Relationships Among the Brain, the Digestive System, and Eating Behavior: Workshop Summary

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Leslie Pray, Rapporteur; Food Forum; Food and Nutrition Board; Institute of Medicine

Relationships Among the Brain, the Digestive System, and Eating Behavior

Workshop Summary

Leslie Pray, *Rapporteur*

Food Forum

Food and Nutrition Board

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

Miguel Alonso-Alonso, Beth Israel Deaconess Medical Center
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Although the reviewers listed above provided many constructive comments and suggestions, they did not see the final draft of this workshop summary before its release. The review of this workshop summary was overseen by **Caswell A. Evans, Jr.** Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteur and the institution.

Contents

1

Introduction[1]

On July 9-10, 2014, the Institute of Medicine's Food Forum hosted a public workshop to explore emerging and rapidly developing research on relationships among the brain, the digestive system, and eating behavior. Figure 1-1 illustrates these complex relationships, as well as the influence of biology and the environment, as described by the speakers throughout the workshop.

Drawing on expertise from the fields of nutrition and food science, animal and human physiology and behavior, and psychology and psychiatry as well as related fields, the purposes of the workshop were to (1) review current knowledge on the relationship between the brain and eating behavior, explore the interaction between the brain and the digestive system, and consider what is known about the brain's role in eating patterns and consumer choice; (2) evaluate current methods used to determine the impact of food on brain activity and eating behavior; and (3) identify gaps in knowledge and articulate a theoretical framework for future research.

The organization of this workshop summary parallels the organization of the workshop presentations and panel discussions. The workshop was divided into four sessions, with a panel discussion at the end of each

[1] This workshop summary is a factual account of the presentations and discussions that occurred during the workshop. All of the information provided here was presented either verbally or visually (on slides) during the workshop. The goal of the workshop was not to reach consensus on any issue or to formulate recommendations. The opinions and suggestions summarized here were those of individual speakers or audience members and should not be construed as reflecting consensus on the part of the Institute of Medicine, the Food Forum, the workshop planning committee, or any other group.

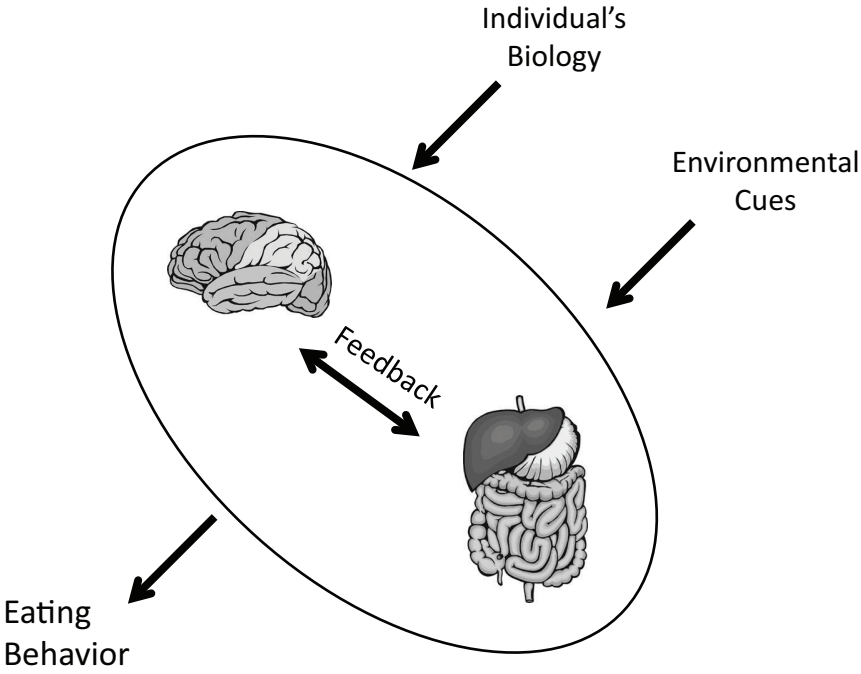


FIGURE 1-1 Relationships among the brain, the digestive system, and eating behavior.
NOTE: Environmental cues include commercial, physical, social, and cultural influences.

session (see the workshop agenda in Appendix B). The panel discussions served to clarify issues, provide additional perspectives, and identify gaps in knowledge.

The workshop began with an exploration of how the presence of food in the gut triggers signals to the brain about nutrient content, character, and volume and how that information, in turn, impacts further food intake. Timothy Moran of Johns Hopkins University explained how most information received by the brain about gastrointestinal contents is derived from vagal afferent feedback signals,[2] some of which come from the stomach and others from the intestine.

While vagal signals from the stomach are different from those arising in the intestine, the two intersect in the hindbrain, where together they play

[2] Vagal afferent signals are signals transmitted toward the central nervous system, in this case from the gastrointestinal tract, via the vagus nerve.

a role in reducing further food intake. Robert Margolskee of the Monell Chemical Senses Center described scientists' discovery of taste-signaling proteins in the gut in the 1990s and what has been learned since then about which gut cells in particular express the taste receptors and how gut-expressed taste proteins contribute to the physiological response to food. Robert Ritter of Washington State University elaborated on some of the information and ideas presented by Moran and explored in greater mechanistic detail how vagal signals activated by gut peptides, cholecystokinin in particular, contribute to the process of satiation and reduce further food intake. Finally, Laurette Dubé of McGill University considered the broader cognitive and social context within which brain-digestive system interactions operate and impact eating behavior. Chapter 2 summarizes these four speakers' presentations and the discussion that followed.

Next, workshop participants explored two recently developed methodologies being used to study the impact of food and food cues on brain activity and eating behavior: (1) neuroimaging and (2) self-report questionnaires. Dana Small of Yale University and the John B. Pierce Laboratory summarized neuroimaging evidence indicating that food cues in the environment can trigger eating even in the absence of hunger. She also described data from rat studies suggesting that the underlying physiological mechanism appears to be a postingestive glucose metabolic effect, as opposed to something sensory. Hisham Ziauddeen of the University of Cambridge highlighted the many assumptions underlying neuroimaging studies on eating behaviors and urged caution when interpreting the study results. Ashley Gearhardt of the University of Michigan explained why and how she and colleagues developed the Yale Food Addiction Scale (YFAS) as a tool for identifying individuals who may be experiencing addictive-like responses to food. She reviewed studies associating addictive-like eating (as identified by the YFAS) with various factors (e.g., neural functioning, impulsivity) implicated in an addictive process. Charles O'Brien of the University of Pennsylvania discussed updates to the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5), criteria for substance use disorder (formerly "dependence") and the challenge of applying DSM criteria originally developed for use with drugs to a substance like food. Chapter 3 summarizes these four speakers' presentations and the discussion that followed.

Throughout the workshop, participants expressed varying opinions regarding how to interpret existing evidence from neuroimaging and self-report questionnaires and whether it is appropriate to characterize certain eating behaviors (or foods) as addictive. In the latter half of the workshop, an entire session was organized around counterpoint presentations on whether the drug and alcohol addiction model is appropriate for food. Nicole Avena of Mount Sinai School of Medicine and Peter Rogers of the

University of Bristol, respectively, argued for and against use of the addiction model with food. Chapter 4 summarizes the presentations and discussion that took place during that session.

Much of the workshop discussion revolved around how the brain processes two kinds of food-related signals: (1) satiety signals sent from the digestive system indicating fullness and (2) sensory signals triggered by food in the gut and food cues in the environment. In his concluding presentation, Edmund Rolls of the Oxford Centre for Computational Neuroscience hypothesized that an imbalance between these two systems may contribute to obesity, with sensory signals overriding satiety signals and overstimulating the reward system in the brain. Revisiting Dubé's argument that eating behavior is influenced by the broader context in which the brain and digestive system operate, Rolls suggested that whether the two are imbalanced depends, in part, on "top-down" cognitive processes in the brain that influence how people actually perceive and respond to food rewards. A better understanding of individual differences in sensitivity to food rewards and whether greater sensitivity may contribute to obesity is one of several topics Rolls suggested for future research. Chapter 5 summarizes Rolls's concluding presentation, the concluding panel discussion that followed, and the discussion of strategies for future research.

2

Interaction Between the Brain and the Digestive System

When food enters the mouth and passes through the digestive system, it sends a multitude of interacting signals to the brain, loaded with sensory, nutritive, and other information. In the first session of the workshop, moderated by Danielle Greenberg[1] of PepsiCo, participants discussed how those signals are triggered and how the feedback they provide to the brain impacts further food intake. Workshop participants also considered how higher cognitive functions in the brain, as well as developmental, familial, and environmental factors, influence this complex signaling and feedback system. This chapter summarizes the presentations and discussion of this session, key points from which are highlighted in Box 2-1.

OVERVIEW OF INTERACTIONS BETWEEN THE BRAIN AND THE DIGESTIVE SYSTEM[2]

In his overview of interactions between the brain and digestive system, Timothy Moran focused mainly on signals sent from the gastrointestinal (GI) tract to the brain via the vagus nerve and described how GI peptides released in response to the presence of nutrients trigger vagal nerve activity.

[1] Daniel Greenberg, Ph.D., F.A.C.N., is a Food Forum member and was a member of the workshop planning committee.

[2] This section summarizes the presentation of Timothy Moran, Ph.D., Johns Hopkins University School of Medicine, Baltimore, Maryland.

BOX 2-1
Key Points Made by Individual Speakers

- Timothy Moran explained that the brain receives much of its information about nutrient content and the volume of food consumed from signals sent via the vagus nerve. Vagal fibers in the stomach respond mainly to volume (i.e., stretch and tension), while those in the intestine respond mainly to nutrient content. According to Moran, there is considerable "crosstalk" in the hindbrain between vagal afferent signals and other types of digestive system signals.
- Taste cells in the tongue are among the first cells in the gastrointestinal (GI) tract that come into contact with food. Recently, researchers have identified taste-like cells in the gut and pancreas as well. According to Robert Margolskee, taste-like cells in the gut and pancreas play an important role in integrating physiological responses during digestion.
- As described by Robert Ritter, the gut peptide cholecystokinin reduces food intake by modulating vagal afferent feedback to the brain. According to Ritter, non-GI peptides, such as leptin, and brain neuropeptides can trigger changes in vagal synaptic transmission and help reduce food intake.
- Laurette Dubé urged greater consideration of the broader context within which brain-digestive system interactions operate. Evidence suggests that "higher-level" brain systems and mental processes (i.e., attention, cognition, and free will); the fetal environment and lifelong programming; parenting and other familial influences; and the broader social, commercial, and cultural food environment all can impact food choice and modulate how the brain guides behavior at any given point in time.

Innervation of the GI Tract

The GI tract is innervated both intrinsically and extrinsically. The intrinsic, or enteric, nervous system is embedded in the wall of the digestive tract and is localized primarily in the myenteric plexus and submucosal plexus.[3] The enteric nervous system contributes to overall gastrointestinal motility, nutrient handling, gastric acid secretion, and other functions within the GI tract (Furness, 2012; Mawe and Hoffman, 2013). It is important to note, Moran observed, that when external inputs are cut, that is, when the extrinsic system is denervated, the enteric nervous system still functions and can regulate overall GI function—not in a normal, coordinated way, but in such a way that there is ongoing digestive activity. Thus,

[3] The myenteric plexus and submucosal plexus are networks of neurons located in different areas of the wall of the digestive tract. The myenteric plexus is located between the layers of longitudinal and circular muscle (two layers of muscle involved with propulsive activity within the intestine), while the submucosal plexus is located between the circular muscle layer and the mucosa.

the enteric nervous system is not completely dependent on extrinsic input and can operate in isolation.

Enteric neurons extend across the GI tract and are activated by the presence of nutrients in what Moran described as a "somewhat nutrient-specific" manner, with different nutrients triggering different patterns of activity. Using c-fos, a stainable marker of neural activity, researchers have demonstrated nutrient-induced intrinsic neural activation under a variety of circumstances (Sayegh et al., 2004). Because the same neurons can also be activated by extrinsic activity, with stimulation of vagal afferent fibers (i.e., extrinsic neurons innervating the intestine) producing similar c-fos activation, it is unclear whether nutrient-induced intrinsic effects are an altogether local phenomenon or are dependent in part on stimulation activated by signals from the brain (Zheng and Berthoud, 2000).

Moran emphasized that while intrinsic neural stimulation can be demonstrated under a variety of conditions, it is unclear whether intrinsic neural regulation plays a role in controlling food intake.

Most information received by the brain about GI contents is transmitted via vagal afferent feedback signals. The vagus is one of two major extrinsic innervation sources, the other being the spinal cord (Sengupta, 2006). Spinal cord afferents appear to play more of a role in mediating GI pain than in providing feedback to the brain about nutrient contents, according to Moran.

Vagal Afferent Feedback Signals

Moran described the work of Hans-Rudolf Berthoud and colleagues, which has been instrumental in providing researchers with an understanding of the GI tract's overall vagal afferent innervation. Berthoud and Neuhuber (2000) described three types of vagal afferent endings, each providing a different type of information to the brain: (1) intramuscular array (providing "stretch" information), (2) intraganglionic laminar endings (providing "tension" information), and (3) mucosal terminals (providing "nutrient" information). According to Moran, it has been fairly well demonstrated that intramuscular array terminals measure stretch; that is, as the stomach begins to fill and food enters the small intestine, the presence of that food causes a stretch in the surrounding muscle fibers that activates vagal afferent neurons with intramuscular array endings (Phillips and Powley, 2000). That activation is transmitted to the brain. The intraganglionic laminar endings, which are found primarily in the stomach and in the proximal duodenum, have been hypothesized to measure tension (Phillips and Powley, 2000). The difference between measuring stretch and measuring tension can be confusing, Moran remarked. Stretch is a change in volume, while tension is a change in the surrounding musculature with no change in volume. Many

vagal afferents have both "stretch" and "tension" endings and are able to respond to both stimuli simultaneously. The third type of vagal afferent ending, the mucosal terminal, is located mainly in the intestine, with the endings in close proximity to where nutrients are being absorbed and where various kinds of endocrine cells are releasing their products. "Nutrient" vagal afferents respond to overall nutrient character, not load volume (Berthoud and Neuhuber, 2000; Dockray and Burdyga, 2011).

Vagal afferent innervation of the stomach is different from that of the intestine. In the stomach, the vagal fibers respond primarily to load volume, not chemical composition. According to Moran, it has been demonstrated that single vagal afferent fibers from the stomach become activated when volume is introduced into the stomach (de Lartigue, 2014; Schwartz et al., 1991). Although vagal afferent fibers in the stomach exhibit a range of activity, with some fibers becoming activated in response to small volumes and others requiring larger volumes, together they show a dose–response relationship with load volume: the greater the load volume, the greater the vagal activation. The dose–response relationship is the same regardless of gastric contents (Dockray, 2013; Li, 2007; Mathis et al., 1998; Schwartz and Moran, 1998). Cells innervating the duodenum, on the other hand, show a very different pattern of results, with different contents producing different amounts of activity (e.g., saline versus glucose versus protein).

Gut Peptide Signaling

The small intestine releases a variety of peptides in response to the presence of nutrients. Using cholecystokinin (CCK) as an example, Moran explored the role played by many gut peptides in regulating food intake by mediating the response between nutrient activity in the small intestine and vagal afferent signaling (see Figure 2-1).

Peptides released from endocrine cells in the small intestine can either enter the bloodstream and travel to a distal target cell (i.e., endocrine signaling) or activate a closely located target cell (i.e., paracrine signaling) (Dockray, 2013; Krstic, 1984). Berthoud and colleagues have demonstrated that vagal afferent nerve fibers innervating the gut are located near endocrine cells in the intestinal villae that release CCK in response to the presence of nutrients in the intestinal lumen (Berthoud and Patterson, 1996; Berthoud et al., 1995; Dockray, 2012; Patterson et al., 2002). According to Moran, it has been further demonstrated that, indeed, activation of those very closely located vagal fibers is mediated by CCK release.

Although gastric fibers respond mainly to gastric load, not nutrient content, and intestinal fibers to nutrient content, not load, it has been demonstrated that nutrient activity in the intestine also results in increased activity in fibers innervating the stomach (Schwartz and Moran, 1998;

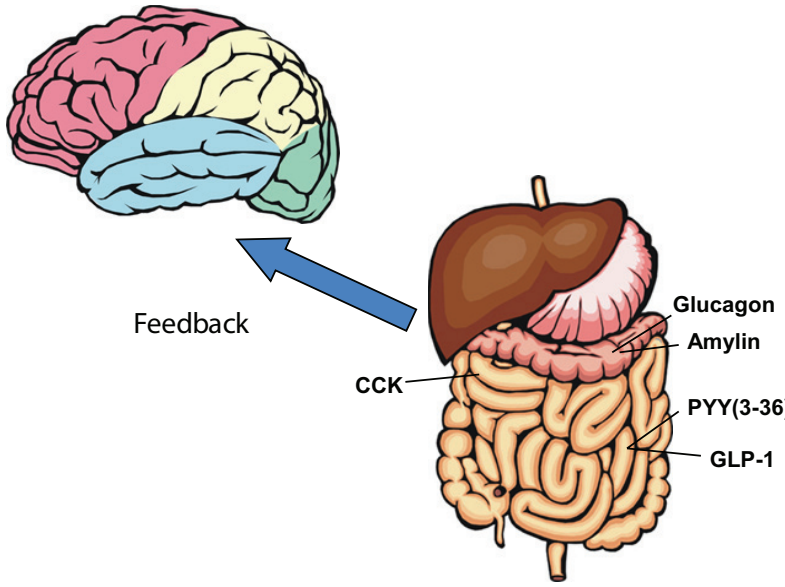


FIGURE 2-1 Much of the feedback received by the brain from the gastrointestinal tract (GI) tract is mediated by peptides released in the gut in response to the presence of nutrients.
NOTE: CCK = cholecystokinin; GLP-1 = glucagon-like peptide-1; PYY = peptide tyrosine tyrosine.
SOURCE: Moran, 2014.

Schwartz et al., 1993) (see Figure 2-2). According to Moran, it is unclear whether that response in the stomach is due to a vagovagal reflex, with signals sent from the intestine to the hindbrain altering gastric tone, or to nutrient-induced release of a peptide in the intestine that circulates and activates the gastric fibers. The effects of load volume and CCK in the stomach appear to be additive, according to Moran. Subthreshold doses of CCK that by themselves are too weak to stimulate vagal afferent activity can stimulate such activity in combination with load volumes.

The ability of CCK to reduce food intake requires an intact vagus nerve. Scientists have shown in rats that removing or cutting the vagal afferent nerves blocks CCK satiety and under some circumstances increases the volume of food consumed.

Crosstalk in the Hindbrain

The vagus nerve enters the brain in an area of the brain known as the caudal medulla, with the vagal afferents and vagal efferents entering struc-

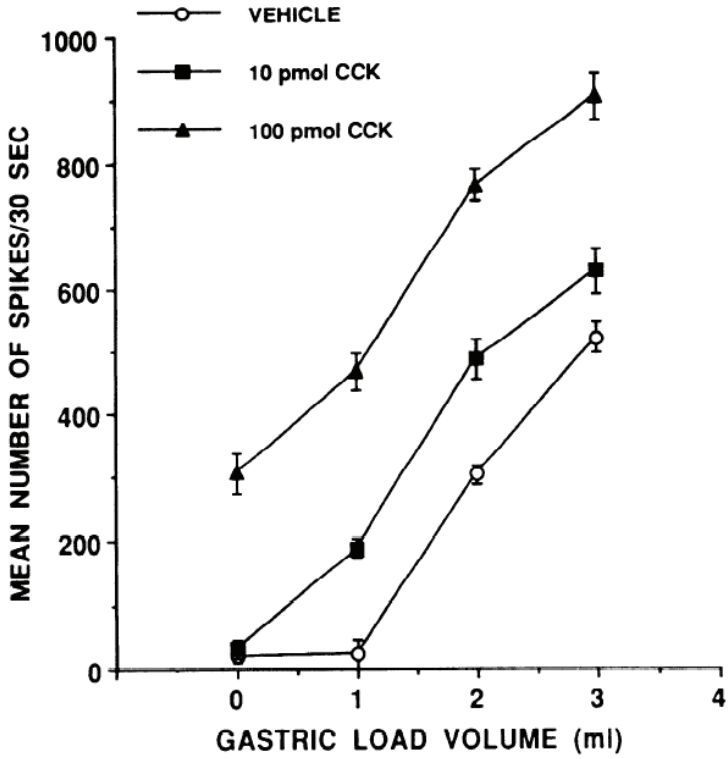


FIGURE 2-2 Cholecystokinin (CCK), a peptide released in the intestine, magnifies the response to gastric load in gastric mechanosensitive fibers.
SOURCE: Reprinted with permission from Schwartz, G. J., P. R. McHugh, and T. H. Moran. 1993. Gastric loads and cholecystokinin synergistically stimulate rat gastric vagal afferents. *American Journal of Physiology* 265(4 Pt. 2):R872-R876.

tures that are immediately adjacent to each other: the vagal afferents enter the nucleus of the solitary tract or nucleus tractus solitarii (NTS), while the vagal efferents enter the dorsal motor nucleus. The adjacency of the vagal afferents and efferents is what allows for some of the vagovagal reflexes that Moran suspects may contribute to some vagal afferent responses. A great deal of what he described as "crosstalk" takes place between the NTS and the dorsal motor nucleus (where the vagal efferents enter), with incoming information from the NTS altering the activity of vagal efferent cell bodies located in the dorsal motor nucleus.

The NTS receives not only information from vagal afferents from the stomach and intestine, but also vagal inputs from the liver and from taste

receptors in the oral cavity. Curious about whether isolating and stimulating individual components of the complex array of signals converging in the NTS would reflect what normally occurs during a meal, Moran and colleagues compared c-fos activation in a real versus a sham feeding[4] situation (Emond et al., 2001). They observed a much greater degree of activation in the taste region of the NTS in the sham feeding situation, suggesting that the brain processes and responds to oral signals differently depending on where in the GI tract nutrients are present. Other kinds of alterations (e.g., nutrients being placed directly into the stomach versus normal feeding through the mouth) have shown similar changes in brain activation (Emond et al., 2001).

HOW TASTE RECEPTORS IN THE GUT INFLUENCE EATING BEHAVIOR[5]

Taste cells in the tongue are among the first cells in the GI tract that come into contact with food. Only recently have scientists discovered taste-like cells in the gut as well. Robert Margolskee provided an overview of taste receptors in the oral cavity and discussed recent research on taste-like receptors in the gut.

Taste Receptors in the Oral Cavity

Oral taste buds—collections of about 50 to 100 specialized epithelial cells—are scattered throughout the oral cavity, primarily in papillae[6] on the front, sides, and back of the tongue. Although oral taste buds are not neurons, they have a number of neuronal properties. Much of the taste transduction cellular machinery is contained within the fingerlike microvilli coating the apical end of each taste bud cell.

Margolskee explained that scientists have identified several different types of taste receptors in the oral cavity, each having a unique taste receptor molecule or set of molecules underlying the taste response (Lindemann, 2001). Over the past decade, work from Margolskee's laboratory, as well as the laboratories of Linda Buck, Nick Ryba, and Charles Zucker, has led to identification of many of the different taste quality receptors. Today, researchers know that the bitter taste receptors involve a family of about 25

[4] Sham feeding involves providing an animal with a liquid diet, which descends through the esophagus but immediately drains out from the stomach, thereby eliminating gastric stretch and intestinal stimulation.

[5] This section summarizes the presentation of Robert Margolskee, M.D., Ph.D., Monell Chemical Senses Center, Philadelphia, Pennsylvania.

[6] Papillae are small structures on the upper surface of the tongue.

to 30 G protein-coupled receptors[7] called the T2Rs (type 2 taste receptors). Sweet receptors, in contrast, involve a dimeric or multimeric combination of T1R2 (type 1 receptor 2) and T1R3 (type 1 receptor 3) receptors, which together respond to a number of sweet compounds, both sugars and noncaloric sweeteners. A related receptor, the umami receptor, involves a combination of T1R1 (type 1 receptor 1) and T1R3 receptors and responds to "savory" tastes such as monosodium glutamate.

The sour and salty taste transduction channels are not as well understood as the bitter, sweet, and umami channels, said Margolskee. Although ENaC[8] certainly plays a role in salty taste transduction, it is involved more with low concentrations of salt. There is likely at least one other transduction channel, as yet unidentified, for high concentrations of salt. The sour taste receptor has a number of candidate channels, including acid-sensing ion channels (ASICs), hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, and polycystic kidney disease (PKD) family member channels, but no one channel has yet been definitively identified.

Taste-Like Cells in the Gut (and Pancreas)

As summarized by Margolskee, researchers recently have identified taste-like cells in the gut that play an important role in integrating physiological responses during digestion. Taste-like cells in the gut are not actual taste cells, although they have a number of characteristics in common with true oral taste cells: they are morphologically similar under both light and electron microscopy and produce many of the same taste signaling proteins. Indeed, the signaling process that occurs in certain types of endocrine cells in the gut is very similar to the transduction process that occurs in oral taste cells (Cummings and Overduin, 2007) (see Figure 2-3). In both types of cells, when G protein-coupled receptors at the apical surface of the cell couple with gustducin and other taste-associated G proteins, they initiate a signal transduction cascade involving multiple signaling enzymes, second messengers (e.g., inositol triphosphate), and channels (e.g., the calcium-activated TRPM5 channel), ultimately leading to neurotransmitter or, in the case of taste-like cells, neuropeptide release. Margolskee explained that one of the differences between taste receptors in the oral cavity and taste-like receptors in the gut is that instead of releasing a true neurotransmitter, taste-like receptors in the gut release neuropeptide hormones, such as GLP-1 (glucagon-like peptide-1).

[7] G protein-coupled receptors are proteins located in the cell membrane that bind extracellular substances and transmit signals from those substances to an intracellular molecule known as a G protein.

[8] ENaC is the epithelial sodium channel, a membrane-bound channel permeable to sodium ions and other substances.

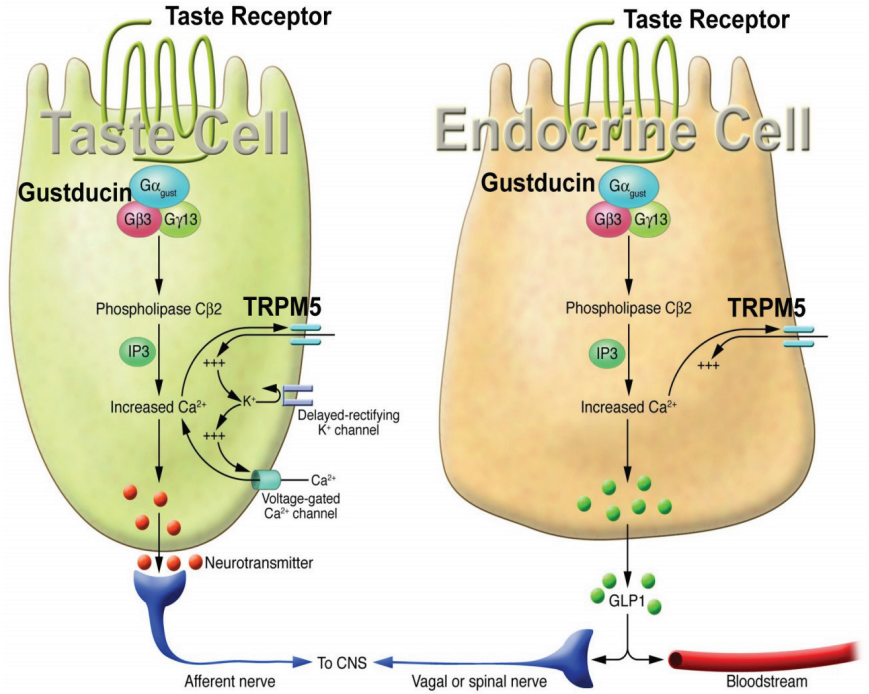


FIGURE 2-3 Oral taste cells ("taste cell") and gut taste-like cells ("endocrine cell") share similar signaling processes.
SOURCE: Modified from Cummings and Overduin, 2007. Reprinted with permission of the American Society for Clincial Investigation, from "Gastrointestinal regulation of food intake," D. E. Cummings and J. Overduin. *Journal of Clinical Investigation* 117(1):13-23, 2007; permission conveyed through Copyright Clearance Center, Inc.

