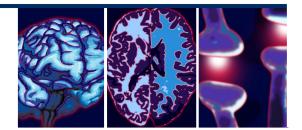
REVIEW



Process addictions in 2012: food, internet and gambling

Yi Zhang^{1,2}, Jie Tian^{1,3}, Karen M von Deneen^{1,2}, Yijun Liu² & Mark S Gold*²

Practice points

- Traditional addiction research mainly focused on alcohol, tobacco and illicit substance use, while more recent studies have begun to focus on behavioral processes such as gambling, sex, excessive internet use and hedonic overeating or food addiction.
- Process and substance addictions are both characterized by an acquired drive and pathological attachment to those activities and drugs. The addicts lose control over their behavior, lie about their behaviors, and more and more time is spent mulling over intrusive thoughts about drugs, cravings and perseverance in obtaining them. Addicts also continue their habits despite loss of health, family and/or their job, or until a serious accident or fatal overdose occurs.
- Food addiction can be defined as a chronic relapsing problem caused by various fundamental factors that increase craving for food or food-related substances leading to a state of heightened pleasure, energy, or excitement. Continued compulsive overeating is not just a cosmetic issue, but instead can lead to metabolic syndrome and Type 2 diabetes, with the possible consequences of organ damage, cardiovascular issues, cancer and pain problems. For these reasons it is not surprising that obesity has become the number one global health problem.
- Pathological gamblers demonstrate diminished brain activity and a blunted response to rewards as well as losses, prompting them to continue seeking rewards. Their responses to gambling-related stimuli indicate increased activity in the region of the brain associated with pleasure processing, mood regulation and risk taking. They also display more risk-taking behavior, impaired decision-making and a hypersensitivity to gambling cues.
- Internet addiction disorder is characterized by a compulsive–impulsive spectrum involving excessive use of or preoccupation with the internet, significant social and/or occupational failures related to internet use and continued excessive use of the internet, despite negative consequences.

Life Sciences Research Center, School of Life Sciences & Technology, Xidian University, Xi'an, Shaanxi 710071, China Department of Psychiatry & McKnight Brain Institute, University of Florida, 100 South Newell Drive, Suite L4-100, PO Box 100256, Gainesville, FL 32610-0256, USA

³Institute of Automation, Chinese Academy of Sciences, Zhong Guancun East Road, No.95, PO Box 2728, Beijing 100190, China *Author for correspondence: Department of Psychiatry, University of Florida College of Medicine, Box 100183, Gainesville, FL 32610-0183, USA; Tel.: +1 352 294 4926; Fax: +1 352 392 8217; msqold@ufl.edu



SUMMARY Traditional addiction studies have focused specifically on the use of chemical substances, while more recent studies have begun to focus on behavioral processes. Process addiction is an addiction to a natural and in many cases essential behavior such as eating and sex. Acquired continued and compulsive overeating is one process addiction similar to other activities or behaviors, such as excessive video gaming, pathological gambling, hypersexuality or excessive internet use where the addict shows loss of control, an inability to stop or modify the activity, and a range of signs and symptoms that can be as debilitating as those associated with substance abuse or addiction. Individuals with process addiction would meet criteria for addiction if their substance of abuse was considered a drug. They present characteristics like other addicts, have a chronic and relapsing course and often the addiction leaves them with loss of health, happiness and a difficulty treating the disease. Gambling has been the least contentious process addiction and will appear in the Diagnostic and Statistical Manual of Mental Disorders. Food and sex have been the most difficult for the field to consider as addictions. However, food may have the clearest, long-standing scientific research behind it. In this review, we provide a summary of the literature on process (behavior) addictions and a discussion of food addiction, as well as pathological gambling and internet addiction disorder.

The concept of addiction originated in the field of substance abuse, which includes alcohol, tobacco, cocaine, marijuana and other drugs that can cause changes in the brain and behavior of the user [1-5]. Researchers have been working in this area for many years [1-5] and have demonstrated that substances of abuse 'hijack' the brain to produce a stereotypical addictive state [6].

In recent decades, researchers have noticed that the concepts they evolved to explain how substance abuse works could be applied to other forms of repeated dysfunctional behaviors, even when these did not involve ingesting any 'addictive' substances. As a result, research has also been extended to the exploration of other potentially addictive processes. An increasing number of studies have begun to focus on behavioral processes such as gambling, sex, excessive internet use or internet addiction disorders (IADs) and food addiction, as well as a variety of other behaviors (shopping, work and exercise) [7-11]. Such behavior is termed a 'process' addiction because it is a type of behavior (a process) that the person is involved with, rather than the substance itself.

