Appetite 107 (2016) 348–361

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Brain regions involved in ingestive behavior and related psychological constructs in people undergoing calorie restriction

Chanaka N. Kahathuduwa [a, b], Lori A. Boyd [a], Tyler Davis [c], Michael O'Boyle [d, e], Martin Binks [a, *]

[a] Behavioral Medicine and Translational Research Lab, Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA
[b] Department of Physiology, Faculty of Medicine, University of Peradeniya, Sri Lanka
[c] Department of Psychological Sciences, Texas Tech University, Lubbock, TX, USA
[d] Department of Human Development and Family Studies, Texas Tech University, Lubbock, TX, USA
[e] Department of Pharmacology and Neuroscience, School of Medicine, Texas Tech University, Health Sciences Center, Lubbock, TX, USA

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form
9 August 2016
Accepted 22 August 2016
Available online 24 August 2016

Keywords:
Calorie restriction
Ingestive behavior
Food-cue reactivity
fMRI

ABSTRACT

Human food intake is regulated by physiological energy homeostatic mechanisms and hedonic mechanisms. These are affected by both very short-term and longer-term calorie restriction (CR). To date, there are parallel discussions in the literature that fail to integrate across these disciplines and topics. First, much of the available neuroimaging research focusses on specific functional paradigms (e.g. reward, energy homeostasis). These paradigms often fail to consider more complex and inclusive models that examine how potential brain regions of interest interact to influence ingestion. Second, the paradigms used focus primarily on short-term CR (fasting) which has limited generalizability to clinical application. Finally, the behavioral literature, while frequently examining longer-term CR and related psychological constructs in the context of weight management (e.g. hedonic restraint, 'liking', 'wanting' and food craving), fails to adequately tie these phenomena to underlying neural mechanisms. The result is a less than complete picture of the brain's role in the complexity of the human experience of ingestion. This disconnect highlights a major limitation in the CR literature, where attempts are persistently made to exert behavioral control over ingestion, without fully understanding the complex bio behavioral systems involved. In this review we attempt to summarize all potential brain regions important for human ingestion, present a broad conceptual overview of the brain's multifaceted role in ingestive behavior, the human (psychological) experiences related to ingestion and to examine how these factors differ according to three forms of CR. These include short-term fasting, extended CR, and restrained eating. We aim to bring together the neuroimaging literature with the behavioral literature within a conceptual framework that may inform future translational research.

Contents

Abbreviations: BOLD, blood oxygen level-dependent; CR, calorie restriction; fMRI, functional magnetic resonance imaging; L/, left; LCD, low calorie diet; R/, right; SWLs, successful weight loss maintainers; VLCD, very low calorie diet.

* Corresponding author. Department of Nutritional Sciences, College of Human Sciences, Texas Tech University, 1301 Akron Street, Box 41270, Lubbock, TX, 79409-1270, USA.
E-mail address: m.binks@ttu.edu (M. Binks).

http://dx.doi.org/10.1016/j.appet.2016.08.112

1. Introduction

Human food intake is regulated by homeostatic mechanisms that balance energy intake and energy expenditure (Berthoud, 2011). Disturbing this energy balance by sustained increases in energy intake contributes to obesity (Berthoud, 2004). Both short and long-term calorie restriction (CR) are common approaches to regulating body weight. Some forms of CR appear to be very effective in inducing weight loss and reducing subsequent drives towards ingestion, while other forms of CR appear to be increasing the risk of subsequent weight gain (Lowe et al., 2006; Markowitz, Butryn, & Lowe, 2008; Martin, O'Neil, & Pawlow, 2006; Martin et al., 2011, pp. 741–755). Therefore, understanding the neurophysiological effects of these various forms of CR could potentially lead to identification of key pathways and connections in the brain that affect human ingestive behavior. Identifying these pathways may potentially outline targets for future pharmacological interventions that aim to control weight gain by affecting food ingestion.

In the present paper we bring together the available behavioral and neurophysiological literature, and attempt to weave them into an evidence-informed, conceptual framework that truly reflects the complexity of human ingestive behavior. We do so by considering three different forms of dietary CR that appear to have contrasting influences on psychological constructs and neurophysiological mechanisms. These include short-term fasting (typically 8–24 h without any food), extended CR (from 3 weeks to several months of CR ranging from 800 to 1500 kcal/day) and the somewhat unique case of restrained eating (RE); the latter involving a maladaptive and at times pathological extended CR strategy to eliminate foods perceived as problematic from the diet in an effort to maintain weight (Lowe et al., 2006; Markowitz et al., 2008). RE has also been shown to be associated with increased ingestion over the longer term and is associated with risk of future weight gain (Lowe et al., 2006; Markowitz et al., 2008).

The effects of fasting, extended CR and RE, on subsequent ingestive behavior, psychological constructs (e.g. craving, hedonic restraint, 'wanting' and 'liking') and body weight have been studied primarily in the context of behavioral intervention studies (Cameron, Goldfield, Finlayson, Blundell, & Doucet, 2014; Gilhooly et al., 2007; Goldstone et al., 2009; Harvey, Wing, & Mullen, 1993; Martin et al., 2006). These at times have demonstrated a somewhat complex and counterintuitive response to CR. For example, in the behavioral literature, fasting has been shown to be associated with increases in cravings (i.e. frequent, intense and irresistible desires to consume particular foods), appetite and overall caloric consumption (Cameron et al., 2014; Goldstone et al., 2009; White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002). However, in response to very-low calorie intake of over 12 weeks duration, reduced cravings have been reported (Harvey et al., 1993; Martin et al., 2006, 2011, pp. 741–755).

Self-report measures are typically used to assess related psychological constructs along with almost all types of CR (Born et al., 2011; Coletta et al., 2009; Stice, Yokum, Blum, & Bohon, 2010), while neuroimaging is frequently used to examine brain responses to food-related stimuli (e.g. Goldstone et al., 2009; Martens et al., 2013; Siep et al., 2009; Stice, Burger, & Yokum, 2013; Uher, Treasure, Heining, Brammer, & Campbell, 2006). Functional magnetic resonance imaging (fMRI), a technique that measures changes in blood oxygen concentrations in response to neural processing, has gained popularity in this discipline within the past decade. The food-cue reactivity paradigm is one of the most frequently used procedures for studying neural responses to food stimuli using fMRI. The food-cue reactivity paradigm involves presentation of food and non-food stimuli (pictures, smells, tastes) that vary in their desirability and often includes simultaneous behavioral ratings of participants subjective reactions to the food (e.g. press a button indicating how "appealing" the stimulus is; Goldstone et al., 2014; Stice et al., 2013; Yokum & Stice, 2013). This is referred to as Food Cue Reactivity.

However, in spite of the recent advances in neuroimaging and resulting improvements in our understating of human ingestive behavior, studies that attempt to better understand the neurophysiology of ingestive behavior in humans are often limited to CR interventions of less than 24 h (e.g. 8–24 h fasting). Notably, much of the neuroimaging literature does not consider extended CR as it relates to brain involvement in the process of ingestive behavior, despite the common use of extended CR in behavioral settings to

induce and maintain weight loss with a limited success (Finer, 2001). This has led to a gap in understanding that has significant implications for translation to applied settings. In fact this disconnect between the neurophysiological and behavioral/intervention literature contributes to the often misguided belief that by persistently attempting to exert behavioral controls, we can override a complex bio behavioral system that we do not as yet fully understand (Michael R Lowe, 2013; Wing, 2014; Wing & Hill, 2001; Wing & Phelan, 2005).

Therefore, the current review attempts to join the somewhat disparate bodies of neuroimaging and behavioral literature in relation to the above mentioned three distinct forms of CR (i.e. fasting, extended CR and restrained eating), to develop a more complete conceptual understanding of the brain's multifaceted role in ingestion and associated psychological processes. Based on the heterogeneity of methodology in the application of CR, populations studied and the limited and often incomplete literature associated with various constructs, we have chosen brain regions that have been implicated in ingestive behavior as a unifying theme. It is anticipated that by doing so we will highlight the structural complexity of the brain and the potential interconnectivity and functional overlaps of these brain regions and associated behavioral constructs as they relate to ingestive behavior. Additionally, we attempt to provide a unifying framework for future studies that will ultimately lead to improved potential for translational efforts by providing a more complete understanding of human experience related to ingestion.

2. Central regulation of ingestive behavior

2.1. Energy homeostasis

Physiological mechanisms of the human body have evolved to maintain energy homeostasis (Berthoud, 2002, 2004). Energy levels in the body are increased by food intake and are depleted through energy expenditure, which includes maintenance of normal physiological functions and volitional physical activity (Berthoud, 2002; Lenard & Berthoud, 2008). Excess energy is stored in adipose tissue as triglycerides and in skeletal muscle and liver as glycogen, buffering the differences in intake and expenditure of energy and maintaining an energy equilibrium (Berthoud, 2004, 2011; Lenard & Berthoud, 2008). The balance between energy intake, energy expenditure and storage is governed by central regulatory mechanisms and both central and peripheral endocrine signals (Berthoud, 2004, 2011; Lenard & Berthoud, 2008). In addition to the neural signals from sensory organs (i.e. those related to vision, hearing, olfaction and gustation), visceral sensory neural signals from the gastro-intestinal tract and endocrine signals provide continuous inputs to these central regulators regarding the status of energy stores (Berthoud, 2002, 2004; Berthoud & Zheng, 2012; Lenard & Berthoud, 2008).

The hypothalamus plays a pivotal role in sensing the *milieu interior* (i.e. the internal environment) (Berthoud, 2002, 2004; Lenard & Berthoud, 2008). Neurons arising from the arcuate nucleus of the hypothalamus, in addition to other regions of the hypothalamus, brainstem, limbic system and several cortical regions, express receptors for chemical messengers of energy balance such as leptin, insulin, ghrelin, GLP-1, cholecystokinin, peptide YY, glucose, free fatty acids and amino acids (Berthoud, 2002). Orexigenic or appetite stimulating (e.g. those expressing receptors for ghrelin) pathways arising in the arcuate nucleus convey neuronal signals to other regions of the brain governing food reward and ingestive behavior, while anorexigenic or appetite inhibiting (e.g. those involving leptin, GLP-1, cholecystokinin, peptide YY, etc.) pathways convey information regarding excess energy. Confirming the above notion, hypothalamic activity has been shown to be associated with changes in energy status of the human body (Liu, Gao, Liu, & Fox, 2000). Lenard and Berthoud (2008) have reviewed the evidence regarding organization and function of these hypothalamic orexigenic and anorexigenic circuits.

2.2. Higher order processing in relation to energy intake

Multiple brain regions and pathways interact to form the complex neurophysiological mechanisms that ultimately determine ingestive behavior. Over the past 2-3 decades, several psychological constructs have been established to enhance our understanding and to promote development of theoretical explanation regarding neural control of human ingestive behavior. The concepts of hedonic restraint, 'liking', food craving, and 'wanting' are some important constructs that allow us to understand the role of the brain in ingestion using common behavioral terms. Even though multiple definitions exists for these constructs and debates continue regarding the validity of the constructs (Havermans, 2011), a basic understanding of these and the neural processes that are postulated to be measured by them could enhance our understanding of human ingestive behavior (Finlayson & Dalton, 2012a, 2012b; Finlayson, King, & Blundell, 2007b).