Margolskee went on to explain that the idea that taste signaling molecules exist in the gut dates back to the mid-1990s, when Dirk Höfer discovered alpha-gustducin (the alpha subunit of the heterotrimeric gustducin protein) being expressed in stomach and intestinal cells that had the general appearance of taste receptor cells (Höfer et al., 1996). Subsequently, Enrique Rozengurt's group identified a number of T2R bitter taste receptors in the stomach and small intestine (Wu et al., 2002). Later, Soraya Shirazi-Beechey found T1R receptors in the gut (Dyer et al., 2005).

In more detailed microscopic studies, Shirazi-Beechey and Margolskee collaborated and found that both T1R2 and T1R3, the two components of the sweet receptor, are present in a small subset of cells lining the small intestinal mucosa and that the cells have the typical appearance of entero-

endocrine cells (Margolskee et al., 2007). Margolskee and his team also collaborated with Josephine Egan at the National Institutes of Health and identified several taste signaling proteins in both human and mouse tissues. They also found essentially the entire taste transduction pathway as it was known to exist in oral taste cells, in gut endocrine cells, and particularly in L cells expressing GLP-1 (Jang et al., 2007).

More recently, Yan Li in Margolskee's laboratory examined co-expression of gustducin-positive endocrine cells from various locations in the small and large intestines and found a roughly equal level of L, K, and L/K co-expression[9] with gustducin in the colon but mainly only K or L/K cells co-expressing with gustducin in other areas (Li et al., 2013). Li also found a number of short chain fatty acids co-expressed with alpha-gustducin in endocrine cells in the colon, including cells activated by the G protein-coupled receptors GPR43 and GPR41. Curious about the potential physiological role of gustducin in the colon, she turned to gustducin knock-out mice and found that short chain fatty acid–stimulated GLP-1 secretion from colon endocrine cells requires alpha-gustducin.

In other collaborative work between Margolskee's laboratory and Shirazi-Beechey's group, the researchers examined SGLT1 (sodium glucose co-transporter 1) expression in two types of knockout mice (Margolskee et al., 2007). SGLT1 is a protein that co-transports glucose and sodium from the gut lumen across the absorptive enterocytes and into the epithelial cells. According to Margolskee, this is typically the rate-limiting step for glucose uptake in the small intestine. Margolskee, Shirazi-Beechey, and colleagues found that SGLT1 mRNA (messenger RNA), SGLT1 protein expression, and glucose uptake activity in wild-type mice all increased when the mice were treated with a high-carbohydrate diet compared with a low-carbohydrate diet. But in knockout mice missing T1R3, a component of both the sweet and umami receptors, there was no difference in SGLT1 between the low- and high-carbohydrate diets. Likewise with gustducin knockout mice, the research revealed no difference in SGLT1 mRNA or protein or glucose uptake activity between the low- and high-carbohydrate diets. According to Margolskee, the evidence suggests that both T1R3 and gustducin are necessary to elicit an increase in SGLT1 in response to dietary carbohydrate and a subsequent increase in glucose uptake activity.

Margolskee described a similar effect observed in knockout mice fed either a low-carbohydrate diet alone or a low-carbohydrate diet supplemented with a noncaloric sweetener (i.e., sucralose) (Margolskee et al., 2007). Wild-type mice showed an increase in SGLT1 mRNA, SGLT1 protein, and glucose uptake activity when their low-carbohydrate diet

[9] L and K cells are types of intestinal enteroendocrine cells. L cells secrete GLP-1; K cells secrete gastric inhibitory peptide (GIP).

was supplemented with a noncaloric sweetener, but knockout mice did not. These results indicate a chemosensory detection pathway in the gut that responds to luminal sugars and luminal sweeteners and leads to the up-regulation of SGLT1 and an increase in glucose uptake activity across the gut.

Margolskee and others have found taste-like receptors not just in the stomach and intestine but also in the pancreas. Margolskee described unpublished data showing the expression of gustducin in pancreatic islet alpha cells and the expression of T1R3 in both alpha and beta cells. The function of these pancreas taste-like receptors is unclear. However, both in vitro data and data from wild-type versus T1R3 knockout mice suggest that these receptors play a role in sweetener-enhanced insulin release.

Oral Taste Cells and the Expression of Gut Proteins

Margolskee noted that researchers have observed a number of gut hormones, including GLP1, GIP (gastric inhibitory peptide), and CCK, expressed in multiple types of oral taste cells. Oral taste cells also express intestinal sugar sensors, such as SGLT1, and pancreatic metabolic sensors (Yee et al., 2011).

Margolskee gave an example of the expression of gut proteins in the oral cavity. Based on studies with T1R3 knockout mice showing a loss of response to noncaloric sweeteners but not to sugars (Damak et al., 2003), he and his colleagues suspected that something else in the oral cavity besides the oral sweet receptor, a T1R2 and T1R3 heterodimer, responds to sugars. They hypothesized the presence of a glucose transport pathway similar to what has been observed in pancreatic beta cells. Indeed, they found that a number of the same pancreatic pathway components were present in oral taste tissue (Yee et al., 2011). Margolskee speculated that gut-like glucose transporters in taste cells may help people and animals distinguish caloric from noncaloric sweeteners.

Taste-Like Receptors in the Gut and Pancreas: Summary of the Science

In summary, Margolskee noted that researchers have identified whole taste signaling pathways in both the gut and pancreas and in both the proximal and distal gut. In the gut, taste elements are expressed in L, K, and L/K cells. In the pancreas, both pancreatic islet alpha and beta cells express taste elements. Gustducin and T1R3 in the gut are involved in the release of GLP-1 and GIP in response to sweeteners and, in the proximal gut, in the regulation of SGLT1 levels. In the colon, gustducin appears to be involved in the release of GLP-1 and GIP in response to short-chain fatty acids. With regard to the role of taste signaling molecules in the pancreas, preliminary

evidence suggests that gustducin and T1R3 are involved in sweetener detection and, under some circumstances, insulin secretion.

GASTROINTESTINAL PEPTIDES, VAGAL AFFERENT SYNAPSES, AND NEURAL MECHANISMS OF SATIATION[10]

Robert Ritter elaborated on information and ideas presented earlier by Timothy Moran and explored in more detail how GI peptides, CCK in particular, provide the brain with information that contributes to the process of satiation and reduces food intake. He focused on CCK because scientists know more about how it modulates vagal afferent activity compared with what is known about other GI peptides.

GI Peptides

GI peptides are localized in specialized enteroendocrine cells scattered among the cells of the absorptive and secretory mucosa of the GI tract, from the stomach through the colon. Nerve fibers pass through the extracellular space beneath the mucosa, into which GI peptide secretion occurs, creating the opportunity for both endocrine and neuronal peptide actions. According to Ritter, although the actions of some GI peptides were discovered in the early 20th century (e.g., 1902 for secretin and 1905 for gastrin), none of the GI peptides were identified as peptides per se until the 1960s and 1970s, when they were synthesized and sequenced. A dozen or more GI peptides have been identified to date. Several are involved in control of food intake, including CCK, which is secreted in the proximal small intestine, and GLP-1, PYY 3-36 (peptide tyrosine tyrosine), and oxyntomodulin, all of which are secreted by L cells in the more distal small intestine and large intestine. CCK, GLP-1, PYY 3-36, and oxyntomodulin all reduce food intake (e.g., Chelikani et al., 2005; Ritter, 2010). Ghrelin, which is released from cells in the gastric mucosa, increases food intake.

Ritter went on to explain that after their secretion from enteroendocrine cells, GI peptides in the blood can broadcast a signal to any tissue with a matching receptor, including tissues in GI organs where the peptides help coordinate digestive function. Early during the digestive process, they contribute to slowing gastric emptying and stimulating pancreatic secretion of enzymes and bicarbonate. Later they facilitate secretion of insulin and the postabsorptive assimilation of nutrients (see the review by Rehfeld, 2011). GI peptides also play an important role in limiting food intake. In Ritter's opinion, food intake can be viewed as yet another part of the digestive

[10] This section summarizes the presentation of Robert Ritter, V.M.D., Ph.D., Washington State University, Pullman.

process, given that reducing food intake limits the inflow of food into the digestive tract during a meal and thereby facilitates the efficient digestion and absorption of what has been eaten. In addition to their impact on GI tissues, GI peptides act on the brain and innervation of the GI tract (see reviews by Banks, 2008; de Lartigue, 2014; and Schwartz, 2010).

According to Ritter, a hallmark of GI peptides is that their secretion and levels in circulation are controlled by nutrients in the GI tract during a meal. When a meal is eaten, levels of GI peptides in the blood rise dramatically (Ellrichmann et al., 2008). Initially, upon entry of nutrients into the intestine, CCK levels rise rapidly to six or seven times their fasting level. Soon thereafter, GLP-1 and PYY 3-36 levels rise as well. The initial rapid rise in CCK levels has been shown to facilitate the release of the other peptides in anticipation of actual direct stimulation of their secretion by nutrients as food moves down through the intestine.

Another hallmark of GI peptides, according to Ritter, is that their impact on the control of food intake is focused on limiting the size and duration of an ingested meal. CCK, GLP-1, and PYY 3-36 all reduce food intake, primarily by reducing meal size and meal duration rather than by decreasing the number of meals initiated (see the review by Ritter, 2010).

The Cellular Mechanisms by Which GI Peptides Modulate Vagal Afferent Activity

Ritter elaborated on what Moran had discussed about CCK reducing food intake through its effect on vagal afferent neurons. According to Ritter, a vagal mode of action characterizes not only CCK but most other GI peptides as well; in fact, their ability to reduce food intake is attenuated or virtually abolished when the abdominal vagus nerve is cut. For ghrelin, however, the stimulatory effect on food intake is more complicated. According to Ritter, ghrelin appears to antagonize the excitatory effects of some of the other GI peptides on vagal afferent firing, although a role for the vagus in actually mediating the increase in food intake through ghrelin is doubtful.

All vagal afferents release glutamate, a neurotransmitter, in the hindbrain. Thus, not surprisingly in Ritter's opinion, CCK-induced reduction of food intake has been shown to be sensitive to antagonism of glutamate receptors in the hindbrain. In fact, antagonism of NMDA-type (*N*-methyl-D-aspartate) glutamate receptors with selective receptor antagonists injected directly into the hindbrain reverses or prevents reduction of food intake by exogenously administered CCK (Wright et al., 2011).

An interesting feature of vagal afferent fibers, according to Ritter, is their very quick release of all available neurotransmitters and failure over time. Susan Appleyard has shown that upon stimulation of vagal afferent

inputs, postsynaptic cells fire but then fail; however, their failure can be reversed by local application of CCK (Appleyard et al., 2005).

In terms of the specific cellular mechanism by which CCK enhances vagal afferent transmission, Ritter has found that CCK activates an enzyme, an extracellular receptor kinase, that phosphorylates synapsin. Synapsins are proteins that bind synaptic vesicles to the cytoskeleton of the neuron; they help control the availability of neurotransmitters for release. When phosphorylated, synaptic vesicles are freed from the cytoskeleton and the availability of transmitters for release is increased. When dephosphorylated, the vesicles remain bound to the cytoskeleton of the neuron and fewer transmitters are available for release (Cesca et al., 2010). Normally, CCK reduces food intake for only a short period of time, about 30 minutes, but inhibiting dephosphorylation of synapsin can extend and enhance the ability of CCK to reduce meal size (Campos et al., 2013). According to Ritter, it is not yet known whether other GI peptides operate in a similar way.

The Impact of Non-GI Proteins on Food Intake

Ritter emphasized that the GI signals controlling food intake are directly related to food that has just been consumed and is in the process of being digested and absorbed. However, other parts of the physiology of an organism provide the brain with indirect information about metabolism that can also impact food intake. Notable among these, said Ritter, is leptin, a protein produced by adipose tissue. Injection of leptin into rats and mice dramatically reduces food intake by reducing meal size, with administration over days or weeks leading to weight loss (Kahler et al., 1998).

Given that leptin acts on the brain to produce reductions in meal size in a manner very similar to that of feedback signals from GI tract hormones such as CCK, Ritter and his colleagues were driven to ask whether vagal afferent function is modulated in any way by leptin. Indeed, interaction between leptin and gut hormones begins in the GI tract, at the peripheral vagal afferents. About 45 percent of vagal afferents that innervate the stomach and small intestine express both CCK and leptin receptors (Peters et al., 2006). It has been shown that leptin and CCK can enhance each other's action, with the combined administration of subthreshold doses of both substances resulting in reduced meal size (i.e., when administered alone, subthreshold doses of either do not reduce meal size) (Peters et al., 2005).

Nevertheless, according to Ritter, there is good evidence that leptin produces major effects on food intake by acting on the hypothalamus, where it activates what are known as POMC (pro-opiomelanocortin) neurons and increases release of alpha-melanocyte-stimulating hormone (alpha-MSH), which then acts on the melanocortin-4 (MC4) receptor (see the review by Ellacot and Cone, 2004). Of interest, Ritter noted, antagonism of the MC4

receptor also attenuates the response to CCK (Sutton et al., 2005; van Swieten et al., 2014).

Ritter and his colleagues have hypothesized that the modulatory effect of leptin occurs at the vagal afferent terminal itself. Evidence to this effect includes MC4 receptor expression by vagal afferents (Wan et al., 2008) and close interaction between vagal afferent neurons and POMC fibers in the hindbrain. Indeed, Campos and colleagues (2014) demonstrated that POMC neurons act at receptors at the first presynaptic element in the visceral afferent communication pathway and that administration of an MC4 agonist into the hindbrain can elevate phosphorylation of synapsin for hours. The ultimate effect, Ritter explained, is that leptin-initiated activation of MC4 enhances vagal afferent transmission and normally, transmission from the vagal afferents to the hindbrain experiences about a 70 percent failure rate. Activation of the MC4 receptor cuts that rate in half. It also decreases the rate of decline of the amplitude of postsynaptic depolarizations that occur in response to vagal stimulation. Essentially, then, MC4 activation increases the fidelity and strength of vagal afferent transmission.

Conclusion

Based on this growing body of evidence, Ritter proposed a model in need of further study: CCK and other gut peptides activate vagal afferents and provide the primary signal for satiation, but the signal is modulated by leptin and perhaps other endocrine signals. Ritter described the vagal afferent ending as a "paintbrush that paints the . . . sensory process of satiety . . . on the hindbrain."

Ritter concluded by emphasizing that several GI peptides are involved with food intake and that they all interact with each other as well as with relevant non-GI hormones to reduce food intake. One of the places where they interact is the first visceral afferent synapse in the nucleus of the solitary tract of the hindbrain, which, he said, is where the experience of satiation begins.

CONTEXTUAL INFLUENCES ON EATING BEHAVIOR[11]

Laurette Dubé considered the different levels of context within which brain-digestive system interactions operate. Specifically, she considered how "higher-level" brain systems and mental processes (i.e., attention, cognition, and free will); the fetal environment and lifelong programming; parenting

[11] This section summarizes the presentation of Laurette Dubé, Ph.D., M.P.S., M.B.A., McGill University, Montreal, Quebec, Canada.

and other familial influences; and the broader social, commercial, and cultural food environment can impact eating behavior.

Impact of "Higher-Level" Brain Systems and Mental Processes on Eating Behavior

"Higher-level" brain systems bearing on cognitive, reward learning, and executive control processes serve as the first-level context within which brain-digestive system interactions operate. Dubé referred workshop participants to two recent reviews of scientists' understanding of that context: (1) Dagher (2012), on brain regions activated during functional magnetic resonance imaging (fMRI) studies of food cue reactivity, and (2) Vainik et al. (2013), on neural behavioral correlates with eating behavior and body mass index (BMI).

Dubé then described in detail two empirical studies she and her colleagues conducted based on the Dutch Eating Behavior Questionnaire (DEBQ), used to assess three types of eating behaviors: restrained, emotional, and external (van Strien et al., 1986). External eating involves a predisposition to ignoring homeostatic signals and reacting primarily to external hedonic cues (Burton et al., 2007; Rodin and Slochower, 1976). Together, the results of these two studies suggest to Dubé that as scientists move forward in their quest to understand eating behavior, they need to study more closely the interactions among the rewarding, executive, and homeostatic control regions of the brain and their psychological and behavioral correlates.

In the first study (unpublished) Dubé described, her research team asked participants to come to the laboratory and work on a puzzle. While working on the puzzle, the participants were interrupted six times to eat chocolate. Some participants were instructed to remain focused on the experience of eating chocolate, others to continue working on the puzzle. The researchers evaluated impact on consumption by measuring self-reported hunger before and after consumption. They found that high-external eaters behaved as expected based on reports in the literature; that is, they experienced a much more intense hedonic response and only a small change in hunger before and after consumption. Low-external eaters, in contrast, experienced a significant decline in hunger before and after consumption when distracted by the puzzle task and not focused on the sensory experience of eating chocolate. This finding reflects their individual predisposition to rely on biological processes more than on environmental cues. When asked to focus on the chocolate, however, low-external eaters experienced no decrease in hunger, their attention to sensory cues seemingly interfering with usual biological signals.

In the second study (Lebel et al., 2008), Dubé and colleagues evaluated change in hunger and fullness before and after consumption among "high

schematics" versus "low schematics." High-schematic eaters score high for all three DEBQ types of eating and are driven by both emotion and external cues, but also show cognitive restraint. In other words, their eating behavior is driven by a full array of mental schemata, attempting to overrule biological processes. Low-schematic eaters score low on all three types of eating. Participants were asked to provide self-reports of hunger and fullness both before and after consuming "comfort food." The researchers found no difference in hunger between the high and low schematics either before or after consumption. However, they did find significant differences in preconsumption fullness and change in fullness (between pre- and postconsumption), with high schematics reporting greater preconsumption fullness and a smaller change in fullness upon eating, and low schematics reporting being less full before consumption and experiencing a greater change in fullness upon eating.

In a third study, Finkelstein and Fishbach (2010) provided participants with a chocolate bar and framed the food as either "healthy" (i.e., chocolate health bar) or "tasty" (i.e., chocolate candy bar). Participants also were either told that their job was to taste the bar (imposed consumption) or asked whether they would like to try it (free choice). The researchers found that participants who were told that the bar was tasty reported similar levels of hunger after consumption regardless of whether consumption was imposed or they were given free choice. In contrast, participants who were told that the bar was healthy reported significantly greater hunger after consumption when consumption was imposed compared with when they were given free choice. Again, for Dubé, these results highlight the need for scientific study of eating behavior and the complex interplay among different brain systems within a broader behavioral context.

Impact of the Fetal Environment on Eating Behavior

Dubé characterized the fetal environment as a key context in biology and behavior. She pointed to the Barker hypothesis as an example. Barker (1990) hypothesized that low birth weight is associated with increased risk of metabolic syndrome, diabetes, and obesity later in life. Dubé pointed workshop participants to a forthcoming review in the *Annals of the New York Academy of Sciences* on intrauterine growth restriction (IUGR) and its impact later in life.

In fact, researchers are finding correlations between IUGR and eating behavior not just later in life but early on as well. A study of 24-year-old women who had been observed over their lifetime showed that low-birth-weight women were consuming more carbohydrates and had higher BMIs (Barbieri et al., 2009). Meanwhile, a study of 27-week-old preterm newborn babies showed that low-birth-weight babies reacted less to sensitivity

tests, postulated as being due to increased need, compared with non-low-birth-weight babies of the same gestational age (Ayres et al., 2012). Numerous other studies have found similar correlations across a wide range of ages (e.g., Crume et al., 2014; Escobar et al., 2014; Kaseva et al., 2013; Lussana et al., 2008; Perälä et al., 2012; Stein et al., 2009).

Dubé and colleagues recently collected self-reported birth weight data for 616 children aged 6 to 12 years from both the children and their mothers and used the DEBQ to measure eating behaviors and daily food consumption. They found that low-birth-weight children showed the same pattern as in the previous literature, with higher consumption of fat and sugar (manuscript under review). They also examined high-birth-weight children—that is, children born with high BMIs—and found that the high-birth-weight children showed more restrained eating and more emotional eating (as defined by the DEBQ) compared with controls, but no difference in external eating (manuscript under review). According to Dubé, both increased restricted eating and increased emotional eating are associated with obesity and high BMIs.

Impact of the Parental/Familial/Home Environment on Eating Behavior

In the same cohort of 616 children aged 6 to 12 years discussed above, Dubé and colleagues also measured attachment (Muris et al., 2001). Attachment is an extensively studied construct in both animals and humans, Dubé explained, with a measure of attachment providing information about the role of the primary caregiver in defining how an animal or person decides to explore beyond what has been programmed at birth. More secure attachment allows child and adult alike to engage with confidence in novel activities, including exploring alternatives to biological programming such as an innate liking for sugar (typical of high-calorie food) and dislike of bitter foods (which typically encompass many nutritious foods, including vegetables). Using 24-hour recall not just for food but also for other healthy and unhealthy eating-related habits, Dubé and colleagues found that children with insecure attachment experienced high eating schematicity for all three DEBQ eating behaviors; greater consumption of salty snacks; lower consumption of water and fruit; and greater likelihood of skipping breakfast, eating out, and eating in front of the television during weekdays. In Dubé's opinion, these findings suggest that more attention should be paid, in both research and practice, to exploring how the early home environment influences a life course of eating behavior.

Other relevant findings include Puhl and Schwartz's (2003) report that parental food rules can influence eating behavior, with some parents using food to reward or punish and encourage or discourage good or bad noneating behavior. Parents applying a control food rule typically use high-calorie

food to encourage good behavior. Dubé cited a study showing higher caloric content, fat, and sugar in the diets of children exposed to parental food control rules. This effect was stronger for children (in particular boys) with an individual predisposition to being responsive to rewarding environmental cues as indexed by the Behavioral Activation System (BAS) scale, with children scoring on the high end of the scale tending to be more sensitive to reward (Carver and White, 1994). Dubé cited Côté and Moskowitz (1998), Lu et al. (2011), and Stroebele and De Castro (2004) as additional relevant studies.

Impact of the Broader Social, Commercial, and Cultural Environment on Eating Behavior

Dubé explained that plentiful correlational evidence collected at the population level over the past few decades links changes in eating behavior and BMI with various changes in the food environment. Examples are the increased availability of processed food, typically with high fat, sugar, and salt content, and increased food advertising (Buijzen et al., 2008; Dhar and Baylis, 2011; Foster et al., 2014; Franco et al., 2009; Kunkel et al., 2004; Powell and Bao, 2009; Powell et al., 2007; Scott et al., 2008).

Dubé argued that it is necessary to examine the effects of the food environment on individual and social processes. She reported results of a study conducted in the Montreal metropolitan area (Buckeridge et al., 2014) that found a correlation between area-level carbonated soft drink sales and median personal income. A decrease of $10,000 in income was associated with almost a five-fold increase in soft drink sales. In another study conducted in Montreal, an individual food environment was defined by a buffer zone around a person's residential address (Paquet et al., 2010). That study demonstrated interactive effects between the density of fast-food restaurants and eating behavior. Individuals scoring low on the BAS were not influenced by the density of fast-food restaurants, while those scoring high on the BAS consumed more fast food when exposed to a higher density of fast-food restaurants. Dubé urged more such studies. She encouraged the use of geographic information systems (GISs) to aid in examining multiple layers of data for the same geographic area.

The Brain-to-Society Model of Eating Behavior

For almost 10 years now, Dubé has been leading a network of McGill University and other scientists in studying eating behavior in its broader context. Together, they developed the Brain-to-Society (BtS) model of eating behavior (Dubé et al., 2008, 2010). The BtS model is based on the premise that eating is a neurobehavior that operates in contexts on different sec-

toral, temporal, and geographic scales. Not only does each contextual level need to be studied by itself in depth, Dubé opined, but the different levels also need to be studied in combination through a systems science framework (Dubé et al., 2012; Hammond and Dubé, 2012).

DISCUSSION WITH THE AUDIENCE

Following Dubé's presentation, the speakers in session 1 participated in a panel discussion with the audience. Questions from the audience spanned a wide range of topics.

Nutrient-Specific Signaling: What Does the Science Say?

During his presentation, Moran had emphasized that vagal afferents innervating the stomach were stimulated by load volume, not content. A member of the audience observed that Moran had presented gastric load data from experiments using glucose and asked whether other macronutrients produced the same effect. Moran replied that he and his research team compared glucose and casein and observed no difference. Additionally, in experiments using pyloric cuffs,[12] no differences in subsequent food intake were observed across loads of different nutrient characters (Phillips and Powley, 1996). Moran reiterated that in the stomach, the reduced food intake response is a response to gastric volume. He pointed to work showing that in the intestine, on the other hand, nutrient content can be sensed and can guide behavior (Sclafani and Akroff, 2012).

While the discussion was on the topic of nutrient-specific responses, Margolskee was asked whether any other macronutrients produce taste-like responses similar to what he and his colleagues observed with the sweet taste-like receptor and response. Margolskee replied that he and his team observed responses in the proximal gut to sugars and sweeteners, triggering the release of the gut hormones GLP-1 and GIP. But in the distal gut, where one would not expect sugars to be reaching, they observed at least some association with short-chain fatty acid responses leading to release of GLP-1 (Li et al., 2013). In Margolskee's opinion, then, different macronutrients do in fact trigger taste-like responses depending on where in the gut the GLP-1–producing L and GIP-producing K cells are located.

With respect to bitter taste, Margolskee said, the evidence for expression of the bitter T2R receptor in the gut is weaker than the evidence for the sweet taste receptor molecules, as is the evidence for a physiological role for bitter taste-like receptors in the gut. With respect to salt, there is good

[12] A pyloric cuff is a device used to tighten the pylorus and prevent food from leaving the stomach, allowing researchers to separate gastric from intestinal factors.

evidence that ENaC is involved in a low sodium concentration response in the oral cavity. Also in the oral cavity, there is likely a different, still unidentified receptor involved in a high sodium concentration response. But according to Margolskee, it is unclear how what is happening in the oral cavity relates to salt-responding cells in the gut.

Taste and Taste-Like Cells: What Does the Science Say?

Several questions were raised about taste and taste-like cells. First, an audience member asked whether tastes have differential effects on reward and subsequent eating behavior. For example, would subsequent eating behavior differ if umami were placed in the gut instead of glucose? And do different amino acids placed in the gut have different satiety potency? The audience member cited evidence from Kunio Torii that monosodium glutamate is particularly effective in the gut in producing satiety and controlling dietary-induced obesity (Yasumatsu et al., 2012). Noting that the umami oral taste system in rats appears to be more specifically sensitive to monosodium glutamate relative to other amino acids than is the case in humans, he asked whether the same is true of the umami gut system.

