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Carving addiction at a new joint? Shared brain vulnerabilities open the way for non-substance addictions

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> "…the…principle…is that of division…according to the natural formation, where the joint is, not breaking any part as a bad carver might…."
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> Socrates, in Plato's Phaedrus [1]

I. Overview

Anna Rose Childress, Ph.D.

The nosologic re-carving of addictions may soon undergo a significant change, reflecting a shift in clinical and research thought about the very essence of these disorders, their critical and necessary elements. Charged with Plato's dictum, working groups for the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM V [2]) are actively considering whether non-substance disorders such as gambling should be classified in the category previously reserved exclusively for substance-related disorders. Though DSM V is not scheduled for final publication until 2012, the possibility of carving addiction at a different joint, somewhere beyond substances, has stimulated spirited exchange and more than a twinge of nosologic anxiety. If ingesting or injecting a substance is no longer a necessary feature for the construct of addiction – how do we find the new boundaries?

At one level, the re-carving of addictions is not new. Substance-related disorders were initially "carved in" under Sociopathic Personality for the first DSM, in 1952 [3], and were still considered Personality Disorders for the next DSM revision, in 1968 (DSM II [4]). They were eventually were "carved out" for independent status in I980 (DSM III [5] and have remained thus for nearly 30 years. But in each of these prior nosologic revisions, the substance-related disorders (whether "carved in" under broader categories, or "carved out", to stand alone) were carved *together*, and defined by substance-taking. In contrast to prior revisions, DSM V is considering whether addictions can be defined apart from drug-taking – a fundamental shift in the way these disorders have previously been viewed.

This "neither-necessary-nor-sufficient" status of substances for the future nosology obliges us to look elsewhere for the carving joint – to look for underlying similarities in the compulsive pursuit of substance and non-substance rewards, rather the single obvious difference. Fortunately, emerging brain, behavioral and genetic data do point to fundamental, mechanistic ways in which substance and non-substance addictions are similar. On the short list of similarities are pre-existing vulnerabilities in the mesolimbic

dopamine reward system, and its failed regulation by frontal regions. As a familiar example, dopamine agonist treatments can trigger compulsive gambling, buying and sexual behavior in a vulnerable subgroup of Parkinson's patients, and these problem behaviors may be intercorrelated [6], [7]. The brain sciences offer strong hope for discovering the new boundaries, the new joint, for the construct of addiction.

The following pieces by Drs. Potenza, Frascella and Brown show how brain tools may be used to parse the new boundaries for non-substance addictions, and the sections relate in three different ways to the emerging nosology. We begin with problem gambling, the non-substance disorder that appears most likely to gain entry into the addictions category for DSM V. As summarized by Dr. Potenza, phenomenologic (compulsive pursuit of gambling reward, despite severe negative consequences), genetic (highly heritable, and often co-morbid with other substance addictions), and brain data (e.g., altered response in reward circuits; poor frontal regulation during exposure to a gambling scenario) argue for including gambling as an addiction [8]. In the case of gambling, biologic data encouraging carving all individuals with the phenotype into the diagnostic category of "addiction".

We next consider the complex problem of obesity. In contrast to gambling, where all those with the phenotype would likely be included in the same diagnostic category, the phenotype of "obesity" or high Body Mass Index (BMI) is recognized to be heterogeneous. A number of brain and metabolic factors control food intake and weight gain; not all individuals who are overweight are "addicted to food". Can we carve a clinically meaningful nosologic distinction among obese individuals? As reviewed by Dr. Frascella, rapidly-advancing brain and genetic data may indeed help us move beyond BMI, enabling us to identify obese individuals who have brain differences (e.g., low D2 receptor availability) paralleling those in drug addiction [9–11]. These individuals may respond to interventions arising from the field of drug addiction (e.g., mu opioid receptor antagonists block reward from drugs such as heroin and morphine, and also blunt the reward from the highly palatable (sweet, high in fat) foods [12–14]). Our nosologic system may eventually use such brain- and treatment-driven endophenotypes to carve subgroups of obese individuals into the category of addiction.

Our final segment, by Dr. Brown, highlights the utility of brain tools for studying powerful appetitive states -- e.g., early romantic infatuation, intense sexual attraction, and attachment, that we define as normal – but that impact the same brain reward circuitry, and share some clinical similarities, with drug addictions. For example, intense romantic attachment is "normal", by definition, because so many humans have experienced it — but it is intensely euphoric, there is strong pursuit of the reward to the exclusion of other activities, and it can lead to poor decision-making (including jealous crimes of passion). As the basic reward circuitry for romantic love and attachment is co-opted by drugs of abuse, studying this "normal" altered state, in a "normal" circuit, may give us guidance about endophenotypes of vulnerability in states that are pathologic. It is possible, for example, that those with greater vulnerability during the "normal" altered states (more frequent or prolonged infatuations, more difficulty moving on after a rejection) are also at greater risk for other dysregulated pathological states, whether substance or non-substance related.

Taken together, these authors encourage us to meet the diagnostic challenges ahead with our best biologic tools, and with an open mind. As we move to carve addiction at a new joint, it will clearly not be meaningful to label as "addiction" every pursuit (food, gambling, sex, shopping, internet, exercise, etc.) that activates brain reward circuits. But it is possible that any of these rewarding pursuits, in the vulnerable individual, may emerge as a clinical problem with brain and behavioral features that display striking similarities to those seen in drug addiction. We can thus seek parallels in clinical progression and even in response to similar treatments. The brain and genetic vulnerabilities that allow pursuit of non-drug

rewards to become pathologic are very likely to be important in the vulnerability to drug addiction. Targeting these shared brain vulnerabilities may accelerate our understanding, and thus our effective treatment, of both substance, and non-substance, addictions.

II. Addiction and Pathological Gambling

Marc N. Potenza, M.D., Ph.D.