Behavioral and substance addictions have many similarities in natural history, phenomenology and adverse consequences [12]. They are both characterized by a drive for and pathological attachment to those activities and drugs [6]. The addicts lose control over their behavior, lie about their behaviors, and more and more time is spent with intrusive thoughts about drugs, cravings and perseverance in obtaining the drugs [6]. Addicts continue their habits despite of loss of health, family and/or their job, or until a serious accident or fatal overdose occurs [6]. In the last few decades, much research has focused on the role of the brain reward system in the development of substance abuse and dependence. Specific components (e.g., the nucleus accumbens $[N_{AC}]$, the ventral tegmental area and the neurotransmitter dopamine [DA]) have been highlighted as key contributors to the addiction process. The brain dopaminergic system has been shown to play an important role in signaling reward and establishing stimulus associations [13]. Food addiction, drug intake, gambling and sexual behavior increase DA release in the striatum and DA receptor antagonists prevent these behaviors [4,7,8,10]. Given that behavioral criteria are utilized to diagnose substance use disorders, it makes intuitive sense to translate the criteria to other problematic behaviors. More recently, research has examined the extent to which other behaviors (e.g., eating, sexual behavior and gambling) are also regulated through this reward circuitry.

Indeed, each of the diagnostic criteria for substance use disorders can be adapted to fit these behaviors. Thus, this opens the door for researchers to study food addiction, hypersexuality, pathological gambling and IAD as addictive processes [6]. In the present paper, we provide a summary of the literature on process (behavior) addictions and a discussion of food addiction, as well as pathological gambling and IAD.

Food addiction

Understanding the processes associated with obesity is a matter of international urgency. Recent findings have indicated that obesity may be a disorder related to addiction [14-16]. Thus, novel and more effective treatments can be utilized to treat obesity as a form of addiction [17,18]. In general, food addiction is associated with substance-related disorders [19] as well as eating disorders, although there is no clear definition for such a condition. It has been suggested that diagnostic criteria for eating and feeding disorders should be included in the proposed 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [101]. The most common definition for food addiction states that it is a chronic condition and is caused by cravings that lead to feeling 'high' when ingesting specific foods [20].

A genetic disorder known as Prader–Willi syndrome is hallmarked by hyperphagia and weight gain early in childhood. Patients with Prader–Willi syndrome have a compulsive tendency to overeat and ingest nonfood substances obsessively [21]. It has been chosen as the genetic model for obesity and has been correlated with food addiction and other addictions as well [22]. One study found that aberrant reward pathways in the brain are involved with metabolism-regulating regions [23].

Researchers have developed an animal model for food (sugar) addiction in rats that closely resembles that seen with drug addiction [24,25]. Hoebel and colleagues reported that sugar has addictive properties similar to psychostimulants and opioids [26]. Specific rat models were used to study sugar binges, which have been closely related to results from other addiction studies involving addictive substances such as sugar and fats [27,28]. Most interestingly, these studies conclude that sugar-addicted rats followed similar behavior patterns as those found in human addicts [29–31].

Most importantly, specifying endocrinological pathways for food addiction is crucial to understanding why people overeat, although there are similarities between food and substance addictions [32]. It has been shown that food and addictive substances share DA pathways in the brain of most living organisms [33,34]. Motivation is regulated by DA along with the reward system and reinforcement [20,35]. This pathway is mostly found in the ventral tegmental area and $N_{\Delta C}$ [36]. The latter region is known to regulate motivation, satiety, salience and food seeking [37]. Volkow et al. provided the first evidence that dopamine in the dorsal striatum is involved in food motivation in humans and demonstrated the ability of methylphenidate to amplify weak dopamine signals [38]. Obese individuals were known to have increased metabolism in the somatosensory cortex [39], meaning that this was where DA was regulated [40]. Specifically, DA D2 receptors play a major role in the regions associated with the reward pathways in the brain [41]. Stice et al. conducted a study that compared obese and lean individuals in response to receiving a chocolate milkshake versus a tasteless solution. The results indicated that obese relative to lean humans had fewer DA D2 receptors in the striatum [42]. In addition, many peripheral metabolic signals, such as insulin, leptin and ghrelin, directly or indirectly interact with midbrain DA pathways [43,44]. Leptin has been shown to decrease reward behavior and increase appetite via the striatum in those that had a leptin deficiency [45]; this hormone regulates ingestion of food by brain pathways involving DA. In one study, when subjects were given ghrelin they responded positively to visual food cues [46]. Another study found that in those who were insulin resistant, there was a greater need for more insulin to achieve the same rewarding effects of food [47].

