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# STUDIES EXPLORE POTENTIAL ORIGINS OF ADDICTION AND TREAMENTS

*Novel therapies for nicotine, heroin, and gambling addiction show promise*

**SAN DIEGO —** Studies released today suggest promising new treatments for nicotine and heroin addiction, and further our understanding of pathological gambling and heroin abuse in those suffering chronic pain. This new knowledge, released at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health, may one day lead to non-pharmaceutical interventions and therapies to treat addiction.

According to the World Health Organization, 15.3 million people worldwide suffer from drug use disorders. A variety of brain areas and processes play a role in addictive behaviors, complicating treatment and costing millions of dollars and lives each year. Today's studies contribute to an understanding of how compulsive disorders like addiction develop and provide new insight into methods to treat addictive behaviors .

The new findings show that:

- Magnetic stimulation of the brain helps some people decrease their smoking, and even quit altogether for up to six months after treatment (Abraham Zangen, abstract 635.03, see attached summary).
- Stimulating an area of the brain associated with drug reward, the subthalamic nucleus, reduces rats' motivation to take heroin (Carrie Wade, PhD, abstract 818.03, see attached summary).
- Chronic pain leads rats already exposed to drugs to take more and higher doses of heroin, suggesting that people with addiction are more susceptible to overdose when in chronic pain (Lucia Hipolito, PhD, abstract 158.05, see attached summary).

Other recent findings discussed show that:

- Drug abuse stresses the brain, and the resulting dysregulation of systems involved in the stress response could contribute to negative feelings that trigger increased drug taking and addiction (George Koob, PhD, presentation 689, see attached speaker summary).
- Research suggests an area of the brain known as the insula may be overactive in people with gambling problems. People with damage to this area were less prone to the motivations of gamblers, providing a clue to identify areas of the brain that are linked to gambling addiction (Luke Clark, PhD, presentation 686.05, see attached speaker summary).
- Pathological gamblers may love a cash payout, but care less about other types of rewards, such as sex or food. Researchers found pathological gamblers showed decreased activity in reward-sensitive brain areas when money wasn't involved (Guillaume Sescousse, PhD, presentation 686.06, see attached speaker summary).

"Non-drug interventions would be an enormous step forward in drug abuse treatment, which currently relies on replacing one drug with another and has an extremely high rate of relapse," said press conference moderator Barry Everitt of the University of Cambridge, an expert in drug abuse research. "Today's exciting results give us new ways of understanding why compulsive conditions such as drug abuse and pathological gambling might arise, and give us targets to explore for non-drug treatment, which would help us treat a population suffering from addiction."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find more information on addiction at *BrainFacts.org*.

– more –

Related Neuroscience 2013 Presentations:

Special Lecture: **Neurocircuitry of Addiction: A Stress Surfeit Disorder**
Wednesday, Nov. 13, 2013, 11:30 a.m.–12:40 p.m., Ballroom 20

History of Neuroscience Lecture: **Reward Circuitry in the Brain**
Tuesday, Nov. 12, 2:30—3:40 p.m., Ballroom 20
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## Abstract 635.03 Summary

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### Magnetically Stimulating the Brain May Help Smokers Quit

Repeated use of a high frequency magnet to stimulate the brain helps some smokers quit for up to six months after treatment, according to early findings presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our research shows us that we may actually be able to undo some of the changes to the brain caused by chronic smoking," said senior author Abraham Zangen, PhD, of Ben Gurion University. "We know that many smokers want to quit or smoke less and this could help put a dent in the number one cause of preventable deaths."

Repeated high frequency Transcranial Magnetic Stimulation (rTMS) is a non-invasive technique that uses magnetic fields to stimulate large areas of neurons in the brain. To investigate how this technique might help smokers reduce their cigarette use, researchers recruited smokers interested in quitting and gave them high frequency rTMS, low frequency rTMS, or placebo treatment for 13 days. They focused on stimulating the prefrontal cortex and the insula, two brain areas associated with nicotine addiction. At the end of the treatment and six months after treatment, study participants reported how much they smoked and how much they craved cigarettes.

Smokers who received the stimiluation decreased the number of cigarettes smoked daily, some quitting entirely. Six months after treatment, researchers followed up with participants and found the effects remained. Overall, participants who received high frequency rTMS smoked less and were more likely to quit, with success rates four times that of the low frequency group and more than six times greater than the placebo group.