A. Introduction

Gambling, defined as placing something of value at risk in the hopes of gaining something of greater value, has been observed across cultures for millennia [15]. Early documents of human behavior show evidence of gambling, including problematic forms of the behavior. Pathological gambling is the diagnostic term used in the current edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV-TR) to describe excessive and interfering patterns of gambling [16]. Pathological gambling is currently grouped with kleptomania, pyromania, trichotillomania, and intermittent explosive disorder in the category of "Impulse Control Disorders Not Elsewhere Classified," although few investigations have studied the extent to which these disorders group together based on biological measures. Inclusionary criteria for pathological gambling share common features with those for substance dependence. For example, aspects of tolerance, withdrawal, repeated unsuccessful attempts to cut back or quit, and interference in major areas of life functioning are reflected in the diagnostic criteria for each disorder. As such, pathological gambling has been termed by some as a "behavioral" on non-substance-related addiction.

B. Clinical and Phenomenological Similarities Between Pathological Gambling and Substance Dependence

In addition to inclusionary criteria common to pathological gambling and substance dependence, other clinical features are shared across the disorders. For example, craving or appetitive urge states are seen in both disorders, both are related temporally to time of last engagement in gambling or substance use [17], and the strength of urges has clinical implications for treatment [18]. Additionally, similar brain regions (e.g., ventral striatum and orbitofrontal cortex) have been found to contribute to gambling urges in pathological gambling and cocaine cravings in cocaine dependence [17, 19]. Pathological gambling and substance dependence are not only frequently comorbid with one another, but also with similar disorders (e.g., antisocial personality disorder) [20, 21]. Similarities also exist with respect to the courses of pathological gambling and substance dependence. Like with substance dependence, high prevalence estimates have been reported for pathological gambling amongst adolescents and young adults and lower estimates amongst older adults [22, 23]. A younger age at gambling onset has been associated with more severe gambling and other mental health problems, similar to data regarding age at first substance use [24, 25]. A "telescoping" phenomenon appears applicable to both pathological gambling and substance dependence [26, 27]. This phenomenon, first described for alcoholism, later for drug addiction and most recently for gambling, refers to the observation that although on average women begin engagement in the behavior later in life than do men, the time frame between initiation and problematic engagement is foreshortened (or telescoped) in women as compared to men [28]. Taken together, these findings indicate many common clinical and phenomenological features between pathological gambling and substance addictions.

C. Genetic Features

Both substance dependence and pathological gambling have been shown to have heritable components [29–31]. Common genetic contributions to pathological gambling and other disorders, including alcohol dependence and antisocial behaviors, have been reported in men

[32, 33]. However, significant portions of the genetic contributions to pathological gambling were also unique from those underlying alcohol dependence and antisocial behaviors, suggesting specific contributions to each disorder. For example, allelic variants in genes coding for enzymes related to alcohol metabolism might be anticipated to be unique to potential risk for alcohol dependence whereas genes related to impulsive propensities might be hypothesized to be shared across disorders [34, 35]. Early investigations into specific molecular genetic contributions to pathological gambling identified common factors in substance dependence and pathological gambling (e.g., the Taq A1 allele of the gene encoding the dopamine D2 receptor) [36]. However, early studies were not typically methodologically rigorous (e.g., did not stratify by racial or ethnic identity and did not include diagnostic assessments), and more recent studies have not replicated some initial findings [37]. As such, more investigation into common and unique genetic contributions to pathological gambling and substance dependence are needed, particularly studies of a genome-wide nature.

D. Personality and Neurocognitive Features

Common personality and neurocognitive features have been described in pathological gambling and substance dependence. Like in individuals with substance dependence [34], features of impulsivity and sensation-seeking have been found to be elevated in people with pathological gambling [35, 38–41]. Pathological gambling, like substance dependence, has been associated with preferential selections of small, immediate rewards over larger delayed ones in delay discounting paradigms [40]. Individuals with pathological gambling like those with drug dependence have been found to make disadvantageous choices on decision-making tasks like the Iowa Gambling Task [42, 43]. However, unique features between substance dependence and pathological gambling have also been reported. For example, one study found that subjects with pathological gambling and alcohol dependence both showed deficits on tasks of time estimation, inhibition, cognitive flexibility and planning [44]. In an independent study, individuals with alcohol dependence and pathological gambling showed similar deficits on aspects of performance on a gambling task and impulsivity task, yet they differed with respect to performance on tasks of executive function on which individuals with alcohol dependence showed greater deficits [45]. These findings suggest that specific features of substance dependence (e.g., chronic exposure to substances) may have specific influences on brain structure and function and related behavior that is not seen in pathological gambling [46–48].

E. Neural Features

The common clinical, phenomenological, genetic, personality and neurocognitive features between pathological gambling and substance dependence might be hypothesized to be reflected in shared neural features [35]. For example, similar brain regions (e.g., ventral striatum and orbitofrontal cortex) have been found to contribute to gambling urges in pathological gambling and cocaine cravings in cocaine dependence [19]. Diminished ventral striatal activation has been observed in individuals with pathological gambling in the processing of monetary rewards during a gambling paradigm [49]. These findings are share similarities with those involving alcohol dependent or cocaine dependent subjects in which diminished ventral striatal activation has been reported during the anticipation of monetary rewards [50, 51].

The ventromedial prefrontal cortex, functionally connected with the ventral striatum, has been implicated in risk-reward decision-making and the processing of monetary rewards [43, 52, 53]. Diminished activation of the ventromedial prefrontal cortex in subjects with pathological gambling was initially reported in studies of gambling urges and cognitive control [41, 54]. A subsequent study found diminished ventromedial prefrontal cortical

activation during simulated gambling, with degree of activation correlating inversely with gambling severity in the subjects with pathological gambling [49]. More recently, subjects with substance use disorders with or without pathological gambling showed diminished ventromedial prefrontal cortical activation during performance of the Iowa Gambling Task [55]. Together, these data suggest dysfunction of ventral fronto-striatal circuitry in pathological gambling and substance dependence that is linked to aspects of reward processing and disadvantageous decision-making.