2.3. Hedonic restraint

The concept of hedonic restraint spans both the neuroimaging literature and to a degree the behavioral literature (dietary restraint). While not identical, they are conceptually similar. Hedonic restraint refers to one's ability to resist eating in the face of highly palatable (e.g. rewarding) foods, or in short to delay reward (Ely, Winter, & Lowe, 2013). In the neuroimaging literature it often refers to the ability to suppress specific impulses generated in reward centers in the brain (Coletta et al., 2009; Ely et al., 2013). Several regions in the cerebral cortex are involved in regulating ingestive behavior via exerting inhibitory control of food intake (i.e. hedonic restraint), with the dorsolateral prefrontal cortex and the inferior frontal gyrus being the primary regions (Berthoud, 2002, 2004, 2011; Coletta et al., 2009). These regions are likely involved in reducing food intake in the context of cognitive influences and social circumstances, and also in the presence of positive influences on food intake exerted by the homeostatic circuits and other cortical regions related to hedonic control (Berthoud, 2002, 2004, 2011; Hare, Camerer, Knoepfle, O'Doherty, & Rangel, 2010; Rudorf & Hare, 2014). Moreover, there is evidence to suggest that the dorsolateral prefrontal cortex modulates activity of brain regions that determine the value (e.g. taste) of a stimulus (Hare, Camerer, & Rangel, 2009). Obesity has been shown to be associated with reduced activation of particularly the dorsolateral prefrontal cortex following a meal, suggesting an obesity-related potential decline in executive control on ingestive behavior (DelParigi et al., 2002; Le et al., 2006).

The behavioral construct, dietary restraint was originally defined by Herman and Mack as an intention to restrict food intake to control body weight (Herman & Mack, 1975). Several scales have been developed to measure dietary restraint (Herman & Mack, 1975; Herman & Polivy, 1980; Stunkard & Messick, 1985; Van Strien, Frijters, Bergers, & Defares, 1986), of which, the restraint scale in the Three Factor Eating Questionnaire described by Stunkard and Messick (1985) has been well-validated and widely used (Williamson et al., 2007). However, little work has been done to examine the effects of CR on the food-cue reactivity of brain regions that are thought to bring about hedonic restraint. In the subsequent sections of this review, we attempt synthesize the limited neuroimaging evidence to address this disconnect.

2.4. 'Liking'

'Liking' is another theoretical construct with multiple definitions. 'Liking' could be defined as a subjective appraisal of the degree to which an individual may find a particular food appealing to them (Finlayson, King, & Blundell, 2007a). Thus, 'liking' depends on the sensory properties of a rewarding stimulus such as food coupled with modifications via learned associations with that food (Berridge, 2009; Finlayson & Dalton, 2012a; Finlayson et al., 2007a). For instance, a generally pleasurable (i.e. 'liked') food could become 'disliked' if it is associated with a negative experience such as ingestion while suffering from a disease such as gastroenteritis and a generally disliked food could become liked if consistently paired with other pleasurable experiences. In behavioral terms, while 'liking' represents a predisposition towards potentially consuming the 'liked' food (vs. another food) it is relatively far removed from an immediate desire to ingest (Finlayson et al., 2007b). Therefore, 'liking' could be operationally defined as a hedonic reaction to the anticipated pleasure of a reward, irrespective of potential acquisition of the reward (Berridge, 2009). Measuring 'liking' in a behavioral setting could at times be challenging due to the difficulties in differentiating 'liking' from pure perception of cues used to trigger 'liking' (Havermans, 2011). However, several instruments exist to date although their validity is often debated (Finlayson & Dalton, 2012a; Havermans, 2011). Reactivity to taste has been used as a measure of 'liking' in animal and infant studies (Grill & Norgren, 1978). Flavor-nutrient pairing and dissociating have been used in animal studies as well as human behavioral and neuroimaging studies to condition and subsequently assess 'liking' (de Araujo, Lin, Veldhuizen, & Small, 2013; Sclafani, 1995; Yeomans, Gould, Leitch, & Mobini, 2009). To date, a reasonable amount of work has been done to recognize the neurophysiological and biochemical processes underlying this theoretical concept. For instance, the orbitofrontal cortex and the insular cortex along with the lateral hypothalamus, shell of the nucleus accumbens and the remaining regions of the ventral striatum are frequently associated with determining the degree of 'liking' for food (Berridge, 2009; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Volkow, Wang, & Baler, 2011). Furthermore, opioid and cannabinoid neurotransmitters and gamma amino butyric acid are thought to be involved in bringing about 'liking' (Volkow et al., 2011). Moreover, the construct of 'liking' has been used extensively to study applied ingestive behavior, such as the effects of CR (Cameron et al., 2014; Goldstone et al., 2009).

2.5. 'Wanting' and food cravings

'Wanting', on the other hand, is defined as the intrinsic motivation towards achieving a rewarding experience (Berridge, 2009; Finlayson et al., 2007b, 2007a). Therefore, 'wanting' is a process where a value is assigned to a particular item of food, after considering associated sensory properties as well as cognitive inputs (Berridge, 1996). Food craving (i.e. a frequent and irresistible desire to ingest a particular type of food) is a construct that is closely related to 'wanting' both conceptually and by definition (Martin, McClernon, Chellino, & Correa, 2011, pp. 741–755; White et al., 2002). While this desire can exist in the absence of the craved food, the relative likelihood of seeking and consuming the craved food is higher than in the case of 'liking' (Berridge, 2009; Finlayson et al., 2007b). Thus, food craving, at times, could be thought as a surrogate measure of 'wanting' (Berridge & Robinson, 2003; Finlayson et al., 2007b; Pelchat, 2002). The incentive driven process of 'wanting' is most likely to be operating in a subcortical mesolimbic level and could occur even in the absence of conscious awareness and cognitive rationale (i.e. implicit 'wanting') (Finlayson et al., 2007b). Dopamine dominates the neural circuitry involved in giving rise to 'wanting' (Volkow et al., 2011). Centers in the brain thought to be involved include the core of the nucleus accumbens, the broader ventral striatum, basolateral amygdala, ventral tegmental area and substantia nigra (Berridge, 2009; Volkow et al., 2011).

In attempting to conceptually localize functionality of these complex constructs, caution is advised. It should be noted that the behaviorally defined constructs of 'liking' and 'wanting', are not entirely distinct neurologically (Berridge, 2009; Havermans, 2011; Volkow et al., 2011). Significant overlaps of 'liking' and 'wanting' exist in the regional brain localization of these functions (Berridge, 2009). In animal models, it has been shown that these two phenomena are potentially controlled by distinct regions in the brain. For example from animal work we are reasonably confident that the area mediating 'liking' in nucleus accumbens is the rostrodorsal quadrant of the medial shell and the region that mediates 'wanting' is localized to the core of the nucleus accumbens (Berridge, 2009; Volkow et al., 2011). However, with human fMRI resolution, we are unable to accurately pinpoint these relatively small areas of functionality, resulting in identifying similar patterns of food-cue reactivity in response to enhancements of both 'liking' and 'wanting' (Born et al., 2011). This overlap in functionality is further complicated by the fact that the rewarding nature of food is typically brought about by a co-existence of both 'liking' and 'wanting' (Berridge, 2009). However, several groups have outlined protocols that appear to be promising in making a clear distinction between these constructs (Finlayson & Dalton, 2012a; Finlayson et al., 2007a).

2.6. Working memory and ingestive behavior

Working memory plays a key role in exerting attention to food-cues (Higgs, 2015; Higgs, Rutters, Thomas, Naish, & Humphreys, 2012). For instance, if an individual is imagining a chocolate, they are more likely to attend to a visual cue of a chocolate compared to an individual who does not hold the image of a chocolate in working memory (Higgs, 2015). This phenomenon has been established in both behavioral (Higgs et al., 2012) and electrophysiological paradigms (Rutters, Kumar, Higgs, & Humphreys, 2015). Thus holding food cues in short term memory for long periods may increase cravings for those particular types of food (Higgs, 2015). Moreover, memories of recent experiences associated with consumption of a particular type of food modulates the degree of 'liking' for that item of food (Higgs, 2015).

2.7. Long-term memory and ingestive behavior

Encoding of food experiences into long-term memory is also of particular importance to the processes of 'wanting' and 'liking' (Higgs, 2015). Primary sensory areas of the cerebral cortex receive inputs and therefore provide continuous information regarding the milieu exterior (i.e. the external environment) (Berthoud, 2002, 2004, 2011; Lenard & Berthoud, 2008). Food-related cues received from the sensory organs are recognized, attended to and compared with relevant memories, especially in the visual, auditory and gustatory association areas (Berthoud, 2002, 2004). The hippocampal formation (which includes the hippocampus, dentate gyrus, subiculum, parasubiculum and entorhinal cortex) plays an important role, along with the primary and association sensory areas, in relating sensory experiences to explicit and semantic memories (Berthoud, 2002; Squire, Stark, & Clark, 2004).

2.8. Execution of ingestive behavior

Efferent signals related to ingestive behavior are brought into effect through the motor areas such as the pre-motor cortex, supplementary motor area and the primary motor cortex in the pre-central gyrus (Dum & Strick, 2002; Fox et al., 2001). These motor regions act as the final common pathway in executing ingestive behavior. Activity observed in these cortical regions in response to food-cues may reflect motor readiness for food ingestion (McCaffery et al., 2009).

Even though a reasonable amount of behavioral evidence exists regarding the effects of several forms of CR on 'liking', 'wanting', food cravings, attention and memory, evidence regarding the effects of different types of CR on the biological processes that are possibly underlying these theoretical constructs are largely limited. Our understanding of the neural and cognitive processes that underlie ingestive behavior could be enhanced by focusing on the actual brain regions and their activity rather than limiting our interpretations to behaviorally measured constructs.

3. Caloric restriction: behavioral intervention studies

In general, energy depletion and subsequent homeostatic hunger, coupled with influences on hedonic mechanisms are believed to combine to increase the drive for food intake following a period of short-term fasting (Schwartz et al., 2003; Woods, Seeley, Porte, & Schwartz, 1998). In behavioral studies this is reported as increased 'liking' and 'wanting' for food. Cameron et al. (2014) examined the effects of fasting for 24 h on 'liking' and 'wanting' as measured by two validated computer-based tests (i.e. Relative Reinforcing Value of Food and Leeds Food Preference Questionnaire) coupled with visual analogue scales measuring both hunger and fullness. In a cross-over design, 15 subjects aged 28.6 ± 4.5 years with a mean BMI of 25.3 ± 1.4 kg/m^2 were exposed to fasting for 24 h 'liking' and 'wanting' for food were rated before and after a meal via exposure to images of food from four categories: high-fat savory, low-fat savory, high-fat sweet and low-fat sweet. A similar paradigm was used with the same subjects in the non-fasted state. Additionally, food intake (grams consumed) and energy intake (kilo-calories) during a post intervention *ad libitum* buffet meal was also measured. The authors reported that both 'liking' and 'wanting' subsided following a meal in the non-fasted state (Cameron et al., 2014). However, 'liking' and 'wanting' for sweet food remained elevated even after intake of food following a 24 h fast. Furthermore, *ad libitum* food intake following the 24 h period of fasting was increased by 74% compared to the food intake in the fed state. This suggests that short-term fasting did in fact result in increased drive to consume, and that this drive may be specific to certain foods (i.e. sweet). Similarly, in a study described in detail in section 4, Goldstone et al. (2009) observed that the subjective appeal for high-calorie food compared to low-calorie food seems to be significantly heightened in the fasting state but not the fed state. Such studies provide insight into the impact that short periods of excessive CR may have on immediate intake. However, they do little to inform regarding the longer term-impact on energy balance.