Different regions of the brain are activated by consummatory food reward rather than by anticipated food reward; there are also differences in obese versus lean individuals [48]. In a satiation to chocolate study, significant gender differences were also found [49]. From this evidence, food addiction and reward mechanisms are interconnected, especially with craving potential [50]. Obesity is known as a reward-deficent condition [51] because DA D2 receptors are found in lower numbers in the obese population [52]. Those with the highest risk of obesity have more activation in somatosensory areas and less activation in the striatum [48].

The food environment has changed dramatically in the USA in the past three decades [53], with larger and less healthy portions of food being served in many food establishments [54]. Logos, cartoons and trademarks associated with hyperpalatable foods become potent stimuli, automatically eliciting mental and physical approach responses [14]. Indeed, highly recognizable food trademarks can trigger brain changes similar to those triggered by drugs or drug paraphernalia when shown to a patient with a substance use disorder [55]. Certain brain networks are responsible for cue-induced eating and appetite induction. A specific food-associated environment to induce eating in healthy humans can shed light on why individuals become addicted to food, overeat and befall obesity. The predominant

regions that have been associated with the drive to eat in both animal and human studies are the hypothalamus, striatum, orbitofrontal cortex, insula, anterior cingulate cortex and amygdala [56]; brain regions consisting of the basolateral amygdala, lateral hypothalamus and medial prefrontal cortex act as a network to regulate eating by learned, motivational cues [57,58].

Pathological gambling

Gambling can be defined as wagering money on a game of chance or some other event for money or other goods or services. Gambling is a common behavior with a large percentage of the US population engaging in some type of gambling within the past few years [59]. It is difficult to calculate the total social costs of gambling, however, Grinols estimated that as much as US\$54 billion is associated with gambling along with increased crime, lost work time, bankruptcies and financial hardships faced by the families of gambling addicts [60].

When gambling behavior becomes compulsive, it is defined as pathological gambling; the behavior starts to interfere with relationships and negatively affects social activities and work performance [61]. Although pathological gambling is classified as an impulse control disorder in the DSM-IV, it is often regarded as a behavioral or nondrug addiction because of its genetic, endophenotypic and phenotypic resemblances to substance dependence [61]. These similarities provide a rationale to change the classification of pathological gambling as an impulse control disorder (DSM-IV) to a new classification as a behavioral addiction in the proposed DSM-V. Given the similarities between substance dependence and gambling, researchers made assumptions and used paradigms similar to those used in substance-use disorder studies. Four important cognitive-emotional processes that are relevant to pathological gambling have been identified [61].

The first of these is reward and punishment processing and its relation to behavioral conditioning. The studies reviewed indicated that pathological gamblers showed decreased blood oxygenation level-dependent responses to nonspecific reward and punishment stimuli in the ventral striatum and ventral medial prefrontal cortex [62]. The next process involves higher salience leading to gambling cravings [63-65], but another study showed decreased brain activation despite the compulsive nature of their craving paradigms [66]. The third is impulsivity, which has been implicated as a vulnerability trait for acquiring pathological gambling and as a consequence of a gambling problem. Using fMRI to examine brain function during performance of the Stroop task, Potenza et al. found that pathological gamblers shared many neural correlates with healthy subjects, but differed in a brain region previously implicated in impulse control disorders [67]. Pathological gamblers showed lower activation in the left middle and superior frontal gyri during processing of incongruent versus congruent stimuli. The fourth process is impaired decision-making that often takes place when pathological gamblers continue gambling in the face of severe negative consequences. One particular study showed that gamblers made riskier decisions, which were regulated by the anterior cingulated cortex [68]. Another similar study resulted in lower superior frontal cortex activity in gamblers when they were given the Iowa Gambling Task [69]. However, more research is needed to elucidate which neurocognitive similarities and differences exist between substance abuse disorders and pathological gambling, and studies directly comparing these disorders to each other and to normal control groups are needed.

