in suggesting new alternatives for treatment of addictions.

Brewer, J. A. and M. N. Potenza (2008). "The neurobiology and genetics of impulse control disorders: relationships to drug addictions." Biochem Pharmacol 75(1): 63-75.

*Abstract:* Impulse control disorders (ICDs), including pathological gambling, trichotillomania, kleptomania and others, have been conceptualized to lie along an impulsive-compulsive spectrum. Recent data have suggested that these disorders may be considered addictions. Here, we review the genetic and neuropathological bases of the impulse control disorders and consider the disorders within these non-mutually exclusive frameworks.

Eisen, S. A., W. S. Slutske, et al. (2001). "The genetics of pathological gambling." Semin Clin Neuropsychiatry 6(3): 195-204.

*Abstract:* Problem and pathological gambling (PG) occurs in about 5% of Americans. Gambling is associated with substantial psychosocial and psychiatric health problems, and the increasing ease of access to gambling may increase its future prevalence. Therefore, it is important to gain greater insight into the causes of PG. Family studies of PG are consistent with a substantial familial impact on vulnerability to PG. However, family studies cannot distinguish genetic from family environmental influences. By contrast, the study of twin pairs permits the genetic and environmental influences on PG to be estimated. The study of gambling behavior among 3,359 twin pair members of the Vietnam Era Twin Registry suggests that: (1) inherited factors explain a substantial proportion of the variance in the report of symptoms of gambling; (2) there is a single continuum of genetic vulnerability that underlies gambling problems of varying severities; and, (3) the co-occurrence of PG with conduct disorder, antisocial personality disorder, and alcohol abuse/dependence is partially explained by genes that influence both PG and these other psychiatric disorders. Neurophysiological correlates of gambling problems and genetically based differences in neurotransmitter systems may provide biological mechanisms that explain the genetic basis for a predisposition to PG.

Ibanez, A., C. Blanco, et al. (2003). "Genetics of pathological gambling." J Gambl Stud 19(1): 11-22.

*Abstract:* Pathological gambling (PG) is an impulse control disorder and a model 'behavioral' addiction. Familial factors have been observed in clinical studies of pathological gamblers, and twin studies have demonstrated a genetic influence contributing to the development of PG. Serotonergic, noradrenergic, and dopaminergic dysfunction have been reported as biological factors contributing to the pathophysiology of PG. Molecular genetic techniques have been used to investigate the role of genetic factors in PG. Molecular genetic research has identified specific allele variants of candidate genes corresponding to these neurotransmitter systems to be associated with PG. Associations have been reported between pathological gamblers and allele variants of polymorphisms at dopamine receptor genes, the serotonin transporter gene, and the monoamine-oxidase A gene. Although preliminary data suggest that some of these differences are gender-specific, more research needs to be performed to substantiate gender-specific genetic contributions to the development of pathological gambling. The review of the current findings on genetics of PG suggests that liability to PG is in part mediated by genetic factors. Additional studies are needed to replicate and extend these findings, as well as to better understand the influence of specific allelic variants to differences in biological and behavioral functioning.

Leeman, R. F. and M. N. Potenza (2013). "A targeted review of the neurobiology and genetics of behavioural addictions: an emerging area of research." Can J Psychiatry 58(5): 260-273.

*Abstract:* This review summarizes neurobiological and genetic findings in behavioural addictions, draws parallels with findings pertaining to substance use disorders, and offers suggestions for future research. Articles concerning brain function, neurotransmitter activity, and family history and (or) genetic findings for behavioural addictions involving gambling, Internet use, video game playing, shopping, kleptomania, and sexual activity were reviewed. Behavioural addictions involve dysfunction in several brain regions, particularly the frontal cortex and striatum. Findings from imaging studies incorporating cognitive tasks have arguably been more consistent than cue-induction studies. Early results suggest white and grey matter differences. Neurochemical findings suggest roles for dopaminergic and serotonergic systems, but results from clinical trials seem more equivocal. While limited, family history and genetic data support heritability for pathological gambling and that people with behavioural addictions are more likely to have a close family member with some form of psychopathology. Parallels exist between neurobiological and genetic and family history findings in substance and nonsubstance addictions, suggesting that compulsive engagement in these behaviours may constitute addictions. To date, findings are limited, particularly for shopping, kleptomania, and sexual behaviour. Genetic understandings are at an early stage. Future research directions are offered.

Lobo, D. S. and J. L. Kennedy (2006). "The genetics of gambling and behavioral addictions." CNS Spectr 11(12): 931-939.

*Abstract:* Behavioral addictions are considered as the repetitive occurrence of impulsive behaviors without consideration of their potential negative consequences. These addictions represent an increasing cost to society and are an important new field of research in psychiatric genetics. There has been a growing body of evidence on the familial aggregation and genetic influences on the development of behavioral addictions and mainly on pathological gambling. The aim of this article is to critically review findings of family and molecular genetic studies on behavioral addictions, focusing

on pathological gambling and commenting on other disorders where appropriate. This review provides a comprehensive approach to genetic studies on behavioral addiction and points out the necessity of expanding the genetic research in this field. Future directions for genetic studies in this field are also discussed.

Lobo, D. S. and J. L. Kennedy (2009). "Genetic aspects of pathological gambling: a complex disorder with shared genetic vulnerabilities." *Addiction* 104(9): 1454-1465.

*Abstract:* AIMS: To summarize and discuss findings from genetic studies conducted on pathological gambling (PG). METHODS: Searches were conducted on PubMed and PsychInfo databases using the keywords: 'gambling and genes', 'gambling and family' and 'gambling and genetics', yielding 18 original research articles investigating the genetics of PG. RESULTS: Twin studies using the Vietnam Era Twin Registry have found that: (i) the heritability of PG is estimated to be 50-60%; (ii) PG and subclinical PG are a continuum of the same disorder; (iii) PG shares genetic vulnerability factors with antisocial behaviours, alcohol dependence and major depressive disorder; (iv) genetic factors underlie the association between exposure to traumatic life-events and PG. Molecular genetic investigations on PG are at an early stage and published studies have reported associations with genes involved in the brain's reward and impulse control systems. CONCLUSIONS: Despite the paucity of studies in this area, published studies have provided considerable evidence of the influence of genetic factors on PG and its complex interaction with other psychiatric disorders and environmental factors. The next step would be to investigate the association and interaction of these variables in larger molecular genetic studies with subphenotypes that underlie PG. Results from family and genetic investigations corroborate further the importance of understanding the biological underpinnings of PG in the development of more specific treatment and prevention strategies.