Margolskee remarked that the umami taste system is highly complex, even in the oral cavity. In addition to significant differences in umami receptors, T1R1 and T1R3, in the oral cavity of rodents versus humans, which may explain some sensory differences between rodent and human preferences for particular amino acids, there is good evidence to suggest that other receptors play a role as well. But it is difficult to tease apart which receptors are involved with which amino acids. In Margolskee's opinion, this is likely as true of umami receptors in the gut as of those in the oral cavity. That being said, while taste receptors in the oral cavity are "pretty good" at distinguishing one nutrient from another—that is, sweet from salty from bitter from umami and so on—preliminary evidence suggests that the gut taste-like receptors may not be as sensitive. Some taste-like cells appear to have both sweet and umami receptors, for example, or both sweet and bitter receptors. Margolskee suggested that some taste-like calls in the gut may be more generalist chemosensory cells rather than what he referred to as "segregationist" cells.

During his presentation, Margolskee briefly touched on the existence and role of taste-like receptors in the pancreas. An audience member asked whether the same pancreatic response that has been observed in wild-type mice—that is, that sucralose promotes insulin release—would be expected in mice or rats that are prediabetic or have type 1 diabetes. Margolskee replied that one would expect the same kind of response, but the question has not been studied.

Margolskee also was asked about oral sensory detection of fat and its effects on physiology. Whether fat is a real taste is still controversial,

Margolskee said; there are some fat receptor candidates, but the evidence is "complicated" and "messy." In his opinion, there is a fat taste and probably an appetitive fat taste that is different from the free fatty acid taste responses. He mentioned work he is doing in collaboration with Anthony Sclafani and John Glendinning (Sclafani et al., 2007) on gustducin and TRPM5 knockout mice, suggesting that there may be oral and postingestive gut endocrine fat sensors tied to some taste proteins. "But a lot of work is yet to be done," he said.

Relative Importance of Examining Tissue-Level Responses Versus Whole-Organism Responses to Food

During his presentation, Ritter emphasized that stimulation of one type of nerve fiber can influence the response of other types of nerve fiber (because of the proximity of different types of nerve endings in the brain). This and other observations led an audience member to ask the panel to comment on whether studying cells or tissues in isolation creates a different impression of brain-digestive system interactions compared with studying whole organisms. Margolskee replied, "Ideally, one would be looking at the whole organism [and] integrative systematic responses. From a practical point of view, we do many reductionist, reduced preparations where we drive the system to be able to see a response, for example, with isolated pancreatic eyelets. We can do things to the eyelets that would be much harder to do in the intact animal model." He noted the struggle to interpret the importance of some of the observed effects of high-potency noncaloric sweeteners on insulin and GLP-1 responses. Whereas he and his research team have shown that high-potency noncaloric sweeteners can drive changes in insulin levels in isolated eyelets, Rebecca Brown's work with noncaloric sweeteners in human subjects has demonstrated an increase in GLP-1 levels but no change in insulin levels (Brown et al., 2009). So the physiological relevance of what Ritter and his team have observed with respect to changes in insulin is questionable. On the other hand, it may be worth considering the possibility that there are long-term effects of many years of high ingestion of high-potency noncaloric sweeteners. Ritter said, "I tried to be fairly cautious in not overinterpreting or overextending from the data, but I think there is something there worth noting and worth considering."

In contrast to the questionable insulin responses, Margolskee said there are some clear systematic physiological responses. He noted Steven Munger's work demonstrating that cephalic phase[13] responses can be driven

[13] The cephalic phase is a phase of gastric secretion that occurs before food enters the stomach.

in isolation with extracted tissues (Geraedts and Munger, 2013). Some cephalic phase responses appear to be "hardwired" into endocrine cells in the gut, Margolskee observed. In sum, he said, "It's a very complex system where we need to understand each of the parts and understand how it functions in totality."

The Role of Animal Models in Understanding Human Eating Behavior

When asked about the use of animal models to study human eating behavior, Dubé opined that many processes can be studied with rats even at the presymbolic level of decision making. She pointed to Peter Shizgal's work on decision making in rats, which has documented how multiple sensory information and biological needs are integrated into a common currency driving the nature and quantity of food choices (Shizgal and Conover, 1996). However, many layers of complexity and diversity must be added in accounting for human choice. Dubé said, "If you want to study human behavior, you need to have all the pieces, but you also need to get the real world context. . . . It's not an either-or. It's a portfolio."

Moran agreed that rats can be used to study more than physiological responses; they also can be used to study dietary preferences. He noted that some of the same fetal outcomes described by Dubé in her presentation can also be shown in rats. He said, "It's likely that a number of these long-term effects are mediated through epigenetic changes, and rodent models really provide a very good vehicle for getting at just what those kinds of specifics are."

The Challenge of Studying Overall Control of Eating: Integrating Homeostatic and Reward Responses to Food Stimuli

An audience member asked how researchers plan to integrate what is known about the homeostatic processes described thus far—that is, all of the various neural mechanisms mediated largely through the vagal nerve and mainly in the hindbrain—with what is known about reward-related dopamine responses in the brain. For example, how can one integrate what is known about individual peptides involved in the control of meal size with what is known about reward processing that goes on in the brain in response to food stimuli? Dubé emphasized that all areas of study contribute information. In her opinion, methodological interfaces could be developed to integrate those pieces of information. When McGill University hosted the first BtS model think tank in 2005, Dubé was struck by the disconnect in people's thinking about the different processes and parts of the brain associated with eating. The situation has changed since then, she said. Still, she encouraged development of an interface protocol and stressed the impor-

tance of having a sense of the system as whole while studying single pieces. Having knowledge of the individual pieces is "absolutely necessary," she said, but it is also necessary to understand those pieces within their larger context. She urged a systems-level approach to moving forward.

Ritter opined that food intake is controlled largely by sensory experiences. Those experiences, he said, "ascend" into the reward areas of the brain and likely influence responses from the GI tract in a "descending" manner. He, too, stressed the importance of gaining a better understanding of the individual pieces and then studying them in their broader context.

Moran added that many of the hormones being studied for their peripheral pathway effects have the ability to cross the blood-brain barrier and directly impact brain reward pathways.

Gut Peptides: Hormone Versus Paracrine Signaling and the Impact of Overall Metabolic State

An audience member noted that many studies have found no relationship between levels of gut hormones circulating in the blood and subjective measures of appetite or food intake. She asked, "Are we going down the wrong path looking at those gut hormones as opposed to knowing that there's that direct effect that's happening in the gut and in the brain?" Moran replied that 20 years ago, one of the arguments against a physiological role for gut hormones in contributing to satiety was a lack of that type of correlational data. However, antagonist experiments have made clear that, rather than a hormonal role, many of these peptides likely play a paracrine role in contributing to satiety. Also, a number of studies have shown that hormones released during one meal do in fact have an effect on meal termination in subsequent meals. Moran explained that many of the positive correlations being seen today are in bariatric surgery conditions, where hormone release is greatly exaggerated because of the anatomical changes associated with the surgery and nutrients accumulate in high concentrations in areas where they normally would not accumulate.

Ritter identified two relevant areas in need of further investigation. The first is the way G protein-coupled receptors display constitutive activity, that is, activity even with very low levels of agonist present, which suggests that the very existence of G protein-coupled receptors facilitates signaling of the nerve. Second is the effect of the metabolic state of an animal or person on hormonal and behavioral response.

Another audience member asked whether some of the "nonsatiety" proteins, such as adiponectin and glucagon, should be studied for their potential role in food intake signaling. She also asked about the role of the liver in appetite regulation and the importance of considering overall metabolic state. Regarding the latter, might some of the lack of correlation

between hormone level in the blood and food intake be related to lack of consideration of overall metabolic state? Ritter agreed that there is much to be learned about the role of multiple cytokines in regulating food intake during both illness and health. He reiterated that overall metabolic state, as well as other contextual and neural factors, needs to be considered when evaluating food intake, overeating, and obesity.

Moran agreed that from a therapeutic standpoint it will be important to understand not just individual signals but the range of signals and their interactions, and how those interactions change across different metabolic states.

Loss of Vagal Afferent Feedback: Obesity and Dementia

Questions were raised about whether loss of vagal afferent feedback may in any way contribute to either obesity or dementia. First, given that obesity can be considered a state of overconsumption, is there any evidence that loss of nutrient-activated vagal afferent feedback contributes to obesity? Ritter replied, "The short answer is yes." Studies in both animals and humans indicate that down-regulation of leptin sensitivity, for example, leads to an increase in meal size. More generally, type of diet (e.g., cafeteria diet) can induce changes in vagal afferent signaling that lead to decreased nutrient sensing and decreased caloric feedback. When asked whether overstimulation or macronutrient content drives decreased sensitivity, Ritter replied that there is evidence for both mechanisms.

An audience member mentioned that her father suffered a brain injury and then gained about 100 pounds in 100 days. In her opinion, "there was a feedback loop that just wasn't working." She asked whether similar malfunctioning feedback loops may contribute to Alzheimer's disease, given its hypothesized relationship with insulin sensitivity (i.e., it has been dubbed by some experts as a "type 3" diabetes). Moran replied that various kinds of brain injuries are known to produce excessive weight, generally in response to excessive food intake. With respect to the relationship between Alzheimer's and a malfunctioning food intake feedback loop, he noted the well-documented relationship between a drop in insulin sensitivity and Alzheimer's and other forms of dementia and the known effect that a drop in insulin sensitivity has on food intake. He said, "There is a deficit in the brain's ability to get the kind of glucose that it needs for normal functioning."

Childhood Development and Obesity

Dubé was asked about the importance of considering upbringing when conducting cross-sectional studies on food intake comparing lean versus

obese individuals. She replied that examining children and their relationships with both food and reward is key to understanding food intake and obesity. This is especially true when applying the addiction model to food. In Dubé's opinion, not only does an excessive focus on addiction processes in food intake fail to account fully for the complex interplay with metabolism and energy balance that is less relevant with, for example, cocaine; it also neglects reinforcement learning processes that are core to reward learning (with or without addiction) and, in the context of food, may certainly be as important at cognitive learning. Dubé emphasized the importance of early exposure to high-calorie, high-fat, and high-sugar foods—or to healthier alternatives—in setting a life course of reinforcement learning that impacts what children learn to like.

Studying the Social Context of Eating Behavior

Dubé also was asked how population-level data, such as the soft drink consumption data that she presented, could be used to generate hypotheses about eating behavior and how better-quality population data could be collected. She replied by emphasizing that the very rigorous standard for collecting population data for epidemiological study needs to be applied in the study of food environments, accounting for sampling and other research methods. She noted that the soft drink data she used in her analysis were predictions based on available private data and that she and her research team used predicted rather than actual data in order to derive population-level estimates and draw inferences at the population level.

3

Assessing the Science Behind Methodologies Being Used to Characterize Food as Addictive

Nutrition researchers are beginning to rely on data from neuroimaging studies and self-report questionnaires to answer questions about how food and food cues impact eating behavior. This chapter summarizes the workshop presentations and discussion that revolved around the use of neuroimaging and the Yale Food Addiction Scale (YFAS) (a self-report questionnaire for identifying "addictive eaters") to characterize eating behavior (or food) as addictive and addictive-like. To start the session, moderator Richard Mattes of Purdue University provided a brief historical overview of energy intake research and the shift in focus toward eating behavior. Box 3-1 highlights key points made by speakers during this session.

A BRIEF HISTORY OF FOOD INTAKE RESEARCH[1]

Although scientists continue to debate whether the nation's obesity problem is driven primarily by changes in energy expenditure versus energy intake, Mattes opined that enough evidence exists to support the hypothesis that energy intake is the primary driver. Based on their use of the doubly labeled water method to measure human energy expenditure, Dale Schoeller, John Speakman, and Klaas Westerterp unanimously and emphatically claim that there has been no change in energy expenditure over the past 15 to 20 years (e.g., Westerterp and Speakman, 2008).

[1] This section summarizes introductory remarks made by Richard D. Mattes, Ph.D., M.P.H., R.D., Purdue University, West Lafayette, Indiana.

BOX 3-1
Key Points Made by Individual Speakers

- Heightened food cue responses in the brain (e.g., responses to pictures or flavors of food), as measured by functional magnetic resonance imaging (fMRI), are associated with higher body mass index (BMI) and can predict feeding behavior and weight gain. According to Dana Small, the underlying mechanism driving brain cue responsivity, at least for carbohydrates, appears to be a postingestive metabolic effect. The greater the expected metabolic effect, the greater is the anticipatory response to food cues.
- Whether neuroimaging evidence reveals anything about eating behaviors, and "food addiction" in particular, is open to debate in Hisham Ziauddeen's opinion. Ziauddeen called attention to key assumptions underlying neuroimaging studies of eating behavior and urged caution when interpreting the study results.
- The Yale Food Addiction Scale (YFAS) is a self-report questionnaire made available in 2009 as a tool for identifying individuals who may be experiencing addictive-like responses to food. The scale is based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV), for diagnosing substance dependence. According to Ashley Gearhardt, addictive-like eating behavior as defined by the YFAS has since been associated in many studies with eating-related problems such as higher current and lifetime BMI and emotional eating. Additionally, Gearhardt outlined how the YFAS has been associated with risk factors and mechanisms implicated in other addictive disorders, such as hyperreactivity of reward-related neural regions to food cues, higher rates of impulsivity, and elevated craving. She noted the importance of replicating existing findings and conducting longitudinal studies. She also emphasized the need to identify which foods may be more likely to trigger an addictive process in humans and suggested that highly processed foods with added fats and refined carbohydrates may be more addictive than more naturally occurring foods.
- "Food addiction" was considered for inclusion in the DSM-5 category for substance use disorder but rejected because of a lack of data, according to Charles O'Brien. O'Brien emphasized that the criteria for substance use disorder were developed based on studies of drug addiction and questioned the appropriateness of "squeezing" what is a normal behavior—eating—into a set of criteria developed for drugs.

Mattes explained that while this claim may seem counterintuitive given how much time people spend watching television and sitting in front of computer screens, people have become heavier and therefore use more energy when they do move. Additionally, when energy expenditure for a large array of terrestrial mammals is plotted against body mass, human data align with what is expected. "What we're doing is not aberrant," Mattes said. Thus, in his opinion, the discussion should revolve around food intake, not energy expenditure.

While limiting the discussion to one side of the equation "should be comforting," Mattes said, "it is not." Measuring food intake is difficult. According to a recent analysis of various iterations of National Health and Nutrition Examination Survey (NHANES) data, not a single study over the past 39 years involved a majority of respondents reporting biologically plausible energy intakes (Archer et al., 2013). That lack of plausibility has led researchers to seek other predictors of intake for use in their studies.

According to Mattes, during the 1950s to 1970s, nutrition research as related to ingestion behavior focused primarily on macronutrients and other factors that tend to influence intermeal interval, not meal size. The focus during the past 15 to 20 years has shifted to gut peptides and their role in controlling meal size (Blundell, 2001; see Chapter 2). Mattes emphasized the need to integrate what has been learned about factors that control eating frequency with what researchers are learning about factors that control portion size. "There really hasn't been much attempt to do that," he said. Absent those data, he observed, researchers have begun to focus more on behavior and, with the advent of new imaging technologies, neurochemistry.

All of this new behavioral and neurochemistry research has raised important questions about characterizing food as addictive. Are there special properties of foods that drive intake to a point where it exceeds energy requirements? Or are there characteristics of consumers that make them especially responsive to whatever interceptive or external stimuli they encounter? "Most likely it's the interaction between these two," Mattes said.

WHAT IMAGING TECHNOLOGIES REVEAL ABOUT FOOD BEHAVIORS: PERSPECTIVE 1[2]

> "The obesity epidemic is a neurobehavioral problem that stems from a vulnerable brain in an unhealthy food environment."
>
> —Giles Yeo

Inasmuch as the brain is a key facet of Giles Yeo's definition of the obesity epidemic, Dana Small began, neuroimaging will be critical to understanding how the modern food environment is engaging appetitive circuits, hedonic circuits, and their interaction. Small discussed how neuroimaging research is being used to understand food cue reactivity and its role in obesity.

[2] This section summarizes the presentation of Dana Small, Ph.D., Yale Medical School, New Haven, Connecticut.

Food Cue Reactivity

Many neuroimaging studies have demonstrated that when shown a palatable food or presented with the aroma or taste of a palatable food, individuals with a high body mass index (BMI) or a genetic predisposition show greater responses in many regions of the brain, particularly dopamine source and target areas. This type of heightened brain-food cue reactivity is important, Small opined, because it predicts eating behavior. In a neuroimaging study in subjects shown pictures of palatable foods, for example, Lawrence and colleagues (2012) demonstrated that response to food cues in the nucleus accumbens, a key reward region of the brain, correlates with subsequent snacking behavior. Notably, this same response was unrelated to self-reported hunger. The researchers also demonstrated that in contrast, a separate circuit involving the ventromedial prefrontal cortex showed no relationship with snacking behavior but a correlation with self-reported hunger. These results demonstrate that distinct responses are associated with hedonic versus homeostatic factors related to feeding. These hedonic responses in regions that may promote eating in the absence of hunger, such as the nucleus accumbens, make sense, Small said, because people can store excess energy as fat for times of famine.

If some circuits, such as the nucleus accumbens, promote eating or are associated with eating without hunger, one would expect the activity level of those circuits to be related to susceptibility to weight gain. Indeed, in a neuroimaging study of individuals taking small sips of chocolate and vanilla milkshake, Geha and colleagues (2013) observed a correlation between responses in the nucleus accumbens, ventral pallidum, and hypothalamus in individuals and change in BMI over the course of a year. In a study of individuals participating in a weight loss trial, Murdaugh and colleagues (2012) found greater activity in the nucleus accumbens among participants who were more likely to gain weight even as they were actively trying to lose weight. Together, these results suggest that food cue reactivity is a powerful predictor of eating behavior and can be used to predict weight gain.

Regulation of Food Cue Reactivity: Importance of Postingestive Signaling

In an effort to understand what regulates food cue reactivity, Small and her research team have been using a "flavor nutrient conditioning" paradigm. Flavor nutrient conditioning has been well studied in animals, largely by Tony Sclafani and his group (Sclafani et al., 1999).

Flavor nutrient conditioning studies typically involve hungry, thirsty rats that are presented on the first day with a sipper containing a particular flavor. When the rat licks the sipper, the lick is detected, a switch is flipped,

the pump turns on, and a nutrient such as glucose is infused directly into the gut. Thus, over the course of the day, the rat has an opportunity to learn to associate the flavor in the sipper with the postingestive effects of the nutrient in the gut. On the second day, the same rat, hungry and thirsty again, is presented with a sipper containing a different flavor. This time when the rat licks the sipper, the lick is detected, a switch is flipped, the pump turns on, and a saline placebo is infused directly into the gut. Over the course of the second day, the rat learns to associate the second flavor with the lack of any postingestive effect in the gut. Then on a subsequent day, the researchers can "ask" the rat which flavor it prefers by making both flavors available and measuring intake. Sclafani and colleagues (1999) showed that rats overwhelmingly preferred a flavor associated with a glucose infusion over a flavor associated with a saline placebo.

Of importance, Small noted, other studies have demonstrated that flavors associated with noncaloric exposures do not condition preference, suggesting that a postingestive effect is necessary to elicit a response (Ren et al., 2010; Yeomans et al., 2008). Other studies also have shown that the association learning that occurs over the course of exposure is highly dependent on dopamine and that blocking dopamine in multiple regions, including in the hypothalamus, the amygdala, and the nucleus accumbens, completely abolishes the learning (Sclafani et al., 2011; Touzani et al., 2010).

While most of the evidence for a postingestive effect comes from rats, Yeomans and colleagues (2008) demonstrated that postingestive effects, but not oral signals, are necessary and sufficient for the formation of flavor preference in humans as well. Because their subjects were human, these researchers did not use the intergastric infusion method. Rather, they administered a pretest during which subjects rated flavors on how pleasant they were, and intake was measured. Then they conducted a series of exposure sessions in which subjects were allowed to associate a novel flavor with a postingestive effect. After the exposure sessions, the researchers conducted a posttest during which, once again, flavors were ranked for pleasantness and intake was measured.

The exposure sessions involved exposing participants to one of three situations. One group received a flavor plus sucrose, a condition with both postoral effects (because sucrose is caloric) and oral effects (because sucrose is sweet). A second group received the same flavor plus maltodextrin, a condition with postoral effects but no oral effects (because maltodextrin is tasteless and odorless to humans). The third group received the same flavor with aspartame, a condition with oral effects but no postoral effects (because aspartame is sweet but has no calories).

The researchers found no change before and after exposure in the ranking of pleasantness or in intake among individuals in the third group—those

exposed to the flavor plus aspartame. However, they found a slight increase in the ranking of pleasantness and a significant increase in intake among those exposed to the flavor plus maltodextrin, and the greatest response in those exposed to the flavor plus sucrose. While the greatest changes were observed when both postoral and oral effects occurred, the lack of change seen in the flavor plus aspartame group and the changes seen in the flavor plus maltodextrin group together suggest that postoral effects by themselves are both necessary and sufficient for inducing flavor-nutrient association learning and for increasing the reward value of a flavor.

Postingestive Signaling: The Role of Glucose Metabolism

Given the evidence accumulated thus far, it appears clear that some postoral effect is a critical signal for flavor-nutrient association learning. What is less clear, Small said, is the nature of such postingestive signals. Ivan de Araujo and colleagues found that intake levels of sweet tastants are controlled by glucose oxidation and its modulatory effects on extracellular dopamine levels in the striatum (Tellez et al., 2013). When mice were allowed to lick and consume glucose, dopamine levels in the striatum increased. In contrast, when mice were allowed to lick and consume glucose while simultaneously being injected with intravenous 2-deoxy-D-glucose, which blocks glucose metabolism, dopamine levels in the striatum remained the same.

These results suggested to Small that glucose metabolism might be the critical signal behind flavor-nutrient conditioning—in other words—that the metabolic impact of glucose metabolism is what drives its reward value. To test whether this is in fact the case, Small and her research team conducted an experiment designed to determine whether responses to calorie-predictive flavors—that is, responses in dopamine source and target regions in the brain—are associated with changes in plasma glucose upon exposure to various flavor-sweetener combinations (de Araujo et al., 2013). Plasma glucose was used as a proxy for glucose oxidation (if glucose is to be used as a fuel, it needs to be present in the plasma). As in the Yeomans et al. (2008) study, there was a pretest in which subjects rated stimuli on pleasantness. In this case, the subjects were presented with 10 noncaloric flavored beverages, each distinctly flavored and distinctly colored. Only those individuals who identified at least three flavors as similarly pleasant continued in the study. Also, because the researchers wanted to use maltodextrin to identify postoral effects in the absence of oral effects (because maltodextrin is flavorless but caloric), subjects who were able to detect maltodextrin were excluded from the study.

Following the pretest, data were collected over the course of four exposure days. Individuals were exposed to two different conditions on alternate

days. On two days they were exposed to one of the noncaloric flavors from the pretest (one of the three flavors that was rated during the pretest as similarly pleasant to others). On the other two days they were exposed to a caloric version of a different flavor (one of the other flavors rated during the pretest as similarly pleasant to others, sweetened with 112.5 calories of maltodextrin).

A typical exposure day involved participants arriving at the laboratory at 11:30 AM. Upon their arrival, a saliva sample was collected, participants were asked to rate their hunger, and a catheter was inserted. Thirty minutes later, the first blood sample was collected and the participants were asked to rate their hunger again. Blood samples were used to measure six metabolic markers: glucose, ghrelin, insulin, trigylcerides, haematocrit, and haemoglobin. Then the participants drank one of the flavored beverages (one day caloric and another day noncaloric). A second blood sample was taken after another 30 minutes, and hunger was rated again. The 30-minute wait was used because 30 minutes postconsumption was about when plasma glucose levels were expected to be at their maximum. Participants would then eat lunch, go home, and return for a similar round of data collection and dinner. At the end of the day, they were sent home with a bottle of flavored beverage to drink at breakfast. Thus, a single exposure day involved three opportunities to learn the association between a flavor and its postingestive effect.

After exposure, the researchers conducted a posttest rating of the pleasantness of the flavors and measured brain responses using functional magnetic resonance imaging (fMRI). They found that after exposure, the flavor to which calories had been added became more pleasant, with participants changing their rating from "like slightly" to "like moderately." In terms of metabolic changes, exposure to the caloric flavor led to greater changes in glucose, ghrelin, and insulin. When the difference in metabolic impact between the caloric and noncaloric beverages was regressed against brain response, the researchers detected only one significant relationship among the six metabolic markers measured, and that was with glucose. In other words, the magnitude of the brain response depended on how much the maltodextrin changed plasma glucose levels during the exposure sessions. Small concluded with an overview of additional studies her laboratory is undertaking to better understand what drives food cue reactivity.

Summary

In summary, Small emphasized that heightened food cue reactivity as assessed by fMRI is associated with BMI and eating in the absence of hunger and is a reliable biomarker of susceptibility to weight gain. Determining what drives food cue reactivity will be critical to understanding how the

modern food environment interacts with the brain to promote obesity. The results obtained by Small's research team are consistent with the hypothesis that at least for carbohydrates, brain food cue reactivity is linked to their utilization as cellular food.

In Small's opinion, better characterization of the metabolic impact of modern carbohydrate-containing foods and beverages will improve scientists' understanding of how those foods and beverages interact with the brain to promote obesity. Small pointed to fat and sugar combinations that have never existed in human evolution until now and to liquid calories as two examples of modern carbohydrate-containing foods and beverages. But many unanswered questions remain.

More generally, Small called for a greater focus on the brain-gut axis, for which imaging will be critical. It is time, she said, to begin integrating the characteristics of foods with their physiological effects in the body and how those physiological effects, in turn, are regulating brain circuits.

WHAT IMAGING TECHNOLOGIES REVEAL ABOUT FOOD BEHAVIORS: PERSPECTIVE 2[3]

Whether imaging data reveal anything about food behaviors, particularly "food addiction," is open to debate in Hisham Ziauddeen's opinion. The answer, he said, depends on what one asks and how one asks it. The question usually is asked in the context of obesity, without which, he suggested, it is doubtful that anyone would think about characterizing food as addictive. Before presenting some examples of how researchers are using neuroimaging to study the complexity of factors that drive energy balance, Ziauddeen provided a conceptual framework to help in understanding how imaging technology data are collected and analyzed.

Key Elements and Assumptions of Cognitive Neuroscience Experiments

Ziauddeen noted that several key assumptions underlie most cognitive neuroscience experiments: (1) there is a phenotype of interest (e.g., "food addiction"); (2) there is a process implemented in the brain that is reliably associated with that phenotype; (3) there is a task that can be used to examine the process; and (4) the method allows for a reasonable examination of the brain processes during the performance of the task.

Two levels of control are inherent in the design of neuroscience experiments. The first is the contrast between the phenotype of interest and a control phenotype. The second is that the task includes a test condition

[3] This section summarizes the presentation of Hisham Ziauddeen, M.R.C. Psych., Ph.D., University of Cambridge, Cambridge, United Kingdom.

and a control condition because most processes imaged are not single-level processes; most are integrated processes. The test condition usually involves manipulating the process of interest, while the control condition involves controlling for all the other processes engaged by doing that task.