Another recent study examined in healthy subjects the neural correlates of the near-miss phenomenon [56]. A near-miss situation occurs when the first two reels of a slot machine stop on the same symbol and then the third reel locks on a non-matching symbol. While anticipating the stopping of the third reel, activation of reward processing brain regions (e.g., striatum) was observed. During the outcome phase, several of these brain regions (e.g., striatum, midbrain region including the ventral tegmental area) showed activation, thus appearing to code these events as reinforcing. A region that showed deactivation (thus appearing to code these events as non-reinforcing) was the ventromedial prefrontal cortex. As ventromedial prefrontal cortical activity has also been linked to loss-chasing in healthy subjects [57], existing data suggest phenomena hypothesized to be associated with the development of pathological gambling are linked to brain regions in which individuals with pathological gambling show functional abnormalities.

F. Treatments

Behavioral and pharmacological treatment strategies for pathological gambling and substance dependence also show similarities. Gamblers Anonymous, based on the 12-step program Alcoholics Anonymous, is the most widely available form of help for individuals with pathological gambling and attendance has been associated with positive treatment outcome [58, 59]. Other behavioral therapies, such as cognitive behavioral therapy, have been adopted from the substance dependence field and shown to be efficacious in the treatment of pathological gambling [60]. Brief interventions, such as those used in medical settings for assistance with smoking cessation, have shown promise in the treatment of pathological gambling [61], as have motivational interventions that have shown success in the treatment of drug dependence [62, 63].

Multiple pharmacotherapies have been investigated in the treatment of pathological gambling [19]. As with drug dependence, serotonin reuptake inhibitors have shown mixed results in controlled trials [19, 64, 65]. Opioid antagonists, such as naltrexone (a drug with approval for the indications of opioid and alcohol dependence), represent the class of drugs that to date has shown the most promise in the treatment of pathological gambling, particularly amongst individuals with strong gambling urges at treatment onset and those with a family history of alcoholism [18]. More recently and based on work in drug dependence [66], glutamatergic agents such as N-acetyl cysteine have been investigated and shown preliminary efficacy in the treatment of pathological gambling.

G. Summary: Addiction and pathological gambling

Pathological gambling and substance dependence show many similarities. Although specific features also likely distinguish pathological gambling from drug dependence (much as specific features distinguish specific forms of substance dependence [29]), existing data suggest a particularly close relationship between pathological gambling and substance dependence that warrant their consideration within a category of addictions.

II. Addiction and obesity

Joseph Frascella, Ph.D.

A. Neurobiological Links between Obesity and Drug Addiction

Introduction—Obesity is increasing significantly and represents a public health concern in both the United States and now worldwide. Current estimates show that about 65% of adults and about 32% of children and adolescents in the U.S. are overweight or obese ([67], [68]). Over one billion adults and 10% of the world's children have been classified as overweight or obese, with consequent decreases in life expectancy as well as increases in adverse consequences such as cardiovascular disease, metabolic syndrome, type 2 diabetes and some cancers (*e.g.,* [69], [70]). The etiology of obesity is extremely complex reflecting varied neurobehavioral factors; however, a growing literature points to the fact that excessive and compulsive eating often can share some of the same processes and behavioral phenotypes with substance abuse and dependence as described in DSM-IV. For example, DSM-IV substance dependence criteria (tolerance; withdrawal; escalation/using larger amounts; persistent desire/unsuccessful effort to reduce use; spending a large amount of time acquiring substance, using it, or recovering from it; sacrificing social, occupational, or recreational activities because of substance use; and continued substance use in the face of persistent or recurrent physical or psychological problems) can be applied in obesity. For some people, food can trigger an addictive process ([71], [72], [73]), and the parallels are so similar that it has been suggested that obesity should be recognized in DSM-V as a mental disorder ([10]; see also [74] for a discussion of the complexities surrounding this notion). With the abundance and availability of highly palatable, calorie-dense foods filled with salt, fats and sugars, these extremely potent reinforcers can be hard to resist, which can lead to nonhomeostatic eating and to obesity.

This review will discuss some of the relevant neurobiological data that reveal the distinct similarities (and differences) between obesity and addiction. The goal is to focus on meaningful comparisons that highlight commonalities and possible connections between both fields of study. As a result, obesity research could potentially inform substance abuse/addiction research and *vice versa*. Despite a growing scientific debate as to the existence of "food addiction" as an important factor driving the current obesity epidemic (see [75–77]), this review will not discuss this construct directly but will instead focus on the parallels between both obesity and addiction in terms of neurobiologic systems that underlie motivational processes in both feeding and drug abuse. These neurobiologic mechanisms can be affected by potent reinforcers resulting in excessive behaviors and a loss of control exhibited in both obesity and addiction. Similarities between obesity and substance addiction might highlight the need to consider a subpopulation of obese individuals consistently with other behavioral addictions.

B. The Brain Reward System: a Common Link between Obesity and Addiction

Increasing evidence, particularly from animal studies, reveals that some of the same brain systems underlie compulsive or excessive eating and drug abuse. The neural systems regulating mammalian energy control and balance are exceedingly complex with many processes and feedback mechanisms that involve distributed regions of the brain. Regulation of normal feeding is mediated by the monitoring of energy needs relative to energy expenditures; when energy expenditures exceed energy intake, systems signal this change and hunger results. Much like substances of abuse, highly palatable foods can serve as potent reinforcers that motivate behaviors (*i.e.,* non-homeostatic eating). The mechanisms underlying excessive food intake leading to obesity, as well as drug seeking leading to addiction, are extremely complex and are influenced by a number of factors (*e.g.,* genetic influences, learning and memory, palatability/liking, stress, availability, developmental, environmental/social/cultural influences) (for review see [9, 78]).