Versini, A., C. LeGauffre, et al. (2012). "Frequency of gambling problems among parents of pathological, versus nonpathological, casino gamblers using slot machines." *Am J Addict* 21(1): 86-95.

*Abstract:* Familial and twin studies suggest the implication of a genetic factor in pathological gambling, but mainly assess probands through treatment settings or advertisements. The question raised here is: are parents of casino pathological gamblers using slot machines more affected with pathological gambling than nonpathological gamblers, all interviewed on site at the same casino? Three hundred and fifty-five casino gamblers on slot machines, which included 96 pathological gamblers, 116 problem gamblers, and 143 nonproblem gamblers, were recruited in situ at the largest casino in the Paris suburbs. We evaluated pathological gambling and two addictive disorders (alcohol dependence and tobacco consumption) in the gamblers and their 690 parents (through the proband). Familial aggregation of pathological gambling was confirmed, with a risk of 3.3 for being a pathological gambler when at least one of the parents has problematic gambling. No familial co-aggregation of pathological gambling with alcohol or tobacco dependence was observed. Pathological gambling is found in excess in the parents of pathological casino gamblers, in accordance with previous aggregation studies devoted to other types of gambling, and with studies recruiting gamblers in different settings.

## Impulsivity

Alvarez-Moya, E. M., C. Ochoa, et al. (2011). "Effect of executive functioning, decision-making and self-reported impulsivity on the treatment outcome of pathologic gambling." J Psychiatry Neurosci 36(3): 165-175.

*Abstract:* BACKGROUND: Impairments in self-regulatory behaviour reflect a deficit in executive functioning and decision-making, as well as higher levels of self-reported impulsivity, and may be involved in the development and maintenance of addictive disorders. We sought to explore the association between self-reported impulsivity and neurocognitive measures, and their association with treatment outcome in pathologic gambling. METHODS: We assessed patients with pathologic gambling using executive functioning and decision-making tests and self-report measures of impulsivity. Patients underwent cognitive-behavioural therapy (CBT) for pathologic gambling. RESULTS: We included 88 patients (8% women) in our study. High self-reported extravagance was associated with poor performance in the Iowa Gambling Task (IGT)-ABCD version. High impulsiveness, low disorderliness, high exploratory excitability (trend), poor backward block span and poor IGT-EFGH scores (trend) predicted dropout. We observed no self-reported or neurocognitive predictors of relapse or number of treatment sessions attended. LIMITATIONS: Most participants were slot-machine gamblers seeking treatment. No follow-up data and no control group were included in the study. The missing sample (i.e., individuals who were recruited and assessed in the pretreatment stage but who chose not to begin treatment) had higher extravagance scores than the final sample. CONCLUSION: Neurocognitive reward sensitivity was related to self-reported overspending behaviour. Self-regulatory impairments (especially rash impulsiveness and punishment sensitivity) and executive dysfunction predicted only dropout of CBT in participants with pathologic gambling. Different neurocognitive processes and personality traits might mediate treatment response to psychological therapy of pathologic gambling according to the specific target variable assessed.

Billieux, J., G. Lagrange, et al. (2012). "Investigation of impulsivity in a sample of treatment-seeking pathological gamblers: a multidimensional perspective." Psychiatry Res 198(2): 291-296.

*Abstract:* Numerous studies have shown that problem gambling is characterised by lack of impulse control. However, they have often been conducted without considering the multifaceted nature of impulsivity and related psychological mechanisms. The current study aims to disentangle which impulsivity facets are altered in pathological gambling. Twenty treatment-seeking pathological gamblers (PGs) and 20 matched control participants completed a self-reported questionnaire measuring the various facets of impulsive behaviours (UPPS Impulsive Behaviour Scale), as well as two laboratory tasks assessing inhibitory control (the go-stop task) and tolerance for delayed rewards (single key impulsivity paradigm). Compared with matched controls, PGs exhibited higher urgency, lower premeditation, impairment in prepotent inhibition, and lower tolerance towards delayed rewards. Nevertheless, complementary profile analyses showed that impulsivity-related deficits found in PGs are highly heterogeneous, and that some PGs are neither impulsive in the impulsivity facets assessed nor impaired in the cognitive mechanisms measured. These findings underscore (1) the necessity to disentangle the construct of impulsivity into lower-order components and (2) that further studies should take into account, in addition to impulsivity-related mechanisms, other psychological factors potentially involved in pathological gambling.

Crewe-Brown, C., A. Blaszczynski, et al. (2013). "Prize Level and Debt Size: Impact on Gambling Behaviour." J Gambl Stud.

*Abstract:* No studies to date have specifically determined the relationship between prize levels, debt size, and impulsivity on reported gambling behaviour on Electronic Gaming Machines (EGM). The present study reports the findings of a pilot study designed to investigate whether or not the likelihood of increasing the size of a bet was related to the level of prize offered and personal debt. The sample consisted of 171 first year psychology students (61 males and 120 females). Participants completed a series of gambling vignettes designed to elicit data on reported bet size according to different prize levels and debt sizes; the Eysenck Impulsivity Scale (Eysenck and Eysenck 1977); the Canadian Problem Gambling Index; and an author-constructed questionnaire eliciting data on demographic and gambling behaviours. Results indicated that as prize levels increase the odds (relative risk) of an individual placing a bet on an EGM and the amount of money reportedly bet tends to increase. A negative relationship between debt size and reported gambling behaviour moderated by prize level was found. No differences were found in the odds of placing a bet according to impulsivity. It was concluded that prize and debt sizes do influence propensities to gamble and level of bets. The findings have implications for restricting jackpot and general prize levels as a responsible gambling strategy designed to reduce motivations to gamble.