The Importance of Task

Although Ziauddeen focused mainly on phenotype and process, he briefly highlighted the importance of task, which in his opinion is highly relevant when considering complex stimuli such as food. As an example, Ziauddeen described a motivational task that he and his research team developed for examining low- or high-fat food versus nonfood (Ziauddeen et al., 2014). The task involved having hungry people squeeze a rubber bulb while in the scanner. They were essentially "playing for lunch," he said. The task produced some very robust neural activation, with the force of the squeeze for high-fat food being significantly greater than the force of the squeeze for nonfood, and the force of the squeeze for all food also being significantly greater than the force of the squeeze for nonfood.

However, a challenge with this task is that findings in the scanner may not be representative of what actually happens. It is unclear how people's responses to images of food while they are in the scanner approximate what happens when they are outside the scanner.

With the aim of gaining better control over what is happening while subjects are in the scanner, Ziauddeen and his team developed another grip force–based task (in process, not published). Using an objective energy density criterion of 250 calories per 100 grams to define high fat or low fat, they had a pilot group of individuals rate pictures of food in terms of how much they liked the foods, how appetizing the foods were, and how healthy or unhealthy they thought the foods were. The researchers then had the participants perform the task that required squeezing a grip force bulb to indicate how much they wanted the item being displayed. After the task, the participants rated the pictures themselves, and these ratings matched well with those of the pilot groups. When the researchers examined the force responses for the food items, there were no differences between high-fat and low-fat effect foods. In other words, once the pictures were controlled such that all foods appeared equally appetizing and equally edible, there were no differences between high-fat and low-fat foods or indeed between healthy and unhealthy foods. This finding is important, as many studies have been conducted by comparing, for example, hamburgers with raw cabbage, Ziauddeen observed, and such high-fat versus low-fat comparisons are confounded by other dimensions such as appetizing versus bland and edible versus not (usually) edible.

Considering the Phenotype

Ziauddeen identified two questions worth keeping in mind when considering the phenotype being evaluated. First, is there a shared similarity between drug addiction and "food addiction"? Second, is there a shared similarity between drug addiction literature and food addiction literature?

Drug Addiction Versus "Food Addiction"

There are at least two views of "food addiction." The first is that certain foods are addictive and activate brain-reward systems in the same way that drugs do. The second is that certain people show a pattern of overeating that resembles drug addiction or drug dependence, with binge eating disorder being the most commonly considered candidate. Similar views can be held on drug addiction: that certain substances are addictive and activate brain-reward systems and that certain people show an addictive or dependent pattern of overconsumption of drugs. However, Ziauddeen noted, the reality is that drug addiction is a combination of an addictive drug and a susceptible individual resulting *over time* in the development of drug addiction or dependence. Drug addiction develops in only about 15 percent of drug users (Anthony et al., 1994). Ziauddeen emphasized the importance of the element of time and the evolution of a syndrome when thinking about an addiction and observed that most people who are thinking about "food addiction" are not thinking about these components of addiction.

Drug Addiction Literature Versus Food Addiction Literature

In the food addiction literature, researchers have examined three "food addiction" phenotypes thus far: (1) obesity; (2) eating disorders, mainly binge eating disorder but also bulimia nervosa on occasion; and (3) food addiction itself, based on the YFAS, which itself is based on the criteria for substance dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (APA, 2000). While obesity is an extremely heterogeneous phenotype, most researchers use BMI as a measure of obesity. With regard to the use of DSM-IV criteria for modeling food addiction, Ziauddeen expressed skepticism and suggested that the criteria be acknowledged for what they are: current best practice consensus guidelines. Also, the DSM-IV criteria are for a behavioral syndrome related to a substance of abuse; they were not designed for a substance such as food that people need to ingest.

That the DSM-IV criteria were not designed for substances that people need to ingest raises a question: For foods, what exactly is the potential substance of abuse? There are several candidates, including high fat, high

sugar, the combination of high fat and high sugar, and refined and processed foods. But all of these potential substances are "terribly imprecise," Ziauddeen said. Without precision, it becomes very difficult to know just what is being studied.

When comparing the DSM-IV criteria for substance dependence (APA, 2000) and their proposed food addiction equivalents (Gearhardt et al., 2009; Volkow and O'Brien, 2007), there are a few things to note, said Ziauddeen. One is that the DSM-IV criteria for substance dependence tend to conflate what are thought of as hallmarks of the addiction syndrome—such as persistent use despite negative consequences, loss of control of consumption, and escalation of use (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004)—with features that relate to chronicity and severity of use of certain drugs, such as tolerance and withdrawal. The DSM-IV tolerance criterion for substance dependence is "increasing amounts of drug are required to reach intoxication"; the withdrawal criterion is "withdrawal symptoms on drug discontinuation, including dysphoria and autonomic symptoms such as shakes and sweats." The proposed food addiction equivalent for tolerance is "increasing amounts of food are required to reach satiety"; the proposed equivalent for withdrawal is "distress and dysphoria during dieting." There are some problematic elements in the DSM-IV criteria that do not map well to food, in Ziauddeen's opinion. He highlighted tolerance and withdrawal not because they are necessarily critical when defining addiction, as they are not associated with all drugs of abuse, but to emphasize the importance of knowing exactly what tolerance and withdrawal mean if they are to be included as proposed food addiction equivalents.

The YFAS, the current tool for defining the food addiction phenotype, is a straight translation of the DSM-IV criteria. However, it is based on adjustments that needed to be made given that food is something people need to ingest, and it uses severity criteria to demarcate what is normal from what extends into the realm of pathology (Gearhardt et al., 2009). While the severity criteria are necessary for this purpose, Ziauddeen's reservations about the YFAS are related to the validity of directly translating the DSM-IV criteria to food and the fact that some of the criteria are not precisely defined (as described on previous page). He also expressed concern about the sample for which the YFAS was developed and validated (Gearhardt et al., 2009). He observed that it was a young and largely nonobese sample. Of even greater concern, the results correlated strongly with a standard measure of eating disorders, suggesting that the YFAS, particularly in this sample, was capturing elements of known eating disorder pathologies rather than any unique syndrome. The YFAS has since been validated in other samples (Davis et al., 2011; Eichen et al., 2013; Gearhardt et al., 2012, 2013b). In these samples, there is a strong concordance with diagnosed binge eating disorder, raising the possibility that the scale may be

measuring the same pathology in another way. Also of concern is that in these studies, significant percentages of the samples endorsed the tolerance and withdrawal criteria, and these are criteria for which the scale itself does not have a clear definition.

In summary, Ziauddeen urged greater consideration of the limitations of phenotypes being studied.

The Processes

Regarding processes at play, neuroimaging studies on food addiction are guided largely by what is known about drug addiction. Broadly and briefly, Ziauddeen described some key models in the drug addiction field. Drug taking starts as voluntary and goal directed but becomes habitual and compulsive over time. Over time, the drug taking sensitizes the dopaminergic systems and makes drug-related cues more salient and motivating. The cues tend to become more rewarding than actual receipt of the reward, which becomes less rewarding. This process has been conceptualized as an enhancement of the anticipation of the drug and a blunting of the consummation of the reward. These changes, which are accompanied by decreases in D2 dopamine receptor levels in the striatum, lead to impairments in the control systems that regulate behavior. Finally, drug taking eventually becomes driven more by the need to prevent the discomfort of withdrawal than by the thrill of taking the drug itself.

Considering the adaptation of this process of drug addiction to foods, Ziauddeen focused on three key questions: (1) Do food cues become more salient and motivating over time? (2) Is there an enhancement of anticipation triggered by the cue, compared with actual receipt of the food? (3) Is there a change in D2 dopamine receptor levels? More broadly, Ziauddeen identified three key contextual issues to consider: (1) the notion that foods and drugs act on the same reward systems; (2) the reality that much of scientists' understanding of drug addiction processes comes from animal neuroscience studies, with many of the ideas not having been fully tested in humans; and (3) the risk of borrowed legitimacy, that is, whether a finding with food that resembles a finding with drugs necessarily means that the food is "addictive." To highlight the latter issue, Ziauddeen referred workshop participants to data presented in Carelli et al. (2000, 2003). Based on recordings of single neurons in the nucleus accumbens, the researchers detected that a very distinct neuronal population responds to water compared with the populations that respond to cocaine. A human imaging study would not have the resolution to capture that difference. Instead, it would probably show similar responses in the same region of the brain. In other words, imaging data showing similar responses in the same region of the brain do not necessarily mean that the same circuits are being engaged.

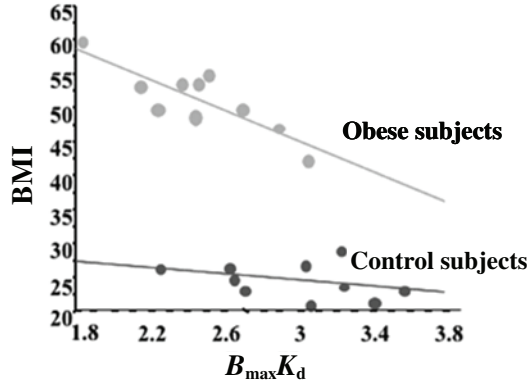
More concerning for Ziauddeen than these contextual issues are two key conceptual questions: (1) Is there an addictive aspect to normal eating behavior? (2) Is there a fundamental addictive mechanism in the brain that controls normal eating? In Ziauddeen's opinion, there is no neural signature of addiction in the brain. He cautioned against observing a neural finding that is different in two different populations—for example, lean versus obese individuals—and assuming that the signature reflects a fundamentally addictive process.

Brief Overview of Neuroimaging Data

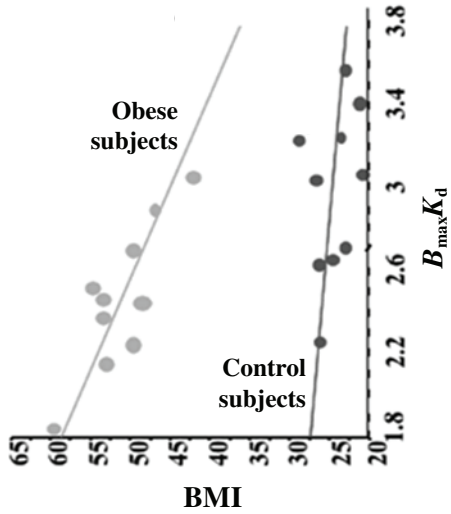
Wang and colleagues (2001) were the first to observe reduced D2 dopamine receptors in the striata of obese individuals. They reported a powerful and compelling graphic, in Ziauddeen's opinion, showing a clear difference in the relationship between D2 binding potential and BMI in morbidly obese (BMI > 40) versus lean (control) subjects (see Figure 3-1a). However, Ziauddeen noted a fair bit of overlap between the findings for the morbidly obese and lean individuals. If the same graphic is flipped on its side (see Figure 3-1b), it is easier to see that D2 receptor levels are fairly comparable for some BMI comparisons (e.g., there is one person with a BMI of about 50 who shows the same D2 receptor levels as a person with a BMI of about 27).

The Wang et al. (2001) finding has been replicated once with a slightly different but similar enough experimental design (de Weijer et al., 2011). However, several other studies have failed to replicate this finding (Dunn et al., 2012; Eisenstein et al., 2013; Haltia et al., 2007), the most striking of these, like Figure 3-1a also from Nora Volkow's laboratory, showing an opposite effect (Dunn et al., 2012). In Ziauddeen's opinion, findings collectively suggest that there is probably a D2 dopamine receptor abnormality in obesity, but thus far at least, only for morbid obesity. For more common levels of obesity, the evidence is unclear.

In a recent review of functional neuroimaging studies examining obesity, binge eating disorder, BMI (as a continuous variable), and food addiction, Ziauddeen and colleagues (2012) found a lack of consistent findings regardless of phenotype studied. The reviewed studies evaluated brain responses to presentation of food, anticipation of food, and consumption of food. Only one of the reviewed studies examined food addiction as a phenotype (Gearhardt et al., 2011c). Even then, Ziauddeen observed, only 2 of the 48 individuals sampled by Gearhardt and colleagues (2011c) actually had food addiction based on YFAS criteria; the others had food addiction symptoms, but not food addiction. Ziauddeen urged acknowledgment of the assumptions of that study—the first being that the YFAS is a valid measure of food addiction, and another being that the YFAS scores reflect



(a)



(b)

FIGURE 3-1 The relationship between D2 binding ($B_{max}K_d$) and BMI in morbidly obese and lean (control) individuals.
NOTE: Graph (b) depicts Graph (a) flipped on its side.
SOURCES: Volkow and Wise, 2005; Wang et al., 2001. Adapted by permission from MacMillan Publishers Ltd.: Nature Neuroscience (Volkow, N. D., and R. A. Wise. 2005. How can drug addiction help us understand obesity? *Nature Neuroscience* 8[5]:555-560), Copyright 2005. Reprinted from *Lancet*, Vol. number 357, Wang, G. J., N. D. Volkow, J. Logan, N. R. Pappas, C. T. Wong, W. Zhu, N. Netusil, and J. S. Fowler, Brain dopamine and obesity, Page No. 354-357, Copyright 2001, with permission from Elsevier.

a continuum of severity (i.e., having two symptoms is worse than having one, having three is worse than having two, and so on). Beyond the fact that only two individuals had a diagnosis of food addiction based on the YFAS, the results are unclear in Ziauddeen's opinion. The individuals were provided with either a chocolate milkshake or a neutral tasteless solution while in the scanner. Based on the model described above from the drug addiction field, one would expect an enhanced anticipatory response to cues that predict the chocolate milkshake and a decreased consumption response to actual receipt of the milkshake in individuals identified as being addicted to food. However, there was no difference in the anticipatory response to the chocolate milkshake between those identified and not identified as having food addiction. Rather, the difference was in the anticipatory response to the neutral cue. Both groups (scoring low and high on food addiction) showed a decreased consumption response.

Future Research

There is little direct neuroimaging evidence to support the idea of food addiction, Ziauddeen concluded. And he suggested that what little direct evidence exists should be interpreted with caution. He called for what he described as a post hoc a priori approach to studying "food addiction": first, define the addictive agent; next, define the behavioral syndrome that relates to that agent; then find a way to measure the syndrome; and finally, examine the syndrome's neurobiology and natural history.

Ideally, the field should conduct long-term prospective studies, Ziauddeen suggested. Most studies conducted thus far have been cross-sectional, which he observed may merely reflect the infancy of the field.

In closing, Ziauddeen commented that the overriding question for him is the purpose of investigating "food addiction." Is it for diagnosis and treatment, for policy change aimed at tackling the obesity crisis, or as a scientific construct for further research? Each of those purposes has not only a different standard of evidence, but also different implications. For example, if developing a clinical diagnosis for "food addiction" is the goal, who would be served as a result and how? Similarly with policy, if the field reaches a point where either an addictive food or a group of people who suffer from a food addiction can be clearly identified, what steps can be taken and what policies can be formulated?

ASSESSING THE VALIDITY OF QUESTIONNAIRES FOR FOOD BEHAVIORS AND ADDICTION[4]

A key goal for Ashley Gearhardt and her research team is to determine whether there is an addictive-like process that may contribute to certain types of problematic eating. The notion that addiction might be playing a role started to gain traction in the early 2000s, according to Gearhardt, for several reasons (Gold et al., 2003; Lilenfeld et al., 2008; Volkow et al., 2013). She explored those reasons and then described the development and validation of the YFAS.

The Notion of Food Addiction

Gearhardt identified several factors that have contributed to the greater scientific attention focused on the notion of "food addiction." First, obesity rates have continued to skyrocket over the past few decades, despite widespread attempts to lose weight that often result in failure. Even the most successful dieters typically regain their lost weight within 2 years, according to Gearhardt. This phenomenon has raised the question of whether an addictive-like process may contribute to this chronic relapsing pattern.

Additionally, there has been greater clinical acknowledgment that binge eating disorder, which entails repeated periods during which people lose control of their food consumption despite a desire to maintain control, is a verifiable mental health issue. Gearhardt noted that many of the phenotypes that present clinically with binge eating disorder resemble what is seen when people present with an addiction: they typically have lost control of consumption, show elevated cravings, and have tried repeatedly to cut down but keep failing. Because many factors that contribute to binge eating disorder are similar to those that contribute to addiction-like disorders, some experts suspect the two disorders may share some common mechanisms, such as impulsivity, reward dysfunction, depression, and issues with emotional regulation. In addition to some potential mechanistic overlap, there are some genetic similarities between binge eating disorder and substance use disorders.

Additionally, there is evidence to suggest neuromechanistic overlap. Gearhardt explained that the reward system in the human brain evolved to ensure that individuals seek out what they need to survive. A common conception about drug addiction is that drugs of abuse are so potent that they are able to hijack the brain's reward system and attribute reward to the addictive substance rather than to things needed for survival. Although

[4] This section summarizes the presentation of Ashley Gearhardt, Ph.D., University of Michigan, Ann Arbor.

humans need to eat, Gearhardt observed that with certain types of food, it appears as though people are eating not to survive but in a hedonically driven manner. She said, "They have lost control of their eating, and they are doing it in a compulsive way."

All of these changes (e.g., rising rates of obesity, acknowledgment of binge eating disorder as a verifiable mental health issue, increases in hedonic eating) have occurred in a changing food environment, with greater availability of ultra-processed foods high in fat, refined carbohydrates (e.g., sugar), and salt (Gearhardt et al., 2012; Monteiro et al., 2010). Gearhardt observed that ultra-processed foods are very different from the foods humans evolved to eat, which included no foods naturally high in both fat and sugar (coconut milk comes the closest, she noted). Foods tend to be either high in sugar, like fruits, or high in fat, like nuts and meats, but not high in both.

The fact that foods have changed over the course of human history, with today's ultra-processed foods being high in both fat and sugar, raises the question for Gearhardt of whether foods have changed over the course of human history in an addictive way, that is, in a way that may trigger an addictive or addictive-like response in certain individuals. She argued that humans have altered the food supply in many of the same ways in which they have made addictive substances in the past. Two of the major mechanisms for accomplishing the latter are (1) increasing the potency, that is, the dose of the rewarding substance, and (2) increasing the speed of absorption and creating a large spike in reward-related responses (Samaha and Robinson, 2005; Verebey and Gold, 1988). When chewed, for example, the coca leaf does not provide a very high dose, nor is it rapidly absorbed into the system. Levels of addiction resulting from chewing a coca leaf are quite small even in places where chewing coca leaves is a common cultural practice. In contrast, when processed and made into a more potent substance that is more rapidly absorbed—that is, when made into cocaine—coca leaf becomes much more addictive. When it is processed even further into crack cocaine, its addictive nature becomes even more intense. Gerhardt noted that the foods people most commonly struggle with and lose control over are ultra-processed foods with elevated potency and elevated speed of absorption into the system. Thus, as with drugs of abuse, these foods may be more likely to trigger an addictive process compared with more naturally occurring foods.

Identifying "Addictive Eaters"

To further investigate the hypothesis that an addictive process contributes to problematic eating, Gearhardt and her colleagues focused on methodologically sound ways of identifying "addictive eaters." When she first started exploring this question, Gearhardt found that existing methods

for identifying addictive eaters were too limiting. One method was self-identification. For example, individuals would be asked if they were "carb cravers" or "chocoholics." But it is not clear what a chocoholic is, given how common the addiction language is in the popular press. Gearhardt asked, rhetorically, whether researchers can consider a response such as "Yes, I am addicted to chocolate" to be evidence of an addiction.

In the past, the most common way of assessing addictive-like eating, according to Gearhardt, was weight status, with obesity being interpreted as evidence for an addiction to food and lean body weight being interpreted as evidence for lack of an addiction to food. But that method raises a number of concerns. First, obesity is a medical endpoint with many causal pathways, including medication side effects, genetics, physical inactivity, and the overconsumption of food. Equating such a highly heterogeneous condition with food addiction likely overidentifies many people. It is like equating cirrhosis of the liver with alcohol addiction, when in fact many people who are not addicted to alcohol have cirrhosis of the liver and many people who are addicted to alcohol never develop that condition. Additionally, the assumption that people with normal BMIs have healthy relationships with food is not necessarily valid. Making that assumption likely underidentifies people who have an unhealthy relationship with food but are not yet obese or who are using such means as purging or excessive exercise to mask their unhealthy relationship with food. In sum, said Gearhardt, using body weight as the only way to predict addictive-like eating behavior results in either over- or underidentification.

A third method used in the past involves defining binge eating disorder as addictive-like eating. Individuals with binge eating disorder show a pattern of consumption that entails losing control and being unable to stop despite wishing to do so. However, observed Gearhardt, there are many differences between binge eating disorder and addictive-like eating. Binge eating disorder involves a discrete period of time in which the individual loses control and is aware that he or she has done so. But with addiction—for example, with cigarette smoking—there are people who chronically and consistently use the addictive substance throughout the day without experiencing any discrete episodic binge. Also, people who are addicted to a substance are not necessarily aware that they have lost control. Most important, Gearhardt noted, binge eating disorder is commonly thought to be a consequence of dietary restraint. That is, people who go on extreme diets and are unable to maintain that level of dietary restraint end up binging. Treating people with binge eating disorder involves minimizing the restraint around eating behavior and teaching them that there is no "good" or "bad" food. From this perspective, it is only the way the person relates to food that is a problem; the attributes of the food (e.g., high sugar, high fat) do not contribute to the eating issues. In contrast, from an addiction perspec-

tive, the characteristics of certain foods may contribute to the problematic eating pattern. For example, highly processed foods with unnaturally high levels of sugar and fat may be more likely to trigger biological and psychological addictive-like responses relative to more naturally occurring foods such as fruits and vegetables. Thus, all foods are not considered equally likely to contribute to problematic eating patterns, and it may be more difficult for someone with addictive-like eating to consume these highly processed foods in moderation compared with other foods. As an example, Gearhardt asked the audience members to think about coming home after a hard day of work and whether they would be more likely to overeat a bowl of strawberries or a bowl of strawberry ice cream from Ben & Jerry's. "There seems to be a difference between these items," she said. Thus, both the mechanisms and treatments for binge eating disorder and addictive-like eating are notably different, which does not make binge eating an optimal proxy for food addiction.

The Yale Food Addiction Scale

Gearhardt and colleagues developed the YFAS to improve the level of specificity in the identification of addictive eaters. They began by considering the relevance of DSM-IV criteria used to diagnose other addictions (APA, 2000). Draft YFAS questions were reviewed by experts who work with addiction, obesity, eating pathology, and binge eating patients to ensure that the questions adequately captured the context and would be clear to test takers. The scale has since been validated in nonclinical, clinical, and epidemiological samples (Flint et al., 2014; Gearhardt et al., 2009, 2012, 2013b). It is currently available in five languages (Meule and Gearhardt, 2014).

Gearhardt acknowledged that DSM-IV is not a perfect document. That said, there are no other agreed-upon criteria for addiction. The DSM-IV criteria have been applied successfully to a wide range of disorders, behaviors, and substances. Even though a heroin addiction looks very different from a cigarette addiction, the same diagnostic criteria have been used to study both disorders. For many years, people argued that cigarettes were not addictive because they did not "look" like heroin—one can legally consume them, one does not get intoxicated when one smokes them, one can smoke them while watching one's children, etc. But as the field moved forward, people began to realize that cigarettes are not just addictive but potentially more addictive than heroin.

Some researchers have suggested that neurobiological rather than behavioral indicators should be used to identify who may or may not be experiencing addictive-like processes in relation to food (Ziauddeen et al., 2012). But Gearhardt noted that it is not currently possible to diagnose known addictions (such as to alcohol) by imaging the brain. Thus, it is even

less plausible to use this means to identify a phenomenon like addictive eating that is still being evaluated. Presently, the field relies on behavioral indicators to diagnose the presence of an addiction, and the YFAS applies this same approach to the identification of addictive-like eating.

Gearhardt also acknowledged that no self-report questionnaire is sufficient to answer whether an addictive process is at play in problematic eating. Indeed, no self-report questionnaire is sufficient to determine whether any mental health disorder exists, especially one as controversial and complex as problematic eating behavior. However, the YFAS can be used, Gearhardt proposed, to identify individuals who may be the most likely to be experiencing an addictive-like response to food and then to evaluate whether mechanisms implicated in other addictions are also contributing to this pattern of problematic eating. Gearhardt stressed the importance of the fact that the YFAS goes beyond weight as a proxy. The focus of the scale is not on weight, but on people's relationships with food. Also important, the word "addiction" is not mentioned on the scale, which should reduce biased answers based on self-identification as a food addict. Thus, while the development of the YFAS does not prove that food addiction is a valid concept, Gearhardt noted, it does provide a more methodologically sound tool than has previously been available for evaluating empirically whether an addictive process is contributing to compulsive eating behavior.

A Review of YFAS Literature

Gearhardt noted that since the YFAS was published in 2009, many studies have used it to examine addictive-like eating. Individuals with addictive-like eating as defined by the YFAS have been shown to have higher current and lifetime BMIs (Flint et al., 2014; Gearhardt et al., 2014a; Pedram et al., 2013); a greater risk for negative health outcomes, such as hypertension, high cholesterol, and diabetes (Flint et al., 2014); more severe binge eating, with a tendency to binge more frequently, and more severe eating disorder pathologies such as emotional overeating (Davis et al., 2011; Gearhardt et al., 2012); elevated craving for certain foods, particularly fatty foods (Gearhardt et al., 2014b); higher emotion dysregulation in general (Gearhardt et al., 2011c); and in children, higher BMI, less satiety responsiveness, and higher emotional eating (Gearhardt et al., 2013a).

Gearhardt proposed that the effects observed in children with addictive-like eating behaviors are among the most important potential outcomes of this work. If certain foods are capable of triggering an addictive response, it is likely that the response will be greater in children than in adults. Children's brains are more plastic, children have not developed the same coping strategies that adults have, and their reward striatal system is more reactive than their executive control system. Children are frequently targeted

for the marketing of unhealthy foods, with children and adolescents seeing approximately 6,000 food commercials a year (Dembek et al., 2014). Gearhardt observed that almost all those commercials are for foods that she suspects lend themselves to an addictive process.

Addictive-like eating as measured by the YFAS also is associated with factors implicated in other addictions, including elevated impulsivity and delay discounting, whereby short-term reward takes priority over long-term consequences (Davis et al., 2011; Jasinska et al., 2012); increased attentional biases for food cues, whereby the food cues become more salient for individuals who report addictive-like eating than for those who do not (Meule et al., 2012); greater risk of developing a substance use disorder following bariatric surgery, which may be indicative of a cross-addiction transfer (Reslan et al., 2014); greater likelihood of having a higher dopamine multilocus genetic profile score, with differences in dopamine signaling being related to genotype (Davis et al., 2013); differential responses to dopamine agonist in the brain (Davis et al., 2013); and patterns of neural response associated with addiction (Gearhardt et al., 2011c).