IAD

The cause of internet addiction is not known and there are currently no consistent criteria for what comprises it. Several criteria have described the disorder as characterized by a compulsiveimpulsive spectrum involving excessive use of or preoccupation with the internet, significant social and/or occupational failures related to internet use, and continued excessive use of the internet despite negative consequences [70,71].

Several studies regarding IAD have been carried out across the world [72-76]. Ko and colleagues identified the neural substances of online gaming addiction via evaluation of the brain areas (anterior cingulated cortex, medial prefrontal cortex, right N_{AC}, orbitofrontal cortex, right dorsolateral prefrontal cortex and right caudate nucleus) associated with the cue-induced gaming urge [73]. As a result, they concluded that visual cues in drug abuse and internet cravings shared neurobiological pathways [73]. Dong et al. investigated response inhibition in people with IAD and their results showed that these addicts had to try harder to finish the inhibition task [74]. IAD subjects had gray matter density deficits in various brain regions [75] and resting state disruption [76]. Yuan et al.

provided evidence indicating that IAD subjects have multiple structural changes in the brain [77]. The gray matter atrophy and white matter fractional anisotropy changes of some brain regions were significantly correlated with the duration of IAD. This evidence does not fully support the concept of IAD, but proved a similarity between IAD and substance disorder in many ways. We propose that IAD should be viewed from the perspective of its similarities with substance abuse especially in the areas of brain reward and inhibitory systems. Much work is needed to be done in the future to provide more evidence to support the concept of internet addiction.

Conclusion & future perspective

Growing evidence indicates that behavioral or process addictions resemble substance addiction across many domains and supports the argument for process behaviors to be conceptualized as addictive. Accumulating evidence has shown that there are a number of shared neural and hormonal pathways, as well as distinct differences in these pathways, that may help researchers discover why certain individuals continue to overeat, despite health risks and other consequences, and become more and more obese. Vulnerability and genetic studies are lacking. However, functional neuroimaging studies revealed that pleasant smelling, looking and tasting food has reinforcing characteristics similar to drugs of abuse. Many of the brain changes reported for hedonic eating and obesity are also seen in various types of addictions with respect to motivation and incentive craving. Animal models of overeating, sugar and fructose corn syrup self administration and other studies have helped redefine the 'globesity' epidemic as a brain disease, like an addiction in many ways. This hypothesis has the additional benefit of making new treatment

developments possible. Rather than targeting appetite, treatments may limit free access to brain reinforcement systems or alter food preferences. Pathological gambling, the most thoroughly studied of the behavioral addictions in man, provides further insight into the relationship of behavioral addiction and substance-use disorder. People who develop problems with internet use may start off using the internet on a casual basis and then progress to using the technology in dysfunctional ways with excessive use. IAD is thought to stimulate the brain reward system in a manner similar to that seen in substance abuse and pathological gambling. In general, subjects with process addiction are characterized by loss of control over their behavior, continue the behavior despite serious negative consequences and spend a great deal of time engaging in the behavior. More research is needed to elucidate which neurocognitive similarities and differences exist between process addiction and substance abuse. It is clear that substantial future research is also needed to understand process addiction in the context of other addictions and to improve efforts for prevention and treatment.

Financial & competing interests disclosure

This work is supported by the China Scholarship Council under grant No. 2010696503 to Y Zhang; the National Natural Science Foundation of China under Grant No. 60901064, 60903127, 31150110171; the Fundamental Research Funds for the Central Universities and the 2010 Independent Investigator Award from the NARSAD Brain and Behavior Research Fund. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest
- Heinz A, Siessmeier T, Wrase J et al. Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. Am. J. Psychiatry 162(8), 1515–1520 (2005).
- 2 Beck A, Schlagenhauf F, Wustenberg T et al. Ventral striatal activation during reward anticipation correlates with impulsivity in