Floden, D., M. P. Alexander, et al. (2008). "Impulsivity and risk-taking behavior in focal frontal lobe lesions." Neuropsychologia 46(1): 213-223.

*Abstract:* Frontal lobe dysfunction may underlie excessively impulsive and risky behavior observed in a range of neurological disorders. We devised a gambling task to examine these behavior tendencies in a sample of patients who had sustained focal damage to the frontal lobes or nonfrontal cortical regions as well as in a matched sample of healthy control subjects. The main objectives of the study were: (1) to behaviorally dissociate impulsivity and risk-taking; (2) to examine potential associations between specific frontal lesion sites and impulsivity or risk-taking; (3) to investigate the influence of reinforcement and trial timing on both behaviors. Our results indicated that patients and controls were equally likely to perform impulsively. Risk-taking performance strategies, however, were related to left ventrolateral and orbital lesion sites. Moreover, risk-taking was also associated with blunted response alteration following a nonrewarded trial. Patients and control subjects showed identical responses to reward-timing manipulations consistent with formal decision-making theory. These findings suggest that ventrolateral and orbital lesions are related to the reward-based aspects of decision-making (risk-taking) rather than to simple response disinhibition (impulsivity). Reduced reaction to the negative consequences of one's actions may underlie this behavior pattern.

Ginley, M. K., J. P. Whelan, et al. (2013). "Exploring a Multidimensional Approach to Impulsivity in Predicting College Student Gambling." J Gambl Stud.

*Abstract:* Impulsivity has been implicated as a contributing factor in the development of gambling problems among college students, but attempts to confirm this relation have been inconsistent. One explanation for these incongruent findings is that impulsivity may be multidimensional and that distinct dimensions differentially predict separate behaviors. Using a large, diverse sample of college students, a factor analysis of self-report measures related to impulsivity revealed a three-factor structure of

Behavioral Activation, Preference for Stimulation, and Inhibition Control that was similar to the structure found by Meda et al. (Behav Pharmacol 20(5-6):390-399, 2009) in a different adult sample. Low risk gamblers and symptomatic gamblers scored significantly lower on Behavioral Activation and Inhibition Control than non-gamblers. Conversely, low risk gamblers and symptomatic gamblers scored significantly higher on Preference for Stimulation. Prevalence of gambling and gambling activity preference for this sample was also assessed.

Knezevic, B. and D. M. Ledgerwood (2012). "Gambling severity, impulsivity, and psychopathology: comparison of treatment- and community-recruited pathological gamblers." *Am J Addict* 21 (6): 508-515.

*Abstract:* BACKGROUND AND OBJECTIVES: Because most studies of pathological gambling gather data from participants recruited from treatment, this study compared community and treatment-enrolled pathological gamblers (PGs) with respect to demographics, gambling severity, impulsivity, and psychopathology. METHODS: One hundred six PGs were recruited as part of two larger studies in Farmington, Connecticut (n= 61) and Windsor, Ontario (n= 45) using radio advertising, word of mouth, and/or newspaper ads, as well as a gambling treatment program at each location. RESULTS: Community (n= 49) and treatment-enrolled (n= 57) PGs did not differ on age, education, gender, race, employment, or marital status. Treatment-enrolled PGs were more likely to report past year illegal behaviors, preoccupation with gambling, and higher scores on the Barratt Impulsiveness Scale (BIS) Attention Impulsivity subscale. Assessment of psychopathology in the Ontario study indicated that treatment-enrolled PGs were more likely to present with Major Depressive and Dysthymic Disorders. Community-recruited PGs in the Connecticut study were overall more likely to present with any substance use disorder relative to their treatment-enrolled counterparts. CONCLUSIONS AND SCIENTIFIC SIGNIFICANCE: Our findings inform intervention and research within the field of pathological gambling. Specifically, the distressing aspects of pathological gambling, such as legal issues, preoccupation with gambling, and depression, may be present more in treatment-enrolled PGs than in those recruited from the community. Such emotional disturbances should be further explored to increase motivation and treatment adherence in PGs. In addition, due to relative absence of overall differences between the groups, research findings utilizing treatment-enrolled PGs may be a good representation of both groups.

Lai, F. D., A. K. Ip, et al. (2011). "Impulsivity and pathological gambling: Is it a state or a trait problem?" *BMC Res Notes* 4: 492.

*Abstract:* BACKGROUND: This study tested 37 Chinese male pathological gamblers and 40 controls to understand the relationship between pathological gambling and impulsivity as a long-term trait or a short-term state in the cognitive and affective domain. RESULTS: Trait impulsivity was measured by the Barratt Impulsiveness Scale-11. State impulsivity in the cognitive and affective domains were measured by the Stroop Color Word Test and the Emotional Conflict Task, respectively. The pathological gamblers scored significantly higher than the controls on the Barratt Impulsiveness Scale-11. However, there were no significant group differences in performance on the Stroop Color Word Test or the Emotional Conflict Task. CONCLUSIONS: Findings clearly show that pathological gambling is associated with trait but not state impulsivity. In other words, pathological gambling is associated with an impulsivity stemming from enduring personality characteristics that lead gamblers to focus on short-

term gains (trait impulsivity) rather than momentary cognitive or affective disinhibition (state impulsivity). Interventions should aim to change pathological gamblers' habitual functioning style by cultivating healthy reflection habits and focusing on long-term rewards.

Lee, H. W., J. S. Choi, et al. (2012). "Impulsivity in internet addiction: a comparison with pathological gambling." Cyberpsychol Behav Soc Netw 15(7): 373-377.

*Abstract:* Internet addiction has been considered to be associated with poor impulse control. The aim of this study is to compare the trait impulsivity of those suffering from Internet addiction with that of individuals suffering from pathological gambling. Twenty-seven patients diagnosed with Internet addiction (age: 24.78+/-4.37 years), 27 patients diagnosed with pathological gambling (age: 25.67+/-3.97 years), and 27 healthy controls (age: 25.33+/-2.79 years) were enrolled in this study. All patients were men seeking treatment. Trait impulsivity and the severity of the Internet addiction and pathological gambling were measured by the Barratt Impulsiveness Scale-11, the Young's Internet Addiction Test, and the South Oaks Gambling Screen, respectively. The Beck Depression Inventory and the Beck Anxiety Inventory were also administered to all subjects. Our results show that those suffering from Internet addiction showed increased levels of trait impulsivity which were comparable to those of patients diagnosed with pathological gambling. Additionally, the severity of Internet addiction was positively correlated with the level of trait impulsivity in patients with Internet addiction. These results state that Internet addiction can be conceptualized as an impulse control disorder and that trait impulsivity is a marker for vulnerability to Internet addiction.