The most effective therapy combined high frequency treatment with a smoking related "cue" (an image with a lit cigarette). The participants who received the smoking cue prior to each rTMS session had even higher levels of abstinence: 44 percent immediately after treatment and 33 percent six months later (up from 28 percent among those who received the high frequency rTMS and no cues).

Research was supported with funds from Tel Aviv University, Sackler Faculty of Medicine, and Brainsway Ltd. Co-author Abraham Zangen serves as a consultant to and has a financial interest in Brainsway Ltd., provider of the deep TMS coils used in this study.

Scientific Presentation: Tuesday, Nov. 12, 3–4 p.m., Halls B–H

635.03, Deep repetitive Transcranial Magnetic Stimulation (rTMS) of the prefrontal cortex and the insula reduces nicotine addiction
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TECHNICAL ABSTRACT: Background: Tobacco smoking is the leading cause of preventable death in developed countries. Several lines of evidence suggest that repeated transcranial magnetic stimulation (rTMS) over the lateral prefrontal cortex (LPFC) and the insula can affect processes involved in nicotine addiction. *Study aim*: To evaluate the effect of high-frequency and low-frequency deep rTMS of the LPFC and insula, with or without presentation of smoking cue, on nicotine addiction.
*Methods*: 115 males and females aged 21-70 who smoked at least 20 cigarettes per day and were motivated to quit smoking were recruited from the general population using advertisements in newspapers and on internet websites. Participants were divided randomly into high-frequency, low-frequency and sham stimulation groups. Each group was subdivided randomly into two subgroups, either presented or not presented with smoking cue, just before the daily TMS session. 13 daily deep rTMS sessions were applied, six months follow-up was then conducted. Deep rTMS sessions were administered using a specific coil over the prefrontal cortex and insula bilaterally. Cigarette consumption was evaluated objectively by measuring cotinine levels in urine samples and subjectively by participants' self-reports. Dependence and craving were evaluated by standard questionnaires. Impulsivity was evaluated by a set of neurocognitive tests.
*Findings*: High frequency Deep rTMS treatment, over the LPFC and Insula, reduced cigarette consumption and nicotine dependence. Presentation of smoking related cue improved the efficacy of the high frequency treatment, resulted with higher reduction in dependence and consumption, and yielded abstinence rate of 44% at the end of the treatment. *Discussion*: Multiple sessions of high frequency stimulation of the LPFC and insula bilaterally with deep rTMS reduces features of cigarette addiction, especially when the craving circuitry is activated by presentation of smoking cues just prior to the stimulation.

**Abstract 818.03 Summary**

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## Deep Brain Stimulation Shows Promise for Treatment of Heroin Abuse

*Therapy approved for use in humans has potential to reduce drive for substance abuse*

Electrically stimulating a specific area in the brain associated with drug reward decreases a rat's motivation to take heroin, according to findings presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"This research takes a non-drug therapy that is already approved for human use and demonstrates that it may be an option for treating heroin abuse," said Carrie Wade, PhD, of the Scripps Research Institute, lead author on the study. "It has been established that this treatment reduces cocaine seeking, and this current study indicates it may be an option for other substance use disorders as well."

The World Health Organization has reported that 9.2 million people worldwide use the opiate drug heroin. Heroin addiction is notoriously difficult to treat, often relying on replacement with other opiate drugs. Previous studies in rats have shown that electrically stimulating the subthalamic nucleus at high frequency can help reduce the rats' motivation to take cocaine, but the new research is the first to examine whether similar stimulation has promise for heroin abuse.

Normally, rats that are allowed to self-administer heroin will show a pattern of escalated drug taking, which models heroin abuse in humans. In this study, the researchers stimulated a region of the brain (the subthalamic nucleus) and allowed rats to self-administer heroin by pressing a lever. After stimulating this brain area, animals took less drugs, did not escalate their intake, and were less motivated to press a lever for a heroin dose.

Research was supported with funds from the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism.