- alcoholics. *Biol. Psychiatry* 66(8), 734–742 (2009)
- Almeida OP, Garrido GJ, Lautenschlager NT, Hulse GK, Jamrozik K, Flicker L. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. *Am. J. Geriatr. Psychiatry* 16(1), 92–98 (2008).
- Du C, Yu M, Volkow ND, Koretsky AP, Fowler JS, Benveniste H. Cocaine increases the intracellular calcium concentration in brain independently of its cerebrovascular effects. J. Neurosci. 26(45), 11522–11531 (2006).
- Zhang Y, Tian J, Yuan K *et al.* Distinct resting-state brain activities in heroin-dependent individuals. *Brain Res.* 1402, 46–53 (2011).
- 6 Gold MS, Merlo L, Bruijnzeel A, Roytberg A, Herkov M. Addiction to drugs, food, gambling, sex and technology: shared causal mechanisms? In: Mental Health in Public Health: The Next 100 Tears. Cottler L, Cottler L (Eds). Oxford Press, NY, USA, 118–148 (2011).
- Reviews studies of behavioral and substance addictions and demonstrates many similarities in natural history, phenomenology, adverse consequences and causal mechanisms.

REVIEW Zhang, Tian, von Deneen, Liu & Gold

- Wareham JD, Potenza MN. Pathological gambling and substance use disorders. Am. J. Drug Alcohol Abuse 36(5), 242-247 (2.010)
- Miner MH, Raymond N, Mueller BA, Lloyd M, Lim KO. Preliminary investigation of the impulsive and neuroanatomical characteristics of compulsive sexual behavior. Psychiatry Res. 174(2), 146-151 (2009).
- Yuan K, Qin W, Wang G et al. Microstructure abnormalities in adolescents with internet addiction disorder. PLoS ONE 6(6), e20708 (2011).
- 10 Zhang Y, von Deneen KM, Tian J, Gold MS, Liu Y. Food addiction and neuroimaging. Curr. Pharm. Des. 17(12), 1149-1157 (2011).
- This article looks at the evidence for food addiction gathered from different perspectives, including animal studies, endocrinology studies, genetic studies, studies on the mesolimbic reward system, and food cues, and how fMRI plays an important role in documenting these findings.
- Grant JE, Potenza MN, Krishnan-Sarin S, Cavallo DA, Desai RA. Shopping problems among high school students. Compr. Psychiatry 52(3), 247-252 (2011).
- Grant JE, Potenza MN, Weinstein A, Gorelick DA. Introduction to behavioral addictions. Am. J. Drug Alcohol Abuse 36(5), 233-241 (2010).
- Spyraki C, Fibiger HC, Phillips AG. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berl.) 79(2-3), 278-283 (1983).
- Gold MS, Graham NA, Cocores JA, Nixon SJ. Food addiction? J. Addict. Med. 3(1), 42-45 (2009).
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. Arch. Gen. Psychiatry 68(8), 808-816 (2011).
- Avena NM, Bocarsly ME, Hoebel BG, Gold MS. Overlaps in the nosology of substance abuse and overeating: the translational implications of 'food addiction'. Curr. Drug Abuse Rev. 4(3), 133-139 (2011).
- Discusses the utility of the concept of 'food addiction' as it may relate to treating certain disordered eating behaviors.
- Volkow ND, Wise RA. How can drug addiction help us understand obesity? Nat. Neurosci. 8(5), 555-560 (2005).
- Edge PJ, Gold MS. Drug withdrawal and hyperphagia: lessons from tobacco and other

- drugs. Curr. Pharm. Des. 17(12), 1173-1179 (2011).
- Warren MW, Gold MS. The relationship between obesity and drug use. Am. J. Psychiatry 164(8), 1268, author reply 1268-1269 (2007).
- Wang GJ, Volkow ND, Thanos PK, Fowler JS. Imaging of brain dopamine pathways: Implications for understanding obesity. J. Addict. Med. 3(1), 8-18 (2009).
- Benarroch F, Hirsch HJ, Genstil L, Landau YE, Gross-Tsur V. Prader-Willi syndrome: medical prevention and behavioral challenges. Child Adolesc. Psychiatr. Clin. N. Am. 16(3), 695-708 (2007).
- von Deneen KM, Gold MS, Liu Y. Food addiction and cues in Prader-Willi syndrome. J. Addict. Med. 3(1), 19-25 (2009).
- 23 Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ. Intracranial abnormalities detected by three-dimensional magnetic resonance imaging in Prader-Willi syndrome. Am. J. Med. Genet. A. 143(5), 476-483 (2007)
- Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. Neuroscience 139(3), 813-820 (2006).
- Gold MS. From bedside to bench and back again: a 30-year saga. Physiol. Behav. 1(104), 157-161 (2011).
- 26 Hoebel BG, Avena NM, Bocarsly ME, Rada P. Natural addiction: a behavioral and circuit model based on sugar addiction in rats. J. Addict. Med. 3(1), 33-41 (2009).
- 27 Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale food addiction scale. Appetite 52(2), 430-436 (2009).
- Gearhardt AN, White MA, Potenza MN. Binge eating disorder and food addiction. Curr. Drug Abuse Rev. 4(3), 201-207 (2011).
- Avena NM. Examining the addictive-like properties of binge eating using an animal model of sugar dependence. Exp. Clin. Psychopharmacol. 15(5), 481-491 (2007).
- Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci. Biobehav. Rev. 32(1), 20-39 (2008).
- Avena NM. The study of food addiction using animal models of binge eating. Appetite 55(3), 734-737 (2010).
- Avena has developed a rat model for sucrose bingeing. This review summarized evidence of 'food addiction' using animal models of binge eating.