Leeman, R. F. and M. N. Potenza (2012). "Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity." Psychopharmacology (Berl) 219(2): 469-490.

*Abstract:* RATIONALE: Pathological gambling (PG) has recently been considered as a "behavioral" or nonsubstance addiction. A comparison of the characteristics of PG and substance use disorders (SUDs) has clinical ramifications and could help advance future research on these conditions. Specific relationships with impulsivity and compulsivity may be central to understanding PG and SUDs. OBJECTIVES: This review was conducted to compare and contrast research findings in PG and SUDs pertaining to neurocognitive tasks, brain function, and neurochemistry, with a focus on impulsivity and compulsivity. RESULTS: Multiple similarities were found between PG and SUDs, including poor performance on neurocognitive tasks, specifically with respect to impulsive choice and response tendencies and compulsive features (e.g., response perseveration and action with diminished relationship to goals or reward). Findings suggest dysfunction involving similar brain regions, including the ventromedial prefrontal cortex and striatum and similar neurotransmitter systems, including dopaminergic and serotonergic. Unique features exist which may in part reflect influences of acute or chronic exposures to specific substances. CONCLUSIONS: Both similarities and differences exist between PG and SUDs. Understanding these similarities more precisely may facilitate treatment development across addictions, whereas understanding differences may provide insight into treatment development for specific disorders. Individual differences in features of impulsivity and compulsivity may represent important endophenotypic targets for prevention and treatment strategies.

Michalczuk, R., H. Bowden-Jones, et al. (2011). "Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report." Psychol Med 41(12): 1-11.

*Abstract:* BACKGROUND: Pathological gambling (PG) is a form of behavioural addiction that has been associated with elevated impulsivity and also cognitive distortions in the processing of chance, probability and skill. We sought to assess the relationship between the level of cognitive distortions and state and trait measures of impulsivity in treatment-seeking pathological gamblers. Method Thirty pathological gamblers attending the National Problem Gambling Clinic, the first National Health Service clinic for gambling problems in the UK, were compared with 30 healthy controls in a case-control design. Cognitive distortions were assessed using the Gambling-Related Cognitions Scale (GRCS). Trait impulsivity was assessed using the UPPS-P, which includes scales of urgency, the tendency to be impulsive in positive or negative mood states. Delay discounting rates were taken as a state measure of impulsive choice. RESULTS: Pathological gamblers had elevated impulsivity on several UPPS-P subscales but effect sizes were largest (Cohen's  $d > 1.4$ ) for positive and negative urgency. The pathological gamblers also displayed higher levels of gambling distortions, and elevated preference for immediate rewards, compared to controls. Within the pathological gamblers, there was a strong relationship between the preference for immediate rewards and the level of cognitive distortions ( $R^2 = 0.41$ ). CONCLUSIONS: Impulsive choice in the gamblers was correlated with the level of gambling distortions, and we hypothesize that an impulsive decision-making style may increase the acceptance of erroneous beliefs during gambling play.

Myrseth, H., R. Tvera, et al. (2012). "A comparison of impulsivity and sensation seeking in pathological gamblers and skydivers." Scand J Psychol 53(4): 340-346.

*Abstract:* The aim of this study was to compare pathological gamblers and skydivers in relation to measures of impulsivity and sensation seeking. The Eysenck Impulsivity Scale - Narrow Impulsiveness Subscale and the Arnett Inventory of Sensation Seeking were administered to pathological gamblers ( $n = 29$ ), skydivers ( $n = 93$ ), and a control group ( $n = 43$ ). A two-way multivariate analysis of variance was conducted to explore differences in impulsivity and sensation seeking between the groups and possible group by gender and group by age interaction effects. The significant effects were further investigated using follow-up univariate analysis of variance. The results showed significant main effects of Group, Gender and Age, and a significant Group by Gender interaction effect. The results showed no statistically significant differences in impulsivity between pathological gamblers and skydivers; however, both groups scored higher than the controls. The skydivers scored higher compared to the pathological gamblers and controls on both sensation seeking subscales. Pathological gamblers scored higher than the controls on the subscale Need for Stimulus Intensity, although lower than the controls on the subscale Need for Novelty. We conclude that skydivers and pathological gamblers do not seem to differ in terms of impulsivity, but that the two groups differ in terms of sensation seeking. Skydivers are hence characterized by more sensation seeking compared to pathological gamblers. Skydiving, as opposed to pathological gambling, is not considered a psychiatric disorder, and skydiving may represent a more non-pathological way to fulfill the need for stimulus intensity.

Patterson, J. C., 2nd, J. Holland, et al. (2006). "Neuropsychological performance, impulsivity, and comorbid psychiatric illness in patients with pathological gambling undergoing treatment at the CORE Inpatient Treatment Center." South Med J 99(1): 36-43.

*Abstract:* INTRODUCTION: Pathologic gambling is a disorder with features that implicate abnormal functioning in brain regions involved in addiction, mood, anxiety, and impulse control disorders. Our goal was to examine brain function with neurocognitive tasks that target these brain regions in patients with pathologic gambling. METHODS: Patients were evaluated for comorbid psychiatric disorders, impulsivity, and performance on reversal-learning and reward-based decision-making cognitive tasks. RESULTS: Patients had higher impulsivity scores and significant deficits on both cognitive tasks compared with controls. All subjects also had comorbid psychiatric disorders, including mood, anxiety, psychotic, and substance abuse. CONCLUSION: The cognitive deficits and impulsivity are consistent with abnormal activity in orbitofrontal-limbic networks. The high level of comorbidity is consistent with the overall severity in these inpatients undergoing treatment, and adds weight to the concept of a fundamental abnormality in this network.