In another study, Martin et al. (2006) compared longer-term (12 week) effects of two different types and amounts of CR 1) a 1200 kcal/day low calorie diet (LCD) derived from typical foods vs. 2) an 800 kcal/day very low calorie diet (VLCD) derived from a balanced nutrition liquid and nutrition bar based total meal replacement. They considered these dietary interventions in terms of cravings (typically associated with 'wanting'), as indexed by the Food Craving Inventory. They reported that both types of CR were successful in decreasing general cravings as well as cravings for sweet, high-fat, starchy and fast food, however this effect was seen to a greater extent in the VLCD as compared with the LCD. Moreover, the effect of the VLCD was seen to persist even during the refeeding phase (6 to 12 weeks) of the intervention, when the VLCD was replaced gradually with a normal diet following the 12-week intervention. Such reductions in food cravings with LCDs and VLCDs were also observed in several other studies that examined the effects of extended CR on food cravings (Harvey et al., 1993; Martin et al., 2011, pp. 741–755). Thus, it appears that 'liking' and 'wanting' for rewarding food are increased with short-term fasting, but food cravings, which appear to be closely related to 'wanting' (Berridge & Robinson, 2003; Finlayson et al., 2007b; Pelchat, 2002), are suppressed with longer duration, and partial CR.

Together, the above findings suggest a methodological disconnect between the disciplines of neuroimaging and behavioral intervention. The majority of human studies designed to better understand the process of human ingestive behavior from a neuroimaging point of view often use short-term fasting paradigms. However, short-term fasting has a very different behavioral consequence than does extended CR. Thus, much of the current neuroimaging literature may not translate or be directly applicable to long-term caloric restriction without comprehensive studies involving extended CR.

4. Caloric restriction: neurophysiological studies

As previously noted, fMRI allows for the study of physiological changes occurring in the brain in response to fasting and extended CR. The technology relies on the increase in oxygenated blood flow to a particular region in the brain (blood oxygen level-dependent; BOLD response), secondary to increased neuronal activity in that region (Poldrack, Mumford, & Nichols, 2011) as a surrogate for measuring neural activation of that region. Using the BOLD signals, one can study the physiological changes occurring in the activation of brain regions in relation to the presentation of a variety of perceptual, cognitive, and behaviorally relevant stimuli (Poldrack et al., 2011). In the case of ingestive behavior, a common methodology involves presentation of food cues (visual, auditory, olfactory or gustatory) and the measurement of the BOLD response to that stimulus. The difference in BOLD responses occurring in response to food-cues compared to nonfood-cues is known as food-cue reactivity. These studies, while somewhat limited in generalizability, nonetheless give us some insight into how the brains of individuals living in food-cue-rich environments (such as Westernized cultures) may be responding to these cues. Thus, differences in food-cue reactivity patterns are widely used to functionally compare and contrast physiological and pathological states in nutritional neuroscience. For instance, differences in food-cue reactivity patterns in obese vs. normal weight individuals have been addressed in a number of studies conducted within the past 10 years (Carnell, Gibson, Benson, Ochner, & Geliebter, 2012). Studies examining physiological effects of fasting and extended CR are also based on contrasts of food-cue reactivity patterns that occur before versus after CR interventions. This section of the review summarizes the direct (and sometimes indirect) evidence emerging from current neuroimaging studies involving the brain regions that are thought to mediate ingestive behavior. By doing so we may inform future research by providing a roadmap to the regions that are most relevant to human ingestion; specifically in the context of varied impacts of caloric restriction and associated changes in related behavioral indices.

4.1. Brain regions involved in ingestive behavior

4.1.1. Hypothalamus

As previously described, one role of the hypothalamus is the

homeostatic regulation of food intake (Berthoud, 2002, 2004; Shin, Townsend, Patterson, & Berthoud, 2011). Moreover, the hypothalamus is thought to be involved in determining the 'liking' of specific foods (Berridge, 2009). Thus, increased 'liking' should result in associated increases in food-cue reactivity of the hypothalamus. While short-term fasting appears to increase 'liking' as measured by behavioral means, this anticipated increase in food-cue reactivity in the hypothalamus has not been directly observed in neuroimaging studies. However, several early fMRI studies suggest that acute energy intake following fasting seem to suppress hypothalamic activity. Liu et al. (2000) examined the resting state fMRI activity of mid-sagittal sections of the brain following a 12 h fast and after administration of a 75 g dextrose load. Administration of the dextrose load was found to suppress the hypothalamic BOLD responses approximately 10 min after ingestion. Smeets, de Graaf, Stafleu, van Osch, and van der Grond (2005) examined this phenomenon by orally administering a solution of glucose (i.e. test solution), a taste-matched aspartame solution (i.e. positive control), an energy-matched maltodextrin solution (i.e. positive control) and a placebo in a randomized 4-way crossover design and performing a mid-sagittal fMRI scan. Only the glucose load resulted in a significant suppression of the ventral hypothalamic activity compared to the placebo. Moreover, only the glucose condition resulted in an early rise in the mean plasma insulin level. Thus, it is possible that hypothalamic activity was suppressed by the acute release of glucose into blood stream. Nevertheless, it is not clear whether this suppression was due to a fasting-associated increase in the baseline hypothalamic activity and a subsequent suppression with the glucose or due to a direct suppression by oral intake of glucose. Therefore, more evidence is required to come to a conclusion regarding the effects of short-term fasting on hypothalamic food-cue reactivity.

However, suppression of hypothalamic activity has been reported in an extended CR intervention extending up to 62 days. In a small study of 6 people with obesity, Rosenbaum, Sy, Pavlovich, Leibel, and Hirsch (2008) conducted a cross-over fMRI study with the aim of examining leptin sensitive changes in energy homeostatic neural circuitry following weight loss. They hypothesized that injection of leptin (a hormone related to increased satiety) would suppress the food-cue reactivity of brain regions thought to be involved in increasing energy intake. Conversely, they predicted that these same regions would show increased activity in response to food-cues, when leptin was not injected. The subjects underwent a liquid-based 800 kcal/day total meal replacement VLCD intervention to achieve a 10% weight loss within a period of 36–62 days. Functional MRI imaging was performed at baseline, following weight loss without injection of leptin (control condition) and following weight loss with the injection of leptin. Hypothalamic activity in the visual food-cue versus non-food-cue contrast was suppressed in the baseline versus control comparison of fMRI food-cue reactivity. Thus, this study provides some evidence to suggest that activation of the hypothalamus occurring in response to food-cues can be suppressed by extended CR. Given the relationship of the hypothalamus to the concept of 'liking' as outlined previously, it may be reasonable to speculate that suppression of hypothalamic activity instantiates a decline in 'liking' found with extended CR in behavioral studies. However some notable limitations must also be considered that may be influencing this relationship. First, the hypothalamus serves multiple roles in regulating food intake including regulation of both homeostatic hunger and satiety (Berthoud, 2002, 2004; Lenard & Berthoud, 2008). Both orexigenic and anorexigenic pathways arise from the hypothalamus (Berthoud, 2002, 2004; Lenard & Berthoud, 2008); thus we expect increased activity of the hypothalamus with the activation of either of these two pathways. Second, the activity of the hypothalamus may be influenced by multiple factors (e.g. stress due to the negative energy balance associated with extended CR; Porter, 1952). Third, a recent animal study conducted by Chen, Lin, Kuo & Knight (2015) suggests that both orexigenic and anorexigenic neurons arising from the arcuate nucleus of the hypothalamus receive real-time inputs regarding the availability of food in the external environment. Moreover, these inputs seem to reverse the hunger-associated heightened orexigenic and suppressed anorexigenic neuronal activity. Thus, alterations in hypothalamic BOLD responses could occur even with the mere presence of sensory food-cues. This potentially explains the detection of alterations in fasting vs. fed state contrasts in hypothalamic activity during resting state fMRI (Liu et al., 2000; Smeets et al., 2005) but not with food-cue reactivity paradigms. Fourth, the hypothalamic nuclei that regulate specific functions are highly compartmentalized (Berthoud, 2002, 2004; Lenard & Berthoud, 2008; Snell, 2010). The resolution of the fMRI images limits our ability to pinpoint these activation patterns to specific regions within the hypothalamus that uniquely serve distinct functions (Poldrack et al., 2011). Fifth, hypothalamic BOLD responses are susceptible to artifacts related to cardiac and respiratory cycles (Napadow et al., 2008). Based on methodological reporting of some fMRI studies one cannot ascertain if there were indeed such artifacts. Finally, some studies have indicated that hypothalamic activity may not be associated with 'liking' (de Araujo et al., 2013). Furthermore, to the best of our knowledge, the hypothesized association of change in 'liking' and the change in hypothalamic food-cue reactivity has not been concluded so far in any clinical neuroimaging study. Therefore, in summary, the above findings are suggestive of the hypothalamus playing an important role in behavioral responses to food, but its exact role(s) is/are not yet known. However, implementing cardio-respiratory gating in fMRI studies and the investigation of potential alterations in structural and functional connectivity (e.g. as assessed by diffusion tensor imaging – DTI and functional connectivity analyses) associated with extended CR between the hypothalamus and other regions involved in ingestive behavior could allow us to further understand the role of the hypothalamus in response to the internal and external food environment.

4.1.2. Orbitofrontal cortex and the broader ventromedial prefrontal cortex

Food-cue reactivity of the ventromedial prefrontal cortex (i.e. primarily the orbitofrontal cortex), which is frequently thought to be involved in 'liking', semantic memory, and associative retrieval (Berridge, 2009; Berthoud, 2002; Fiez, 1997; Ricci et al., 1999), tends to increase following short-term fasting. Goldstone et al. (2009) compared the fMRI visual food-cue reactivity patterns in the fed and fasting states, randomizing 20 non-obese healthy males and females (19–35 years of age). The difference in BOLD signals between high-calorie and low-calorie visual food cues was significantly greater in the fasting (15.9 ± 0.3 h since last meal) than the fed state (1.6 ± 0.1 h since last meal) in both medial and lateral orbitofrontal cortex bilaterally. In a similar study involving 34 healthy female adolescents, which examined the neurophysiological correlates of short-term fasting, Stice et al. (2013) found that differences in BOLD signals in the L/orbitofrontal cortex obtained in response to visually appetizing food-cues vs. non-appetizing food-cues moderately correlated with the hours of fasting, which ranged from 1 to 16 h. Furthermore, food-cue reactivity of the orbitofrontal cortex was greater in the fasting state compared to the satiated state even when taste-cues were used rather than visual food-cues. Malik, McGlone, Bedrossian, and Dagher (2008) studied fMRI visual food-cue reactivity in 20 non-obese subjects, of whom 12 subjects were scanned in the fed state before and after receiving injections of ghrelin while 8 subjects were scanned twice in the fed state

without receiving ghrelin. Injection of ghrelin mimics fasting even in the fed state as it is a hormone that is associated with hunger and is found to be increased with fasting and decreased with food intake. It is important to note that the hypothalamus has receptors for circulating ghrelin and binding of ghrelin increases the activity of hypothalamic orexigenic pathways, thus increasing the overall drive to ingest. Contrast in BOLD responses of the ghrelin vs. control conditions observed by Malik et al. (2008) was significantly higher in the orbitofrontal cortex in food-cue vs. non-food-cue contrast suggesting that mimicking a physiological state of hunger by injection of ghrelin could result in a similar activation of orbitofrontal cortex as seen in the fasting state. The latter study suggests that Ghrelin may be an important mediator of the observed responses to food cues.