Central to the motivation and drive in the acquisition of certain foods as well as abused substances is the brain reward system. This highly evolved system involves an extremely complex neurobiologic network, particularly the mesolimbic dopamine (DA) system – the ventral tegmental area in the midbrain and its projections to the nucleus accumbens, amygdala, ventral striatum, hippocampus, and medial prefrontal cortex (*e.g.,* [79–83]). How effective a substance (or food) is in stimulating the brain's reward system influences the likelihood of future intake of that substance (or food). The brain reward system is linked to feeding circuits mediating energy balance and control.

Dopamine release in the nucleus accumbens has been shown after administration of most substances of abuse and is thought to mediate the rewarding properties of drugs (*e.g.,* [84–95]). Similarly, when we ingest foods, dopamine is released, and animal studies have long shown that the release of dopamine occurs in the nucleus accumbens and ventral tegmental area (*e.g.,* [96–102]). Further studies have shown that dopamine release in the nucleus accumbens is a direct function of the rewarding properties of food, and dopamine release varies as a function of food palatability [97, 103, 104]. Such work reveals the link between palatability, reward, and dopamine, all of which can interact with normal homeostatic appetitive states. Pleasantness and palatability of the food also can be dissociated from hunger (*e.g.,* [13], [105]).

The characterization of the neurobiological relationship between taste and reward is critical in the understanding of the affective aspects to feeding, motivation and food preference. The corticolimbic pathways that mediate motivational factors for food project to the hypothalamic nuclei, and the connection of these systems regulates hunger and satiety [106, 107]. Other findings suggest that sensory activity from a food stimulus is processed by way of limbic projections to the nucleus accumbens [108]). Another brain area that has been shown to be involved in the reward or pleasurable aspects of food and other stimuli is the orbitofrontal cortex (*e.g.,* [80, 82, 83, 105, 109–113]). Many of these systems involved in food reward overlap with those affected by abused substances. Both palatable food and drugs are highly rewarding, and both are mediated through the dopamine system.

Although the dopamine system plays a key role in reward processing, other systems are also important. A growing literature suggests that the endocannabinoid system directly modulates reward and drug seeking (*e.g.,* [114–121]). Similarly, the endogenous opioid system is involved in reward processing [122, 123], and both the endogenous cannabinoid and opioid systems interact to mediate brain reward (see [120]). Similar to the effects of these two systems on reward and drug seeking, studies have revealed a link between the endogenous cannabinoid and opioid systems in feeding and in the regulation of food intake (*e.g.,* [124], [13, 125–127]; for review see [128, 129]). Recently, opioid systems mediating palatability and reward value of food were shown to be neurobiologically distinct ([130]).

C. Clinical Brain Imaging Findings

Much of the evidence presented linking both has been from animal studies reporting direct measures of the neurobehavioral aspects of feeding and drug seeking. Overlapping mechanisms and functional processes underlying both obesity and addiction are being elucidated in a growing number of human brain imaging studies. Normal food intake is regulated by homeostatic processes and is also influenced by the same rewarding or motivational processes that also control drug seeking. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) methods have provided powerful tools to determine brain structures, transmitter systems, and functional circuits involved in food and drug reward processing.

Studies in humans have paralleled animal work by characterizing the involvement of the dopamine system in substance abuse, specifically through the relationship between brain dopamine levels in the nucleus accumbens and the rewarding properties of drugs of abuse. Volkow and colleagues [131] showed that the reinforcing effects of psychostimulant drugs in humans were related to increased brain dopamine levels, and the subjective perception of reward/pleasure was positively correlated with amount of dopamine released. Also overall levels of dopamine D2 receptors predicted individual differences in the reinforcing effects of psychostimulant drugs – that is, low dopamine D2 receptor levels correlated with greater reinforcing effects of the drug [132] Studies of dopamine release in response to food, or food-associated stimuli, have similarly shown that when healthy, food-deprived subjects are presented with favorite foods, dopamine is released during the presentation of food-related cues 38, [133], as well as after consumption of the meal. The amount of dopamine released (in dorsal, but not ventral, striatum) correlates with meal pleasantness [110], suggesting that dorsal striatum may mediate food reward in healthy individuals 38, [133]. This finding of food reward/motivation being mediated in the dorsal striatum but notventral striatum (an area involved in drug reward) reveals a distinction in processing between food and drugs of abuse. The dorsal striatum has been shown to be important in feeding (*e.g.,* [134], [84]) and is consistent with findings of increased regional cerebral blood flow in the dorsal striatum during the ingestion of chocolate; blood flow in this region correlated positively with pleasantness ratings ([111]).

Craving is a characteristic feature to both obesity and addiction. It may underlie overeating and drug abuse, and interferes with maintenance of abstinence. Several studies exist attempting to characterize the functional correlates of food pleasantness or food desirability (e.g., [135], [111], [110], [11], [136]); however, relatively few have assessed food craving directly. Pelchat *et al.* ([137]) studied brain activation to food craving and found craving-related changes in the hippocampus, insula, and caudate. In another study, chocolate cravers were compared to non-cravers, and cravers showed greater activation in reward areas such as the medial prefrontal cortex, anterior cingulate, and ventral striatum ([138]). Many of the areas activated in food craving are somewhat overlapping with brain areas in drug craving studies, such as the anterior cingulate (*e.g.,* [139], [140], [141], [142], [143], [144], [145], [146], [147]), ventral striatum (*e.g.,* [142], [147]), hippocampus (*e.g.,* [141], [147]); insula (*e.g.,* [141], [148], [144], [142], [143], [146], [147]), and dorsomedial and dorsolateral prefrontal cortex (*e.g.,* [139], [149]; [145]; [146], [147]). It should be noted that in these brain imaging studies of drug craving, individuals tested were dependent on drugs, whereas in the food craving studies, healthy subjects were tested. Therefore, studies assessing craving in obese individuals are needed. Many studies, however, have been conducted to determine brain responses to food and food cues and have probed the reward system in obese populations. Dysfunctional food reward processing in these individuals is thought to contribute to and represent a neurobiological substrate to pathological eating and obesity.