Shao, R., J. Read, et al. (2013). "Shifts in reinforcement signalling while playing slot-machines as a function of prior experience and impulsivity." Transl Psychiatry 3: e235.

*Abstract:* Electronic gaming machines (EGMs) offer significant revenue streams for mercantile gambling. However, limited clinical and experimental evidence suggests that EGMs are associated with heightened risks of clinically problematic patterns of play. Little is known about the neural structures that might mediate the transition from exploratory EGM play to the 'addictive' play seen in problem gamblers; neither is it known how personality traits associated with gambling activity (and gambling problems) influence reinforcement processing while playing EGMs. Using functional magnetic resonance imaging in healthy participants, we show that a single episode of slot-machine play is subsequently associated with reduced amplitudes of blood-oxygenation level-dependent signals within reinforcement-related structures, such as the ventral striatum and caudate nucleus, following winning game outcomes; but increased amplitudes of anticipatory signals within the ventral striatum and amygdala while watching the game reels spin. Trait impulsivity enhanced positive signals within the ventral striatum and amygdala following the delivery of winning outcomes but diminished positive signals following the experience of almost-winning ('near-misses'). These results indicate that a single episode of slot-machine play engages the well-characterised reinforcement-learning mechanisms mediated by ascending dopamine mesolimbic and mesostriatal pathways, to shift reward value of EGMs away from game outcomes towards anticipatory states. Impulsivity, itself linked to problem gambling and heightened vulnerability to other addictive disorders, is associated with divergent coding of winning outcomes and almost-winning experiences within the ventral striatum and amygdala, potentially enhancing the reward value of successful slot-machine game outcomes but, at the same time, modulating the aversive motivational consequences of near-miss outcomes.

Takano, Y., N. Takahashi, et al. (2010). "Big losses lead to irrational decision-making in gambling situations: relationship between deliberation and impulsivity." PLoS One 5(2): e9368.

*Abstract:* In gambling situations, we found a paradoxical reinforcing effect of high-risk decision-making after repeated big monetary losses. The computerized version of the Iowa Gambling Task

(Bechara et al., 2000), which contained six big loss cards in deck B', was conducted on normal healthy college students. The results indicated that the total number of selections from deck A' and deck B' decreased across trials. However, there was no decrease in selections from deck B'. Detailed analysis of the card selections revealed that some people persisted in selecting from the "risky" deck B' as the number of big losses increased. This tendency was prominent in self-rated deliberative people. However, they were implicitly impulsive, as revealed by the matching familiar figure test. These results suggest that the gap between explicit deliberation and implicit impulsivity drew them into pathological gambling.

Weinstock, J., C. E. Massura, et al. (2013). "Professional and pathological gamblers: similarities and differences." *J Gambl Stud* 29(2): 205-216.

*Abstract:* Although much recent research has focused on the gambling practices and psychosocial functioning of pathological gamblers, few investigations have examined the characteristics of professional gamblers. The current project sought to address this gap in the literature by conducting a quantitative comparison of professional and pathological gamblers. Pathological gamblers were recruited and balanced with professional gamblers on demographic variables and preferred gambling activity. A total of 22 professional gamblers and 13 pathological gamblers completed an extensive self-report battery including instruments assessing demographics, gambling behaviors and problems, other psychiatric disorders, current psychosocial functioning, recent stressful events, personality characteristics, and intelligence. Pathological and professional gamblers reported similar rates of gambling frequency and intensity and types of games played. Pathological gamblers endorsed poor psychosocial functioning, whereas professional gamblers reported a rate of psychiatric distress within a normative range. Pathological gamblers also reported lower gambling self-efficacy, greater impulsivity, and more past-year DSM-IV Axis I disorders than professional gamblers. The results of the present study shed light on the unique circumstances of professional gamblers, as well as underscore important differences between such individuals and pathological gamblers that could prove fruitful in future research and intervention and prevention efforts.

## Neuropsychology

Conversano, C., D. Marazziti, et al. (2012). "Pathological gambling: a systematic review of biochemical, neuroimaging, and neuropsychological findings." *Harv Rev Psychiatry* 20(3): 130-148.

*Abstract:* Pathological gambling is an emerging psychiatric disorder that has recently gained much attention because of its increasing prevalence and devastating personal, familial, and social consequences. Although its pathophysiology is largely unknown, the shared similarities with both addiction and obsessive-compulsive spectrum disorders have suggested the possibility of common psychobiological substrates. As with many other psychiatric disorders, it is believed that pathological gambling may result from the interplay between individual vulnerability and environmental factors. The aim of this article is to offer a comprehensive review of the main neurobiological aspects of pathological gambling, with particular attention to neuropsychological and related findings. A deeper understanding of the biological correlates of pathological gambling is required in order to develop effective treatment strategies.

el-Guebaly, N., T. Mudry, et al. (2012). "Compulsive features in behavioural addictions: the case of pathological gambling." Addiction 107(10): 1726-1734.

*Abstract:* AIMS: To describe, in the context of DSM-V, how a focus on addiction and compulsion is emerging in the consideration of pathological gambling (PG). METHODS: A systematic literature review of evidence for the proposed re-classification of PG as an addiction. RESULTS: Findings include: (i) phenomenological models of addiction highlighting a motivational shift from impulsivity to compulsivity associated with a protracted withdrawal syndrome and blurring of the ego-syntonic/ego-dystonic dichotomy; (ii) common neurotransmitter (dopamine, serotonin) contributions to PG and substance use disorders (SUDs); (iii) neuroimaging support for shared neurocircuitries between 'behavioural' and substance addictions and differences between obsessive-compulsive disorder (OCD), impulse control disorders (ICDs) and SUDs; (iv) genetic findings more closely related to endophenotypic constructs such as compulsivity and impulsivity than to psychiatric disorders; (v) psychological measures such as harm avoidance identifying a closer association between SUDs and PG than with OCD; (vi) community and pharmacotherapeutic trials data supporting a closer association between SUDs and PG than with OCD. Adapted behavioural therapies, such as exposure therapy, appear applicable to OCD, PG or SUDs, suggesting some commonalities across disorders. CONCLUSIONS: PG shares more similarities with SUDs than with OCD. Similar to the investigation of impulsivity, studies of compulsivity hold promising insights concerning the course, differential diagnosis and treatment of PG, SUDs, and OCD.