Fasting was also seen to increase gustatory food-cue reactivity of the orbitofrontal cortex. Haase, Cerf-Ducastel, and Murphy (2009) conducted a study to compare the effects of fasting for 12 h and satiation on fMRI reactivity to 6 different types of taste-cues (i.e. sucrose, saccharin, caffeine, citric acid, guanosine 5-monophosphate and sodium chloride) in 18 healthy, non-obese young-adult males and females. An increased BOLD response was seen in Brodmann area 11 in the orbitofrontal cortex in response to the tastes of sucrose, caffeine and citric acid in the fasting condition compared to the satiated control condition.

However, the food-cue reactivity of the ventromedial prefrontal cortex was seen to decrease in the context of extended CR (Bruce et al., 2014; Rosenbaum et al., 2008). In two studies designed to consider broader topics, the control groups were exposed to an extended CR intervention. Findings of the control groups are relevant to our discussion here. First, Rosenbaum et al. (2008) described a significant reduction in BOLD responses in the L/ventromedial prefrontal cortex (Brodmann area 10 and 11) after achieving a 10% weight loss compared to the baseline. Bruce et al. (2014) examined 16 obese participants aged 23–52 years who underwent a moderate CR intervention for 12 weeks as part of a behavioral weight loss intervention. Subjects were scanned using a food-cue reactivity paradigm before and after the behavioral weight loss intervention in both fed and very brief fasting (4 h) states. In a graphical representation, the authors indicated a reduction in the fasted-state food-cue reactivity of the R/ventromedial prefrontal cortex (Brodmann area 9 and 10) after the 12 week dietary intervention, compared to the baseline. Thus, extended CR appear to be suppressing the ventromedial prefrontal cortical activity.

Therefore, considering results of all the above studies fasting for up to 24 h seems to increase both gustatory and visual food-cue reactivity of the ventromedial prefrontal cortex. Particularly, the orbitofrontal region of the ventromedial prefrontal cortex is involved in storing associations between visual cues and associated reward or punishment (Berthoud, 2002). The observed increased activity in the orbitofrontal cortex associated with highly appealing food-cue presentation in the fasted state is thus suggestive of this region's involvement with rewarding experiences. Furthermore, as described in section 2, the orbitofrontal cortex is involved in determining 'liking' (Berridge, 2009). This finding is consistent with the results of Cameron et al. (2014) and Goldstone et al. (2009), discussed in Section 3, suggesting that fasting may be increasing 'liking' by a mechanism that acts through the orbitofrontal cortex. However, extended calorie restriction seems to suppress the food-cue reactivity of the orbitofrontal cortex. This may be associated with suppressed overall salience to ingestion seen with extended CR.

One limitation impacting these conclusions involves the susceptibility of fMRI signals of the orbitofrontal cortex regions to air-tissue interface artifacts caused by the frontal sinuses which severely reduce signal-to-noise ratio (Deichmann, Gottfried, Hutton, & Turner, 2003; Poldrack et al., 2011). Deichmann et al. (2003) described a method to limit this problem by optimizing the image slice orientation via increasing the tilt-angle of the head to 30°. Since the tilt-angel is not described in most fMRI studies, we do not know if these precautions have been implemented and thus findings related to the orbitofrontal cortex need to be cautiously interpreted. Therefore, even though the evidence suggests that fasting increases food-cue reactivity of the orbitofrontal cortex, we emphasize the need to improve methods to decrease the signal-to-noise ratio and for more detailed methodological reporting in future fMRI studies examining this region. Yet, another limitation in the literature that restricts our ability to conclude a relationship between the changes in food-cue reactivity in the orbitofrontal cortex along with the changes in behavioral constructs is the lack of direct evidence to suggest this conclusion. This disconnect of behavioral and neuroimaging studies needs to be addressed in future studies.

4.1.3. Dorsolateral prefrontal cortex

As opposed to the ventromedial prefrontal cortex, the dorsolateral prefrontal cortex is primarily involved in exerting inhibitory control over hedonic drives leading to food intake. Accordingly, alterations in visual food-cue reactivity of the dorsolateral prefrontal cortex was not observed with short-term fasting in the majority of studies (Frank et al., 2010; Goldstone et al., 2009; Malik et al., 2008; Martens et al., 2013; Siep et al., 2009; Stice et al., 2013). However, in a study conducted by Uher et al. (2006), increased taste-cue reactivity was seen in the dorsolateral prefrontal cortex. In fact, they conducted an fMRI study, including 18 healthy men and women aged 20–44 years, to compare both visual and taste food-cue reactivity in a fed state and following a 24-h fast. They found significant activation in the L/dorsolateral prefrontal cortex region (Brodmann area 44), in the chocolate milk versus tasteless solution contrast for the fasting state compared to the fed state. Increased taste-cue reactivity was seen in the L/inferior frontal gyrus (Brodmann area 47) in the study conducted by Haase et al. (2009) as well. Therefore, the taste-cue reactivity, but not the visual food-cue reactivity, of dorsolateral prefrontal cortex may also be increasing in response to fasting. Given that the dorsolateral prefrontal cortex, particularly Brodmann area 47, is involved in working sensory memory and associative retrieval (Burton, LoCasto, Krebs-Noble, & Gullapalli, 2005; Fiez, 1997; Ricci et al., 1999), increased taste-cue reactivity in the fasting state compared to the fed state may be due to the increased neural resource allocation necessary to retrieve memories of food associated with the taste cues being presented.

Food-cue reactivity of the dorsolateral prefrontal cortex was also increased in the context of extended CR (Rosenbaum et al., 2008). In the previously described study, Rosenbaum et al. (2008) reported increased visual food-cue reactivity in the R/and L/middle frontal gyri (Brodmann area 9) and the L/inferior frontal gyrus region in the food-cue vs. non-food-cue contrast following an extended CR intervention in an obese population. However, a recently published study that specifically examined for dorsolateral prefrontal cortical activity (Weygandt et al., 2015) failed to demonstrate a relationship between dietary calorie restriction for 12 weeks and change in BOLD responses in a food-related delay discounting task. Nevertheless, as suggested by Rosenbaum et al. (2008), extended CR may be associated with enhanced food-cue reactivity in the dorsolateral prefrontal cortex, possibly contributing to the enhancement of inhibitory control of hedonic and homeostatic drives to ingest in calorie restricted individuals. However, as with previously described brain regions, literature lacks direct evidence indicating associations between changes in dietary restraint and alterations in

visual food-cue reactivity of the dorsolateral prefrontal cortex seen with extended CR. A study that addresses this limitation is needed to confirm the empirical relationships.

4.1.4. Anterior cingulate cortex

Among its multiple functions, the anterior cingulate cortex is considered to be involved in calculating food reward, selectively attending to food-cues and maintaining motivation for food intake (Berthoud, 2004, 2011; MacDonald, Cohen, Stenger, & Carter, 2000). In keeping with these functional roles, food-cue reactivity of the anterior cingulate cortex seems to increase with fasting. Martens et al. (2013) examined the effect of fasting for 10 h on fMRI visual food-cue reactivity, in 20 overweight and 20 normal weight subjects. A significant stimulus (food vs. non-food contrast) x condition (fasting vs. satiated) x group (overweight vs. normal weight) interaction was seen in the anterior cingulate cortex. Subsequent analyses indicated that the food-cue reactivity of the anterior cingulate cortex is increased in the fasted state compared to the satiated state in the food vs. non-food visual stimulus contrast. This effect was exaggerated in the overweight subjects compared to the normal weight controls. Similarly, reactivity of the anterior regions of the L/posterior cingulate cortex (also involved in exercising selective attention to sensory stimuli and reward assessment) was also stronger in response to images of high-calorie food in the fasting state compared to the satiated state in the study conducted by Siep et al. (2009). Therefore, the anterior cingulate cortex, which is involved in reward calculation, selective attention and motivation (Berthoud, 2004, 2011; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; MacDonald et al., 2000), seems to be critically involved in the increased responsivity to food-cues during fasting, despite the lack of direct combined neuroimaging and behavioral evidence to confirm this conclusion.

On the other hand, the food-cue reactivity of the anterior cingulate cortex was seen to be suppressed following extended CR. Rosenbaum et al. (2008) described previously, and Murdaugh, Cox, Cook, and Weller (2012) reported a significant suppression in visual food-cue reactivity of bilateral anterior cingulate cortex (Brodmann areas 24 and 32) following the extended calorie weight loss intervention. These findings suggest that the food-cue reactivity of the anterior cingulate cortex is suppressed with CR induced weight loss. Taken together, these findings, while not completely conclusive, are suggestive of an important role for the anterior cingulate cortex, in reward calculation and motivation towards food intake, which appear to decrease with extended CR.

4.1.5. Insula

The role of the insula in ingestive behavior has been a focus of interest due to the fact that it is believed to be involved in taste perception and determining 'liking' for food (Berridge, 2009; Phan, Wager, Taylor, & Liberzon, 2002; Volkow et al., 2011). Several studies have explored this possibility in relation to fed versus fasted states. In the previously described study, Haase et al. (2009) found taste reactivity of the L/insula was greater following fasting compared to the fed state. Uher et al. (2006) and Goldstone et al. (2009) found similar results. food-cue reactivity of the insula was also seen to increase bilaterally when ghrelin was injected to mimic a state of hunger, compared to when saline was injected in subjects who were fed (Malik et al., 2008). Therefore, the activity of the insula, which is involved in taste perception and determining the degree of 'liking' for food (Berridge, 2009; Volkow et al., 2011), increases with fasting. It is not clear whether the increase in food-cue reactivity is due to enhanced 'liking' *per se* or due to increased activation of memories and selective attention to an expected or an already received taste stimulus. A study that examines the relationship between change in 'liking' and alteration in insular food-cue reactivity may provide insight into this issue. However, in keeping with the theme of contrasting results from fasting versus extended CR, the insular food-cue reactivity was not seen to be significantly affected with extended CR in the previously described studies conducted in individuals with obesity (Bruce et al., 2014; Murdaugh et al., 2012; Rosenbaum et al., 2008).

4.1.6. Amygdala

The amygdala is made up of at least 20 nuclei with varying functions, including regulation of 'wanting' (Berridge, 2009; Paton, Belova, Morrison, & Salzman, 2006; Phan et al., 2002). Following the pattern of cerebral reactivity described so far, food-cue reactivity of the amygdala seems to increase in response to fasting, yet decline with extended periods of CR. Examining the effects of fasting on visual food-cue reactivity, Goldstone et al. (2009) demonstrated increased reactivity of bilateral amygdala to visual high-calorie food-cues compared to low-calorie food-cues while fasting. Haase et al. (2009) reported a similar increase in the gustatory food-cue reactivity of the amygdala. Malik et al. (2008) also found positive correlations between the food-cue reactivity of bilateral amygdala and subjective hunger following injection of ghrelin (mimicking fasting). Nevertheless, in line with the common pattern of activation associated with extended CR in this review, Rosenbaum et al. (2008) described a suppression in the activity of the L/amygdala to food-cues following weight loss brought about by extended CR. Unfortunately, as has been the case throughout this review, few studies have examined extended CR, which significantly limits the conclusions that may be drawn. However, based on these preliminary observations, it is reasonable to speculate that during fasting, the increased activity of the amygdala may be related to increased 'wanting' and conversely, that suppression of food-cue reactivity in the amygdala with extended CR may be associated with suppression of 'wanting'. Nevertheless, it should be emphasized that these relationships cannot be confirmed until these specific associations are found in clinical neuroimaging studies.