For example, brain responses to anticipatory and consummatory food reward were found to be different in obese versus lean individuals. Obese subjects showed a significantly greater brain activation during both anticipated and actual consumption of food in primary gustatory cortex, in somatosensory cortex, and anterior cingulate [150]. A decreased activation in the caudate was found in obese versus lean individuals during consumption, which was thought to possibly indicate reduced dopamine receptor availability. Also, as a function of BMI, increased activation to anticipatory food reward was found in the temporal operculum and dorsolateral prefrontal cortex, and increased activation in the insula and frontoparietal operculum was found to consummatory food reward. These results show a distinct difference in processing of food stimuli in obese versus lean individuals. Greater responses to food presentation, coupled with a decreased striatal response during consumption, were posited as a potential neurobiological marker of risk for overeating and obesity.

In another study, the relationship between obesity and hypofunctioning of the dorsal striatum was related to the presence of the A1 allele of the *Taq*I gene [151]. The negative relation between striatal response to food intake and BMI was significantly greater in those individuals with the A1 allele (see also [152]). It was suggested that this difference was possibly related to the reduced dopamine D2 levels in the striatum of obese individuals, thereby compromising dopamine signaling, which could lead to overeating to compensate for a reward deficiency. Additionally, individuals with this dopamine D2 receptor gene polymorphism were shown to have a deficit in learning from errors in a feedback-based learning task. Dopamine D2 receptor reduction has been related to decreased sensitivity to negative action consequences [153]. Studies have also suggested that the dopamine D2 receptor *Taq*I A1 polymorphism is related to substance abuse (*e.g.,* [154–156]). Recently, a significantly higher prevalence of the dopamine D2 receptor *Taq*I A1 allele polymorphism was found in methamphetamine-dependent individuals as compared to a comparison group [157]. Substance-dependent individuals with this polymorphism also had cognitive deficits, scoring significantly lower on executive function measures.

Despite these results showing a decreased responsiveness in the dorsal striatum, a structure important in habit learning (e.g., [158]; [159]; [160]), Rothemund et al. [161] found that during food ingestion high-calorie food selectively activated the dorsal striatum along with other areas such as anterior insula, hippocampus, and parietal lobe in obese women as compared to normal-weight individuals indicating a possible higher reward anticipation and motivational salience in obesity. Differences in the motivational potency of food cues and the reactivity of the reward system were also found in obese individuals. High-calorie foods elicited significantly greater activation in the brain areas mediating motivational and emotional responses to food and food cues (medial and lateral orbitofrontal cortex, amygdala, nucleus accumbens/ventral striatum, medial prefrontal cortex, insula, anterior cingulate cortex, ventral pallidum, caudate, putamen, and hippocampus) for obese versus normal-weight individuals [162]. The authors suggest that their results are consistent with the hypothesis that those brain networks showing hyperactive responsiveness to food cues in obesity are also hyperactive to drug cues in addiction.

A critical question remains as to whether obese individuals have a hyper-responsiveness in brain reward regions important to food reward or if they, in fact, have a hypo-responsive reward circuitry. Stice et al. [163] review behavioral and brain imaging evidence for both models. They conclude that much, but not all, of the data suggest that obese compared to lean individuals report greater pleasure and show great activation in gustatory and somatosensory cortex in response to food anticipation and consumption. This heightened activation in these brain areas could increase vulnerability to overeating. They further hypothesize that overeating may lead to a down-regulation of receptors in the striatum, which could further drive individuals to consume highly palatable/high-calorie foods, all of which could contribute to obesity. It should be noted that some of the discrepant (hyperactive versus hypoactive brain regions) results could be due to methodological differences. For example, some studies assessed brain activations when subjects were in a state of hunger, whereas others studies did not. Food preference, history of eating disorders, eating patterns, and present diet are important factors in such studies (see [162]), and control for such factors is not consistent across studies. Also, it was suggested that brain activation results could be different depending on different functional states; that is, resting versus when exposed to food or food stimuli [150]. For example, a study of regional brain metabolism at rest revealed differences between lean and obese individuals. Obese individuals had a significantly higher resting metabolic activity than lean individuals in brain regions underlying sensations of the lips, tongue and mouth [164]. The authors concluded that this enhanced activity in brain regions involved with the sensory processing

of food in obese individuals could place them at risk for an increased motivational drive for food.

In a recent study of functional connectivity within the reward network in response to high- and low-calorie food stimuli, Stoeckel et al. [165] found abnormal connectivity in obese individuals compared to normal-weight controls. Specifically, a reduced connectivity was found in response to food cues from the amygdala to the orbitofrontal cortex and nucleus accumbens, which is thought possibly to produce deficient modulation of the affective/emotional aspects of food reward value thereby resulting in a lack of devaluation of foods following consumption leading to an enhanced food drive leading. An increased orbitofrontal cortex to nucleus accumbens connectivity was found in obese individuals also thought to contribute to an enhanced drive to consume foods. In a drug study, an enhanced resting state connectivity between the nucleus accumbens and orbitofrontal cortex was found in substance addiction and was thought to contribute to a stronger salience value of drugs [166].

Reward processing is an important factor in obesity, but other processes are also involved. Satiety signaling also plays a significant role in the control of food intake. Brain measures have shown differential signaling to meal satiation; that is, cerebral blood flow changes in response to a meal were different in lean compared to obese individuals. Limbic/paralimbic areas and prefrontal cortex responded differently as a function of low versus high BMI, Obese individuals responded to satiation with a greater activation in the prefrontal cortex and a larger deactivation of limbic and paralimbic areas (frontal operculum, hippocampal formation, insula, orbitofrontal cortex, temporal pole), striatum, precuneus, and cerebellum (*e.g.*, [167–169]).