Goudriaan, A. E., J. Oosterlaan, et al. (2004). "Pathological gambling: a comprehensive review of biobehavioral findings." Neurosci Biobehav Rev 28(2): 123-141.

*Abstract:* In this review, findings of biobehavioral research into pathological gambling (PG) are discussed, focusing on neuropsychological, psychophysiological, neuroimaging, neurochemical and genetic studies. Neuropsychological studies indicate deficiencies in certain executive functions. Psychophysiological studies indicate that arousal in PG is of importance when reward is present. Neuroimaging studies point to abnormalities in brain functioning. Recent research into the neurochemistry of PG indicates that abnormalities exist in different neurotransmitter systems. Finally, genetic studies indicate the existence of abnormal dopamine receptor genes in PG. Methodological and theoretical factors that may explain discrepancies between studies include differences in screening and assessment, heterogeneity of gambling problems and different underlying cognitive or motivational mechanisms. Results from the PG studies fit in with recent theoretical models of addiction and PG, which stress the involvement of brain reward pathways, neurotransmitter abnormalities, the frontal cortex and the psychophysiological stress system. A framework for future studies is suggested, indicating the need for studies that integrate knowledge from different research areas, and that employ stricter diagnostic screening methods and inclusion of clinical control groups.

Grant, J. E., B. L. Odlaug, et al. (2012). "Telescoping phenomenon in pathological gambling: association with gender and comorbidities." J Nerv Ment Dis 200(11): 996-998.

*Abstract:* The course of pathological gambling (PG) in women has been described as having a later age of initiation but a shorter time to problematic gambling ("telescoped"). This study examined evidence for telescoping and its relationship with comorbidities. Seventy-one treatment-seeking

individuals with PG underwent a diagnostic interview to examine gambling behaviors, age at initiation of gambling, and time from initiation to meeting criteria for PG. The women had a higher mean age at gambling initiation compared with that of the men (mean [SD] age, 31.3 [13.0] years, compared with 22.4 [7.9] years;  $p = 0.0003$ ) and a significantly shorter time from initiation of gambling to meeting the criteria for PG (8.33 [8.7] years compared with 11.97 [9.1] years;  $p = 0.0476$ ) after controlling for demographic and clinical variables. This study presents evidence for a gender-specific course of PG unrelated to psychiatric comorbidities and suggests a need for greater clinical focus on the gender differences of gambling behavior.

Hur, J. W., N. Shin, et al. (2012). "Do pathological gambling and obsessive-compulsive disorder overlap? a neurocognitive perspective." *CNS Spectr* 17(4): 207-213.

*Abstract:* OBJECTIVE: Pathological gambling (PG) is a severe and persistent pattern of problem gambling that has been aligned with obsessive-compulsive disorder (OCD). However, no study has compared the neurocognitive profiles of individuals with PG and OCD. METHODS: We compared neurocognitive functioning, including executive function, verbal learning and memory, and visual-spatial organization and memory among 16 pathological gamblers, 31 drug-naive OCD subjects, and 52 healthy controls. RESULTS: The only neurocognitive marker common to both groups was increased fragmentation errors on the Rey-Osterrieth Complex Figure Test (ROCF). The PG subjects showed increased nonperseverative error on the Wisconsin Card Sorting Test and organization difficulties in the ROCF, whereas the OCD subjects revealed longer response times on the Stroop test and retention difficulties on the immediate recall scale of the ROCF. CONCLUSIONS: A more careful approach is required in considering whether PG is a part of the OCD spectrum, as little evidence of neurocognitive overlap between PG and OCD has been reported.

Maclaren, V. V., J. A. Fugelsang, et al. (2011). "The personality of pathological gamblers: a meta-analysis." *Clin Psychol Rev* 31(6): 1057-1067.

*Abstract:* This review summarizes studies of pathological gambling and personality. Meta-analyses were conducted on 44 studies that reported personality traits of pathological gamblers ( $N = 2134$ ) and nonpathological gambling control groups ( $N = 5321$ ). Effect size estimates were calculated for 128 comparisons and organized according to the factors associated with two integrative accounts of personality. Four of the meta-analyses examined traits that have previously been found to load on the Urgency, Premeditation, Perseverance, and Sensation Seeking aspects of impulsivity (Whiteside & Lynam 2001). Substantial effects were found for traits associated with Negative Urgency (Cohen's  $d = .99$ ) and Low Premeditation ( $d = .84$ ), but not for Low Perseverance or Sensation Seeking. A second set of meta-analyses examined broad domains of personality that have previously been found to load on Negative Affect, Positive Affect, Disagreeable Disinhibition, and Unconscientious Disinhibition (Markon, Krueger, & Watson, 2005). Substantial effects were found for Unconscientious Disinhibition ( $d = .79$ ), Negative Affect ( $d = .50$ ), and Disagreeable Disinhibition ( $d = .50$ ), but not Positive Affect. It was concluded that these individual personality characteristics may be important in the etiology of pathological gambling. The personality profile implicated in the etiology of pathological gambling is similar to that found in a recent meta-analysis of substance use disorders (Kotov, Gamez, Schmidt, & Watson, 2010). These results suggest that pathological gambling may be part of a broad cluster of

externalizing psychopathology, and also call into question the current classification of pathological gambling as an Impulse Control Disorder in the DSM-IV.

Odling, B. L., L. R. Schreiber, et al. (2012). "Personality disorders and dimensions in pathological gambling." *J Pers Disord* 26(3): 381-392.

*Abstract:* Comorbid DSM-IV Axis II personality disorders appear to be common in pathological gambling (PG) and may contribute to the chronic problems often associated with the disorder. This study sought to examine the relationship between PG, personality disorders, and impulsivity in a sample of pathological gamblers. Personality assessments included the SCID-II, Eysenck Impulsiveness Questionnaire, Tridimensional Personality Questionnaire, and Barratt Impulsiveness Scale. A total of 77 individuals with DSM-IV PG were included in this study, of which 35 (45.5%) met criteria for at least one personality disorder. Specific aspects of impulsivity were associated with certain personality disorders in PG when grouped by cluster, yet the presence of a personality disorder was not positively correlated with gambling severity. It remains unclear how the presence of a personality disorder and aspects of impulsivity may affect treatment outcome. Further exploration of these disorders and dimensions of personality may encourage a more inclusively global treatment approach.