- 32 Avena NM, Gold MS. Food and addiction sugars, fats and hedonic overeating. Addiction 106(7), 1214-1215, discussion 1219-1220 (2.011)
- Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage 19(4), 1709-1715 (2003).
- Liu Y, von Deneen KM, Kobeissv FH, Gold MS. Food addiction and obesity: evidence from bench to bedside. J. Psychoactive Drugs 42(2), 133-145 (2010).
- Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 363(1507), 3191-3200 (2008).
- In this paper, the authors integrated findings from PET imaging studies on dopamine's role in drug abuse/addiction and in obesity and propose a common model for these two conditions.
- Wise RA, Bozarth MA. Brain reward circuitry four circuit elements 'wired' in apparent series. Brain Res. Bull. 12(2), 203-208 (1984).
- Bassareo V, di Chiara G. Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. Eur. J. Neurosci. 11(12), 4389-4397 (1999).
- Volkow ND, Wang GJ, Fowler JS et al. 'Nonhedonic' food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. Synapse 44(3), 175-180 (2002).
- Wang GJ, Volkow ND, Felder C et al. Enhanced resting activity of the oral somatosensory cortex in obese subjects. Neuroreport 13(9), 1151-1155 (2002).
- Huttunen J, Kahkonen S, Kaakkola S, Ahveninen J, Pekkonen E. Effects of an acute D2-dopaminergic blockade on the somatosensory cortical responses in healthy humans: evidence from evoked magnetic fields. Neuroreport 14(12), 1609-1612 (2003).
- Wise RA. Role of brain dopamine in food reward and reinforcement. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 361(1471), 1149-1158 (2006).
- Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Science 322(5900), 449-452 (2008).
- Myers MG, Cowley MA, Munzberg H. Mechanisms of leptin action and leptin resistance. Annu. Rev. Physiol. 70, 537-556 (2008).



- 44 Abizaid A, Liu ZW, Andrews ZB et al. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J. Clin. Invest. 116(12), 3229–3239 (2006).
- 45 Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. *Science* 317(5843), 1355 (2007).
- 46 Malik S, McGlone F, Bedrossian D et al. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 7(5), 400–419 (2008).
- 47 Anthony K, Reed LJ, Dunn JT et al. Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? *Diabetes* 55(11), 2986–2992 (2006).
- 48 Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J. Abnorm. Psychol. 117(4), 924–935 (2008).
- 49 Smeets PA, de Graaf C, Stafleu A, van Osch MJ, Nievelstein RA, van der Grond J. Effect of satiety on brain activation during chocolate tasting in men and women. Am. J. Clin. Nutr. 83(6), 1297–1305 (2006).
- 50 Kalra SP, Bagnasco M, Otukonyong EE, Dube MG, Kalra PS. Rhythmic, reciprocal ghrelin and leptin signaling: new insight in the development of obesity. *Regul. Pept.* 111(1–3), 1–11 (2003).
- 51 Blum K, Braverman ER, Holder JM et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive and compulsive behaviors. J. Psychoactive Drugs 32(Suppl. i–iv), 1–112 (2000).
- 52 Wang GJ, Volkow ND, Logan J et al. Brain dopamine and obesity. Lancet 357(9253), 354–357 (2001).
- 53 Avena NM, Gold MS. Variety and hyperpalatability: are they promoting addictive overeating? Am. J. Clin. Nutr. 94(2), 367–368 (2011).
- 54 Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in food locations and sources among adolescents and young adults. *Prev. Med.* 35(2), 107–113 (2002).
- 55 James GA, Gold MS, Liu Y. Interaction of satiety and reward response to food stimulation. *J. Addict. Dis.* 23(3), 23–37 (2004).