4.1.7. Ventral striatum and nucleus accumbens

The nucleus accumbens and the broader ventral striatum are involved either directly or indirectly in determining both 'liking' and 'wanting' (Berridge, 1996, 2009; Berthoud, 2002, 2004). They are thought to be involved in 'calculating' the degree of 'wanting' after considering inputs from the cortical regions that determine 'liking,' and exert executive control and also after receiving inputs from the homeostatic circuitry (Berthoud, 2002, 2004). In addition, being an important component of the reward circuitry, the nucleus accumbens itself is made up of nuclei that are involved in determining 'liking' (Berridge, 1996, 2009). food-cue reactivity of the ventral striatum has been found to increase with both fasting (Goldstone et al., 2009) and when ghrelin was injected during a fed state to simulate hunger (Malik et al., 2008). Additionally, the response to fasting of reward-related ventral tegmental area and the substantia nigra were observed to be similar (Malik et al., 2008). Thus, the food-cue reactivity of the ventral striatum, ventral tegmental area and substantia nigra seem to increase with short-term fasting. However, the activity of these regions that are often thought to be involved in determining 'liking', 'wanting' and the ultimate food reward was not affected by extended CR.

4.1.8. Hippocampal formation, fusiform cortex and visual cortex

The hippocampus and the parahippocampal gyrus are involved in the storage of explicit and semantic memories related to ingestive behavior (Strange, Fletcher, Henson, Friston, & Dolan, 1999). Furthermore, these regions along with areas such as the occipital cortex (Malik et al., 2008; Murdaugh et al., 2012) and the fusiform

gyrus (Malik et al., 2008; Rosenbaum et al., 2008; Siep et al., 2009; Uher et al., 2006) are involved in visual object and face perception and associated selective visual attention (Dumoulin & Hess, 2007). The food-cue reactivity of the hippocampal formation and the parahippocampal gyrus, was found to increase in response to fasting and decrease in response to extended CR (Haase et al., 2009; Malik et al., 2008; Murdaugh et al., 2012; Rosenbaum et al., 2008). The food-cue reactivity of the fusiform cortex and the visual cortex was also increased with fasting and suppressed with extended CR (Haase et al., 2009; Malik et al., 2008; Murdaugh et al., 2012; Rosenbaum et al., 2008). Increased activity of these areas during fasting is most likely to signify increased activation of memories related to food intake and increased visual attention to food-cues related to the memories; whereas in the case of extended CR, decreased activity seems to be associated with reduced activation of memories and therefore decreased visual attention to such food-cues. However, there is a notable confounding factor that is typically unaccounted for in such studies. The image banks used in many fMRI studies involving food-cue reactivity paradigms, particularly along with CR interventions, do not appear to contain images of food and control images (i.e. images of objects, blurred images, etc.) that are matched in terms of color and shape with the food items. However, it should also be noted that several recent neuroimaging studies have attempted to address this limitation by presenting images of food and objects that are comparable in color and topography in order to dissociate the processing of basic visual properties like color and shape, compared to those specific properties related to processing of images of food *per se* (Blechert, Meule, Busch, & Ohla, 2015; Martens et al., 2013). Implementing similar or equivalent paradigms (i.e. shape and color matched food and control images) in future fMRI studies that aim to examine the effects of CR will likely improve our understanding of the effects of extended CR on activity of the regions involved in visual information processing and visual memory.

4.1.9. Primary motor cortex and pre-motor cortex

The primary motor cortex executes motor responses and the pre-motor cortex region modulates the activity of the primary motor cortex (Dum & Strick, 2002; Fox et al., 2001). These regions are involved in determining motor readiness to ingest and the execution of ingestive behavior (McCaffery et al., 2009). Visual food-cue reactivity of R/PCG (pre-motor cortex region) was found to positively correlate with length of absolute fasting in hours (Stice et al., 2013). However, food-cue reactivity of the motor regions in the brain were suppressed with extended CR. Rosenbaum et al. (2008) described a suppression in food-cue reactivity of bilateral pre-central gyri, involving the L/pre-motor cortex and Brodmann area 9 on the right side following extended CR. In this study, real food and non-food objects were shown to each subject in a pre-randomized order, while the fMRI images were acquired. The subjects did not perform any motor responses. Thus, the increased food-cue reactivity in the motor cortices are likely to be due the reactivity of the regions in response to food stimuli, rather than due to activation of the motor cortical regions during execution of a motor response. Therefore, fasting seems to increase the food-cue reactivity of motor regions involved in ingestive behavior, indicating motor readiness to consume. However, in the case of extended caloric restriction, food-cue reactivity of motor cortical- and reward-related regions appears to be suppressed. This is particularly interesting as many studies fail to adequately consider influences of the motor aspects of behavior, preferring to focus on matters more "psychological" in nature such as 'liking' and 'wanting'. Some research groups have used reaction times to food-cues as a measure of explicit 'wanting' (Finlayson et al., 2007b, 2007a). However, a neuroimaging study that examines the correlations between changes in food-cue reactivity in the motor regions and changes in reaction times in visual food-cue reactivity paradigm in fasting and extended CR interventions is needed to confirm these conclusions and establish the importance of the motor regions in ingestive behavior.

5. Restrained eating: a special case of CR

The evidence outlined above involves CR by intentional intervention. However, there is a unique ingestive phenomenon observed in the literature that is worthy of consideration as the genesis of the caloric restriction is believed to be at least in part, a pathological (and typically unsuccessful) attempt to control calorie intake, typically through the elimination of specific foods or food categories (Lowe et al., 2006; Markowitz et al., 2008). The basis is a belief that ingesting these foods will 'trigger' extreme ingestive dysregulation. Thus, restrained eating is defined as effortful restriction of energy intake for the purpose of weight loss or maintenance (Markowitz et al., 2008). However, restrained eaters are not always engaged in hypocaloric dieting in the naturalistic setting and at times are consuming considerable calories from this restricted range of "allowed" foods (Lowe et al., 2006; Markowitz et al., 2008; Stice, Cooper, Schoeller, Tappe, & Lowe, 2007). Thus, restrained eating is not always synonymous with CR and in fact is considered a risk factor for future weight gain (Lowe et al., 2006; Markowitz et al., 2008). Nonetheless it is important to understand RE in the context of the current discussions as there are distinct patterns of food-cue reactivity seen in this group of individuals. Therefore, we emphasize in our review of this literature, the similarities and differences in food-cue reactivity patterns associated with extended CR and RE (which also represents an extended CR strategy).

As described in Section 4, food-cue reactivity of the regions that are primarily exerting executive inhibitory control over ingestion (i.e. dorsolateral prefrontal cortex and inferior frontal gyrus) was enhanced following extended CR in one study. This phenomenon was noticeably evident in individuals with increased hedonic restraint. Successful weight loss maintainers (SWLs) are individuals who were successful in maintaining a weight loss of at least 13 kg for more than 1 year (McCaffery et al., 2009; Wing & Hill, 2001). Restraint scores (i.e. measures of hedonic restraint in relation to ingestive behavior) of SWLs are significantly higher than typical obese and normal weight subjects (Sweet et al., 2012). McCaffery et al. (2009) compared the visual food-cue reactivity of 17 SWLs, with 16 obese and 18 normal weight subjects. Both SWLs and normal weight controls demonstrated increased food-cue reactivity to high-energy food-cues in the dorsolateral prefrontal cortex, bilaterally, compared to the obese subjects who were not SWLs. In a study conducted by the same group (Sweet et al., 2012), gustatory food-cue reactivity of the posterior L/inferior frontal gyrus was seen to be increased in SWLs compared to normal weight and obese subjects, measured both 20–40s and 40–60s after stimulation of the tongue with a lemon lollipop. Consistent with the above finding, several studies have documented positive correlations between restraint scores and food-cue reactivity of the prefrontal cortex and the L/inferior frontal gyrus. Burger and Stice (2011), found a moderate correlation between restraint scores and the activity of the bilateral superior and middle frontal gyri in response to the taste of a milk-shake compared to a tasteless solution. Demos, Kelley, and Heatherton (2011) also described increased visual food-cue reactivity in the superior frontal gyrus and the L/inferior frontal gyrus in obese subjects with higher restraint scores compared to those with lower restraint scores. Sweet et al. (2012) also reported a positive correlation between the restraint scores and the gustatory food-cue reactivity of the L/inferior frontal gyrus

in response to a gustatory stimulus. These findings taken in composite suggest that the prefrontal cortex activity of restrained eaters increases to a greater extent compared to normal weight and obese controls when responding to food cues. However, with extended CR, even previously non-restrained people with obesity seem to develop a higher level of inhibitory control over food intake as evidenced by the literature reviewed in the previous section. Thus, it is unclear whether this gain in inhibitory control is primarily due to CR, weight loss and associated alterations in overall metabolism, or the prolonged lack of exposure to stimulating food-cues during extended CR interventions. This question needs to be addressed in future studies.

Previously we noted that in contrast to the prefrontal cortex, food-cue reactivity of the anterior cingulate cortex was seen to decrease with extended CR, providing a possible explanation for the reduction in 'wanting' associated with extended CR. Interestingly, this pattern was also evident in studies conducted with restrained eaters. SWLs were also found to have decreased reactivity in the anterior cingulate cortex region in response to both images of high-energy food (McCaffery et al., 2009) and gustatory food-cues (Sweet et al., 2012) compared to obese controls. Furthermore, the activity of the anterior cingulate cortex of the obese controls was greater than that observed in the sustained weight-loss maintainers (Sweet et al., 2012). The anterior cingulate cortex is a higher-level brain center that governs incentive salience (Berthoud, 2002, 2004, 2011). As evidenced by neuroimaging findings, food-cue reactivity of the anterior cingulate cortex appears to be lower in restrained eaters compared to individuals with lower levels of hedonic restraint. Thus, the food-cue reactivity of the anterior cingulate cortex appears to be lower in both restrained eaters and obese individuals who have undergone extended CR, while the food-cue reactivity of the dorsolateral prefrontal cortex appears to be higher in both groups of individuals. The decrease in food-cue reactivity of the anterior cingulate cortex therefore may be associated with the increase in the inhibitory activity of the prefrontal cortex.

The insula is a cortical region involved in determining 'liking' (Berridge, 1996, 2009). In the studies reviewed in section 4, insular food-cue reactivity was not seen to be affected by extended CR. However, McCaffery et al. (2009) concluded that subjects who were obese but are currently maintaining weight loss successfully through dieting tend to show increased visual food-cue reactivity in the L/insula compared to obese controls. Similarly, the reactivity of bilateral insular cortices to taste of a lemon-flavored lollipop was correlated with the restraint scores (Sweet et al., 2012). Similar results are reported in other studies involving insular food-cue reactivity of subjects with high restraint scores who were on a diet (Demos et al., 2011). Thus, the insular food-cue reactivity of self-restrained dieters seems to be greater than non-restrained people with obesity. This suggests that 'liking' for food in self-restrained dieters may be greater. Therefore, in spite of the inhibition of food intake brought about by higher degrees of hedonic restraint (as evidenced by increased activity of the dorsolateral prefrontal cortex and the inferior frontal gyrus), restrained eaters may also be developing (and or trying to overcome) a greater level of 'liking' for food. Overriding of the hedonic control of this 'liking' may be a potential mechanism leading to violation of dietary restrictions and weight regain following weight-loss in some individuals.