Teed, M., K. A. Finlay, et al. (2012). "Sympathetic magic and gambling: adherence to the law of contagion varies with gambling severity." *J Gamb Stud* 28(4): 691-701.

*Abstract:* This study assessed adherence to the law of contagion by 118 undergraduate students (39 males). Participants were students who played a slot machine game after viewing a prior player who seemed to be winning ("lucky" condition) or losing ("unlucky" condition). Adherence to the law of contagion was assessed by the selection of the coin holder used by a "lucky" prior player and the avoidance of the coin holder used by an "unlucky" prior player. Contagion varied directly with scores on the Problem Gambling Severity Index and scores on the Luck/Perseverance subscale of the Gamblers' Belief Questionnaire (Steenbergh et al. in *Psychol Addict Behav* 16(2):143-149, 2002). Gamblers high in problem severity chose the "lucky" coin holder and avoided the "unlucky" coin holder significantly more than gamblers low in problem severity. Problem gamblers, therefore, exhibit evidence of magical thinking related to the transfer of a "lucky" essence. The same was the case for individuals with a strong level of belief that sheer continuation in gambling (luck perseverance) results in success and for individuals who believe that luck is a personal rather than a situational characteristic. All three variables (problem gambling severity, luck perseverance and personal luck) had direct effects on behavior reflecting irrational magical thinking. A belief that knowledge or skill has a role in successful gaming was unrelated to magical thinking. These findings suggest potential foci for cognitive interventions with problem gamblers and those with non-skill based evidence of irrational thinking.

## Pharmacological treatment

Achab, S. and Y. Khazaal (2011). "Psychopharmacological treatment in pathological gambling: a critical review." *Curr Pharm Des* 17(14): 1389-1395.

*Abstract:* Given the rates of pathological gambling and its impact on affected individuals and their relatives, effective treatments are needed. There are, however, no approved pharmacological treatments for pathological gambling. This paper describes the development of pharmacological treatments for pathological gambling and is based on a review of the literature published in the past 10 years. Important studies were carried-out on antidepressants, mood stabilizers, and antipsychotic agents. In the absence of comorbid psychiatric disorder, these studies did not conclude to the efficacy of these psychotropic drugs. A possible efficacy of opiate antagonist treatment for pathological gambling has been replicated in a number of placebo-controlled studies. Preliminary results on N-acetyl cysteine, Memantine and Topiramate produced significant improvement for pathological gamblers and may open new avenues for treatment.

Grant, J. E., S. R. Chamberlain, et al. (2010). "Memantine shows promise in reducing gambling severity and cognitive inflexibility in pathological gambling: a pilot study." Psychopharmacology (Berl) 212(4): 603-612.

*Abstract:* RATIONALE: Although pathological gambling (PG) is relatively common, pharmacotherapy research for PG is limited. Memantine, an N-methyl D-aspartate receptor antagonist, appears to reduce glutamate excitability and improve impulsive decision making, suggesting it may help individuals with PG. OBJECTIVE: This study sought to examine the safety and efficacy of Memantine in PG. METHODS: Twenty-nine subjects (18 females) with DSM-IV PG were enrolled in a 10-week open-label treatment study of memantine (dose ranging from 10 to 30 mg/day). Subjects were enrolled from January 2009 until April 2010. Change from baseline to study endpoint on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) was the primary outcome measure. Subjects underwent pre- and post-treatment cognitive assessments using the stop-signal task (assessing response impulsivity) and the intra-dimensional/extra-dimensional (ID/ED) set shift task (assessing cognitive flexibility). RESULTS: Twenty-eight of the 29 subjects (96.6%) completed the 10-week study. PG-YBOCS scores decreased from a mean of 21.8 +/- 4.3 at baseline to 8.9 +/- 7.1 at study endpoint ( $p < 0.001$ ). Hours spent gambling per week and money spent gambling both decreased significantly ( $p < 0.001$ ). Subjects also demonstrated a significant improvement in ID/ED total errors ( $p = 0.037$ ) at study endpoint. The mean effective dose of memantine was 23.4 +/- 8.1 mg/day. The medication was well-tolerated. Memantine treatment was associated with diminished gambling and improved cognitive flexibility. CONCLUSIONS: These findings suggest that pharmacological manipulation of the glutamate system may target both gambling and cognitive deficits in PG. Placebo-controlled, double-blind studies are warranted in order to confirm these preliminary findings in a controlled design.

Grant, J. E. and S. W. Kim (2006). "Medication management of pathological gambling." Minn Med 89(9): 44-48.

*Abstract:* Pathological gambling has received little attention from clinicians and researchers despite prevalence rates similar to or greater than those of schizophrenia and bipolar disorder. This article summarizes the phenomenology and associated psychopathology of this public health problem and presents results of studies of 3 types of pharmacological agents used to treat this disorder: serotonin reuptake inhibitors, opioid antagonists, and mood stabilizers.

Grant, J. E., B. L. Odlaug, et al. (2012). "Pharmacological Treatments in Pathological Gambling." Br J Clin Pharmacol.

*Abstract:* AIMS: Pathological gambling (PG) is a relatively common and often disabling psychiatric condition characterized by intrusive urges to engage in deleterious gambling behavior. Although common and financially devastating to individuals and families, there currently exist no formally approved pharmacotherapeutic interventions for this disorder. This review seeks to examine the history of medication treatments for PG. METHODS: A systematic review of the 18 double-blind, placebo-controlled pharmacotherapy studies conducted for the treatment of pathological gambling was conducted. Study outcome and the mean dose of medication administered was documented in an effort to determine a preferred medication choice in this population. RESULTS: A variety of medication classes have been examined in the treatment of PG with varying results. Antidepressants, atypical antipsychotics, and mood stabilizers have demonstrated mixed results in controlled clinical trials. Although limited information is available, opioid antagonists and glutamatergic agents have demonstrated efficacious outcomes, especially for individuals with PG suffering from intense urges to engage in the behavior. CONCLUSIONS: Given that several studies have demonstrated their efficacy in treating the symptoms associated with PG, opioid antagonists should be considered the first-line treatment for PG at this time. Most published studies, however, have employed relatively small sample sizes, are of limited duration, and involve possibly non-representative clinical groups (e.g., those without co-occurring psychiatric disorders). Response measures have varied across studies. Heterogeneity of PG treatment samples may also complicate identification of effective treatments. Identification of factors related to treatment response will help inform future studies and advance treatment strategies for PG.