Given the importance of the dopamine system in substance abuse and addiction, Wang et al. [11] assessed brain dopamine D2 receptors in severely obese (BMI between 42 and 60) individuals. Findings revealed that striatal dopamine receptors were significantly lower in these individuals, and an inverse relationship was found between D2 receptor levels and BMI – that is, lower levels of receptors correlated with higher BMI. The authors suggested that this dopamine deficiency in these obese individuals might contribute to and perpetuate pathological eating to compensate for the decreased dopamine signal in these systems, consistent with the notion of “reward deficiency”. Alternatively, given the generality of the decrements of dopamine D2 receptors, it has been posited that reductions in the dopamine system may be a marker for vulnerability or predisposition to excessive or addictive behaviors [11]. As mentioned previously, Stice et al.’s ([150], [151]) findings of a reduced caudate activation in obese versus lean individuals during food consumption are consistent with reduced dopamine receptor availability in the dorsal striatum. Similarly, drug-addicted individuals, across a range of addictions to different drug classes, have shown clear disturbances in the dopamine system, particularly in terms of reduced striatal dopamine receptors in cocaine [170–172], methamphetamine [173, 174], alcohol [175–177], nicotine [178], and heroin [179] addicted individuals. Decreases in dopamine transporters also were also found in cocaine [170, 180], methamphetamine [173, 181, 182], alcohol [183], and nicotine [184] addicted individuals.

The exact relationship between low dopamine D2 receptor levels and the risk for overeating/obesity is not well characterized. Having previously established that striatal dopamine D2 receptors levels are lower in obese individuals, Volkow *et al.* [185] confirmed this result and explored the relationship between these decrements and activity in the prefrontal cortical brain regions that have been implicated in inhibitory control in a group of morbidly obese individuals. In obese individuals, as compared to control individuals, lower dopamine D2 receptor availability was associated with decreased metabolic activity during food

consumption in prefrontal areas (*i.e.,* dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate, and also the somatosensory cortex. The authors hypothesized that excessive eating could result as the consequence of lower striatal dopamine D2 receptors influence on those prefrontal mechanisms involved in inhibitory control. Furthermore, the association between striatal dopamine D2 receptors and somatosensory cortical metabolism was thought to reflect enhanced food palatability and food reward. Similar findings and association between receptor availability and metabolism had been observed in drug-addicted individuals [170, 174, 186], and the loss of inhibitory control and the compulsive drug-seeking in these individuals were suggested to be related to the changes in striatal dopamine function and orbitofrontal cortex metabolism.

These studies reveal that decreases in glucose metabolism levels in prefrontal regions might potentially contribute to obesity because these areas are important in executive function and cognitive/inhibitory control. Thus, deficits in these processes along with increased drive states could lead to the inability to terminate reinforcing behaviors, like over consuming palatable foods or abusing addictive drugs, even in the face of negative health consequences. Recent work has further probed prefrontal metabolic activity to assess its direct relationship with BMI. In healthy adults, a negative correlation was found between BMI and baseline brain glucose metabolism in both prefrontal areas and in the anterior cingulate gyrus [187], and both of these areas notably have been suggested to be directly involved in drug addiction. Memory and executive function were also assessed, and a similar inverse relationship between prefrontal metabolism and performance on executive function and verbal learning was found. This finding of decreased cognitive function in obesity is consistent with a growing literature showing that elevated BMI is associated not only with adverse health outcomes, but also adverse neurocognitive and neuropsychological outcomes in adults (*e.g.,* [188–191]), including a reduction in mental flexibility and capacity for sustained attention in obese individuals [192]. Interestingly, these same findings, however, were not found in children and adolescents [193].

These functional findings were extended in studies that assessed how obesity might be associated with regional brain structure. In a morphometric assessment of brain volumes in obese individuals versus lean individuals, reductions in gray matter density were found in several brain areas (*i.e.,* postcentral gyrus, frontal operculum, putamen, and middle frontal gyrus) that have been implicated in taste regulation, reward, and inhibitory control [194]. Similarly, in a large sample of healthy individuals, a significant negative correlation was found between BMI and both global and regional gray matter volume, but in men only [195]. This study was supported by another investigation of brain volume in healthy adults as a function of BMI. Obese individuals showed overall smaller whole brain and total gray matter volumes than normal or overweight individuals [196], and the authors suggested that these morphometric differences in brain might account for the inverse relationship between cognitive function and BMI that has been found.

These findings in obese individuals are very consistent with a fairly large literature in substance-dependent individuals revealing structural and functional abnormalities in frontal cortical regions. Gray matter reductions have been documented in prefrontal cortical regions in polysubstance abusers [197], in frontal (cingulate gyrus, orbitofrontal cortex), insular, and temporal cortical [198–201] and in cerebellar [202] regions in cocaine abusers, as well in prefrontal, insular, and temporal cortical regions in opiate-dependent individuals [203]. These similar and multiple systems that are affected in both obesity and addiction demonstrate both the extent and complexity of circuits involved.

D. Summary: addiction and obesity

The study of the neurobiological systems underlying obesity and addiction show some compelling parallels. A growing body of research, particularly relatively recent findings using brain imaging, has documented both structural and functional changes in important areas that underlie behavioral regulation, reward and reward processing, executive function, and decision making. Alterations in neurobiological systems can lead to dysfunctional processing and consequent highly motivated behaviors (non-homeostatic eating/drug seeking) that contribute to obesity and addiction. The identification of, and highlighting of, such commonalities in these processes might yield new perspectives on obesity and addiction with the ultimate possibility that new, intersecting clinical approaches and strategies for treatment (and prevention) might be developed. Finally, such similarities might highlight the need for consideration of obesity within the new DSM-V.

IV. Addiction and sex, romantic love and attachment

Lucy L. Brown, Ph.D.