As discussed in section 4, food-cue reactivity of the nucleus accumbens and the broader ventral striatum were not affected by extended CR in the reviewed studies. In spite of these observations, Demos et al. (2011) in a study comparing visual food-cue reactivity among chronic dieters and non-dieters, found an increase in the activity in the nucleus accumbens bilaterally among non-dieters while food-cue reactivity of the L/nucleus accumbens of chronic dieters was seen to decrease. However, when the dieters were exposed to a high calorie milk-shake, violating their diet, food-cue reactivity of the nucleus accumbens was seen to increase bilaterally. Both nucleus accumbens and the broader ventral striatum are key areas involved in determining the degree of 'wanting' and contributing to the calculation of reward of a food (Berridge, 2009; Volkow et al., 2011). Thus, suppression of the reactivity of the nucleus accumbens and the ventral striatum in dieters appears to be associated with suppression of 'wanting' and the anticipated reward of a food. However, according to Demos et al. (2011), violation of hedonic suppression seem to be associated with an increase in the food-cue reactivity in the nucleus accumbens. Persistence of a higher degree of 'liking' (as evidenced by increased insular activity) despite increased hedonic restraint (as evidenced by increased activity of the prefrontal cortex) may be suppressing the activity of the reward-calculating nucleus accumbens in successful dieters with higher restraint scores. When dieting is violated, due to the lack of inhibition brought about by the prefrontal cortex, the activity of the nucleus accumbens may be increasing resulting in a higher incentive salience. This potential mechanism may play an important role in the violation of diets and resulting weight gain seen following completion of some dietary interventions for obesity. Taken as a whole, food-cue reactivity of the nucleus accumbens and the broader ventral striatum appear to be suppressed in restrained eaters. Violation of diets, however, seems to increase the food-cue reactivity in these regions.

Another interesting phenomenon observed in restrained eaters was the increased food-cue reactivity in the motor cortical regions. As discussed in Section 4, extended CR seems to suppress motor cortical food-cue reactivity. However, a contradictory finding is reported by McCaffery et al. (2009) who described increased motor cortical food-cue reactivity, particularly in the mouth region (Fox et al., 2001), indicating a higher motor readiness to consume despite hedonic restraint. This inconsistency deserves further attention if we are to better understand the role of motor cortices in restrained eating.

6. Conclusions, limitations and future directions

In our review we sought to consolidate the findings from somewhat compartmentalized and at times contradictory areas of the research literature. Our goal is to propose a unified and evidence-informed conceptual framework that may assist researchers in developing a clearer understanding of the complex experience of human ingestive behavior. The neuroimaging and behavioral findings reviewed, were often times incomplete and methodologically heterogeneous. In addition, the populations sampled were typically diverse (normal weight, obese, mixed). Thus when possible we noted BMI associated comparisons. As such this review does not claim to be the definitive 'explanation', but rather, is intended to provide evidence based insights into how the human brain reacts to dietary restriction and perhaps to highlight where the extant literature conceptually converges, which in turn may provide new and novel paths for future research.

Table 1 summarizes the neurophysiological effects of fasting, extended CR and restrained eating examined in this review. Generally speaking, fasting was observed to be associated with increased food-cue reactivity in the brain regions involved in determining 'liking' (orbitofrontal cortex, insula, ventral striatum), 'wanting' and food reward calculation (nucleus accumbens, broader ventral striatum, amygdala and anterior cingulate cortex), visual attention and memory (hippocampus, fusiform cortex and visual cortex) and motor execution (primary motor cortex and pre-motor cortex).

Table 1
Food-cue reactivity patterns of the brain seen with fasting, extended calorie restriction and restrained eating.

Region in the brain	Alteration in food-cue reactivity			Function(s) of the region
	Fasting	Extended CR	Restrained eating	
Hypothalamus		↓(Rosenbaum et al., 2008)		Homeostatic regulatory center of food intake, 'liking' (Berridge, 2009; Berthoud, 2002, 2004)
Dorsolateral prefrontal cortex	↑(Haase et al., 2009; Uher et al., 2006)	↑(Rosenbaum et al., 2008)	↑(Burger & Stice, 2011; DelParigi et al., 2007; McCaffery et al., 2009; Sweet et al., 2012)	Hedonic restraint, executive control, working memory (Berthoud, 2004, 2011; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004)
Orbitofrontal cortex	↑(Goldstone et al., 2009; Haase et al., 2009; Malik et al., 2008; Stice et al., 2013)	↓(Bruce et al., 2014; Rosenbaum et al., 2008)	↓(DelParigi et al., 2007)	'Liking', semantic memory, associative retrieval (Berridge, 2009; Berthoud, 2002; Fiez, 1997; Ricci et al., 1999)
Inferior frontal gyrus	↑(Haase et al., 2009)	↑(Rosenbaum et al., 2008)	↑(Demos et al., 2011; Sweet et al., 2012)	Working sensory memory, associative retrieval (Burton et al., 2005; Fiez, 1997)
Anterior cingulate cortex	↑(Frank et al., 2010; Martens et al., 2013; Siep et al., 2009)	↓(Murdaugh et al., 2012; Rosenbaum et al., 2008)	↓(McCaffery et al., 2009; Sweet et al., 2012)	Reward calculation, executive control, motivational drive, emotion regulation (Berthoud, 2011; Davidson et al., 2002; MacDonald et al., 2000)
Insula	↑(Goldstone et al., 2009; Haase et al., 2009; Malik et al., 2008; Uher et al., 2006)		↑(Demos et al., 2011; McCaffery et al., 2009; Sweet et al., 2012)	Taste perception, 'liking', emotional recall (Berridge, 2009; Phan et al., 2002; Volkow et al., 2011)
Amygdala	↑(Goldstone et al., 2009; Haase et al., 2009)	↓(Rosenbaum et al., 2008)		'Wanting', reward processing, classical conditioning, fear and anxiety (Berridge, 2009; Paton et al., 2006; Phan et al., 2002)
Nucleus accumbens and broader ventral striatum	↑(Goldstone et al., 2009; Malik et al., 2008)		↓(Demos et al., 2011)	'Liking', 'wanting', reward calculation (Berridge, 2009)
Ventral tegmental area/substantia nigra	↑(Malik et al., 2008)			Reward expectation, reward prediction and reward processing (Darbaky, Baunez, Arecchi, Legallet, & Apicella, 2005; Zellner & Ranaldi, 2010)
Hippocampal formation	↑(Haase et al., 2009; Malik et al., 2008)	↓(Murdaugh et al., 2012; Rosenbaum et al., 2008)	↓(DelParigi et al., 2007; McCaffery et al., 2009)	Long-term memory, short-term memory, working memory, relational memory, episodic memory, associative memory, semantic memory, motivational drive (Squire et al., 2004; Strange et al., 1999)
Fusiform cortex	↑(Malik et al., 2008)	↓(Murdaugh et al., 2012; Rosenbaum et al., 2008)	↓(DelParigi et al., 2007; McCaffery et al., 2009)	Visual object (food-cue) perception (Dumoulin & Hess, 2007)
Visual cortex	↑(Malik et al., 2008)	↓(Murdaugh et al., 2012; Rosenbaum et al., 2008)	↓(McCaffery et al., 2009; Schur et al., 2012)	Visual object (food-cue) perception (Dumoulin & Hess, 2007)
Pre-motor cortex and primary motor cortex	↑(Stice et al., 2013)	↓(Rosenbaum et al., 2008)	↑(McCaffery et al., 2009)	Voluntary movement planning and execution (Dum & Strick, 2002; Fox et al., 2001)

Note. Fasting, absolute refrainment from intake of food for periods extending up to 48 h; Extended calorie restriction (CR), limitation of intake of calories to less than 1500 kcal/day over a period that is greater than 3 weeks; Restrained eating, effortful restriction of energy intake for the purpose of weight loss or maintenance.

It is important to note however that with extended CR, food-cue reactivity of those regions determining 'liking' were only minimally affected, while the food-cue reactivity of all regions involved in food-reward calculation and 'wanting', retrieving memories related to food rewards, and other regions involved in perception and execution of motor behavior were found to be suppressed. Moreover, food-cue reactivity of the dorsolateral prefrontal cortex and inferior frontal gyrus was seen to increase with extended CR, which may be indicative of these regions exercising executive hedonic control over the homeostatic and hedonic impulses to ingest. Together, these neurophysiological alterations provide plausible explanations for reductions in 'cravings' that are associated with extended CR.

In the special case of RE, food-cue reactivity patterns of certain areas of the brain appear to be similar to the patterns seen with extended CR. While they are successfully engaged in a diet, restrained eaters seem to suppress incentive salience for food intake by increasing inhibitory control to ingest when encountering food-related cues, as evidenced by increased food-cue reactivity in the prefrontal cortex. However, in contrast to the unaffected insular food-cue reactivity and suppressed motor cortical food-cue reactivity seen with extended CR, restrained eaters seem to have heightened levels of 'liking' (as evidenced by increased food-cue reactivity of the insula) and motor readiness to ingest (as indicated by increased food-cue reactivity in the primary motor cortex). Thus, when a diet is violated, sensory stimuli related to food may potentially contribute to increased 'liking' as the insula and the operculum (i.e. the primary taste cortex) are closely interactive. Once the overall 'liking' surpasses the inhibitory control of the prefrontal cortex, incentive salience is likely to increase (as evidenced by increased food-cue reactivity of the nucleus accumbens), resulting in increased consumption. While studies are yet to be conducted to examine the food-cue reactivity patterns of restrained eaters who have failed to control their weight; these observations when expanded within a broader theoretical context, provide a potential neurophysiological explanation for the increased risk of weight gain observed among restrained eaters. Future studies should therefore target the neurophysiological mechanisms associated with increased caloric consumption following dietary violation in restrained eaters.

Some shortcomings of the current review are largely based on limitations of the body of available literature as this is a somewhat nascent field of inquiry. Even though we present summaries of cerebral food-cue reactivity patterns observed along with three distinct types of ingestive behavior, the studies examining the effects of fasting, extended CR and restrained eating differ considerably based on subject characteristics, methods, quantification of CR, and temporal nature of the designs. They also often fail to adequately account for reductions in *in vivo* exposure to food cues and weight loss subsequent to CR. Furthermore, though our review

extrapolates from the combined studies to formulate plausible explanations, no single, well-controlled and adequately powered study examining the effects of fasting or extended CR has completely captured the complex relationships proposed here.

In summary, neuroimaging studies of food-cue reactivity suggest that patterns of activation across brain regions that process sensory food-cues, influence hedonic drives, and govern motor control differ between types of CR. Comparing across these CR types indicates that: 1) fasting results in increased food-cue reactivity in regions associated with sensory processing, hedonic response, and motor control, 2) extended CR results in increased activation in regions associated with inhibitory control, and 3) restrained eating exhibits properties associated with both thus resulting in increased food-cue reactivity in regions associated with inhibitory control and hedonic response. The latter may partially explain why restrained eating is associated with a risk of future weight gain. Also, the behavioral literature suggests that short-term fasting may increase the desire to eat while extended CR may suppress food cravings, which further highlights the fact that a unique, yet not uncommon subset of the population (restrained eaters) may utilize specific food targeted hedonic restraint in an effort to control ingestive behavior.