Scientific Presentation: Wednesday, Nov. 13, 3–4 p.m., Halls B–H

818.03, Attenuation of compulsive-like heroin self-administration with high frequency stimulation of the subthalamic nucleus
**C. L. WADE**[1], E. BREYSSE[2], D. O. HERNANDEZ[1], *G. F. KOOB[1], C. BAUNEZ[2], O. GEORGE[1]; [1]The Scripps Rsrch Inst., LA JOLLA, CA; [2]UMR7289 CNRS & Aix-Marseille Univ., Marseille, France

TECHNICAL ABSTRACT: Interest in using deep brain stimulation to manage and treat neurological and psychiatric disorders such as Parkinson's disease, obsessive compulsive disorder, severe depression and recently drug addiction is increasing due to the reversibility of the stimulation. It has previously been shown that both lesions of the subthalamic nucleus (STN) and high frequency stimulation (HFS) of the STN decrease cocaine responding in a progressive ratio (PR) session, and it also decreases the time spent in a cocaine-paired chamber in a conditioned place preference test. The effect of STN HFS on escalation of drug intake, a hallmark of drug addiction, remains to be investigated. However, evidence that STN HFS modulates GABAergic and glutamatergic excitability supports the hypothesis that the effects of STN HFS on cocaine intake may be extended to other drugs of abuse. Our objective was to test the specific hypothesis that STN HFS decreases heroin escalation and motivation for self-administration. First, we tested STN HFS in heroin self-administration in a short access group (nondependent, non-compulsive-like responding-ShA) and a long access group (dependent, compulsive-like responding- LgA), Second, we examined STN HFS on self-administration in a Progressive Ratio in both short and long access sessions. We found that heroin self-administration was decreased in ShA (3hr) sessions. In LgA (12 hr) sessions, we found that, when stimulated, rats did not escalate heroin intake over a 2-week period. In both ShA and LgA groups, animals subjected to STN HFS showed significant decreases in breakpoints in a PR session. Finally, we examined the effects of STN HFS on locomotor activity and found no differences between prestimulation and during stimulation. Altogether, this study extends the results observed with cocaine to heroin by demonstrating that STN HFS attenuates heroin escalation. This suggests that treatment of addiction with STN HFS may be a useful non-drug therapy for substance abuse.

**Abstract 158.05 Summary**

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## History of Drug Abuse May Increase Risk of Pain Medication Overdose and Dependency

*Animals accustomed to heroin are less sensitive to painkillers and took more medication when in pain*

A new animal study suggests a history of drug abuse may increase the risk of pain medication dependency and overdose when treating chronic pain. This research was presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our findings reveal an important link between pain and drug abuse," said Lucia Hipolito, PhD, lead author of the study from Columbia University. "This is especially important when you look at treating pain in patients with a history of opioid abuse (i.e. heroin, morphine). Our research shows that in these patients, chronic pain could trigger escalating use of drugs, which may lead to the abuse of prescription pain medications and increased risk of drug overdose."

In studies gathered from around the world, the World Health Organization has shown that 13.5 million people take opioid drugs, and 9.2 million of them use heroin. Chronic pain is also a global problem, and afflicts between 10 percent and 50 percent of the population of some countries, resulting in many people with chronic pain who also have a history of opiate use or abuse.

Hipolito and her research group, led by J.A. Moron Concepcion, PhD, examined how chronic pain impacts the brains of rats that were able to self-administer the opiate heroin — a model for heroin dependency in humans. When facing chronic pain, rats who had access to low doses of heroin appeared to be less sensitive to the drug's effects, while those with access to higher doses administered more heroin over time. This may indicate that the rats were less sensitive to the pleasurable effects of heroin when in chronic pain.

Additionally, researchers found that the different reaction to heroin in rats with chronic pain may be due to the release of dopamine. In normal rats, heroin caused a large release of dopamine, a chemical that produces feelings of pleasure, but in rats with chronic pain, the dopamine reaction was muted at low doses and increased at high doses. The results suggest that chronic pain may cause animals to prefer to take more of the higher doses of heroin to feel the same effects as low doses without pain. This study suggest that for people with chronic pain and a history of drug dependency or abuse, the condition could result in reduced sensitivity to prescription painkillers, prompting abuse, and the potential for overdose of pain medication or other drugs.

Research was supported with funds from the National Institutes of Health.

Scientific Presentation: Sunday, Nov. 10, 8–9 a.m., Halls B–H.