Grant, J. E. and M. N. Potenza (2010). "Pharmacological treatment of adolescent pathological gambling." Int J Adolesc Med Health 22(1): 129-138.

*Abstract:* Adolescents as a group appear to constitute a high-risk population for gambling problems. Given the rates of adolescent problem gambling and its impact on affected individuals and their families, effective treatments are important. There are, however, no pharmacological treatments for pathological gambling in children, adolescents, or adults that are currently approved by the United States Food and Drug Administration (FDA). Additionally, no studies have investigated directly the safety and efficacy of pharmacological treatments for pathological gambling in adolescents. This article reviews the literature on effective treatments in adults with pathological gambling, describes the safety data for the use of these drugs in adolescents, and provides a rationale for future studies to investigate the efficacy and tolerability of pharmacotherapies for pathological gambling in adolescents.

Iancu, I., K. Lowengrub, et al. (2008). "Pathological gambling: an update on neuropathophysiology and pharmacotherapy." CNS Drugs 22(2): 123-138.

*Abstract:* Neurobiological research has shown the potential involvement of serotonergic, dopaminergic and opioid dysfunction in the pathophysiology of pathological gambling. In this review, we present current theories of the neuropathology of pathological gambling, paying particular attention to the role of the neural circuitry underlying motivation, reward, decision-making and

impulsivity. This review also presents a literature review of current pharmacological treatment strategies for pathological gambling, such as selective serotonin reuptake inhibitors (SSRIs), opioid receptor antagonists, anti-addiction drugs and mood stabilizers, and also discusses the role of nonpharmacological interventions. A hypothetical model of the clinical subtypes of pathological gambling is presented, e.g. the impulsive subtype, the obsessive-compulsive subtype and the addictive subtype. This model attempts to integrate current knowledge in the field of pathological gambling regarding neuropathology, psychiatric co-morbidity, family history, genetics, course of illness, gender and response to pharmacological treatment. Finally, it is proposed that the existence of possible clinical subtypes of pathological gambling may provide a potential framework for matching the various subtypes with specific pharmacotherapies.

Pallesen, S., H. Molde, et al. (2007). "Outcome of pharmacological treatments of pathological gambling: a review and meta-analysis." J Clin Psychopharmacol 27(4): 357-364.

*Abstract:* Although several qualitative reviews on pharmacological interventions for pathological gambling have been published, no quantitative review of this field has been conducted. **METHODS:** Studies of pharmacological interventions of pathological gambling were identified by computer searches in the PsychINFO and MEDLINE databases covering the period from 1966 to July 2006, as well as from relevant reference lists. The inclusion criteria were as follows: the target problem had to be pathological gambling, the interventions were pharmacological, the study was written in English, and the study reported outcomes particularly pertaining to gambling. A total of 130 potential studies were identified of which 16 met the inclusion criteria. A total of 597 subjects were included in the outcome analyses of these studies. The grand mean age was 43.3 years. The overall proportion of men was 62.8%. The included studies were coded for outcome measures of pathological gambling. For each condition, means and SDs for gambling-related outcome measures were compiled at 2 points in time: baseline and posttreatment. **RESULTS:** At posttreatment, the analysis showed that the pharmacological interventions were more effective than no treatment/placebo, yielding an overall effect size of 0.78 (95% confidence interval, 0.64-0.92). A multiple regression analysis showed that the magnitude of effect sizes at posttreatment was lower in studies using a placebo-control condition compared with studies using a predesign/postdesign without any control condition. Effect sizes were also negatively related to the proportion of male participants in the included studies. No differences in outcome between the 3 main classes of pharmacological interventions (antidepressants, opiate antagonists, mood stabilizers) were detected. **CONCLUSION:** Pharmacological interventions for pathological gambling may be an adequate treatment alternative in pathological gambling.

Toneatto, T., B. Brands, et al. (2009). "A randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of concurrent alcohol use disorder and pathological gambling." Am J Addict 18(3): 219-225.

*Abstract:* The efficacy of naltrexone as a treatment for concurrent alcohol abuse or dependence and pathological gambling was evaluated in a randomized, double-blind, placebo-controlled trial. Fifty-two, mostly male, subjects were recruited from the community and received 11 weeks of medication during which cognitive-behavioral counseling was also provided. No significant group differences were found on any alcohol or gambling variable (ie, frequency, quantity, expenditures) at post-treatment or at the one year follow-up. However, a strong time effect was found suggesting that

treatment, in general, was effective. The use of naltrexone to treat concurrent alcohol use and gambling problems was not supported.

van den Brink, W. (2012). "Evidence-based pharmacological treatment of substance use disorders and pathological gambling." Curr Drug Abuse Rev 5(1): 3-31.

*Abstract:* This review summarizes our current knowledge of the pharmacological treatment of substance use disorders and pathological gambling using data mainly from randomized controlled trials and meta-analyses regarding these randomized controlled trials. The review is restricted to the selection of first and second line pharmacological treatments for smoking, alcohol dependence, opioid dependence, cocaine dependence, cannabis dependence and pathological gambling. It is concluded that great progress has been made in the last three decades and that currently evidence-based pharmacological treatments are available for smoking cessation, alcohol and opioid dependence and pathological gambling. At the same time a series of existing and new pharmacological compounds are being tested in cocaine and cannabis dependence. The review concludes with a summary of additional strategies to increase the effect size of already available pharmacological interventions, including polypharmacy, combining pharmacotherapy with psychotherapy and psychosocial support, and improved patient-treatment matching.