Overview

Sex, romantic love, and attachment: each of these has addictive qualities; all are part of the human reproductive strategy; all rely on brain reward systems identified in animal and human studies. Childress et al. [204] suggested that natural reward systems might be used when addicts view cues that induce craving, and Kelley [205] has reviewed how systems associated with drug addiction are also associated with reward and motivation. Is the physiology of natural strategies for the survival of the species the basis for addiction disorders? Is the euphoria of sex and romantic love a normal level of intense pleasure experienced with drugs of abuse? Is the contentment and safety of attachment the normal action of a system activated by drugs of abuse, and the reason for repeated use? Available evidence strongly suggests that substance abuse neurophysiology may be based on survival mechanisms and their mesolimbic reward systems associated with sex, romantic love and attachment.

Medical research places addictions in the context of disorders, not as a part of natural and productive behaviors. It may be advantageous to consider behaviors like substance abuse as existing on one end of a continuum. In moderation, these behaviors are necessary. In the extreme, they can be dangerous and counter-productive. If they are based on survival systems, then the underlying physiological systems must be complex and redundant, exist at many levels of the brain, and be especially difficult to moderate. It should not be surprising that we would never “forget” the feeling of sexual arousal, satisfaction, attraction to a specific individual to reproduce with, or the attachment to mother, child, and mate. Evolution would select for that memory to be stable and long-lasting, and for those who seek out sex. It would not be surprising that moderating a survival system is difficult. Thus, although drugs of abuse may change molecular events to produce destructive addictions [e.g. 205, 206, 207], and although there are individual differences in addiction susceptibility [e.g. 207, 208–210], the systems may be difficult to control in most people because they evolved for survival.

Potenza [211] provides a useful definition of addiction in his paper discussing non-substance-related conditions. It is well described as a “loss of control over a behavior with associated adverse consequences.” The behavior is impulsive and obsessive, and includes the feeling of craving. Diagnostic criteria for substance dependence include life interference, tolerance, withdrawal, and repeated attempts to quit. These descriptions can be applied to situations in human sexual and attachment relationships.

The Sex Drive

Sex is necessary for the survival of any species. The sex act is the final common pathway for reproduction. Humans almost universally describe sex as pleasurable and it could be considered the primal non-drug reward process. Some people claim they are addicted to it [212, 213]. It occupies their thoughts and time so much, that it has a negative impact on the rest of their lives. It is often an impulsive behavior that cannot be controlled, in both positive and destructive circumstances. Evidence from human brain imaging suggests that sexual arousal and orgasm affect the mesolimbic reward system. Areas affected are the amygdala, ventral striatum (including accumbens), medial prefrontal cortex and orbitofrontal cortex [214–216]. These regions are all implicated in drug abuse [e.g. 217, 218–220]. Also, activity in the ventral tegmental area (VTA) was correlated with perceived sexual arousal in women [215], an area associated with cocaine high [221]. In areas not directly associated with reward, sex-related neural activity was found in the ventromedial hypothalamic area/ tuberoinfundibulum, paraventricular n., insular cortex, and several neocortical areas [214–216, 222]. Animal studies suggest that hypothalamic brain activity during the sexual response could depend on opioid receptors [223, 224] and norepinephrine [225, 226]. Finally, testosterone and estrogen affect sexual arousal, and testosterone can induce obsessive thoughts about sex. Testosterone is a controlled substance for its abuse potential. Animals will self-administer it [227]. In summary, involvement of mesolimbic reward areas in the sex drive in humans, and the possible opioid involvement in the sexual response are particularly interesting in the context of drug abuse. However, there is also a strong rationale for more emphasis on the roles of sex hormones and hypothalamic control in drug abuse.

Romantic Love

Fisher has hypothesized that romantic love is a developed form of a mammalian drive to pursue preferred mates [228, 229], thus being an essential aspect of the human reproductive strategy and a strong influence on human behavior. Individuals in the early stages of romantic love often exhibit addicted characteristics. They are obsessed by the other person so that their lives are oriented around them; they can be impulsive and lose control over their thoughts and behavior; they may abandon family to be with the beloved. In extreme cases, they commit homicide and/or suicide if love appears to be withdrawn. The focus on the other person can be dangerous to them and others. We found in a brain mapping study that early-stage romantic love activates the VTA of the midbrain and the caudate nucleus, suggesting that it does, indeed, use brain systems that mediate mammalian reward and drives, and is not so much an emotion as a survival motivation [230]. Participants in love also showed deactivation in the amygdala. In addition, the longer the relationship, the more activity in the ventral pallidum and insular cortex [230]. Furthermore, we looked at young adults who had been recently rejected in love [231], arguably the group showing the greatest “addiction” to another person, experiencing craving, poor self-regulation, painful affect, isolation, disordered sense of self-worth and most likely to do harm to themselves. In them, we found activation of the VTA similar to the early-stage romantic love group, suggesting that the sight of the sweetheart is still rewarding, but also in the accumbens nucleus, and in several regions where Risinger et al. [232] reported activity correlated with craving in cocaine addicts. These areas include the accumbens core, an area of the accumbens-ventral pallidum, and an area deep in the middle frontal gyrus [232].

Also, we looked at a group of individuals who had been in long-term marriages (average 20 yrs) and claimed to feel the “high” of early-stage love [233] They, too, showed activation in their VTA when they viewed their beloved, but also their experience involved the accumbens, and the ventral pallidum, areas shown to be essential for pair-bonding in prairie voles [234, 235]. In addition, the experience of long-term love involved the bed nucleus of the stria terminalis, and the area around the paraventricular nuclei of the hypothalamus,

suggesting that longer-term love that includes pair-bond attachment may involve important hormone systems such as oxytocin and vasopressin. These two hormones are important for pair-bonds in voles [234, 235].

In summary, feelings of romantic love use reward and motivation systems consistently, across individuals and across circumstances of the love experience. Love includes obsessive behaviors and can ruin lives, just as substance abuse does. Like sex, love may involve hypothalamic hormone control systems. Like sex, it is acting at midbrain, hypothalamic and ventral striatum levels, and uses subcortical areas associated with reward.