Regarding this last association, Gearhardt and colleagues (2011c) found that women with higher scores on the YFAS exhibited elevated activation in the dorsolateral prefrontal cortex, medial orbitofrontal cortex, and amygdala during anticipatory cues for foods. When the women started to actually consume the food, the researchers observed less activation in the lateral orbital cortex, a brain region implicated in cognitive control. This same pattern of neural response has been identified in other types of addictions. Gearhardt explained that with addiction, the reward system often stops responding to nonaddiction cues; that is, it becomes hyposensitive, with the only cue activating it being the addictive cue. Gearhardt and colleagues (2011c) found that addictive-like eaters expressed that same hypoactive response to other stimuli, but when they were shown a milkshake cue, their neural response increased to a more normative level. That finding is consistent with what has been observed with other addictive disorders. Notably, Gearhardt said, she and her team controlled for BMI, so the effects "occurred above and beyond" BMI. In the future, Gearhardt would like to test these findings in a sample with more severe levels of food addiction, as few participants in this study met the clinical cut-off point for food addiction. Given the large effect sizes found in this study, it is likely that more severely addicted eaters may exhibit even more differences in neural function in response to food cues and consumption.

Next Steps

A first next step will be to examine DSM-5 and see whether the current thinking about addictive-like eating reflects scientists' changing understand-

ing of addiction. Also, Gearhardt would like to know how people interpret the YFAS questions and whether a clinical interview would yield more clinical specificity. Most important, existing findings need to be replicated and longitudinal studies need to be conducted.

The field is in its infancy; the YFAS was developed only 5 years ago. So, suggested Gearhardt, it is no surprise that there are many gaps in the literature. But now that scientists have a better understanding of who additive-like eaters may be, they can begin to test more mechanisms, such as tolerance and withdrawal. Do additive-like eaters show signs of tolerance? Do they show signs of withdrawal?

Finally, which foods are at issue? Gearhardt opined that the term "food addiction" is a misnomer. There appears to be a certain subclass of food that people struggle with—foods that are processed and designed to be as hedonically rewarding as possible. But which foods in particular are capable of triggering an addictive-like response? Answering this question and determining the socioeconomic implications (e.g., living in a neighborhood of lower socioeconomic status and having access only to certain types of foods) will be "incredibly important" for treating and preventing obesity and eating disorders, Gearhardt said. Understanding how obesity is framed—for example, the difference between framing it as a problem related to personal responsibility as opposed to a problem potentially caused by an addictive-like response to food—will also have important implications for treatment and prevention.

In closing, Gearhardt made a call for continued research funding in this area. Conducting this type of research is challenging, she noted, not only because of the controversial nature of the topic, but also because the topic often cuts across multiple funding bodies.

DSM-5: SUBSTANCE-RELATED AND ADDICTIVE DISORDERS[5]

Charles O'Brien observed that his perspective on the workshop topic comes from having spent more than 40 years treating people with unquestioned addiction. He began working in the field of addiction during the Vietnam War, when few people knew anything about addiction, especially its clinical aspects, because there had been so little research in the area. O'Brien served as chair of the substance use disorders section of the most recent DSM update, DSM-5, published in 2013. He discussed differences between DSM-IV and DSM-5 criteria for a substance use disorder diagnosis and the relevance of the criteria to food.

[5] This section summarizes the presentation of Charles P. O'Brien, M.D., Ph.D., University of Pennsylvania, Philadelphia.

Changes in DSM-5

O'Brien explained that the committee responsible for updating the substance use disorders section of DSM-5 attempted to keep the changes to a minimum (APA, 2013). Several candidate "addictions" were proposed for addition to DSM-5, food addiction being among them. Eventually, the committee decided that food addiction should not be added, but that binge eating disorder should be retained. Sex addiction was also proposed but similarly rejected. The most likely new candidate for inclusion at some point is Internet gaming disorder, which is becoming an important clinical problem in many countries worldwide. It was included in Section III of DSM-5 (i.e., as a potential diagnostic category requiring further research). As more data accumulate, it may be added as an actual diagnosis. O'Brien suggested that Internet gaming disorder may be a useful model for food addiction.

The DSM-5 criteria for substance use disorder begin with tolerance and withdrawal. Both of these criteria used to be considered signs of opioid addiction (APA, 2013), but they can also occur when medications are used appropriately under a physician's prescription. Thus, tolerance and withdrawal can be considered normal responses to drugs administered repeatedly that act on the nervous system (i.e., antidepressants, opioid analgesics, antianxiety drugs, and antihypertensive drugs). The DSM-5 substance use disorder committee decided that tolerance and withdrawal should not be used as criteria for addiction if the substance in question has been prescribed by a physician as a form of treatment. O'Brien noted that that exclusion is one of the changes from DSM-IV (APA, 2000).

All of the other DSM-5 criteria for substance use disorder besides tolerance and withdrawal deal with loss of control (APA, 2013). "Control is really a big thing," O'Brien said. It is considered essential for drug addiction and is important for "food addiction" as well, which is why, in the view of the DSM-5 substance use disorder committee, binge eating disorder comes the closest among eating problems to "food addiction." Another change in the DSM-5 criteria for substance use disorder is the addition of craving for the substance. Craving was added based on brain imaging data showing that people who are in treatment for any kind of addiction tend to have a craving for the substance that can last for years. The long-term "memory" of addiction has also been studied extensively in rats, according to O'Brien. The other criteria for substance use disorder are all classic signs of addiction: loss of ability to cut down, spending excessive time acquiring the substance, giving up other activities for the substance, using the substance despite its negative effects, failure to fulfill major role obligations, recurrent use in hazardous situations, and continued use despite consistent social or interpersonal problems.

An overall goal of DSM-5 was to make psychiatric diagnoses more neuroscience based (APA, 2013). Unfortunately, in O'Brien's opinion, researchers have spent years searching for biomarkers for psychiatric disorders but have yet to identify any that serve the same clinical purpose as that served by metabolic disorder and cardiology biomarkers. In fact, according to O'Brien, the need for biomarkers is why the National Institute of Mental Health launched its Research Domain Criteria (RDoC) project.

While the field lacks sufficiently reliable biomarkers, it does have very good animal models. In terms of "food addiction," animal models show both similarities and differences in central nervous system responses to drugs of abuse and sweet foods. In work from Friedbert Weiss's laboratory, for example, rats were allowed to self-administer either sweetened condensed milk, which is an intensely sweet substance, or alcohol. With both substances, the rats demonstrated a high level of self-administration and self-administered until the substance was no longer available. However, the animals showed an important difference during the reinstatement period of the experiment, that is, when the rats were provided with the same self-administration tool but with no actual substance available. Rats previously exposed to alcohol continued to try to self-administer even though they were not actually getting any alcohol. The rats previously exposed to sweetened condensed milk, on the other hand, did not continue to try to self-administer. The same was true of cocaine: during the reinstatement period, the rats reinstated quickly to cocaine but not to sweetened condensed milk. Together, these results suggest that the self-administration value of sweetened condensed milk does not last as it does with alcohol or cocaine, even though all three substances are activating the same part of the brain—the nucleus accumbens and ventral striatum.

O'Brien emphasized that while human brain imaging is useful (in fact, gambling was added to the DSM-5 list of addictions based on human brain imaging data), correlation between a report of pleasure and activation of the brain reward structures is expected and is not evidence that the pleasure in question is an addiction.

Factors that need to be considered before adding a new disorder to DSM-5 include a clinical need that is common and severe enough to warrant a new diagnosis, the potential for harm, the potential for treatment, and whether the condition meets the criteria for a mental disorder. O'Brien noted that the substance use disorder committee spent a great deal of time debating the last of these factors. The field of psychiatry has been criticized for overmedicalizing behaviors. For example, some people think that social anxiety disorder could be characterized as shyness and that making shyness a diagnosis robs the world of diversity. Someone diagnosed with social anxiety disorder can be treated with medication and can become more relaxed and sociable. O'Brien asked, rhetorically, "Is that good or bad?"

DSM and the YFAS

The "big issue" with the YFAS, in O'Brien's opinion, is taking a clinical problem from one field and trying to "squeeze" it into another. Changing the concepts and terminology used in one field so they can be used in another is particularly problematic with addiction because there has always been a certain amount of debate about the words used for the different concepts and various aspects of addiction. The addiction criteria in DSM-IV are based on classic opioid addiction and studies with opioids dating back to the 1930s and 1940s. Other forms of addiction are based on that addiction. O'Brien suspects that the developers of the YFAS will do a good job of adapting the scale to DSM-5. But is "squeezing" something meant for drugs into something that is normal behavior for people (i.e., eating) a good idea, he asked, especially since the goal for food obviously cannot be abstinence?

Compounding the challenge is the fact that the word "addiction" has been misused for many years now, and not just in the clinic. O'Brien cited articles about the president saying that the United States is "addicted" to oil and about women being "addicted" to pink. He said, "You could say I am addicted to skiing because I really get euphoric when I see a field of powdered snow. I am sure that if I were in a brain scanner, you would see activation of my ventral striatum and nucleus accumbens. But does that mean it is an addiction?"

In O'Brien's opinion, for the addiction model to be useful with food, the issue of severity needs to be addressed. For example, O'Brien suggested that severity might be based on some degree of complication, such as diabetes or morbid obesity. When he entered the field of addiction research, the only way to measure severity was the number of bags of heroin someone used daily, and the goal was to try to get that person to go from a 10-bag-per-day habit to a 2-bag-per-day habit. That approach is not very useful, he said. Most people with a heroin habit typically have multiple other problems. So the Addiction Severity Index (ASI) was developed in the 1970s as a way to measure severity based on those other problems as well, not just drug use. Today, the ASI is used worldwide and is available in more than 20 languages. It covers seven categories of problems, or domains: drug use, alcohol use, medical problems, employment problems, legal problems, family problems, and psychiatric problems (see Figure 3-2). In DSM-5, severity for substance use disorders is based on the number of symptoms a person has, with a maximum of 11.

Conclusion

In conclusion, O'Brien observed that there is a group of well-intentioned people who already think that food addiction is a diagnosis and needs to be

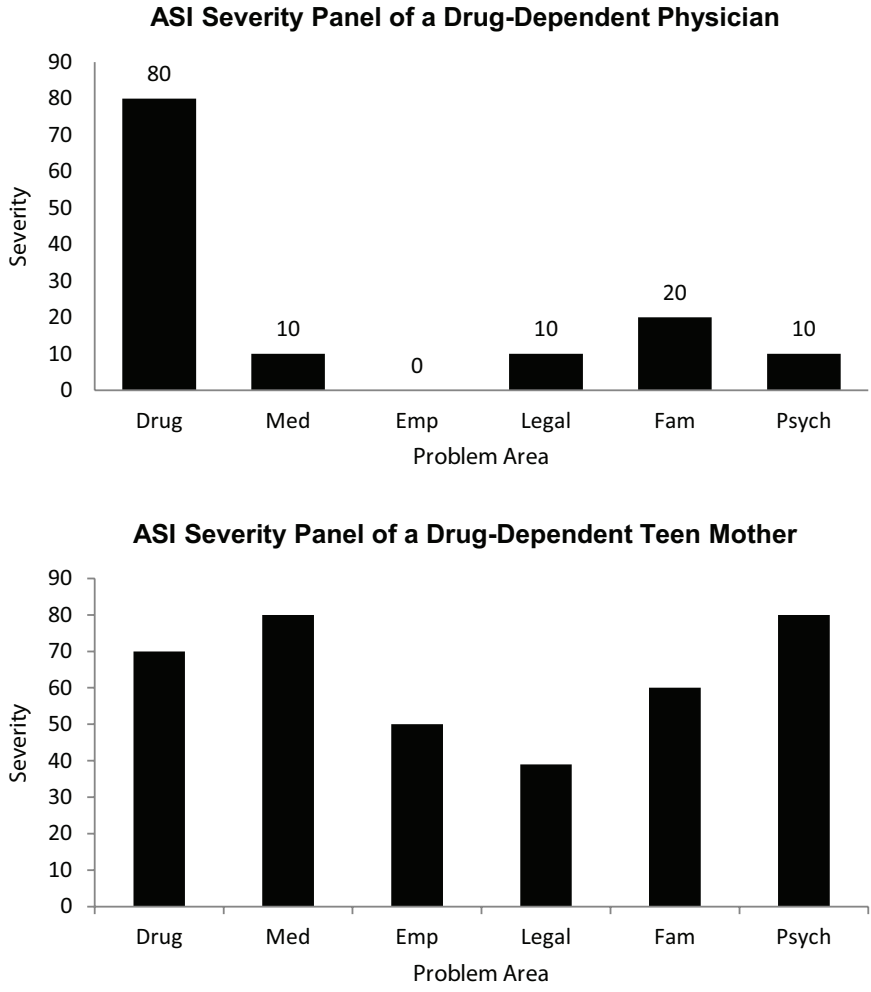


FIGURE 3-2 Severity of symptoms for six of the seven problem areas, or domains, associated with addiction, based on the Addiction Severity Index (ASI), for two individuals.
NOTE: Emp = employment/support; Fam = family/social; Med = medical; Psych = psychiatric.
SOURCE: O'Brien, 2014.

treated. "We have to be cautious," he warned. "[A diagnosis of food addiction] has to be founded on science rather than on enthusiasm."

DISCUSSION WITH THE AUDIENCE

Following O'Brien's presentation, the speakers from the afternoon session participated in a panel discussion with the audience. Questions covered a wide range of topics.

Identifying the Potentially Addictive (or Addictive-Like) Substance in Food: A Key Research Challenge

An audience member observed that discussions of drug addiction generally do not revolve around drug addiction per se; rather, the focus usually is on addiction to specific drugs, such as cocaine, heroin, and so on. The audience member asked whether there is a specific food-related chemical reaction that is having an impact when the brain's reward system overrides its satiety system.

Gearhardt replied that such knowledge does not yet exist for food. Evidence from animal models suggests that sugar may be a possibility. But studies in humans are "really just beginning," Gearhardt observed. Food is complicated in so many ways. A Pop-Tart, for example, has some 60 ingredients, and it is difficult to tease them apart. Gearhardt suspects that the combination of extremely high levels of refined carbohydrates, fat, and salt is likely what is triggering the response observed in the brain, but much more data and science are needed to answer this question.

Ziauddeen agreed that having a clearly identifiable substance is "critical." An assumption underlying the DSM-IV criteria is that an addictive substance exists and that the behavioral criteria apply within the context of using that substance. With food, it is not yet clear what is being consumed that is important. Presently, researchers are accumulating evidence on behavior based on a potential agent that has yet to be identified; all potential substances are being lumped together. With drugs, researchers are beginning to accumulate evidence for other elements besides the behavioral syndrome of addiction that characterize an addiction. However, they are able to do so only because they have a substance as a starting point. "I think it is important to actually clarify what the agent is to use any of this [food-related evidence] meaningfully," Ziauddeen said. "I do not mean this as criticism, as in, we have no substance [and] therefore there is no addiction. But I think the fact that there is no substance is very much of a problem."

The Modern Diet: High-Fat/High-Sugar Combinations

In her presentation, Gearhardt emphasized the high-fat/high-sugar content of modern foods not found in any naturally occurring foods. A member of the audience pointed out that human breast milk has the highest sweetness content of any mammalian milk and a fat content equivalent to cow's milk, goat's milk, and certain other milks. Small agreed that human milk is a high-fat/high-sugar substance, but observed that it is probably unique among naturally occurring foods in this regard.

The same audience member also commented on the historical use of fruit/nut combinations and observed that the combination of milk and honey, for example, goes back at least several thousand years. In response, Small said the relevant historical scale is hundreds of thousands of years, not thousands of years, and those kinds of mixtures do not extend far enough back in time to influence the evolution of the system. She repeated what she had emphasized during her presentation: modern foods challenge human physiology in a way that has not been seen over the course of time until now.

Later, another audience member observed that creative sugar/fat combinations have been in the human diet at least for decades or hundreds of years and asked why such an increase in obesity has been seen only recently. Small replied that she was unaware of any research on the origin of the current trend in increasing weight and its relationship to the introduction of high-fat/high-sugar combinations in the diet. She stressed the importance of looking at other components of the environment that may contribute to increasing weight. In addition to access to ultra-processed foods, examples of other factors that may contribute to increasing weight include stress, lack of sleep, and loss of insulin sensitivity because of reduced physical activity. "Perhaps we hit a critical mass of these things," she said.

At another point in the discussion, an audience member asked the panelists to elaborate on the potential role of stress and whether the dramatic rise in obesity over the past several decades might be cortisol related. The audience member mentioned single mothers who work hard during the day and "eat hard" at night. Small pointed to work by Rajita Sinha showing that people with high cortisol levels in the morning, an indicator of chronic stress, exhibit higher cue reactivity. Small reiterated that addictive-like eating behavior is a confluence of multiple factors. "It is not just the nature of the food product," she said.

In Ziauddeen's opinion, there are clear differences between the foods available today and those available 50 or 100 years ago. He suspects that highly palatable high-fat/high-sugar foods are stressing human physiology in novel ways and are likely to be having public health consequences. However, none of that necessitates invoking an addictive mechanism, he said. "[Foods] can be 'bad' even if they are not addictive," he noted.

Ultra-Processed Foods: What Makes Them "Addictive"?

In reference to Gearhardt's statement during her presentation that substances that are absorbed more rapidly have a higher abuse potential, Timothy Moran expressed puzzlement at the relationship between that hypothesis and ultra-processed foods. In other words, what is it about ultra-processed foods that makes them potentially addictive? Is it a taste phenomenon, or is there a metabolic effect? Gearhardt replied that her research team is currently investigating that question. Based on the drug addiction literature and experiments conducted with sham feeding, she suspects that a metabolic effect is involved. But it is very challenging to disentangle responses to a sweet flavor from responses to absorption of a high glycemic load into the system.

Pressing for more clarity, Moran asked about refined versus complex carbohydrates in particular, which he said empty from the stomach at exactly the same rate and therefore have the same effect on releasing insulin. Thus, they should have similar metabolic consequences. How does one of those foods (refined carbohydrates) produce a "phenomenon" (addiction-like process) that the other (complex carbohydrates) does not produce?

Gearhardt reiterated that what differentiates foods with and without addictive-like characteristics is an open question, especially when one is comparing, for example, breakfast cereals of whole and refined grains. When she thinks about what differentiates foods that do and do not trigger addictive-like responses, she tends to think along the lines of a banana, which has a decent amount of sugar but also has fiber, water, and other components and is eaten much less quickly than a handful of jelly beans with the same sugar content that is tossed into the mouth. A multitude of food characteristics need to be examined, she said, to make that differentiation.

Richard Mattes added that if absorption is an issue, the question arises of why fat is being considered alongside sugar. Fats and sugars are quit disparate in their rate of absorption. Small explained that while the physiological response is clearly going to be different with different macronutrients—for example, with fat modulating reward circuits via different pathways compared with glucose—exactly what is going on at a mechanistic level in the gut to trigger those different signals is unclear. Nor is it clear how those separate signals interact in the brain.

The Nature of Addiction: Are Substances Addictive, or Are People Susceptible to Addiction?

Robert Ritter stated that his understanding of addiction is that a substance produces a change in the nervous system, which in turn evokes

addictive behaviors. But do those changes necessarily arise from the use of food substances? Might it be the case that people who become addicted have an underlying problem that results in the expression of addictive behavior?

Ziauddeen responded that at least in the case of drug addiction, predisposing factors increasingly are being viewed as important. He pointed to work by Karen Ersche demonstrating that siblings of cocaine users show similar baseline vulnerabilities to drug dependence with respect to brain structure, personality, and such variables as impulsivity and inhibitory control. The onset of addiction in many cases may begin with these preexisting vulnerabilities. Ziauddeen described addiction as a "combination of an individual and a substance."

Addiction as a Continuum

An audience member observed that several speakers had mentioned or discussed activation of reward centers in the brain in response to or in association with the YFAS scores, but that as far as he could tell from what was presented, much of the data show a fair amount of variation in the intensity of response. He said, "In the public eye, addiction is thought of like a light switch. It is on or it is off. But your data show a continuum." He asked the panelists to comment.

Gearhardt replied, "The evidence does not suggest that there is this very discrete line: you are an addict or you are not." People show a range of addictive responses, from none to subclinical to clinically severe. For example, only about 10 to 15 percent of people who use alcohol actually show a full-blown clinical level of addiction. Many people show subclinical responses. But all those subclinical responses drive up the overall public health cost of alcohol, which is the third leading cause of preventable death. A concern with the potentially addictive nature of certain ultra-processed foods, Gearhardt said, is that the vast majority of people are not (or would not be) fully addicted. Enough people may show enough of an addictive response, enough of a craving, that they consistently eat 100 or 200 more calories daily than they homeostatically need. This level of additional caloric intake on a daily basis is enough to move an individual from a normal weight category to an overweight or obese category, eventually creating a significant public health problem.

O'Brien added that research conducted between the publication of DSM-IV and the preparation of DSM-5 yielded evidence that addiction is a gradual process. The fact that it is a gradual process, or a continuum, is why its diagnosis is now based on number of symptoms. That said, in O'Brien's opinion, there is no such thing as a mild addiction. Rather, addiction is a progressive disorder, with many different variables impacting the

outcome, not the least of which is genetics. In fact, according to O'Brien, of all mental disorders, addiction carries the strongest evidence for a genetic basis. He urged greater consideration of genetic makeup in future research.

Extrapolating from Drugs to Foods

In her presentation, Gearhardt had compared the ultra-processing of foods to the processing of the coca leaf into the more refined and more potent cocaine and crack cocaine. Ziauddeen found that to be, as he said, "quite an appealing" narrative. But he questioned the parallel with foods. For example, does the refinement of complex carbohydrates into highly refined sugars increase their potency? Even in the addiction field, the process is not quite as straightforward or inevitable. People choose potencies that suit them. Not all people who use a substance choose to use a high-potency version of that substance.

O'Brien noted that this issue of potency is another of the significant difficulties in extrapolating from drugs to food. The oral mechanism of food consumption makes it very different from either intralung or intravenous administration of addictive drugs. Substantial differences in addiction potential are related to route of administration, O'Brien said. The coca leaf was used for some 5,000 years "without much trouble," he noted, but changing the route of administration "caused it to become a terrible drug." Cocaine reaches the brain very quickly.

More generally, O'Brien asked, what is to be gained when differences between drugs and foods are ignored and the two are "squeezed" together? Would it be better to set food up as a separate category?

Gearhardt agreed that the oral consumption of food is different from other, more intensive routes of administration. But alcohol is consumed orally as well. In fact, some people think of alcohol as an addictive-like food. It provides calories, which the body needs. Alcohol is good evidence, in Gearhardt's opinion, that an oral route of administration does not necessarily mean that addiction cannot occur. With respect to whether food should be placed in a separate category, in Gearhardt's opinion, doing so entails risks. She pointed to research on tobacco and statements in the 1980s and 1990s that tobacco was too different from heroin and other drugs to be considered addictive. Some people wanted to place tobacco in a separate category and apply the term "habit forming" instead.

Liquids Versus Solids: Different Gut-Brain Relationships?

During her presentation, Small had described a study showing that the relationship between caloric load and metabolic response differs for liquids versus solids, a difference that she said likely influences regulation of cue

reactivity. An audience member asked whether there was a corresponding brain imaging component of the "salad study." Small said, "Not yet."

Small also was asked why she chose to use salads as the solid food and whether the liquid-solid difference observed might be attributable to a difference in macronutrient content, with the salads containing few sweet components and the beverages containing many. Small replied that the salad dressing was sweetened with the same sweetener used in the beverage—maltodextrin. In fact, the dressing was basically the same flavor but a thicker substance. That said, she agreed that the difference in metabolic response could be attributable to a macronutrient difference. She and her team are following up on that possibility.

Cultural and Familial Factors to Consider

The panel was asked whether anything can be learned from cultural differences in taste preferences—for example, the greater emphasis in Asian cuisine on umami and lesser emphasis on sweet. In response, Gearhardt remarked that how one eats and when one eats may be relevant. She observed that having socially constrained periods for use of an addictive substance is a way to keep that substance from becoming a widespread problem—for example, using wine only during church services or in certain social settings. When a cultural definition of when it is appropriate to use a substance erodes, addictive-like behaviors increase. Today's snacking and eating in the car or at the computer may be an example of that type of cultural change, Gearhardt said. In her opinion, sitting down at meals appears to have been more prominent 40 or 50 years ago than it is today.

An audience member observed that today's children eat more unsupervised meals than children of past generations and questioned whether insufficient parenting skills related to etiquette, the use of utensils, and so on may be contributing to unhealthy eating behaviors in children. She suggested conducting future eating behavior studies with children aimed at determining whether the occurrence of family meals (as opposed to unsupervised meals) may make a difference. Gearhardt pointed to work by Julie Lumeng and Alison Miller on the relationship between child–parent interactions and different eating-related outcomes. These researchers are finding that certain parenting techniques do help, but eating-related outcomes depend on many other factors as well. For example, obesity is especially problematic in areas of low socioeconomic status, where access to food and the ability to find good child care are limited. Also, children vary in their sensitivity to food advertising. Gearhardt agreed that the American culture is shifting, with family meals not being what they used to be, but there are other factors at play as well.

The Need for Larger Studies

Edmund Rolls observed that researchers studying disorders such as autism and schizophrenia are conducting brain imaging analyses of very large databases (e.g., studies with 500 patients and 500 controls) and looking for differences. He suggested that researchers studying eating behavior adopt a similar approach, that is, collect brain imaging data in a very large database and look for correlations with individual questions from the YFAS. In the same studies, researchers could also look for biomarkers that correlate either with the activation seen in the brain imaging or responses to the questions. Rolls suggested further that such an approach would not necessarily have to be in the form of one large study. Rather, it could involve multiple teams collecting and contributing data from 20 to 50 subjects. He asked the panel whether they thought this would be a useful approach to determining whether there is a subclass of people who could be described as "addictive."

Gearhardt replied that such a large study across multiple sites would be "really wonderful." An important question to consider is the nature of the indicators that would be used to identify addiction. Gearhardt repeated what she had emphasized during her presentation about the use of BMI alone being insufficient. Behavioral indicators associated with addiction would be necessary, but the measures across sites would need to be similar.

Ziauddeen echoed that "[such research] is a great idea." The one thing to keep in mind, in his opinion, is that such studies are based on specific phenotypes being examined and specific imaging data being collected. Several levels of specification are required before the data can actually be collected.

Imaging Studies of Eating Behavior: How Far Has the Methodology Advanced?

Mattes observed that new technologies often experience a "honeymoon" period when researchers use a "shotgun" approach to discovery. He asked whether the field of imaging is at a point yet where researchers should be generating hypotheses about how certain manipulations are expected to activate specific areas of the brain.

Ziauddeen replied that he would like to see the field move to the point where researchers can conduct an intervention and determine its effect without measuring that effect as a change from baseline. But the field is not at that stage yet, in his opinion. Presently, researchers can use imaging reasonably well within a controlled test/retest paradigm. That is, they collect baseline data, apply an intervention, then measure the change from baseline.

According to Small, however, at least some researchers are trying to conduct hypothesis-driven imaging studies. For example, several studies have demonstrated a relationship between dorsal striatum activation in response to a milkshake and BMI. That is, as BMI increases, the response decreases. But among individuals at risk for obesity, there is no decreased response. Small and her research team have been testing some (unnamed) compounds to see whether they can reverse that effect (i.e., increase response in the dorsal striatum that is believed to be caused by adiposity or a high-fat/high-sugar diet).