158.05, Effects of CFA-induced chronic inflammatory pain on opioid self-administration and accumbal dopamine release in heroin dependent rats
***L. HIPOLITO[1]**, L. VIRAG[1], R. WHITTINGTON[1], S. COMER[2], J. A. MORON CONCEPCION[1]; [1]Anesthesiol., Columbia Univ., New York City, NY; [2]Dept. of Psychiatry and substance abuse, Columbia Univ., New York, NY

TECHNICAL ABSTRACT: The use of opioid-based therapies in patients with chronic pain is a challenge in the medical practice because of drug abuse liability. This problem is magnified in the case of patients with a previous history of opioid abuse, leading to reduced treatment of pain conditions in this population. The most recent National Survey on Drug Use and Health report revealed that approximately 7 million people used prescription pain relievers for non-medical purposes and highlights a possible link between the current increase in heroin use and the nonmedical use of prescription pain relievers, suggesting a potential association between pain reliever misuse and heroin use. Surprisingly, few studies have investigated how chronic inflammatory pain could alter opioid intake patterns and none of them have focused on an opioid-dependent population. In the present study, we investigated the effect of chronic inflammatory pain on heroin (50 μg/kg/infusion) self-administration under fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. Moreover, we investigated the neurochemical changes induced by chronic inflammatory pain in the dopamine mesolimbic pathway by using the in vivo microdialysis technique. Our results indicate that s.c. injections of complete Freund's adjuvant (CFA) in the hind paw induces chronic inflammatory pain and impacts the motivation for heroin self-administration under a PR schedule by reducing the breakpoint. Moreover, sensitivity to heroin appears to be altered since the dose response curve within a session showed a clear deviation from the expected linear response. Animals injected with CFA increased their intake when tested with high doses (100 and 200 μg/kg/infusion) than for the low dose (50 μg/kg/infusion) in comparison with control animals. Finally, in vivo microdialysis studies supported these findings.

Animals injected with CFA showed a significant reduction in the heroin-induced DA release in nucleus accumbens (NAc) vs control animals. In conclusion, these results suggest that chronic inflammatory pain can alter the motivational properties of heroin by affecting DA release in the NAc. Moreover, this effect is associated with a change in the self-administration pattern for high doses of heroin. Overall, these results suggest that chronic inflammatory pain may produce a rightward shift in the rewarding properties of heroin, such that higher doses of heroin are needed for reliable rates of self-administration. Therefore, these data suggest that chronic inflammatory pain induces changes in the VTA-NAc pathway that in turn may facilitate opioid dose escalation in order to maintain the rewarding properties of the drug.

**Speaker Summary (689)**

**Speaker: George Koob, PhD** (858) 784-7062
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Lecture: **Neurocircuitry of Addiction: A Stress Surfeit Disorder**
Wednesday, Nov. 13, 11:30 a.m.–12:40 p.m., Ballroom 20

Drug addiction, including addiction to alcohol, nicotine and illicit drugs produces an enormous cost to society in economic cost, medical cost, social cost and human suffering. The thesis to be elaborated by my presentation is that activation of the brain systems that mediate stress is a key component of the disease of addiction.

Drug addiction has been conceptualized as a chronically relapsing disorder of compulsive drug seeking that includes loss of control in limiting intake and continuing to seek and take drug despite serious adverse consequences. Such compulsive drug taking in addiction moves through three stages: binge/intoxication (active drug taking), withdrawal/negative affect (temporary abstinence from taking drugs), and craving (the desire for drugs that leads to relapse during prolonged abstinence from taking drugs) that involve changes in the drive for excessive drug taking and/or loss of control in limiting drug intake.

Drug addiction, for many years, was thought to be driven largely by feeling good mediated by activation of the brain pleasure systems. However, another powerful drive for drug-seeking in addiction is where one takes the drug in order not to feel bad, in other words, by alleviating drug withdrawal. This process of taking drugs to avoid feeling bad during withdrawal is called negative reinforcement. The withdrawal state that makes one take drugs to avoid feeling bad is called a negative emotional state (anxiety, stress- like state, irritability, feeling down, feeling like nothing other than drugs is pleasurable). The argument here is that excessive use of drugs leads to negative emotional states that drive such drug seeking by activating the brain stress systems within areas of the brain historically known to mediate emotions and includes the stress/fear-mediating amygdala and reward-mediating basal ganglia. Two key chemicals (neurotransmitters) activated within these brain areas are corticotropin-releasing factor (CRF) in the amygdala and the dynorphin-κ opioid system in the basal ganglia, both of which mediate anxiety-like behavior, fear conditioning (CRF), and dysphoria-like behavior (dynorphin- -κ opioid) in animal models. Increases in activity of CRF in the central nucleus of the amygdala and dynorphin in the basal ganglia occur in animal models of addiction. CRF receptor antagonists and kappa opioid antagonists block compulsive-like drug taking in animal models. Thus, brain stress response systems are hypothesized to be activated by excessive drug intake, to be activated even further during repeated withdrawals, and to persist into protracted abstinence.