Attachment

The mother-child relationship reveals attachment systems, and the importance of attachment behaviors to our survival [236, 237]. Strathearn et al. [233] used fMRI to study mothers looking at images of the faces of their infants. They found activation associated with the mothers' own child compared to an unknown child in areas typically associated with reward and drug high and craving: the VTA, amygdala, accumbens, insula, medial prefrontal cortex and orbitofrontal cortex. They also found hypothalamic activation [238], but in an area different from sexual arousal [214] and long-term love [233].

Flores has suggested that addiction is an attachment disorder [239, 240]. He uses Bowlby's (1973) assertion that attachment is a drive in its own right, thus making it part of a mammalian survival system. Without normal attachment, emotional regulation is compromised and individuals are vulnerable to addictive compulsions. Monkeys raised in isolation have difficulties in a social environment later, but also binge on food and water, and consume more alcohol than normal monkeys [e.g. 241]. Human individuals who lose a spouse are at greater risk of death, themselves, than the general population; in the first year one of the greatest causes of death is alcohol-related events [242]. The association of isolation in development, or loss of a spouse, with alcohol use and other addictions has implications for addiction treatment [240]. For example, successful treatment approaches often use healthy social relationships to break addictions, like the alcoholics anonymous program. To break the cycle of alienation and isolation that accompanies, and may be the cause of addictions, group therapy can be especially therapeutic, and the experience of secure attachment appears to produce better self-regulation [240]. The association of attachment with reward and survival systems, and its behavioral relevance to addiction treatment make it an especially interesting reward system for future study.

Drug Addiction, Lust, Love and Attachment

Brain mapping studies have looked at the effects of acute drug injections and drug cues on neural activity in reward systems [e.g. 204, 218, 221, 243]. In one study that scanned cocaine addicts under the two conditions of drug cues and erotic images (sex cues), the amygdala was affected in both states [244]. The amygdala was affected by sexual arousal, orgasm, romantic love and attachment stimuli [215, 216, 230, 238]. Areas consistently associated with the cocaine "high" are the VTA, amygdala, accumbens (positive or negative response), orbitofrontal and insular cortex [221, 243]. Areas associated with cocaine craving are the accumbens, ventral pallidum and orbitofrontal cortex [221, 243]. These areas associated with drug high and craving were also affected by sex, love and attachment. Differences between drug cues and reproductive system reward systems may be in the ventral pallidum, where mothers' activation to a picture of their child was more anterior and dorsal than for sex, cocaine cues or romantic love. Also, sex cues and drug cues were associated with different sides of the ventral striatum [244]. Thus, the survival systems may differ from drug abuse substrates by using different regions of, or sides of, reward areas, and more hypothalamic areas.

Summary—Functional brain imaging studies of sex, romantic love and attachment provide ample evidence for an extended but identifiable system central to natural, non-drug reward processes and survival functions. The natural reward and survival systems are distributed throughout the midbrain, hypothalamus, striatum, insular, and orbitofrontal/prefrontal cortex. Brain areas that control essential hormones for reproductive capacity, childbirth and water balance as well as brain areas that are rich in dopamine and opioids appear to be involved. The overlap of classic reward brain areas involved in sexual arousal, love and attachment is complete (VTA, accumbens, amygdala, ventral pallidum, orbitofrontal cortex). Although brain imaging drug abuse studies have not yet implicated hypothalamic and hormonal control areas in addiction, they may be involved, and may deserve more research attention. The main thesis, here, however, is that the widely distributed levels of substance abuse-associated systems, because they are survival systems, may require several simultaneous biochemical and behavioral approaches. The side of the brain responsive to the different cues can differ, and there are differentially activated subregions in large areas like the accumbens and orbitofrontal cortex. However, a speculation is justified that associates survival-level natural rewards with substance addictions, expanding the brain systems to be addressed in therapy, and increasing our understanding of the necessary tenacity of the behaviors.

V. SUMMARY

As these three authors illustrate, the increased availability of powerful brain and genetic tools has opened new era in the diagnostic classification for addictions. For the first time since the diagnostic manuals were developed more than half a century ago, a diagnosis of "addiction" will likely not require substance-taking – previously a *sine qua non* for the category. Boundaries for the construct will be carved somewhere beyond substances. Exactly where is not yet clear – but as the authors demonstrate, characterizing shared brain vulnerabilities for the compulsive pursuit of substance and non-substance rewards may aid not only in carving diagnostic boundaries, but in the etiologic understanding and treatment of these difficult disorders.

One anticipated clinical benefit of the broadened diagnostic boundaries is hypothesis-driven testing of "cross-over" medications -- agents found helpful for substance addictions may be tried in non-substance disorders, and vice-versa. Examples include use of the opioid antagonist naltrexone, a treatment beneficial for opiate addiction [245] (and for a genetic sub-group of Caucasian male alcoholics [246]), now being tried as a monotherapy for gambling [18] and as a combination therapy (with bupropion) for obesity [247]. GABA B agonists such as baclofen have shown preclinical (cocaine, opiates, alcohol and nicotine, [248–251]) and clinical [252–255] promise in substance addictions, but may also have "cross-over" promise for over-consumption of highly palatable (especially high-fat) foods [75, 256] [257]. Conversely, novel agents such as the orexin antagonists, though initially studied in food reward paradigms, may have a much broader impact, including cocaine and heroin reward [258–260].

Future carvers of addiction nosology will make use of the results from such "cross-over" therapeutics to help refine the construct and its boundaries. Effective, specific biological treatments often help to re-carve diagnostic boundaries. A case in point is the historical diagnostic distinction between anxiety and depression. As serotonin-specific reuptake inhibitors often show benefit for both anxiety and depression, these disorders are increasingly viewed as overlapping "spectra", rather than clearly dichotomous disorders. It can be anticipated that the addictions may undergo a similar re-carving, if the same biologic interventions are effective against the compulsive pursuit of substance and non-substance rewards. Though our nosology has thus far compartmentalized these problems, we may soon

carve addiction at a new joint that will greatly benefit our hypotheses, our clinical research, and most importantly, our patients.

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