While on the topic of imaging studies, Mattes observed that most neuroimaging data are presented as dichotomous outcomes. An area of the brain is either activated or not. Mattes asked whether imaging studies are expected to gain specificity such that one will be able to observe graded responses like those being sought with behavioral measures. Ziauddeen replied that in fact, many imaging studies rely on regression analyses. For example, the studies described by Small during her presentation were regression analyses with BMI on the x-axis and gradation of activation responses on the y-axis. However, Ziauddeen agreed that many neuroimaging studies ask dichotomous questions and that the field needs to move toward greater use of continuous measures.

Reliability of the YFAS Scores

When asked by Mattes about a test-retest correlation for the YFAS over extended periods of time, Gearhardt noted that a student of hers is currently collecting those data. The YFAS has been tested more for validity than for reliability, she said.

The Concept of "Food Addiction": Implications for the Future

A member of the audience asked: If some day it is decided, based on the evidence, that fat and sugar are addictive, given that both fat and sugar are "absolutely required" by the human body, then what? What will the implications be for the food system? Small agreed that fat and sugar are necessary for the human body, but people do not need to be consuming them at today's levels. She expressed the hope that 20 years from now, researchers will have identified which mechanisms in the human body are being overtaxed by high-fat/high-sugar foods in the modern diet and will know how to change those foods in a way that reduces their addictive potential while maintaining their palatability. She encouraged collaboration with food industry scientists.

Also looking toward the future, another audience member asked about the clinical implications of food addiction should it become recognized as

a diagnosis at some point in the future. What would be done differently? Gearhardt explained that the cognitive-behavioral approach currently used with people who have binge eating disorder is based on cues and identification of what triggers those cues. One of the goals is to help individuals avoid situations, such as being in an extreme fasting state, that trigger binge eating. The current approach is based on the notion that there are no "good" versus "bad" foods. For example, if a person has a problem with chocolate, a therapist may suggest actually eating some chocolate and not being so restrictive. Rarely does the therapist try to help someone abstain altogether from eating chocolate or another problem food, such as french fries. If food addiction is recognized as a diagnosis at some point in the future, Gearhardt foresees a different treatment approach—one based on identifying which foods trigger the addictive response and helping people moderate their intake of or in some cases abstain from eating certain types of foods.

In response, O'Brien insisted that those approaches are already being taken. An official diagnosis of addiction, in his opinion, would not change the current psychotherapeutic approaches.

4

Future Directions: Is the Addiction Model for Drugs and Alcohol Appropriate for Food?

Moderator Joseph Levitt[1] opened the third session of the workshop by highlighting the popularity of the term "food addiction" not only in the media but also in the medical community. The notion that some foods may have addictive qualities now occupies a space next to low fat, low carb, and gluten-free in the American search for simple solutions to the obesity crisis, Levitt said. He observed that during the Korean War, malnutrition was the number one medical reason for rejection from military service; today, more than half a century later, the number one medical reason for rejection from military service is obesity (Christeson et al., 2010). "That is an enormous change," Levitt said. But the question raised by Eric Decker[2] earlier during his introductory remarks needs to be addressed: Is addiction the proper model for examining overeating, overweight, and obesity?

Throughout the workshop, participants expressed varying opinions about how to interpret existing evidence for addictive-like eating behavior from neuroimaging studies based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). Some participants argued that existing evidence suggests that at least some eating behaviors, namely binge eating, can be characterized as addictive, while others opined that the data in this regard are inconclusive (see Chapter 3). The third session of the workshop, summarized here, comprised two counterpoint

[1] Joseph Levitt, J.D., is with Hogan Lovells US LLP, Washington, DC.

[2] Eric Decker, Ph.D., University of Massachusetts Amherst, is a member of the Food Forum and was chair of the workshop planning committee.

BOX 4-1
Key Points Made by Individual Speakers

- In rats, overconsumption of sugar and other highly palatable foods has been associated with drug-like alterations in the brain (including the repeated release of dopamine), signs of withdrawal and craving, and cross-sensitization with drugs of abuse, according to Nicole Avena. Avena urged care in defining the concept of addiction. Rather than the extreme loss of control typically associated with addiction (e.g., heroin use), she proposed that addiction to palatable foods may be more in line with the milder and less pronounced loss of control associated with the most commonly abused and addictive substance available—cigarettes. She argued that studying "food addiction" adds to the field of obesity research, and in no way does it preclude the legitimacy of any of the other multiple factors contributing to overeating and obesity.
- While evidence presented by Avena and others shows an overlap between brain mechanisms and behaviors associated with foods and those associated with drugs, Peter Rogers cautioned that such an overlap is not evidence for addiction. Rather, some of the brain chemistry changes being observed when rats overeat may actually reflect a "positive" attempt to reduce continued overeating. Rogers proposed that the evidence does not support the case for addiction, and he opined that the addiction model may be counterproductive.

presentations on the appropriateness of applying the addiction model for drugs and alcohol to eating behavior. Box 4-1 highlights key points made by speakers during this session.

THE ADDICTION MODEL IS APPROPRIATE FOR USE WITH FOOD[3]

Echoing what several other participants had previously said or implied, Nicole Avena identified obesity as "one of the main reasons why we are all here today." Researchers have been trying for some time, she said, to understand how the concept of "food addiction" might play into the many factors contributing to the rising obesity epidemic. After providing an overview of factors contributing to obesity, she described her own research, along with other supporting studies, on the characterization of food addiction using a rat model. She noted that her work in the field extends back to when she was a graduate student with Bart Hoebel at Princeton University.

[3] This section summarizes the presentation of Nicole Avena, Ph.D., Mount Sinai School of Medicine, New York, New York.

Why Are So Many People Overweight or Obese?

A majority of the U.S. population is overweight or obese. Not only are overweight and obesity associated with multiple comorbid health concerns, such as heart disease and diabetes, but they also have significant psychological, social, and economic consequences (IOM, 2012; Tsai et al., 2011). But why, Avena asked, are so many people overweight and obese despite all the education and warnings they receive? Why do so many people have such a difficult time regulating their body weight? Avena emphasized that obesity is an endpoint, with no singular cause and many factors at play. For example, portion sizes have increased over the past several decades. Also, acquiring food today is much easier than it was for our hunter-gatherer ancestors. Other contributing factors include today's sedentary lifestyles, genetic vulnerability, social norms regarding food, and stress and endocrine factors. Avena's research program is focused on the taste of food and how food as reward may also be contributing to the obesity epidemic.

What Is a Food?

Avena raised the question: What is a food? She showed images of nutrition labels for two "foods"—one obviously baby carrots, with the only listed ingredient being "whole baby carrots, frozen, unprepared," and the other unidentifiable by its long list of ingredients. The latter turned out to be Pop-Tarts. Avena suggested that before discussing how to determine whether certain foods can meet the criteria for being "addictive," the term "food" may need to be defined or characterized differently from how it currently is.

Avena also suggested that it is necessary to consider what is meant by "eating." There are multiple reasons why people eat—for hunger but also for hedonic purposes, that is, not because they are hungry but because they derive pleasure from eating or tasting a food. Avena clarified that when she describes research on "food addiction," she is referring to hedonically driven eating. The types of foods often eaten for hedonic purposes tend to be hyperpalatable, ultra-processed foods that contain many added sugars, fats, and other ingredients (Monteiro et al., 2011).

There are pathways in the brain that reinforce natural behaviors, such as sexual and feeding behaviors, causing individuals to engage in the behaviors repeatedly. Drugs of abuse activate those same pathways, according to Avena. Highly palatable foods, she said, activate brain reward systems beyond what is seen when healthy food is eaten (e.g., with rats, their rat chow), and instead act in ways that could potentially be putting these systems into "overdrive" (Avena and Gold, 2011). Given the overlaps in neural circuitry associated with eating and with drug use and abuse, the

empirical question Avena and her research team have been asking for many years is: Could some people be "addicted" to eating highly palatable foods rich in sugar and fat in ways that resemble drug addiction, and could such out-of-control eating result in increased body weight and obesity in some individuals?

Empirical Studies of Food Addiction Using Animal Models

Avena's research involves the use of animal models to determine whether DSM-IV and DSM-5 criteria for substance use disorders (APA, 2000, 2013) apply when the substance in question is a highly palatable food instead of a drug. That is, instead of giving animals drugs, she and her research team give them delicious foods to eat. Avena emphasized that not all of the DSM-IV or DSM-5 criteria need to be met for diagnosis of a substance use disorder. Also of note, Avena was drawn to the use of animal models because they allow researchers to examine biological correlates of behavior often impossible to study in humans.

Avena started her inquiry into food addiction by looking at sugar (Avena et al., 2008b). She chose sugar for several reasons, including the fact that Americans consume on average 22 teaspoons of added sugar daily (NCI, 2010). Studies suggest that sugar appears to be one of the ingredients many people find particularly problematic, such that they have difficulty regulating the intake of foods rich in sugar when they try to cut back. There also have been several studies finding a correlation between sugar intake and obesity. Thus, for Avena, sugar appeared to be a good ingredient to examine first.

In one study conducted by Avena's group (Rada et al., 2005), rats were given access to standard rat chow plus a sugar solution for 12 hours a day for 21 days and were observed to drink more sugar over time. By the end of the 3-week period, these rats were bingeing on the sugar solution and showed evidence of tolerance as they were consuming more and more each day, which suggests that an increased amount was needed to achieve the same effect (Rada et al., 2005). This bingeing behavior was particularly apparent during the first hour of access to the sugar solution following the 12-hour period of abstinence. Of interest, Avena noted, rats provided with chow and sugar ad libitum (one of the control groups) did not show this escalation in daily intake. Other control groups included rats that had access to sugar only on days 1, 2, and 21 of the experiment and rats that had 12-hour daily access to chow only (no sugar). It was only the rats that were bingeing on the sugar daily that showed increased intake over time.

Avena and her team were curious about whether the overconsuming rats in the test group were releasing dopamine in a way that was consistent with consuming a food or a drug. A hallmark of drugs of abuse is that they

can cause a release of dopamine in reward-related regions of the brain, such as the nucleus accumbens, every time they are administered. Food also can cause the release of dopamine, according to Avena, but the dopamine release normally wanes when the food is no longer novel and an individual becomes habituated to it. She and her team found that, indeed, rats that were overconsuming the sugar solution were releasing dopamine every time they had access to the sugar. This was as true on day 21 as it was on day 2. Rats in the ad libitum control group and the control group that drank the sugar solution only occasionally, on the other hand, did not show the same release of dopamine over time, nor did the rats that consumed chow and no sugar (Rada et al., 2005). According to Avena, these results suggest that there is something about sugar such that when rats overconsume it, they release dopamine in a drug-like way.

Other studies have shown that rats that overconsume sugar show physical signs of withdrawal, distress, and anxiety when the sugar is taken away or when they are administered an opioid antagonist, which blocks opioid receptors in the brain (Avena et al., 2008b; Colantuoni et al., 2001). Additionally, the reward-related regions of their brains show a decrease in dopamine levels, coupled with an increase in acetylcholine (Avena et al., 2008a). According to Avena, a similar dopamine-acetylcholine imbalance has been seen during withdrawal from many drugs of abuse, including cocaine, nicotine, and morphine.

Craving is a difficult behavior to assess with animal models, in Avena's opinion. She considers it a highly subjective, psychological characteristic. Nonetheless, several researchers have assessed features of craving in rats in an effort to understand its biological basis (Avena et al., 2005; Grimm et al., 2005; Krasnova et al., 2014; Oswald et al., 2011). Oswald and colleagues (2011) provided M&Ms to rats that were either prone or resistant to binge eating, the catch being that the rats had to cross an electrified shock grid to get to the M&Ms. The researchers found that the rats prone to binge eating endured greater magnitudes of shock to obtain the treat relative to their binge-resistant counterparts. Other studies have shown that following an abstinence period, rats prone to bingeing on sugar increase their intake of sugar when it is made available (Avena et al., 2005) and work harder to gain access to sugar-associated cues (Grimm et al., 2005).

Avena and her team also studied cross-sensitization between overconsumption of sugar and drugs of abuse (Avena and Hoebel, 2003; Avena et al., 2004). They found that animals with a history of overeating sugar became hyperactive when administered a very low dose of amphetamine, a potent dopamine agonist, instead (Avena and Hoebel, 2003). Animals without a history of overeating sugar, on the other hand, did not show the same hyperactivity in response to the same dose of amphetamine. These results suggest to Avena that there is something about sugar consumption,

presumably the effect it is having on the dopamine system, that causes even a very low dose of amphetamine to have this effect. Greater evidence of cross-sensitization was observed when rats with a history of overconsuming sugar were provided with alcohol instead of sugar; they drank more alcohol than did control rats that were exposed to sugar, but did not overconsume it (Avena et al., 2004).

Avena mentioned that many other food addiction studies have focused on sugar-fat combinations and combinations of other foods. Many researchers have used as a test condition the cafeteria diet, whereby rats have been provided a wide variety of high-fat, high-sugar foods, as well as healthy foods. For example, Geiger and colleagues (2009) found that animals on a cafeteria diet became overweight or obese and when provided amphetamine in vivo or in vitro, released much more dopamine than chow-fed control rats. Moreover, when their cafeteria diet was replaced with regular lab chow, the rats did not show an increase in release of dopamine. Only when their cafeteria diet was reintroduced did these rats again show an increase in dopamine release. According to Avena, these results suggest that the cafeteria diet had changed the rats' brains in a way that was similar to what is seen in rats that overeat sugar and that caused the animals to react to healthy food differently from the way the rats maintained on a healthy diet reacted.

Issues to Consider

Since this was a debate, Avena identified several issues raised by critics of this work to consider, or reconsider, in moving forward. First is the notion put forth be some experts that the construct of food addiction is "distracting" and diverts attention from the main causes of overeating and obesity (Rogers, 2013). According to those critics, obesity is better viewed as being due to a "toxic" environment (Rogers, 1999). Avena said, "I couldn't agree more that a toxic environment is certainly a big part of this." That said, she reiterated that overeating and obesity have multiple contributing factors and that research on "food addiction" does not preclude the legitimacy of any other factor; thus, there is no reason to consider it "distracting."

Additionally, critics have noted that the construct of food addiction may be fitting for individuals with binge eating disorder but not for understanding obesity. That is a valid criticism, in Avena's opinion, given that much of the laboratory work done to date has aligned food addiction with binge eating. To further understand how the food addiction construct may be helpful for understanding obesity, Avena reminded the audience that care is necessary in defining addiction. Usually when people think about addiction, they think about an extreme loss of control (Altman et al., 1996). But

quoting Rogers (2013), Avena stated that while an extreme loss of control may characterize binge eating, it does not describe well the repeated failure to resist energy-rich foods in large portions that gradually contribute to weight gain. Avena remarked that many people think of the typical addict as someone lying in a gutter with no job and no family. But in reality, the typical addict in American society is a mom driving her kids to soccer practice and smoking cigarettes—someone who is likely a fully functioning individual for whom withdrawal syndrome is not physically life-threatening. Avena suspects that addiction to palatable foods may be more like addiction to cigarettes than to drugs of abuse, and thereby produce the same type of milder and less pronounced loss of control that is associated with smoking.

Finally, some critics argue that stigma may be conferred when a person is diagnosed as a "food addict." Again, this is a valid concern in Avena's opinion, but scientific data suggest it is unfounded. She pointed out that recent studies suggest that the stigma conferred by being labeled a "food addict" is no greater and may even be less than that associated with being labeled "obese" (DePierre et al., 2013; Latner et al., 2014).

THE ADDICTION MODEL IS NOT APPROPRIATE FOR USE WITH FOOD[4]

Peter Rogers's interest in the appropriateness of the addiction model for use with food stems from his interest in understanding human appetite and weight control and his work in caffeine psychopharmacology. During his talk, he questioned the definition of addiction, evidence for "food addiction" from animal and human studies, and the usefulness of "food addiction" in explaining and reducing overeating. But first, he noted that in his opinion, caffeine illustrates very well the distinction between dependence and addiction. Most people who consume caffeine—who he suggested represent the majority of people on the planet—are dependent on it. If they become tolerant to its psychostimulant effects and it is withdrawn, they become fatigued and tired. But few people who consume caffeine experience the extreme loss of control that is characteristic of addiction.

Also to set the stage for his talk, Rogers displayed a headline from a June 2013 edition of the *Metro (UK)*: "Potatoes Give You 'Drug Fix.'" The article read: "You might not have to shoot . . . it up to get a fix. But food is just as addictive as heroin and nicotine, research suggests. Substance abuse and high-glycemic foods—such as white bread and potatoes—trigger the same brain mechanism as that linked to addiction, according to Boston Children's Hospital. They apparently cause excess hunger and stimulate

[4] This section summarizes the presentation of Peter Rogers, Ph.D., M.Sc., B.Sc., University of Bristol, Bristol, United Kingdom.

reward and craving in parts of the brain." Rogers questioned whether those ideas and that sort of reporting help encourage healthier eating or weight loss.

What Is Addiction?

There are several ways to define addiction, noted Rogers. The *Concise Oxford English Dictionary* (Stevenson and Waite, 2011) defines it as a "a fact or condition of being physically dependent on a particular substance," a definition that Rogers observed is aligned with how other workshop speakers had defined it. Other definitions are milder and imply something that someone simply likes to do frequently or is particularly interested in. For example, when people say they are "addicted" to soap operas, they mean that watching soap operas occupies a large amount of their time. And people who call themselves "chocoholics" usually are communicating that they probably eat more chocolate than they would like to rather than indicating a serious problem with that substance.

Rogers's preferred definition of (drug) addiction comes from Altman and colleagues (1996): "Addiction is restricted to the extreme or psychopathological state where control over drug use is lost." He emphasized the importance of "extreme state" and "loss of control." Additionally, Altman and colleagues (1996) define (drug) dependence as "the state of needing a drug to function within normal limits; it is often associated with tolerance and withdrawal [symptoms], and with addiction as defined above." They state, "Tolerance, sensitization, withdrawal and craving are phenomena that may accompany dependence." Rogers emphasized that dependence and craving, while associated with addiction, are not necessary for addiction.

A Counterargument to the Case for Food Addiction

As a "scaffolding" for his talk, Rogers referred to Gearhardt and colleagues' (2011a)[5] synopsis of the case for food addiction (emphasis added by Rogers):

> The food environment has changed dramatically with the influx of *hyperpalatable foods* that are engineered in ways that appear to surpass the rewarding properties of traditional foods (e.g., vegetables, fruits, nuts) by increasing fat, sugar, salt, flavors and food additives to high levels (Table 1). *Foods share multiple features with addictive drugs.* Food cues

[5] Reprinted with permission. Gearhardt, A. N., C. M. Grilo, R. J. DiLeone, K. D. Brownell, and M. N. Potenza. Can food be addictive? Public health and policy implications. *Addiction* 106(7):1208-1212. Copyright © 2011. [1] = Volkow et al., 2008; [2] = Blumenthal et al., 2010; [3] = Avena et al., 2008b; [4] = Johnson and Kenny, 2010.

> and consumption can activate neurocircuitry (e.g., meso-cortico-limbic pathways) implicated in drug addiction [1,2]. *Animals given intermittent access to sugar* exhibit behavioral and neurobiological indicators of withdrawal and tolerance, cross-sensitization to psychostimulants and increased motivation to consume alcohol [3]. Rats consuming *diets high in sugar and fat demonstrate reward dysfunction associated with drug addiction,* downregulation of striatal dopamine receptors and compulsive eating, including continued consumption despite receipt of shocks [4].

Rogers identified several key points of this summary worth reconsidering (i.e., the points in italics above), one of them being that foods share multiple features with addictive drugs. That argument, he explained, is based on an observed overlap between the brain mechanisms and behavioral processes involved in eating and those involved in psychoactive drug use or abuse. In Rogers's opinion, that overlap by itself is not evidence of addiction; it merely shows that drugs of abuse have engaged some of the same mechanisms engaged by eating. It is often argued further that addictive drugs "hijack" those mechanisms, the implication being that drugs of abuse have particularly potent effects on those mechanisms and that foods have less potent effects. In Rogers's opinion, that same point could be used to argue that foods therefore pose a relatively low risk of addiction.

Another argument put forth for the case of food addiction, one based on animal evidence, is that consumption of certain foods—those high in sugar and fat—causes reward dysfunction and sets in motion a vicious cycle of further overeating. That is, the changes that occur in the reward pathways of the brain lead to overconsumption, which leads to further brain changes, and so on. Again, the argument goes, there is a parallel with the effects of addictive drugs. The argument is based on evidence such as that reported by Johnson and Kenny (2010), who showed that rats exposed to a cafeteria diet of chocolate, pound cake, sugar frosting, and a variety of other energy-dense foods experienced increased body weight compared with rats fed a standard laboratory diet. Additionally, by implanting electrodes in the rats' brains that delivered rewarding stimulation when the rats pressed a lever, the researchers found that the rats on the cafeteria diet had a higher current threshold; that is, they experienced less reward for the same amount of stimulation compared with rats fed standard lab chow. The researchers interpreted their results as evidence of brain dysfunction.

In Rogers's opinion, there is an alternative to Johnson and Kenny's (2010) "vicious cycle" conclusion. He suggested that the higher current threshold in the rats fed the cafeteria diet was a "positive adaptation" to limit further weight gain; that is, as the rats gained weight, they became less interested in eating. He traced his alternative explanation back to a 1983 study in which he offered rats either a variety of energy-dense foods or fat,

specifically lard, along with their standard diet (Rogers, 1985). Initially, rats in both groups showed an increase in body weight. Over time, however, the rats' food intake decreased and their rate of weight gain plateaued. Rogers argued that the increased weight gain produced a negative feedback effect on appetite. When the rats were returned to their chow diet, they underate. Rogers interpreted their undereating to mean that the rats were no longer being stimulated by energy-dense palatable foods. While not discounting the significance of what he described as "our toxic obesogenic environment," Rogers identified energy density as a major contributor to overconsumption, with energy-dense foods being less satiating on a calorie-for-calorie basis than energy-dilute foods and therefore more rewarding (Ledikwe et al., 2006; Stubbs et al., 1995).

Other studies, such as that of Epstein and Shaham (2010), have shown that rats exposed to addictive drugs experience a reduced brain stimulation reward similar to that experienced by the rats on a cafeteria diet in Johnson and Kenny's (2010) study. Although the extended access to drugs caused a similar progressive disruption of the brain reward system, the reduction in brain stimulation reward declined rather rapidly when the drugs were withdrawn. That was not the case with the Johnson and Kenny (2010) rats fed a cafeteria diet, whose "reward dysfunction" persisted for a long time.

In summary, in Rogers's opinion, Johnson and Kenny's (2010) conclusions can be rewritten in a more positive way (see Figure 4-1). Their

"The development of obesity in extended access rats was closely associated with ~~a worsening deficit~~ **reduced** brain reward* ~~dysfunction~~." (p. 635)

"~~Reward deficits~~ **Reduced reward** in overweight rats may reflect ~~counter~~adaptive decreases in baseline sensitivity of brain reward circuits to oppose their ~~over~~stimulation by ~~palatable~~ food. Such ~~diet-induced~~ **obesity-induced** reward hyposensitivity may help ~~contribute to~~ **oppose** the development of obesity by ~~increasing~~ **decreasing** the motivation to **eat** ~~consume high-reward 'obesogenic' diets to avoid or alleviate this state of negative reward~~." (p. 639)

*Refers to electrical self-stimulation of a brain area known to be involved in the control of eating.

FIGURE 4-1 Conclusions of Johnson and Kenny (2010), as reworked by Peter Rogers.
NOTE: Reprinted with permission from MacMillan Publishers Ltd.: *Nature Neuroscience* (13[5]:635-641), Copyright (2010).

observations, he said, do not point to dysfunction. Rather, they point to a functioning system whereby increased weight causes changes that oppose further weight gain.

Based on these animal studies and some parallel observations in humans, the case has been made that deficits in food reward mechanisms underlie human obesity and that individuals increase their consumption of palatable foods in an attempt to overcome that loss of food reward (Gearhardt et al., 2011b). According to that argument, one would expect to see increased food consumption in response to decreased brain dopamine. However, in a human study that involved reducing brain dopamine function by depleting the amino acid precursors to dopamine—tyrosine and phenylalanine—from the test subjects' diets, Hardman and colleagues (2012) demonstrated the reverse: reduced dopamine function was associated with, if anything, a decrease in consumption of palatable food ($p < 0.06$). In Rogers's opinion, these results further support the idea that the changes in brain reward being observed in animal studies reflect adaptive changes that counter overeating.

Another argument for food addiction is the common occurrence of reported food cravings. Because of the association between craving and addiction, it has been suggested that perhaps an addictive process underlies those cravings (Gearhardt et al., 2011b). In Rogers's opinion, however, craving is a normal part of the eating experience and reflects the result of an attempt to resist eating certain foods (Rogers and Smit, 2000). He explained that it is normal for people to develop an appetite for a food, such as chocolate, as a result of being reminded of chocolate, being in a place where they recently consumed chocolate, being in a mood similar to their mood the last time they consumed chocolate, or otherwise experiencing something associated with chocolate. But if people who develop an appetite for chocolate deny themselves the chocolate—for example, because they have gained a few pounds recently—the thought of eating chocolate does not necessarily go away. If anything, the thought becomes more elaborated to the point where it could be called a craving. Rather than a craving being related to the food being craved and a cause of eating, Rogers views it as a consequence of restraint.

Many of these counterarguments, Rogers said, can be linked to some of John Davies's (1997) ideas in *The Myth of Addiction*. While some readers may regard Davies's book as an extreme view of addiction—his essential argument being that addiction is a social construct—Rogers opined that the book makes for compelling reading. Among other arguments, Davies proposes that the idea of addiction may actually be unhelpful in relation to trying to change behavior.

Attribution of Food Addiction: Helpful or Unhelpful?

It has been argued that one way in which the attribution, or label, of food addiction may be helpful is by reducing the stigma of overweight and obesity and encouraging more support for obesity treatments. There is some evidence that this is indeed the case (Hoyt et al., 2014; Latner et al., 2014; Lund et al., 2011). For example, Hoyt and colleagues (2014) found that being exposed to the notion that obesity is a disease helped reduce body image dissatisfaction. However, the researchers also found that the same individuals expressed reduced concern about weight and higher-calorie food choices. Such results suggest to Rogers that while the attribution of food addiction may reduce stigma, it also diminishes personal responsibility and motivation to change (Ogden and Wardle, 1990).

Rogers and colleagues have themselves collected preliminary data on the effects of attribution of food addiction. They provided participants with a variety of passages either confirming or disconfirming the existence of food addiction, but told the participants to read the passages and comment on the font type, writing, and other features not related to the content. Then they provided the participants with high-fat cookies, crisps, breadsticks, and grapes. They found that participants who had been primed with the idea that food addiction is a valid construct on average ate a little more food but mainly showed more variable intake than participants who had not been primed with that idea.

In summary, in Rogers's opinion, attributing overeating to food addiction may be counterproductive, at least for some people, with respect to successful eating control.

Food Addiction and Obesity

Rogers echoed the remarks of other workshop participants that most people who are obese do not display addictive-like eating behavior. In a study of the relationship between weight status and food addiction as defined by the Yale Food Addiction Scale (YFAS),[6] a little over one-third of obese individuals met the YFAS criteria for food addiction (Meule, 2011). Another study found that only about 8 percent of obese individuals met the criteria (Pedram et al., 2013). Rogers suggested that perhaps the best case for food addiction is binge eating. But again, whether binge eating is a "food addiction" depends on the definition of addiction. In a study of 79 women with a diagnosis of binge eating disorder, Cassin and von Ranson (2007) found that most of the women were "food-addicted" based on one set of criteria for addiction, but fewer than half were "food-

[6] See Chapter 3 for a discussion of the YFAS.

addicted" based on a more stringent set of criteria. Binge eating may look like addictive behavior, and there is a known association between binge eating and obesity, such that people with binge eating disorder are more likely to be obese (Pike et al., 2001). Nonetheless, the prevalence of binge eating disorder is much lower than the prevalence of overweight and obesity (Striegel-Moore and Franko, 2003).