Compelling evidence exists to argue that the brain stress systems, a heretofore largely neglected component of dependence and addiction, play a key role in engaging the transition to addiction and maintaining addiction once initiated. Thus, stress can cause addiction and addiction can cause stress. A role of the brain stress systems in addiction not only provides insight into the neurobiology of the emotional misery of addiction but also provides novel targets for the treatment of addiction.

Funding for this research was provided by the National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, National Institute of Diabetes and Digestive and Kidney Diseases, and the Pearson Center for Alcoholism and Addiction Research.

**Speaker Summary (686.05)**

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**Neural Substrates of Distorted Cognition in Gambling Addiction (686.05)**
Minisymposium: *Pathological Choice: The Neuroscience of Gambling and Gambling Addiction*
Wednesday, Nov. 13, 8:30–11 a.m., Room 28A

Patients with focal brain damage affecting a region called the insula have been found to be insensitive to two distinct errors of thinking that occur in gambling games, and are linked to problematic gambling behavior.

In a collaborative study between researchers at the University of Cambridge, the University of Iowa and the University of Southern California, gambling behavior was examined in several groups of neurological patients with brain injury affecting different areas: the ventromedial prefrontal cortex (vmPFC, n=17), the insula (n=8) and the amygdala (n=7), as well as healthy controls and patients with mixed damage elsewhere in the brain. The researchers focused on two psychological distortions that occur across many forms of gambling: the effects of 'near-miss' outcomes (where a loss looks similar or 'close' to a jackpot win) and the 'gambler's fallacy' (believing that a run of one event means that a different event is due, such as a run of heads in a coin-flipping task). These effects were elicited using two computerized gambling tasks: a slot machine simulation was used to deliver near-misses, and a roulette simulation was used to model the gambler's fallacy.

We saw a specific disruption of both effects in the group with insula damage: these patients showed an abolition of the gambler's fallacy, and failed to show the normal motivational response to near-misses. While the group with vmPFC damage are known to have difficulties in their 'real life' decision making that in some respects resembles problem gamblers, the two gambling distortions were unaffected in the patients with vmPFC damage. We infer that the insula may be overactive in people with gambling problems, who appear to be more prone to these erroneous thoughts during gambling play. Our ongoing project is testing this hypothesis using fMRI in pathological gamblers performing these two tasks.

Gambling is a widespread form of recreation that around three-quarters of the population engages in at least occasionally. It becomes excessive in a minority of those involved, and the formal psychiatric diagnosis of 'pathological gambling' occurs in around 1percent of the population. Since it was first recognized in 1980, pathological gambling has been considered in the 'impulse control disorders', but the DSM5 has announced an important decision to reclassify the disorder into the addictions category, based on several lines of evidence for shared disease mechanisms. As pathological gambling is the only non-substance addiction in this new category, it is the prototype for the 'behavioral addictions.'

Our broad approach to studying gambling aims to characterize the psychological factors that occur during gambling play and how these processes are disrupted in people with gambling problems. We consider disordered gambling as arising from a combination of individual risk factors and features of the games themselves. To study individual factors, we have investigated neurocognitive function (focusing on impulsivity and compulsivity) and dopamine neurotransmission (with 11C-raclopride PET imaging) in pathological gamblers attending the National Problem Gambling Clinic in London.

To study the games themselves, we use simplified gambling games to investigate how different factors influence subjective ratings of the game, risk-taking behavior, and persistent play. We have previously shown that gambling near-misses increase the motivation to gamble, and using functional MRI, these events recruit overlapping brain regions to gambling wins, despite their objective status as losses. Behaviorally, the gambler's fallacy is evident in healthy participants as reduced choice of either color (e.g. red) as function of the prior run length of that color (e.g. four successive red outcomes). In the treatment of pathological gambling, it may be possible to target these distortions through either psychological or pharmacological therapies.