The findings of our review highlight the need to conduct comprehensive and adequately powered randomized controlled trials to examine simultaneously, the neurophysiological and behavioral/psychological relationships between extended CR and the human brain. At the outset, if the field is to achieve translationally significant findings, an over-reliance on short-term fasting paradigms must be replaced by more translationally focused approaches. At minimum, future studies should more closely examine how the brain responds to extended periods of CR that more closely resemble common weight loss practices. While several recently published manuscripts have examined the effects of bariatric surgery on cerebral food-cue reactivity using fMRI; these studies are limited in number (Bruce et al., 2014; Ionut, Burch, Youdim, & Bergman, 2013; Miras & le Roux, 2013; Scholtz et al., 2014). Similarly, only a few groups have studied the effects of pharmacological interventions on food-cue reactivity among individuals with obesity (Schlögl et al., 2013; van Bloemendaal et al., 2014). Additionally, examination of a wider variety of interventions (e.g. major behavioral weight loss intervention trials) in the context of their impacts on neurophysiology in humans remains relatively sparse. These types of investigations are an essential next step if we are to fully understand mechanisms underlying their clinical impact and subsequently improve such interventions.

In terms of other methodological limitations of the existing body of literature, there are several that if addressed, would strengthen our understanding. First, efforts should be made to improve methodological reporting. Documenting scanning parameters, and providing detailed specifications of the image banks and image selection/validation process are essential to accurate interpretation and replication of findings. In addition, issues of relatively low scanner resolution, image distortions, and other scanning artifacts (e.g., the need for cardiac and respiratory gating of the brainstem, hypothalamus, etc.) must also be routinely employed.

Moreover, the present review suggests that we move away from the tendency in the current fMRI/ingestive behavior literature to treat processes in the brain as functionally segregated when they in fact are highly integrated. Thus, it would be timely to examine the effects of dietary interventions in terms of structural and functional connectivity between the described regions of interest using methods such as DTI and functional connectivity analyses. In terms of the food-cue reactivity paradigms themselves, more attention should also be paid to matching the shape, color and texture of the control images to the food cue images being used in a given study, and to include a wider range of hedonic valence in both the food and non-food images (as opposed to simply 'neutral objects'). This will allow us to better pinpoint the salient 'food-related reward' as opposed to 'general reward reactivity.'

Studies focused on short-term fasting paradigms, or that fail to comprehensively consider complex neurohumoral and psychological influences on human ingestive behavior will do little to solve the primary issue of our time; obesity. This review represents a call to focus our attention on translationally oriented models that will inform the development of novel, comprehensive, behavioral and pharmacological approaches to obesity.

Conflicts of interest

The authors have no potential conflict of interest to declare.

Authors' contributions

CNK – designed the review, conducted the review and wrote the paper.

LAB – conducted the review.

TD – wrote the paper.

MO – wrote the paper.

MB – designed the review, conducted the review, wrote the paper and had primary responsibility for final content.

Acknowledgments

The authors wish to thank Shao-Hua Chin and Kelli Kaufman for helping to organize the references and Blake Johns for assisting in proof reading the manuscript.

References

de Araujo, I. E., Lin, T., Veldhuizen, M. G., & Small, D. M. (2013). Metabolic regulation of brain response to food cues. *Current Biology, 23*(10), 878–883.

Berridge, K. C. (1996). Food reward: Brain substrates of wanting and liking. *Neuroscience & Biobehavioral Reviews, 20*(1), 1–25.

Berridge, K. C. (2009). 'Liking' and 'wanting' food rewards: Brain substrates and roles in eating disorders. *Physiology & Behavior, 97*(5), 537–550. http://dx.doi.org/10.1016/j.physbeh.2009.02.044.

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences, 26*(9), 507–513.

Berthoud, H.-R. (2002). Multiple neural systems controlling food intake and body weight. *Neuroscience & Biobehavioral Reviews, 26*(4), 393–428.

Berthoud, H.-R. (2004). Neural control of appetite: Cross-talk between homeostatic and non-homeostatic systems. *Appetite, 43*(3), 315–317.

Berthoud, H.-R. (2011). Metabolic and hedonic drives in the neural control of appetite: Who is the boss? *Current Opinion in Neurobiology, 21*(6), 888–896.

Berthoud, H. R., & Zheng, H. (2012). Modulation of taste responsiveness and food preference by obesity and weight loss. *Physiology & Behavior, 107*(4), 527–532. http://dx.doi.org/10.1016/j.physbeh.2012.04.004.

Blechert, J., Meule, A., Busch, N. A., & Ohla, K. (2015). Food-pics: An image database for experimental research on eating and appetite. *Food Cravings*, 40.

van Bloemendaal, L., IJzerman, R. G., Jennifer, S., Ten Kulve, J. S., Barkhof, F., Konrad, R. J., et al. (2014). GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes, 63*(12), 4186–4196. http://dx.doi.org/10.2337/db14-0849.

Born, J. M., Lemmens, S. G., Martens, M. J., Formisano, E., Goebel, R., & Westerterp-Plantenga, M. S. (2011). Differences between liking and wanting signals in the human brain and relations with cognitive dietary restraint and body mass index. *The American Journal of Clinical Nutrition, 94*(2), 392–403.

Bruce, A. S., Bruce, J. M., Ness, A. R., Lepping, R. J., Malley, S., Hancock, L., et al. (2014). A comparison of functional brain changes associated with surgical versus behavioral weight loss. *Obesity (Silver Spring), 22*(2), 337–343. http://dx.doi.org/10.1002/oby.20630.

Burger, K. S., & Stice, E. (2011). Relation of dietary restraint scores to activation of reward-related brain regions in response to food intake, anticipated intake, and food pictures. *Neuroimage, 55*(1), 233–239. http://dx.doi.org/10.1016/j.neuroimage.2010.12.009.

Burton, M. W., LoCasto, P. C., Krebs-Noble, D., & Gullapalli, R. P. (2005). A systematic investigation of the functional neuroanatomy of auditory and visual phonological processing. *Neuroimage, 26*(3), 647–661.

Cameron, J. D., Goldfield, G. S., Finlayson, G., Blundell, J. E., & Doucet, E. (2014). Fasting for 24 hours heightens reward from food and food-related cues. *PLoS One, 9*(1), e85970. http://dx.doi.org/10.1371/journal.pone.0085970.

Carnell, S., Gibson, C., Benson, L., Ochner, C. N., & Geliebter, A. (2012). Neuroimaging and obesity: Current knowledge and future directions. *Obesity Reviews, 13*(1), 43–56. http://dx.doi.org/10.1111/j.1467-789X.2011.00927.x.

Chen, Y., Lin, Y. C., Kuo, T. W., & Knight, Z. A. (2015). Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell, 160*(5), 829–841.

Coletta, M., Platek, S., Mohamed, F. B., van Steenburgh, J. J., Green, D., et al. (2009). Brain activation in restrained and unrestrained eaters: An fMRI study. *Journal of Abnormal Psychology, 118*(3), 598.

Darbaky, Y., Baunez, C., Arecchi, P., Legallet, E., & Apicella, P. (2005). Reward-related neuronal activity in the subthalamic nucleus of the monkey. *Neuroreport, 16*(11), 1241–1244.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology, 53*(1), 545–574.

Deichmann, R., Gottfried, J. A., Hutton, C., & Turner, R. (2003). Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage, 19*(2 Pt 1), 430–441.

DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M., et al. (2007). Successful dieters have increased neural activity in cortical areas involved in the control of behavior. *International Journal of Obesity (London), 31*(3), 440–448. http://dx.doi.org/10.1038/sj.ijo.0803431.

DelParigi, A., Gautier, J. F., Chen, K., Salbe, A. D., Ravussin, E., Reiman, E., et al. (2002). Neuroimaging and obesity. *Annals of the New York Academy of Sciences, 967*(1), 389–397.

Demos, K. E., Kelley, W. M., & Heatherton, T. F. (2011). Dietary restraint violations influence reward responses in nucleus accumbens and amygdala. *Journal of Cognitive Neuroscience, 23*(8), 1952–1963. http://dx.doi.org/10.1162/jocn.2010.21568.

Dumoulin, S. O., & Hess, R. F. (2007). Cortical specialization for concentric shape processing. *Vision Research, 47*(12), 1608–1613.

Dum, R. P., & Strick, P. L. (2002). Motor areas in the frontal lobe of the primate. *Physiology & Behavior, 77*(4), 677–682.

Ely, A. V., Winter, S., & Lowe, M. R. (2013). The generation and inhibition of hedonically-driven food intake: Behavioral and neurophysiological determinants in healthy weight individuals. *Physiology & Behavior, 121*, 25–34.

Fiez, J. A. (1997). Phonology, semantics, and the role of the left inferior prefrontal cortex. *Human Brain Mapping, 5*(2), 79–83.

Finer, N. (2001). Low-calorie diets and sustained weight loss. *Obesity Research, 9*(S11), 290S–294S.

Finlayson, G., & Dalton, M. (2012a). Current progress in the assessment of 'liking'vs.'wanting'food in human appetite. Comment on '"You Say it's Liking, I Say it's Wanting..."'. On the difficulty of disentangling food reward in man'. *Appetite, 58*(1), 373–378.

Finlayson, G., & Dalton, M. (2012b). Hedonics of food consumption: Are food 'liking'and 'wanting'viable targets for appetite control in the obese? *Current Obesity Reports, 1*(1), 42–49.

Finlayson, G., King, N., & Blundell, J. E. (2007a). Is it possible to dissociate 'liking'and 'wanting'for foods in humans? A novel experimental procedure. *Physiology & Behavior, 90*(1), 36–42.

Finlayson, G., King, N., & Blundell, J. E. (2007b). Liking vs. wanting food: Importance for human appetite control and weight regulation. *Neuroscience & Biobehavioral Reviews, 31*(7), 987–1002.

Fox, P. T., Huang, A., Parsons, L. M., Xiong, J.-H., Zamarippa, F., Rainey, L., et al. (2001). Location-probability profiles for the mouth region of human primary motor–sensory cortex: Model and validation. *Neuroimage, 13*(1), 196–209.

Frank, S., Laharnar, N., Kullmann, S., Veit, R., Canova, C., Hegner, Y. L., et al. (2010). Processing of food pictures: Influence of hunger, gender and calorie content. *Brain Research, 1350*, 159–166. http://dx.doi.org/10.1016/j.brainres.2010.04.030.

Gilhooly, C. H., Das, S. K., Golden, J. K., McCrory, M. A., Dallal, G. E., Saltzman, E., et al. (2007). Food cravings and energy regulation: The characteristics of craved foods and their relationship with eating behaviors and weight change during 6 months of dietary energy restriction. *International Journal of Obesity (London), 31*(12), 1849–1858. http://dx.doi.org/10.1038/sj.ijo.0803672.

Goldstone, A. P., Prechtl de Hernandez, C. G., Beaver, J. D., Muhammed, K., Croese, C., Bell, G., et al. (2009). Fasting biases brain reward systems towards high-calorie foods. *European Journal of Neuroscience, 30*(8), 1625–1635. http://dx.doi.org/10.1111/j.1460-9568.2009.06949.x.