DISCUSSION WITH THE AUDIENCE

Following Rogers's talk, both speakers participated in a panel discussion with the audience. Questions spanned a range of topics.

Intermittent Feeding in the Rat Model: Relevance to Human Eating Behavior

In her presentation, Avena had discussed results of her research with animal models aimed at determining whether DSM-IV and DSM-5 criteria for substance use disorders apply when the substance of desire is a highly palatable food instead of a drug. Edmund Rolls asked her why intermittent access to food was an important part of her rat model. What is happening when food is removed? Is the animal becoming stressed? How relevant is that type of forced removal of food to humans? Would anti-anxiety drugs abolish the observed phenomena?

The intermittent access, Avena explained, is a sort of "limited extended access." The rats have their food and sugar available for the majority of the time they are awake and active, but are unable, for example, to get up in the middle of the night and eat. Although many people tend to think of humans as living in an ad libitum food environment, with constant access to food, humans engage in self-limiting eating patterns in many ways. People tend to eat in meals, and many who are trying to lose weight restrict their intake. In Avena's opinion, the intermittent pattern used in her research caused the animals to eat in a way similar to how people who are having problems losing weight may eat.

With respect to whether anti-anxiety drugs would reverse the pattern, Avena replied that she and her team have not studied this question. They have studied some other types of pharmacological compounds, such as baclofen (a muscle relaxant also shown by some studies to assist in the treatment of alcoholism) and baclofen in combination with naltrexone (an opioid receptor antagonist), which have been shown to mitigate the effects of overeating.

Avena was asked whether overall consumption for rats with intermittent access to food was any different from overall consumption for rats allowed to eat ad libitum. She replied that, yes, the rats with intermittent access to

food not only binged when food was reintroduced into their environment but also consumed more food over the entire 24-hour period compared with the rats with ad libitum access.

Danielle Greenberg commented that even in the absence of thirst, rats drink vast quantities of water when food is provided only intermittently. It is a phenomenon known as schedule-induced polydipsia. Greenberg asked Avena whether her interpretation of the rats' sugar-bingeing behavior when provided intermittent access to food is valid given that the same thing happens with water. Greenberg replied that an important control would be an intermittent feeding schedule whereby the rats would be provided with water only. Without that control, it is impossible to know whether the overconsumption of sugar water observed by Avena and her team is any different from schedule-induced polydipsia. Avena replied that she and her team typically include a control group that has intermittent access to chow only (no sugar), and these animals do not show the addiction-like brain changes and behaviors seen when rats are overeating sugar. Thus, it does not appear that intermittent access alone is responsible for the observed effects.

Sensory-Specific Satiety: Its Relationship to Overeating and Obesity

When asked whether sensory-specific satiety contributes to obesity, Avena replied that it is unclear whether people who are obese or are overeating are experiencing dampened sensory-specific satiety or becoming satiated by one particular food and then switching to another. Rogers remarked that food variety contributes to overconsumption, although the extent of its role is not clear. In his opinion, overconsumption is possible even with a very narrow range of food variety. In fact, even a single energy-dense food can promote overconsumption, at least in animals.

Sensory Components of Foods and Addictive-Like Eating

The speakers were asked whether any research is under way to determine whether other aspects of foods besides their ingredients, such as their sensory and visual appeal, may contribute to addictive-like eating. For example, if one were to dye a hamburger and its bun green, would that dissuade some people from overeating? Avena replied that much of what is going on with addictive-like eating in humans is related to conditioning to food cues. Food cues serve, in many ways, to reinforce or encourage some eating behaviors. In fact, Avena sees this even in rats. After just a few days of access to highly palatable foods, rats learn when to expect food. They become conditioned to the researchers walking into the room to give them Cheez Doodles or M&Ms. Avena remarked that it is important to keep the effect of these cues on eating behaviors in mind when thinking about how

foods are packaged and marketed. It is possible, for example, that simply seeing a specific food or beverage package can affect the brain reward system in a way that primes someone to want to eat the food.

Rogers disagreed to some extent. However effectively cabbage is packaged, for example, he does not believe it could ever become a binge food. He stressed the importance of the characteristics of the foods themselves. In his opinion, energy density is key. Taste characteristics are important as well. Many foods people like tend to have sweet and salty tastes. Rogers views packaging as something that merely reminds people of the value of the food in terms of its energy density and taste.

Sugars Versus Artificial Sweeteners: Dopamine Release and Overeating

Avena was asked whether there is any evidence that her sugar model in rats is applicable to artificial sweeteners. She replied that artificial sweeteners are difficult to study in rats because rats do not taste them the same way that humans do. For example, rats cannot detect the taste of aspartame. However, Avena and her team have done relevant work with sugar sham feeding, whereby they provide the animals with a sugar-containing food that they can taste and ingest but not necessarily digest (because it exits through the stomach via a gastric cannula). This work has revealed that sweet taste alone is sufficient to elicit the dopamine release associated with the addiction-like behaviors. Of interest, Avena noted that other researchers have observed the same release of dopamine in reward regions of the brain when sugar is infused into the gut. She remarked that consuming caloric sugar produces a "double whammy" effect because dopamine is released in response to both the taste and postingestive effects of surgar, whereas artificial sweeteners stimulate only some dopamine release in response to the sweet taste.

When asked whether it would be possible to test the effects of artificial sweeteners in primates, Rogers commented that in some ways, such research has already been conducted. Many human studies have compared the appetite and long-term body weight effects of beverages (or foods) sweetened with artificial sweeteners and the effects of sugar-sweetened beverages (or foods) or water. In Rogers's opinion, all of the evidence to date converges on the notion that "intense sweeteners" help people eat less and lose body weight. (Rogers noted that he prefers the term "intense sweetener" over "artificial sweetener," because some so-called artificial sweeteners arguably are not artificial.)

Overeating, Obesity, and Socioeconomics

An audience member observed that people in communities of lower socioeconomic status, in which food is purchased at corner stores and not

in supermarkets where fresh foods are abundant, appear to develop an attachment to highly palatable foods and an apparent aversion to healthy foods. She asked whether there is a solution to this problem. Avena observed that she has seen much of this behavior in Harlem and noted that several organizations in New York City are making efforts to educate children about the importance of seeking out fruits, vegetables, and other healthy foods.

Rogers agreed that education is important and added that convenience and access are also parts of the problem. Many so-called healthy foods require more skill and equipment to prepare relative to many energy-dense foods. Rogers pointed to the replacement of french fries with apple slices in children's meals by McDonald's as a successful example of nudging eating behavior in a healthier direction. Fergus Clydesdale, University of Massachusetts Amherst, noted that some healthy foods are in fact available in frozen or canned form.

Another audience member observed that the higher rate of obesity in resource-poor communities is a much larger problem than a lack of education. Most of these communities are so stressed that it does them a disservice to "simply say that you can educate them out of this." Avena reiterated the importance of education but also agreed that to think that education will be enough is "overly ambitious and overly hopeful." She said, "We need to think beyond that and think outside the box in terms of how we might diversify some of our approaches."

Rogers remarked that obesity shows the same socioeconomic patterning as other unhealthy behaviors, including drug use and alcoholism, and agreed that stress in certain communities may underlie those unhealthy behaviors. But there are other elements as well, in his opinion. He pointed to attitude as a potential problem, with studies in the United Kingdom showing that in some communities obesity is considered the norm and diabetes is considered an inevitable part of getting older. Thinking about those unhealthy conditions as normal or inevitable, in his view, probably undermines the idea that one can or should try to change one's behavior. He suggested developing approaches to tackle those attitudes.

Pleasure Versus Addiction: Neuroimaging Evidence

A member of the webcast audience observed that listening to jazz music has been shown to elicit the same dopamine response in the striatal system as that activated by consumption of hedonically pleasing foods. He asked whether, given that observation, Avena was willing to make the argument that listening to jazz music is addictive. Or are current biological methods unable to distinguish between addiction and pleasure?

Avena replied that she did not think this observation warrants calling

listening to jazz an addiction and reiterated that no single feature defines a substance as addictive. While palatable foods are known to activate brain reward systems, so are many other pleasurable activities. But whether those pleasurable activities are addictive depends on how the reward systems are engaged; the extent to which they are engaged; and whether other concomitant features of addiction manifest, as has been shown with palatable foods. She said, "When we talk about addiction, we are talking about a multifaceted, multifeatured issue that we need to study from multiple angles."

For Rogers, it is useful to think of the addiction risk posed by a substance. He cited a case report of "carrot addiction" in the *Australian and New Zealand Journal of Psychiatry* (Kaplan, 1996). In his opinion, carrots pose a low risk of addiction. Yet Rogers noted that, as this report demonstrates, it is possible to show addictive behavior in relation to eating carrots.

5

Integrating the Evidence

As elaborated throughout this summary, much of the workshop discussion revolved around how on the one hand, food triggers satiety signals from the digestive system to the brain indicating fullness, or hunger, while on the other hand, food and food cues also send sensory signals that activate the brain reward system. In his closing presentation, Edmund Rolls brought these ideas together and explored how sensory and satiety signals are integrated in the brain. Moreover, bringing the discussion full circle and touching on the concept of context that Laurette Dubé had introduced earlier in the workshop, Rolls explored how "higher-level" cognitive factors influence how people actually perceive and respond to all of these signals being received by the brain. This chapter summarizes his closing presentation and the discussion that followed. Box 5-1 highlights key points made by Rolls.

FOOD REWARD, APPETITE, SATIETY, AND OBESITY[1]

Rolls hypothesized that obesity is related to an imbalance between the satiety and sensory-produced reward neural systems, with the latter overriding the former as a function of individual differences in cognitive control. He described eating as an output of the interaction in the brain of satiety signals, all of the various sensory inputs (taste, smell, texture, sight) that are con-

[1] This section summarizes the concluding presentation of Edmund T. Rolls, D.Phil., D.Sc., Hon.D.Sc., M.A., Oxford Centre for Computational Neuroscience, Oxford, United Kingdom. Rolls mentioned Fabian Grabenhorst as a major contributor to the work that he discussed.

BOX 5-1
Key Points Made by the Concluding Speaker

- Edmund Rolls hypothesized that obesity is related to an imbalance between the satiety and sensory-produced reward neural signals, with the latter overriding the former. There are individual differences in the potency of reward signals. Moreover, cognition can influence the reward effects of food. Evidence from nonhuman primate and human studies suggests that all food-related sensory stimuli, including taste, olfactory, and visual stimuli, converge in the brain in the orbitofrontal cortex and amygdala, where the reward value of the food is computed and then modulated by gut satiety signals. Top-down cognitive control appears to be expressed in the same area of the brain as well.
- In Rolls's view, given that humans are generally dominated by sensory inputs with high reward value, a key challenge for the food industry is to create highly palatable foods with low energy density.

verted into reward signals, and cognitive factors that modulate food reward (see Figure 5-1). He noted that satiety signals have been "genetically set" for tens of thousands of years, but that many of the sensory and cognitive effects of food have changed considerably over just the past 30 years with the increased availability of a wide variety of very highly palatable foods.

As far as which parts of the brain play a role in food intake, Rolls pointed to the orbitofrontal cortex and amygdala in the temporal lobe as being important sites of convergence for sensory inputs from the primary taste cortex (taste), the olfactory cortex (smell), the visual cortex (sight), and the somatosensory cortex (texture). For example, the taste pathway in primates, which enters via the brain stem and passes through the primary taste cortex, ends in the orbitofrontal cortex and amygdala. Neurons in the primary taste cortex do not actually respond to the input they are receiving. They simply "tell" the brain what the stimulus is independently of how "nice" or "pleasant" it is. Only when that signal reaches the orbitofrontal cortex and amygdala is its reward value represented. The same is true of other sensory signals as well.

In primates, the same areas of the brain—the orbitofrontal cortex and amygdala—also receive satiety signals, which enter by way of the lateral hypothalamus and brain stem to influence the reward value of food-related sensory stimuli. Also in primates, "top-down" cognitive processes have major influences on activity in the orbitofrontal cortex and amygdala and affect the way taste and other sensory stimuli are processed. Cognitive modulation of reward value is important, Rolls said, in determining how people respond in any situation.

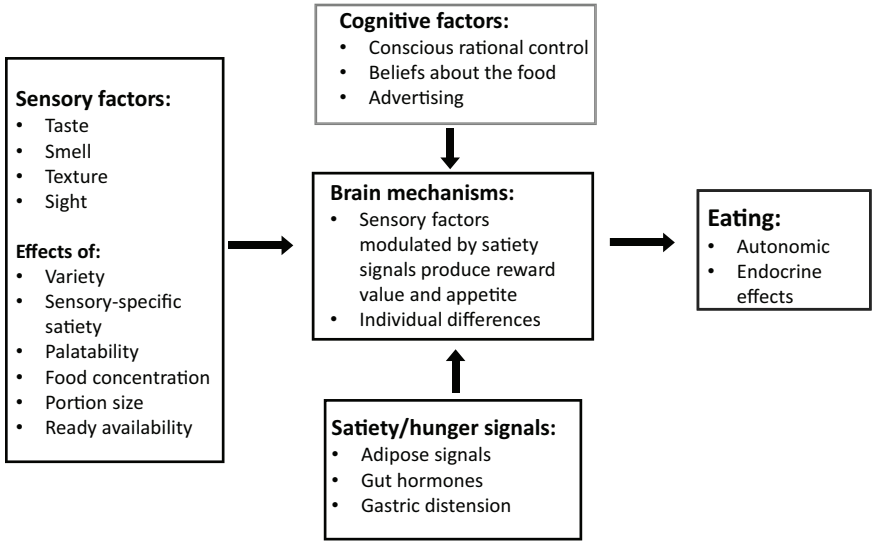


FIGURE 5-1 Rolls's framework for integrating all of the different food-related inputs in the brain and their effects on eating behavior.
SOURCE: Rolls, 2011. Reprinted by permission from Macmillan Publishers Ltd. on behalf of Cancer Research UK: International Journal of Obesity (London) (Rolls, E. T. 2011. Taste, olfactory and food texture reward processing in the brain and obesity. *International Journal of Obesity [London]* 35[4]:550-561), copyright 2011.

Sensory Signals and Reward

Sensory neurons are highly selective. Rolls showed data illustrating the selectivity of a single taste neuron that responds to glucose sweetness but not to salt, sour, or water and that can even differentiate between glucose sweetness and fruit juice. In a study of the macaque orbitofrontal cortex, Rolls and colleagues (1989) demonstrated that a single glucose-sensitive neuron increased from a baseline firing rate of a few spikes per second to 20 spikes per second when the monkey was fed glucose. As the monkey was fed more glucose, eventually the firing rate of that same neuron decreased to zero, as did the monkey's feeding behavior. But the same neuron tested with fruit juice (black currant juice) continued to respond even after it had stopped responding to glucose. Rolls and his team interpreted these results as evidence for sensory-specific satiety, with the reward value of the glucose decreasing to a point where the monkey started rejecting the glucose but still responded to fruit juice. According to Rolls, the same phenomenon has been demonstrated repeatedly in humans.

Of importance, it is only in the orbitofrontal cortex, not the primary taste cortex, where taste reward value is represented. In a related study, Rolls and colleagues (1989) demonstrated that when fed glucose to satiety, neurons in the primary taste cortex continued to fire at the same rate even as those in the orbitofrontal cortex slowed to zero. Rolls described the orbitofrontal cortex as the "reward antenna on the world." It "tells" the brain about the various details of food based on the responses of all the different orbitofrontal cortex neurons, with each neuron responding to a different combination of taste, odor, texture, and temperature stimuli. For example, one neuron might respond to glucose and fruit juice but not to sodium and monosodium glutamate, another to viscosity but not to taste, another to fat texture but not to viscosity, and so on (Verhagen et al., 2003). Together, the population of neurons in the orbitofrontal cortex produces information about a rich variety of reward stimuli and provides for sensory-specific satiety related to specific combinations of stimuli.

As another example of the selectivity of sensory neurons, Rolls and colleagues (1999) demonstrated that not only does the orbitofrontal cortex contain oral fat texture-specific neurons, but those neurons contribute to sensory-specific satiety. When test monkeys were fed cream, their fat texture-specific neurons fired until the monkeys became satiated on the cream. But after the neurons stopped responding to the cream, they continued to respond to glucose. In Rolls's opinion, the fact that some neurons in the orbitofrontal cortex respond to fat texture but not to other textures has important implications for the food industry: low energy-dense foods could be made highly palatable through the incorporation of substances that trigger a fat texture response (Rolls et al., 1999, 2003; Verhagen et al., 2003).

Rolls emphasized that food rewards in the orbitofrontal cortex are a neuronal representation of stimulus value that have nothing to do with behavioral responses (Grabenhorst and Rolls, 2011; Rolls and Grabenhorst, 2008). In other words, the responses tell people "how nice things are, but not what to do about them." At least that is the case with nonhuman primates, based on the evidence.

As far as human evidence goes, in one of Rolls's early human neuroimaging studies, people were provided either tomato or chocolate to taste and later fed to satiety with that food (Kringelbach et al., 2003). The researchers found for both foods that the measured signal in the orbitofrontal cortex was high before the individuals became satiated and then decreased upon satiation, as did the pleasantness rating of the food. Moreover, either food could trigger sensory-specific satiety. After subjects were fed to satiety with tomato, their brain still responded to chocolate, and vice versa.

In another human imaging study, de Araujo and Rolls (2004) observed significant representation of oral fat texture in the anterior cingulate cortex

and ventral striatum that was independent of viscosity. They also observed a convergence of responses to oral fat and sucrose in the most anterior part of the cingulate cortex. Grabenhorst and colleagues (2010) found a linear relationship between a fat texture signal in the orbitofrontal and anterior cingulate cortex measured with magnetic resonance imaging (MRI) and the signal's subjective pleasantness rating.

The Processing of Reward: Modulation by Cognition

If an individual is provided with an ambiguous stimulus—such as the chemical compound isovaleric acid, whose odor is similar to that of some cheeses, such as brie, but is also similar to body odor—the brain responds differently depending on how the stimulus is described (de Araujo et al., 2005). With isovaleric acid, for example, if one were told that what one was smelling was brie, one would believe that it was brie. But if one were told that it was soldiers' socks, one would believe that it was soldiers' socks. Based on these different responses to the same stimulus, Rolls wanted to know where in the brain sensory and reward information is being influenced by cognition. Does the flavor reward representation travel up into some cognitive area, or does cognition travel down into the reward system? Evidence indicates the latter.

By delivering isovaleric acid into the nose of test individuals using an olfactometer, Rolls and colleagues observed greater activation in the pregenual cingulate and orbitofrontal cortex when individuals were told that what they were smelling was cheese compared with when they were told it was body odor (de Araujo et al., 2005). In a control condition, in which individuals were provided with no actual odor but told that what they were smelling was either cheese or body odor, the response to cheese was still greater than the response to body odor, but there was a much lesser top-down effect than when there was also a bottom-up signal from the odor. Rolls interpreted these results to mean that cognitive effects, such as descriptions of food in advertising, affect the parts of the brain that represent pleasantness and reward value.

Top-down attention matters, too. In another human imaging study, participants were delivered monosodium glutamate taste and were told to rate either its pleasantness or intensity (Grabenhorst and Rolls, 2008). The instructions were intended to set the brain up for performing different tasks with the same taste. The researchers observed a greater brain response in the orbitofrontal cortex and pregenual cingulate cortex among individuals instructed to rate pleasantness, with the signal being linearly related to the pleasantness of the taste. When subjects were instructed to rate intensity, on the other hand, the researchers observed a greater response in the insular taste cortex, again with the signal being linearly related to the intensity of

the taste. In other words, Rolls explained, when one is interested in how intense a taste is, or what a taste is, one's processing in the primary taste cortex is turned up, whereas when one is interested in how pleasant a taste is, one's processing in the orbitofrontal cortex is turned up. In Rolls's opinion, again, these results have implications for the food industry: it is important to know how drawing attention to any one property of a food is going to impact hedonic versus perceptual processing in the brain.

Rolls also has been curious about where in the brain differences among individuals in liking a food are represented. Are those differences represented in the sensory processing system (e.g., primary taste cortex) or in the hedonic system (ventral striatum, pregenual cingulate cortex, orbitofrontal cortex)? Rolls and McCabe (2007) conducted an experiment with chocolate cravers, identified as such using a standard food-craving questionnaire. They delivered liquid chocolate into the mouth and measured responses to the sight of chocolate as well as to chocolate in the mouth. They found no difference between cravers and noncravers in the primary taste cortex, suggesting that whatever separates cravers from noncravers is not involved with sensory processing. However, there was a difference in the pregenual cingulate cortex, with chocolate in the mouth producing a much larger response in cravers than in noncravers in the ventral striatum, and the sight of chocolate producing a much larger response in cravers than in noncravers in the pregenual cingulate cortex and orbitofrontal cortex. These results suggest to Rolls that individual differences in whether a food is liked are expressed in the hedonic system but not in the sensory analysis system. Rolls opined that understanding individual differences in brain responses to highly pleasant foods may help scientists understand the mechanisms that drive the liking of particular foods, food decision making, and food intake.

Summary and Future Directions

In summary, Rolls noted that all of the various food-related sensory stimuli, including taste, olfactory, and visual stimuli, converge in the brain in the orbitofrontal cortex and amygdala, where the reward value of the food is computed and modulated by gut satiety signals. Moreover, sensory rewards are biased by top-down cognitive or attentional control. The next step for the brain is decision making, said Rolls: "Once you have computed that something is nice, you then make a decision about what you are going to do about it." He did not elaborate, but referred workshop participants to his book *Emotion and Decision-Making Explained* (Rolls, 2014).

Rolls identified several topics to consider for future discussion, all of which revolved around the problem of obesity and whether obesity overstimulates the food reward system in the brain (Rolls, 2011, 2012, 2014). He pointed to early work by Stanley Schachter suggesting that people who

are obese may be more sensitive to the reward properties of food. In Rolls's opinion, there is considerable individual variation in sensitivity to different types of reward stimuli as a result of natural selection. In other words, he said, "We are all slightly different in the rewards that we find attractive." He suggested future large-scale imaging studies aimed at examining brain responses in relation to body mass index (BMI). It would also be extremely interesting, in his opinion, to know whether people who are obese are more sensitive to the reward value of food, and perhaps less sensitive to the satiating property of food.

Rolls identified palatability and variety as two additional factors to consider when evaluating whether obesity may be related to overstimulation of the food reward system. Enhanced palatability in the human diet may lead to an imbalance between sensory reward and satiety signals, and enhanced variety may lead to increased food intake as a result of satiety's being partly sensory-specific.

In general, Rolls opined, "humans are dominated by these sensory inputs produced by food that make it pleasant and rewarding." It can take humans a week or two to adjust their response to satiety signals following a change in the energy density of their diet.

Most of what Rolls described during his talk was what he called the brain's "pleasure system," which computes how "nice" something is and gives rise to goal-directed action. But humans also have what he called an explicit "reasoning system." For example, a person can decide not to eat ice cream because doing so may lead to obesity. The two systems have different goals. The goal of the reasoning system is to produce long-term optimal behavior using advance planning. The goal of the pleasure system is short-term reward, with the reward value of a stimulus being influenced by its adaptive value during evolution. The two systems may be in competition, said Rolls. Again, individual variation is important, in his opinion: "Some individuals may be more susceptible to advice and operation of the explicit, cognitive, reasoning control system."

In conclusion, Rolls opined that the "mismatch hypothesis" appears reasonable. According to this hypothesis, food palatability, availability, variety, and exposure through advertising have increased food reward in the past 30 years, while satiety signals have remained unchanged, and this "mismatch" is contributing to overeating. The challenge for the food industry, assuming that the mismatch hypothesis holds, is to create "healthier" but still highly palatable foods, said Rolls.

CONCLUDING DISCUSSION WITH THE AUDIENCE

The workshop concluded with an open discussion in which all speakers were invited to the stage to answer questions from the audience. Questions addressed a range of topics.

Sensory Versus Metabolic Effects of Stimuli: What Does the Science Say?

There was some discussion of the relative importance of sensory versus metabolic effects on food preferences. Richard Mattes commented on what is now a substantial literature showing that for salt and fat and, less compellingly, sugar, preferred levels are determined more by sensory exposure than by metabolic effect. For him, this suggests that there is nothing "special" about high-salt versus low-salt or high-fat versus low-fat diets; rather, preference is determined by what one has been exposed to and is familiar with. Mattes thinks this is an important point to address given that some people suggest there is a special quality about salt, fat, or sugar that may be driving eating behavior.

Rolls replied, "The primary determinant of reward value is what comes into the mouth in tiny quantities." Based on sham feeding experiments with rats, animals show a preference for sucrose even when no food is reaching the gut. If the concentration of sucrose is increased, consumption will also increase until it reaches a sickly sweet point at which consumption drops. Rolls said these kinds of results are essential to understanding how rewards guide behavior (see Rolls, 2014). Tiny quantities of substance in the mouth act as a potent reward signal. In the gut, on the other hand, large quantities are needed to produce a reward. That said, although fundamental reward selection is produced by sensory receptors in the mouth, preferences can be conditioned by postingestive consequences such as sickness or by the metabolic energy value of food.

Dana Small agreed that sensory information is critical in determining behavior. But the reason it is critical, in her opinion, is that it is a conditioned cue associated with postingestive metabolic effects. If a rat is exposed to artificial sweetener over time, especially in a hungry state, and learns that the artificial sweetener is not associated with a positive postingestive effect, the dopamine response to that artificial sweetener will disappear, and the rat will stop consuming it.

The Slow Process of Weight Gain: Implications for the Concept of "Food Addiction"

Mattes commented on the small percentage of people in the general population, about 5 percent, who would be classified by the Yale Food

Addiction Scale (YFAS) as "food-addicted," compared with the 65 percent of the general population who are overweight or obese. Not only would only a small proportion of people who are overweight or obese be classified as food-addicted, but also, in his opinion, most people who are obese are not "gluttonous." Most people reach that weight category by gaining half a kilo to a kilo per year. Addiction, on the other hand, refers to an overconsumption that Mattes termed "really remarkable." Nor is weight gain in people who are obese steady. There are long periods of time when their weight is stable, and then it goes up, then another stable period, and so on.

Ashley Gearhardt responded that it is important to distinguish between someone who is addicted and the impact of an addictive substance on public health. With every addictive substance, only a small percentage of people, 5 to 10 percent, become fully addicted. If the focus was only on that small percentage, the actual public health cost would not be captured in any way, especially for legal, cheap, easily accessible, and heavily advertised substances. Most people who consume an addictive substance do not become addicted, but do overconsume and do have a tendency at times to overindulge in a way that is more likely to occur than with something that is not addictive. Gearhardt's concern with ultra-processed foods is that if they have the capacity to trigger an addictive response, most people will show a subclinical level of overconsumption that will have a significant public health cost.