Our ongoing work using functional MRI in pathological gamblers is funded by the Medical Research Council.

**Speaker Summary (686.06)**

**Speaker: Guillaume Sescousse, PhD** 0031 024 36 10618
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**Do Pathological Gamblers Suffer From a Distorted Sensitivity to Reward?**

Minisymposium: *Pathological Choice: The Neuroscience of Gambling and Gambling Addiction*
Wednesday, Nov. 13, 8:30–11 a.m., Room 28A

Our research shows that pathological gamblers have a blunted sensitivity to non-monetary rewards such as sex, which is visible at both the behavioral and brain levels. This state of affairs might create a motivational imbalance in favor of monetary rewards, and might ultimately contribute to compulsive gambling.

Pathological gambling is a psychiatric condition characterized by compulsive gambling in the face of negative consequences. It affects about 1–2 percent of the Western population, similar to schizophrenia. Since last May, it has been officially recognized as the first behavioral addiction in the DSM-5, the international reference manual for psychiatric diagnoses. However, the brain mechanisms underlying this disorder remain largely elusive. A popular and intuitive hypothesis is that gamblers would suffer from an aberrant sensitivity to reward. This hypothesis has been tested repetitively in the past 10 years, using brain imaging as a way to probe the reactivity of the brain "reward circuit" when confronted to gambling cues and monetary gains. However, while half of these studies have reported a hyper-sensitivity of the reward circuit in gamblers, the other half has revealed a hypo-sensitive reward circuit in the same population. It is thus currently difficult to draw general conclusions from these studies.

In this context, we set out to investigate an alternative hypothesis: what if, instead of an aberrant sensitivity to monetary rewards, gamblers had a blunted sensitivity to non-monetary rewards such as food or sex? Such an imbalance would create a biased preference for monetary rewards, which might in turn explain the powerful attraction of gambling. To test this idea, we designed a game in which people could either win money or see pleasant erotic pictures if they were fast enough in a rapidity task. Reaction times allowed us to measure the motivation for each type of reward. We recruited 18 pathological gamblers and 20 healthy participants and asked them to play this game inside an fMRI scanner while we recorded their brain activity.

Behaviorally, gamblers were less motivated by erotic pictures than by monetary gains, whereas healthy participants were equally fast for both rewards. This blunted motivation for non-monetary rewards was further observed at the brain level, within a key structure of the reward circuit called the ventral striatum. During the reward anticipation phase, gamblers showed greatly diminished brain responses to erotic cues compared to monetary cues in this structure, whereas brain activity levels were similar in healthy participants. Importantly, this difference in brain reactivity to monetary versus erotic cues was larger in more severe gamblers, suggesting that it constitutes a genuine "marker" of this addiction.

Finally, we examined the brain responses to reward outcomes - that is when participants received the actual rewards. We focused on the orbitofrontal cortex, another key structure of the brain reward circuit. In previous studies, we have found an interesting dissociation in this structure: while the posterior part responds exclusively to erotic rewards, the anterior part responds exclusively to monetary rewards. We think this reflects a broader dissociation between primary rewards such as food and sex, which have an innate value and are crucial for survival, and secondary rewards such as money and power, whose value needs to be learned and can be exchanged against lower-level rewards. In the present study, we found that the posterior orbitofrontal cortex was activated by erotic rewards in both groups as expected, but was also activated by monetary rewards in gamblers. Thus, it is as if the brain of gamblers interpreted money as a primary reward. This idea is consistent with the fact that pathological gamblers seem to pursue money not necessarily for what it can buy — that is as a secondary reward — but for its own sake, as if it were intrinsically reinforcing.

Together, our results point to a distorted sensitivity to reward in pathological gamblers. From a clinical perspective, they suggest that enhancing the saliency of non-monetary rewards may be a fruitful strategy as part of a therapeutic approach. In addition, they suggest that reappraising money as a secondary reward - that is as a tool and not as an intrinsic source of pleasure - could also represent an interesting complementary approach.

This work was supported by the Fyssen Foundation, the Interministerial Mission for the Fight Against Drugs and Drug Addiction, the French National Institute of Health and Medical Research, and the French Foundation for Medical Research.