- 56 Tataranni PA, DelParigi A. Functional neuroimaging: a new generation of human brain studies in obesity research. Obes. Rev. 4(4), 229–238 (2003).
- 57 DeFalco J, Tomishima M, Liu H et al. Virus-assisted mapping of neural inputs to a feeding center in the hypothalamus. Science 291(5513), 2608–2613 (2001).
- 58 Petrovich GD, Canteras NS, Swanson LW. Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. *Brain Res. Brain Res. Rev.* 38(1–2), 247–289 (2001).
- Welte JW, Barnes GM, Wieczorek WF, Tidwell MC, Parker J. Gambling participation in the U.S. – results from a national survey. J. Gambl. Stud. 18(4), 313–317 (2002).
- 60 Grinols E. Gambling in America: Costs and Benefits. Cambridge University Press, Cambridge, UK, 63, 297–302 (2004).
- 61 van Holst RJ, van den Brink W, Veltman DJ, Goudriaan AE. Brain imaging studies in pathological gambling. *Curr. Psychiatry Rep.* 12(5), 418–425 (2010).
- Reviews the neuroimaging research on pathological gambling. These imaging studies focused on reward and punishment sensitivity, cue reactivity, impulsivity and decision-making.
- Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat. Neurosci.* 8(2), 147–148 (2005).
- 63 Crockford DN, Goodyear B, Edwards J, Quickfall J, El-Guebaly N. Cue-induced brain activity in pathological gamblers. *Biol. Psychiatry* 58(10), 787–795 (2005).
- 64 Goudriaan AE, de Ruiter MB, van den Brink W, Oosterlaan J, Veltman DJ. Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addict. Biol. 15(4), 491–503 (2010).
- Miedl SF, Fehr T, Meyer G, Herrmann M. Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. *Psychiatry Res.* 181(3), 165–173 (2010).
- 66 Potenza MN, Steinberg MA, Skudlarski P et al. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Arch. Gen. Psychiatry 60(8), 828–836 (2003).
- 67 Potenza MN, Leung HC, Blumberg HP et al. An fMRI stroop task study of ventromedial

- prefrontal cortical function in pathological gamblers. *Am. J. Psychiatry* 160(11), 1990–1994 (2003).
- 68 Hewig J, Kretschmer N, Trippe RH et al. Hypersensitivity to reward in problem gamblers. Biol. Psychiatry 67(8), 781–783 (2010).
- 69 Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT. Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. *Hum. Brain Mapp.* 28(12), 1276–1286 (2007).
- 70 Ko CH, Yen JY, Chen CC, Chen SH, Yen CF. Proposed diagnostic criteria of internet addiction for adolescents. *J. Nerv. Ment. Dis.* 193(11), 728–733 (2005).
- 71 Block JJ. Issues for DSM-V: internet addiction. *Am. J. Psychiatry* 165(3), 306–307 (2008).
- 72 Cao F, Su L, Liu T, Gao X. The relationship between impulsivity and Internet addiction in a sample of Chinese adolescents. *Eur. Psychiatry* 22(7), 466–471 (2007).
- 73 Ko CH, Liu GC, Hsiao S *et al.* Brain activities associated with gaming urge of online gaming addiction. *J. Psychiatr. Res.* 43(7), 739–747 (2009)
- Identifies the neural substrates of online gaming addiction through evaluation of the brain areas associated with the cue-induced gaming urge.
- 74 Dong G, Zhou H, Zhao X. Impulse inhibition in people with internet addiction disorder: electrophysiological evidence from a Go/ NoGo study. *Neurosci. Lett.* 485(2), 138–142 (2010).
- 75 Zhou Y, Lin FC, Du YS et al. Gray matter abnormalities in internet addiction: a voxel-based morphometry study. Eur. J. Radiol. 79(1), 92–95 (2011).
- 76 Liu J, Gao X, Isoken O et al. Increased regional homogeneity in internet addiction disorder: a resting state functional magnetic resonance imaging study. Chin. Med. J-Peking. 123(14), 1904–1908 (2010).
- 77 Yuan K, Qin W, Wang G et al. Microstructure abnormalities in adolescents with internet addiction disorder. PLoS ONE 6(6), e20708 (2011).

Website

101 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-V). www.dsm5.org