Is the Focus on Addiction Diverting Attention from Other Biological Processes at Play?

Laurette Dubé suggested that the focus on addiction may be distracting experts from considering and understanding all of the biological processes at play. For example, she emphasized the importance of reinforcement in how people react to food. "We learn to like what we are exposed to," she said. Food is different from nicotine, opium, and other addictive substances in the sense that it is the only substance connected to sensory processing.

Food Versus Alcohol

When asked about what can be learned from alcohol given that it can be considered both a drug of abuse and a food, Dubé replied that alcohol has some of the same sensory aspects as food but that its "nutrient dimension" is much less complex. Rolls added that alcohol intake obviously is not driven by the energy one derives from drinking it. Charles O'Brien added that alcoholism is among the most highly gene-driven addictions and that some alcoholism in families is influenced by variants of the opioid receptor.

Mention of alcohol prompted an audience member to comment on a

study showing increased alcohol consumption in bariatric surgery patients 2 years after surgery. The phenomenon appears to be limited to gastric bypass patients. Gastric banding, a purely restrictive procedure that does not involve rewiring the gastrointestinal tract, has not been associated with increased uptake of alcohol. The researchers in the cited study interpreted their findings to mean that gastric bypass patients, but not gastric banding patients, experience more rapid alcohol absorption and speculated that perhaps a more rapid rate of absorption provides greater reward. The audience member asked the panel to comment on (1) whether they agreed with the interpretation that increased alcohol intake following gastric bypass surgery could be due to faster absorption of alcohol, and (2) why the phenomenon occurs 2 years, and not 1 year, after surgery.

Timothy Moran agreed that the researchers' interpretation was one possibility and noted that with some other addictive compounds, the more rapidly they are absorbed, the more addictive they are. In terms of the time period, putting a large amount of calories into the intestine quickly immediately after gastric bypass produces a very negative sensation. Food consumption following surgery tends to increase significantly at about the 1-year mark. The 2-year time period may simply reflect the system being accustomed to that kind of more rapid delivery of calories.

Hisham Ziauddeen remarked that the case of gastric bypass is probably more complicated on several levels. For example, he noted all the hormonal changes that occur fairly early following the surgery and even before any weight loss. He suspects that much of what is going on during those 2 years is not yet understood. He mentioned recent studies reporting an increased risk of suicide in patients who had undergone gastric bypass surgery, which he believes may reflect more pathologies beyond what is happening in the gut or with substances.

The Food Environment on College Campuses

When children leave home and go to college, they generally gain weight. The panel was asked how they would advise college administrators to change the food environment on college and university campuses. Dubé commented on the complexity of the problem. There are ways to design the environment in a way that encourages healthier eating—for example, by not placing high-fat/high-sugar foods near the cashier—but such changes need to be made in light of what is necessary to maintain sufficient sales. Creating demand for healthier eating in the individual is also important. College is a highly stressful experience. Students need to be nurtured and educated about healthy eating. Then, at the policy level, there needs to be greater investment in those who are financially able to create healthy foods in a way that meets customer demand.

Rogers described the "freshman 15" as a natural experiment that demonstrates how eating and body weight are under environmental control. There is a long history of research in this area, he said. Such changes in weight are viewed as a function of how different the new environment is compared with the old, modified by individual experience. Rogers added that going to college is a major change in lifestyle that represents, for some people, a "step" in the stepwise trajectory to obesity.

Moran added that college cafeterias are very different from what they were like 40 years ago. Then, students were presented a tray and were served. Now, colleges are competing to provide extensive choices.

For Dubé, the complexity of the issue highlights the need for more evidence not just on the brain, food, or nutrition, but also on all of the complex factors that make up society. She said, "I would strongly promote the idea that the science and evidence that are needed need to be expanded to those domains in a very urgent manner."

"Food Addiction" as a Risk Factor for Obesity

An audience member asked what weight of evidence would be needed to support the hypothesis that addiction is a risk factor for obesity. Gearhardt replied that at this point, scientists do not have enough evidence regarding the potential level of impact of an addictive-like process on obesity. The field is still in its infancy, she said. Results of some studies suggest a risk. But most of these studies are small, not nationally representative, and not longitudinal. In Gearhardt's opinion, the field needs larger studies that are nationally representative and longitudinal. Ziauddeen cautioned, however, that scientists have a long way to go in terms of defining endpoints before those studies can be conducted.

Pursuing Pleasure or Avoiding Displeasure?

According to an audience member, experiments with rats have demonstrated that the drive to avoid displeasure is stronger than the drive to pursue pleasure. But is this true in humans? When patients with addictions of one form or another struggle with compulsive behaviors that enable them to avoid displeasure, what is the decision-making process that is occurring at that time? What is known about the avoidance of displeasure during the decision-making process that takes place in choosing between a healthy food and a high-fat/high-sugar food?

Avena replied that her work with rats has shown that animals actually are willing to inflict displeasure on themselves to get to M&Ms and other foods. But when restricted from sugar or highly palatable foods, they show behaviors suggesting that they are not happy. Rather, they show signs of

depression, anxiety, and distress; the symptoms are mild, but they are present. Is that displeasure perhaps fueling poor food choices the next time they have access to food? It is a good question, Avena said—one in need of empirical study.

Rolls noted (as in Rolls, 2014) that the field of neuroeconomics is beginning to tackle just these sorts of issues. That is, how are benefits and costs weighed during the decision-making process, what trade-off occurs in the brain between planning for the future and seeking short-term gain, and what is the genetic basis of impulsive decision making?

Ziauddeen mentioned George Koob's description of the avoidance of the dysphoria of withdrawal as "the dark side of addiction" (Koob and Le Moal, 2005). It is an interesting idea to consider, he said. Studies with drugs have shown that continued drug seeking in people who are addicted to drugs helps ameliorate many negative effects associated with not taking drugs. This is true even with drugs like cocaine, which is not associated with prominent physical withdrawal. It is probably a relevant phenomenon to consider with food given the multiplicity of factors involved in eating behavior.

In Rogers's opinion, a desire to eat chocolate probably is not overridden by concern that one may develop heart disease in 20 or 30 years. But it may be overridden by concern that one may gain some weight in the near future as a result. Rogers encouraged a closer examination of how the experience of eating and the experiences that people have immediately after they have eaten can be used to help gain control over what are perceived as problematic foods. For example, the sequence of events that some people experience when eating "forbidden" or "naughty" foods includes not only pleasure but also regret soon after having eaten. In the United Kingdom, efforts are under way to encourage healthy eating by communicating messages such as "eating healthy will make your skin look better."

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A

Abbreviations and Acronyms

ASI	Activation Severity Index
BAS	Behavioral Activation System
BMI	body mass index
BtS	Brain-to-Society
CCK	cholecystokinin
DEBQ	Dutch Eating Behavior Questionnaire
DSM-IV (or 5)	*Diagnostic and Statistical Manual of Mental Disorders* (Fourth or Fifth Edition)
ENaC	epithelial sodium channel
fMRI	functional magnetic resonance imaging
GI	gastrointestinal
GIP	gastric inhibitory peptide
GIS	geographic information system
GLP-1	glucagon-like peptide-1
GPR	G-protein coupled receptor
IUGR	intrauterine growth restriction

MC4	melanocortin-4
MRI	magnetic resonance imaging
mRNA	messenger RNA
NHANES	National Health and Nutrition Examination Survey
NTS	nucleus of the solitary tract or nucleus tractus solitarii
POMC	pro-opiomelanocortin
PYY	peptide tyrosine tyrosine
RDoC	Research Domain Criteria project
SGLT1	sodium glucose co-transporter 1
TRP M5	transient receptor potential cation channel subfamily M member 5
YFAS	Yale Food Addiction Scale

B

Workshop Agenda

Relationships Between the Brain,
Digestive System, and Eating Behavior
July 9-10, 2014

National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC
Auditorium

Day 1: July 9, 2014

8:00 AM **Registration**

8:30 **Welcome and Introductions**
Eric Decker, Ph.D., *Food Forum Member, Workshop Planning Committee Chair*

SESSION 1—INTERACTION BETWEEN THE BRAIN AND THE DIGESTIVE SYSTEM

8:45 **Session 1 Introduction**
Moderator: Danielle Greenberg, Ph.D., *Food Forum Member, Workshop Planning Committee Member*

9:00 **Overview of Interactions of the Brain and Digestive System**
Timothy Moran, Ph.D., *Johns Hopkins University*

9:30 **Taste Receptors in the Gut: How They Influence Eating Behavior**
Robert Margolskee, M.D., Ph.D., *Monell Chemical Senses Center*

10:00 **BREAK**

10:30 **Gut Peptides and the Control of Eating Behavior**
Robert Ritter, V.M.D., Ph.D., *Washington State University*

11:00 **Contextual Influences on Food Intake**
Laurette Dubé, Ph.D., M.P.S., M.B.A., *McGill University*

11:30 **Moderated Panel and Audience Discussion with Session 1 Speakers**

12:30 PM **LUNCH**

SESSION 2—ASSESSING THE SCIENCE BEHIND METHODOLOGIES BEING USED TO CHARACTERIZE FOOD AS ADDICTIVE

1:30 **Session 2 Introduction**
Moderator: Richard Mattes, Ph.D., M.P.H., R.D., *Purdue University*

1:45 **What Can Imaging Technologies Tell Us About Food Behaviors?**
- Perspective 1: Dana Small, Ph.D., *Yale University*
- Perspective 2: Hisham Ziauddeen, M.R.C.Psych., Ph.D., *University of Cambridge*

2:45 **BREAK**

3:15 **Assessing the Validity of Questionnaires for Food Behaviors and Addiction**
- Perspective 1: Ashley Gearhardt, Ph.D., *University of Michigan*
- Perspective 2: Charles O'Brien, M.D., Ph.D., *University of Pennsylvania*

4:15 **Moderated Panel and Audience Discussion with Session 2 Speakers**

5:15 **Adjourn**

Day 2: July 10, 2014

8:00 AM **Registration**

8:15 **Welcome and Recap of Day 1**
Eric Decker, Ph.D., *Food Forum Member, Workshop Planning Committee Chair*

SESSION 3—FUTURE DIRECTIONS: IS THE ADDICTION MODEL FOR DRUGS AND ALCOHOL APPROPRIATE FOR FOOD?

8:30 **Session 3 Introduction**
Moderator: Joe Levitt, J.D., *Hogan Lovells*

8:45 **The Food Addiction Model *Is* Appropriate for Use with Food**
Nicole Avena, Ph.D., *Columbia University*

9:15 **The Food Addiction Model *Is Not* Appropriate for Use with Food**
Peter Rogers, Ph.D., M.Sc., *University of Bristol*

9:45 **Moderated Panel and Audience Discussion with Session 3 Speakers**

10:15 **BREAK**

CONCLUDING SESSION

10:30 **Concluding Session Introduction**
Moderator: Sophie Kergoat, Ph.D., *Workshop Planning Committee Member*

Closing Presentation
Edmund Rolls, D.Phil., D.Sc., Hon.D.Sc., M.A., *Oxford Centre for Computational Neuroscience*

11:00 **Moderated Conversation with Workshop Speakers and Audience**

12:00 PM **ADJOURN**

C

Speaker Biographical Sketches

Nicole Avena, Ph.D., is assistant professor of pharmacology and systems therapeutics at Ichan School of Medicine, Mount Sinai, New York City. She has published more than 60 scholarly journal articles on topics related to diet, nutrition, and overeating. Her research achievements have been recognized by the New York Academy of Sciences, the American Psychological Association, and the National Institute on Drug Abuse. Dr. Avena received a Ph.D. in psychology and neuroscience from Princeton University in 2006 and completed a postdoctoral fellowship at Rockefeller University.

Eric Decker, Ph.D., is currently a professor and head of the Department of Food Science at the University of Massachusetts Amherst. Dr. Decker is actively conducting research to characterize mechanisms of lipid oxidation, antioxidant protection of foods, and the health implications of bioactive lipids. He has authored more than 325 publications, and he is listed as one of the most highly cited scientists in agriculture. Dr. Decker has served on numerous committees for institutions such as the U.S. Food and Drug Administration, the Institute of Medicine, the Institute of Food Technologists, the U.S. Department of Agriculture, and the American Heart Association. Recognition for his research includes awards from the American Oil Chemists Society, the Agriculture and Food Chemistry Division of the American Chemical Society, the International Life Science Institute, the Royal Society of Chemistry, and the Institute of Food Technologists. Dr. Decker is a member of the Institute of Medicine's Food Forum. He obtained his M.S. and Ph.D. in food science and nutrition from Washington State University and the University of Massachusetts Amherst, respectively.

Laurette Dubé, Ph.D., M.P.S., M.B.A., holds the James McGill Chair of Consumer and Lifestyle Psychology and Marketing at the Desautels Faculty of Management, McGill University. Dr. Dubé is founding chair and scientific director of the McGill Center for the Convergence of Health and Economics. Her research investigates the cognitions, affects, and behavioral economic processes underlying consumption and lifestyle behavior and brings complexity sciences to bear in examining how such knowledge can inspire more effective communication, successful health-sensitive innovation, and ecosystem transformation for convergence between health and economics. Dr. Dubé has authored numerous scientific publications in both books and journals. Her work has been cited in *Maclean's*, *The Globe and Mail*, *USA Today*, *The Wall Street Journal*, and *The Economist*. A fellow of the Royal Society of Canada, she received her Ph.D. from Cornell University, an M.P.S. in marketing and management from Cornell University, an M.B.A. in finances from École des Hautes Études Commerciales (Montreal), and a B.Sc. in nutrition from Laval University.

Ashley Gearhardt, Ph.D., is an assistant professor of clinical psychology at the University of Michigan. While working on her doctorate in clinical psychology at Yale University, Dr. **Gearhardt became interested in the possibility** that certain foods may be capable of triggering an addictive process. To explore this possibility further, she developed the Yale Food Addiction Scale to operationalize addictive-like eating behavior, which recently has been linked with more frequent binge eating episodes in clinical populations, increased prevalence of obesity, and patterns of neural activation implicated in other addictive behaviors. Dr. Gearhardt also investigates the impact of certain components of the food environment, such as food advertising, on obesity risk through the use of multimethod approaches (e.g., neuroimaging, eye tracking). She is currently directing the Food and Addiction Science and Treatment laboratory to further evaluate whether an addictive-like mechanism contributes to certain types of problematic eating behavior. Dr. Gearhardt received her Ph.D. in clinical psychology at Yale University.

Danielle Greenberg, Ph.D., F.A.C.N., is nutrition director in PepsiCo's Research and Development organization. At PepsiCo she is responsible for providing scientific expertise on issues concerning beverages, nutrition, and health. Dr. Greenberg joined PepsiCo as part of the Public Affairs and Science and Regulatory Affairs groups and was responsible for communications both internally and externally in the areas of nutrition and scientific affairs. She began her career as an academic researcher and was an associate professor in the Department of Psychiatry at Cornell University Medical College. Her area of research was the physiology of obesity, with specific

focuses on how dietary fats lead to satiety, the role of fat intake in obesity, the satiating potency of dietary fats, how fats control food intake, how brain gut peptides work in hunger and fullness, and the neural processes mediating food intake. Prior to joining PepsiCo, Dr. Greenberg worked for Nutrition 21, a science-driven nutritional products company. She is a fellow of the American College of Nutrition and of The Obesity Society. She received a Ph.D. in biological psychology from the City University of New York.

Joseph Herskovic, Ph.D., is based in Omaha, Nebraska. During his 23 years in the food and beverage industry, he has created, led, or been part of five sensory evaluation departments, including departments at Frito-Lay, Uncle Ben's, Seagram's, Product Dynamics, and ConAgra Foods. For 7 years he conducted research on nicotine addiction and smoking cessation at the University of California, Los Angeles, School of Medicine and the Duke University School of Medicine as an assistant research psychologist and director of clinical trials, respectively. Dr. Herskovic has published in the areas of neuroscience, psychology, psychopharmacology, and sensory science and has taught university-level short courses on sensory discrimination testing. He holds a Ph.D. in neuropsychology from the City University of New York.

Sophie Kergoat, Ph.D., is senior research scientist at the Wrigley Company (a subsidiary of Mars Inc.) in Chicago, with responsibility for developing scientific support in human behavior and brain activity. This work involves the identification of new areas for product innovation, the coordination of external and internal studies to provide scientific and clinical support for scientific claims, and the development of relationships with consultants and research organizations. Dr. Kergoat is currently working to develop a platform of research focused on the effect of gum chewing on various aspects of the human physiology. She joined Mars Inc. Europe in 2007 as a research scientist to undertake research projects in human behavior and to develop leading-edge cognitive sciences technology using world-class expertise. This work encompassed areas ranging from the effectiveness of consumer communication to understanding of consumer behavior to such areas as scientific and external affairs. Previously, Dr. Kergoat held a position as lecturer in human sciences at the University Paris Descartes and at the University of Basse-Normandie and collaborated with a team of researchers at C.N.R.S. (National French Scientific Center) in Paris. She holds a Ph.D. in cognitive science from University Paris Descartes in partnership with the Berchet Company and a professional degree in psychology (neuropsychology).

Joseph Levitt, J.D., is a partner at Hogan Lovells US LLP in Washington, DC. Mr. Levitt is a 25-year veteran of the U.S. Food and Drug Administration (FDA); he served as director of FDA's Center for Food Safety and Applied Nutrition (CFSAN) for 6 years. He counsels numerous food companies and trade associations in food safety, labeling, and compliance matters and in how to work effectively with FDA. He is a recognized expert in the Food Safety Modernization Act, including all phases of its development and implementation. While serving as CFSAN director, Mr. Levitt led successful efforts to modernize food safety regulation and enhance the security of the U.S. food supply. He also initiated a revitalization of FDA's nutrition program. During his earlier FDA tenure, while in the Office of the Commissioner, he helped streamline the new drug review process and launch the agency's food labeling initiative. Additionally, he served as deputy director for regulations and policy at FDA's Center for Devices and Radiological Health. Mr. Levitt began his FDA career in the Office of Chief Counsel. He has received a Top Tier ranking from Chambers for food and beverage lawyers. While at FDA he received numerous honors and awards, including three Presidential Executive Rank Awards. More recently, he received the FDA Distinguished Alumni Award. Mr. Levitt earned his bachelor's degree, magna cum laude, from Cornell University and his J.D. degree, cum laude, from Boston University School of Law.

Robert F. Margolskee, M.D., Ph.D., is director of the Monell Chemical Senses Center, where he joined the faculty in 2009. Dr. Margolskee's long-standing research focus is on the molecular mechanisms of taste transduction, utilizing molecular biology, biochemistry, structural biology, electrophysiology, and transgenesis to study the mechanisms of signal transduction in mammalian taste cells. More recently he has been studying the chemosensory functions of taste-signaling proteins in gut and pancreatic endocrine cells. Dr. Margolskee has made numerous seminal discoveries in the taste field, including the identification and molecular cloning of taste-specific receptors and G proteins. In 1992, his laboratory discovered gustducin, a taste cell-expressed G protein. Subsequently, Dr. Margolskee demonstrated that gustducin is critical to the transduction of compounds that humans consider bitter, sweet, or umami. Much of his current work is focused on taste-like cells of the gut and endocrine properties of taste cells. In 2007, Dr. Margolskee published two papers in the *Proceedings of the National Academy of Sciences of the United States of America* shedding light on how the gut "tastes" nutrients, a new area of research with important implications for diabetes and obesity. Most recently his group identified the previously elusive adult taste stem cells. Among Dr. Margolskee's honors and awards are the Monell Mastertaste-Manheimer Award and the International Flavors and Fragrances (IFF) Award. He received his A.B. in

biochemistry and molecular biology from Harvard University and his M.D. and Ph.D. in molecular genetics from Johns Hopkins University.

Richard D. Mattes, Ph.D., M.P.H., R.D., is a distinguished professor of nutrition science at Purdue University, adjunct associate professor of medicine at the Indiana University School of Medicine, and affiliated scientist at the Monell Chemical Senses Center. His research focuses on the areas of hunger and satiety, regulation of food intake in humans, food preferences, human cephalic phase responses, and taste and smell. At Purdue University, Dr. Mattes is director of the Ingestive Behavior Research Center and director of the Public Health Program. He also holds numerous external responsibilities, including serving as associate editor of the *American Journal of Clinical Nutrition* and serving on the editorial boards of the *British Journal of Nutrition, Chemosensory Perception*, the *Ear, Nose, and Throat Journal*, and the journal *Flavour*. Dr. Mattes has received multiple awards, most recently the Babcock-Hart Award from the Institute of Food Technologists. He has authored more than 225 publications. Dr. Mattes earned an undergraduate degree in biology and an M.P.H. from the University of Michigan and his Ph.D. in human nutrition from Cornell University.

Timothy Moran, Ph.D., is the Paul R. McHugh Professor of Motivated Behaviors and vice chair and director of research in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine. Dr. Moran's research interests are in brain/behavior relationships as they apply to motivated behaviors. His work has focused on brain/gut peptides as feedback controls of meal size and how they interact with neural systems involved in overall energy balance and reward processing, in particular how they may go awry in eating disorders and obesity. Additional projects examine how gestational and early developmental factors can bias metabolic and neural programming to contribute to obesity and stress reactivity and the effects of exercise on diet preference and overall energy balance. Dr. Moran has been active in leadership roles in The Obesity Society and the Society for the Study of Ingestive Behavior. He received his Ph.D. in biopsychology from Johns Hopkins University and has been on the faculty at the Johns Hopkins University School of Medicine since 1984.

Charles P. O'Brien, M.D., Ph.D., is the Kenneth E. Appel Professor of Psychiatry at the University of Pennsylvania. He also established and directs a clinical research program that has had a major impact on the treatment of addictive disorders. His work involves discovery of central nervous system changes involved in relapse, new medications, behavioral treatments, and instruments for measuring the severity of addictive disorders. Dr. O'Brien

led the discovery of the effects of alcohol on the endogenous opioid system and developed a completely new treatment for alcoholism. He was elected to the Institute of Medicine in 1991 and has received numerous research and teaching awards as well as an honorary doctorate from the University of Bordeaux. Dr. O'Brien is past president of the American College of Neuropsychopharmacology and the Association for Research in Nervous and Mental Disease. He earned his M.D. and Ph.D. degrees from Tulane University.

Robert C. Ritter, V.M.D., Ph.D., is professor of integrative physiology and neuroscience in the College of Veterinary Medicine at Washington State University. Dr. Ritter investigates neural and endocrine controls of appetite and body weight. He is especially interested in how signals from the gastrointestinal tract and body fat alter food intake and metabolism by modulating neural signaling in the hindbrain. Dr. Ritter is very interested in how neurotransmitters and hormones trigger short- and long-lasting neuroplastic changes in the hindbrain and how such changes produce alterations in feeding behavior that favor weight gain or weight loss. His experimental approach to these issues is multidisciplinary and collaborative, combining neuroanatomy, cell and molecular biology, electrophysiology, and behavioral testing. Dr. Ritter is active in a number of scientific societies and currently serves on the executive board for the Society for the Study of Ingestive Behavior. He is a member of the editorial board of the *American Journal of Physiology* and has been a regular member of National Institutes of Health study sections, including the Neuroendocrinology, Neuroimmunology, Rhythms and Sleep study section, on which he currently serves. Dr. Ritter received his doctorate in veterinary medicine from the University of Pennsylvania and his Ph.D. in biology from the University of Pennsylvania.

Peter Rogers, Ph.D., M.Sc., B.Sc., is professor of biological psychology at the School of Experimental Psychology, University of Bristol. His research focuses on nutrition and behavior, and a large part of this work is concerned with how physiological, learned, and cognitive controls on appetite are integrated. The results are relevant to identifying the causes of obesity and disordered eating and to understanding food choice, food craving, and food "addiction." Dr. Rogers also works on dietary effects on mood and cognition; this work includes research on how food consumption affects alertness and attention, as well as studies of longer-term influences of diet on psychological health. Dr. Rogers links his research to his third area of interest—the psychopharmacology of caffeine. His research on this ubiquitously consumed substance began with questions about how preferences for caffeine-containing drinks develop and now focuses on caffeine's psycho-

stimulant, anxiogenic, and motor effects. Caffeine provides a good example of the distinction between dependence and addiction. When frequent caffeine consumers interrupt their habit for more than half a day, they function below par (dependence), but this does not cause a strong compulsion to consume caffeine. Dr. Rogers received his B.Sc. in biology and M.Sc. in experimental psychology at the University of Sussex and his Ph.D. in eating behavior at the University of Leeds.

Edmund T. Rolls, D.Phil., D.Sc., Hon.D.Sc., M.A., is director of the Oxford Centre for Computational Neuroscience, Oxford, United Kingdom, and a professor in computational neuroscience in the Department of Computer Science, University of Warwick, United Kingdom. Dr. Rolls is a neuroscientist with research interests in computational neuroscience, including the operation of real neuronal networks in the brain involved in vision, memory, attention, and decision making; functional neuroimaging of vision, taste, olfaction, feeding, control of appetite, memory, and emotion; neurological disorders of emotion; psychiatric disorders, including schizophrenia; and the brain processes underlying consciousness. These studies include investigations in patients and are performed with the aim of contributing to understanding of the human brain in health and disease and treatment of its disorders. Dr. Rolls has published more than 530 research papers (many available at www.oxcns.org) and 11 books on these topics. He qualified in preclinical medicine at the University of Cambridge and received a D.Phil. and D.Sc. in neuroscience from the University of Oxford.

Dana Small, Ph.D., is professor of psychiatry at Yale Medical School, visiting professor in the Institute of Genetics at the University of Cologne, and a fellow of the John B. Pierce Laboratory. Dr. Small's research interests are in the neurophysiology of feeding, chemical senses, neuroimaging, dopamine, addiction, motivation, psychophysics, stress, and obesity. She has served on the executive committee of the Association for Chemoreception Sciences since 2008 and on the board of the Society for the Study of Ingestive Behavior since 2011. Dr. Small is also a member of the scientific advisory boards for the Helmholtz Alliance's "Imaging and Curing Environmental Metabolic Diseases" and "Nudge-it," a European-based alliance aimed at understanding decision making in food choice. She also serves on the editorial boards of *Molecular Metabolism*, *Biological Psychiatry*, *Chemosensory Perception*, *Neuroimage: Clinical*, and *Frontiers of Human Neuroscience*. In recognition of her contributions to the fields of flavor and ingestive behavior, Dr. Small received the Ajinomoto Award for Research in Gustation in 2003, the Moskowitz Jacobs Award for Research Excellence in the Psychophysics of Taste and Smell in 2005, the Firmenich Flavor and Fragrance Science Award in 2007, and the Ruth Pike Award for contribu-

tions to nutrition research in 2010. She received her Ph.D. in clinical psychology from McGill University in 2001.

Hisham Ziauddeen, M.R.C.Psych., Ph.D., is a psychiatrist working in the Health Neuroscience group in the Department of Psychiatry at the University of Cambridge. Dr. Ziauddeen's research focuses on the role of the brain reward system in normal and abnormal eating behavior, using neurobehavioral, functional neuroimaging, and experimental medicine approaches. His current work is looking at the mechanisms of antipsychotic-induced weight gain in patients who are prescribed these medications. Along with his colleague Dr. Paul Fletcher, Dr. Ziauddeen has critically examined the food addiction model both in the scientific literature and in science comedy. He received his Ph.D. from the University of Cambridge.