Goldstone, A. P., Prechtl, C. G., Scholtz, S., Miras, A. D., Chhina, N., Durighel, G., et al. (2014). Ghrelin mimics fasting to enhance human hedonic, orbitofrontal cortex, and hippocampal responses to food. *The American Journal of Clinical Nutrition, 99*(6), 1319–1330.

Grill, H. J., & Norgren, R. (1978). The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. *Brain Research, 143*(2), 263–279.

Haase, L., Cerf-Ducastel, B., & Murphy, C. (2009). Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage, 44*(3), 1008–1021. http://dx.doi.org/10.1016/j.neuroimage.2008.09.044.

Hare, T. A., Camerer, C. F., Knoepfle, D. T., O'Doherty, J. P., & Rangel, A. (2010). Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. *The Journal of Neuroscience, 30*(2), 583–590.

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science, 324*(5927), 646–648.

Harvey, J., Wing, R. R., & Mullen, M. (1993). Effects on food cravings of a very low calorie diet or a balanced, low calorie diet. *Appetite, 21*(2), 105–115.

Havermans, R. C. (2011). "You Say it's Liking, I Say it's Wanting…". On the difficulty of disentangling food reward in man. *Appetite, 57*(1), 286–294.

Herman, C. P., & Mack, D. (1975). Restrained and unrestrained eating1. *Journal of Personality, 43*(4), 647–660.

Herman, C. P., & Polivy, J. (1980). Restrained eating. *Obesity*, 208–225.

Higgs, S. (2015). Cognitive processing of food rewards. *Appetite*.

Higgs, S., Rutters, F., Thomas, J. M., Naish, K., & Humphreys, G. W. (2012). Top down modulation of attention to food cues via working memory. *Appetite, 59*(1), 71–75.

Ionut, V., Burch, M., Youdim, A., & Bergman, R. N. (2013). Gastrointestinal hormones and bariatric surgery-induced weight loss. *Obesity, 21*(6), 1093–1103.

Lenard, N. R., & Berthoud, H. R. (2008). Central and peripheral regulation of food intake and physical activity: Pathways and genes. *Obesity (Silver Spring), 16*(Suppl 3), S11–S22. http://dx.doi.org/10.1038/oby.2008.511.

Le, D. S. N., Pannacciulli, N., Chen, K., Del Parigi, A., Salbe, A. D., Reiman, E. M., et al. (2006). Less activation of the left dorsolateral prefrontal cortex in response to a meal: A feature of obesity. *The American Journal of Clinical Nutrition, 84*(4), 725–731.

Liu, Y., Gao, J. H., Liu, H. L., & Fox, P. T. (2000). The temporal response of the brain after eating revealed by functional MRI. *Nature, 405*(6790), 1058–1062.

Lowe, M. R. (2013). The importance of behavioral anchoring in neuroimaging studies of obesity. *The American Journal of Clinical Nutrition, 97*(3), 451–452.

Lowe, M. R., Annunziato, R. A., Markowitz, J. T., Didie, E., Bellace, D. L., Riddell, L., et al. (2006). Multiple types of dieting prospectively predict weight gain during the freshman year of college. *Appetite, 47*(1), 83–90. http://dx.doi.org/10.1016/j.appet.2006.03.160.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835–1838.

Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metabolism, 7*(5), 400–409. http://dx.doi.org/10.1016/j.cmet.2008.03.007.

Markowitz, J. T., Butryn, M. L., & Lowe, M. R. (2008). Perceived deprivation, restrained eating and susceptibility to weight gain. *Appetite, 51*(3), 720–722. http://dx.doi.org/10.1016/j.appet.2008.03.017.

Martens, M. J., Born, J. M., Lemmens, S. G., Karhunen, L., Heinecke, A., Goebel, R., et al. (2013). Increased sensitivity to food cues in the fasted state and decreased inhibitory control in the satiated state in the overweight. *The American Journal of Clinical Nutrition, 97*(3), 471–479.

Martin, C. K., McClernon, F. J., Chellino, A., & Correa, J. B. (2011). Food cravings: A central construct in food intake behavior, weight loss, and the neurobiology of appetitive behavior. *Handbook of behavior, food and nutrition*. Springer.

Martin, C. K., O'Neil, P. M., & Pawlow, L. (2006). Changes in food cravings during low-calorie and very-low-calorie diets. *Obesity, 14*(1), 115–121.

Martin, C. K., Rosenbaum, D., Han, H., Geiselman, P. J., Wyatt, H. R., Hill, J. O., et al. (2011). Change in food cravings, food preferences, and appetite during a low-carbohydrate and low-fat diet. *Obesity (Silver Spring), 19*(10), 1963–1970. http://dx.doi.org/10.1038/oby.2011.62.

McCaffery, J. M., Haley, A. P., Sweet, L. H., Phelan, S., Raynor, H. A., Del Parigi, A., et al. (2009). Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *The American Journal of Clinical Nutrition, 90*(4), 928–934. http://dx.doi.org/10.3945/ajcn.2009.27924.

Miras, A. D., & le Roux, C. W. (2013). Mechanisms underlying weight loss after bariatric surgery. *Nature Reviews Gastroenterology and Hepatology, 10*(10), 575–584.

Murdaugh, D. L., Cox, J. E., Cook, E. W., 3rd, & Weller, R. E. (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage, 59*(3), 2709–2721.

Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E. N., & Barbieri, R. (2008). Brain correlates of autonomic modulation: Combining heart rate variability with fMRI. *Neuroimage, 42*(1), 169–177. http://dx.doi.org/10.1016/j.neuroimage.2008.04.238.

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron, 33*(5), 815–826.

Paton, J. J., Belova, M. A., Morrison, S. E., & Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature, 439*(7078), 865–870.

Pelchat, M. L. (2002). Of human bondage: Food craving, obsession, compulsion, and addiction. *Physiology & Behavior, 76*(3), 347–352.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331–348.

Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2011). *Handbook of functional MRI data analysis*. Cambridge University Press.

Porter, R. (1952). Alterations in electrical activity of the hypothalamus induced by stress stimuli. *American Journal of Physiology—Legacy Content, 169*(3), 629–637.

Ricci, P. T., Zelkowicz, B. J., Nebes, R. D., Meltzer, C. C., Mintun, M. A., & Becker, J. T. (1999). Functional neuroanatomy of semantic memory: Recognition of semantic associations. *Neuroimage, 9*(1), 88–96.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443–447.

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *The Journal of Clinical Investigation, 118*(7), 2583–2591. http://dx.doi.org/10.1172/JCI35055.

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. *The Journal of Neuroscience, 34*(48), 15988–15996.

Rutters, F., Kumar, S., Higgs, S., & Humphreys, G. W. (2015). Electrophysiological evidence for enhanced representation of food stimuli in working memory. *Experimental Brain Research, 233*(2), 519–528.

Schlögl, H., Kabisch, S., Horstmann, A., Lohmann, G., Müller, K., Lepsien, J., et al. (2013). Exenatide-induced reduction in energy intake is associated with increase in hypothalamic connectivity. *Diabetes Care, 36*(7), 1933–1940.

Scholtz, S., Miras, A. D., Chhina, N., Prechtl, C. G., Sleeth, M. L., Daud, N. M., et al. (2014). Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding. *Gut, 63*(6), 891–902. http://dx.doi.org/10.1136/gutjnl-2013-305008.

Schur, E. A., Kleinhans, N. M., Goldberg, J., Buchwald, D. S., Polivy, J., Del Parigi, A., et al. (2012). Acquired differences in brain responses among monozygotic twins discordant for restrained eating. *Physiology & Behavior, 105*(2), 560–567. http://dx.doi.org/10.1016/j.physbeh.2011.09.008.

Schwartz, M. W., Woods, S. C., Seeley, R. J., Barsh, G. S., Baskin, D. G., & Leibel, R. L. (2003). Is the energy homeostasis system inherently biased toward weight gain? *Diabetes, 52*(2), 232–238.

Sclafani, A. (1995). How food preferences are learned: Laboratory animal models. *Proceedings of the Nutrition Society, 54*(02), 419–427.

Shin, A. C., Townsend, R. L., Patterson, L. M., & Berthoud, H. R. (2011). "Liking" and "wanting" of sweet and oily food stimuli as affected by high-fat diet-induced obesity, weight loss, leptin, and genetic predisposition. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 301*(5), R1267–R1280. http://dx.doi.org/10.1152/ajpregu.00314.2011.

Siep, N., Roefs, A., Roebroeck, A., Havermans, R., Bonte, M. L., & Jansen, A. (2009). Hunger is the best spice: An fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behavioural Brain Research, 198*(1), 149–158. http://dx.doi.org/10.1016/j.bbr.2008.10.035.

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate. *Brain, 124*(9), 1720–1733.

Smeets, P. A., de Graaf, C., Stafleu, A., van Osch, M. J., & van der Grond, J. (2005). Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories. *The American Journal of Clinical Nutrition, 82*(5), 1011–1016.

Snell, R. S. (2010). *Clinical neuroanatomy*. Lippincott Williams & Wilkins.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279–306. http://dx.doi.org/10.1146/annurev.neuro.27.070203.144130.

Stice, E., Burger, K., & Yokum, S. (2013). Caloric deprivation increases responsivity of attention and reward brain regions to intake, anticipated intake, and images of palatable foods. *Neuroimage, 67*, 322–330. http://dx.doi.org/10.1016/j.neuroimage.2012.11.028.

Stice, E., Cooper, J. A., Schoeller, D. A., Tappe, K., & Lowe, M. R. (2007). Are dietary restraint scales valid measures of moderate-to long-term dietary restriction? Objective biological and behavioral data suggest not. *Psychological Assessment, 19*(4), 449.

Stice, E., Yokum, S., Blum, K., & Bohon, C. (2010). Weight gain is associated with reduced striatal response to palatable food. *The Journal of Neuroscience, 30*(39), 13105–13109.

Strange, B., Fletcher, P., Henson, R., Friston, K., & Dolan, R. (1999). Segregating the functions of human hippocampus. *Proceedings of the National Academy of Sciences, 96*(7), 4034–4039.

Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *Journal of Psychosomatic Research, 29*(1), 71–83.

Sweet, L. H., Hassenstab, J. J., McCaffery, J. M., Raynor, H. A., Bond, D. S., Demos, K. E., et al. (2012). Brain response to food stimulation in obese, normal weight, and successful weight loss maintainers. *Obesity (Silver Spring), 20*(11), 2220–2225. http://dx.doi.org/10.1038/oby.2012.125.

Uher, R., Treasure, J., Heining, M., Brammer, M. J., & Campbell, I. C. (2006). Cerebral processing of food-related stimuli: Effects of fasting and gender. *Behavioural Brain Research, 169*(1), 111–119. http://dx.doi.org/10.1016/j.bbr.2005.12.008.

Van Strien, T., Frijters, J. E., Bergers, G., & Defares, P. B. (1986). The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. *International Journal of Eating Disorders, 5*(2), 295–315.

Volkow, N. D., Wang, G. J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: Implications for obesity. *Trends in Cognitive Sciences, 15*(1), 37–46. http://dx.doi.org/10.1016/j.tics.2010.11.001.

Weygandt, M., Mai, K., Dommes, E., Ritter, K., Leupelt, V., Spranger, J., et al. (2015). Impulse control in the dorsolateral prefrontal cortex counteracts post-diet weight regain in obesity. *NeuroImage, 109*, 318–327.

White, M. A., Whisenhunt, B. L., Williamson, D. A., Greenway, F. L., & Netemeyer, R. G. (2002). Development and validation of the food-craving inventory. *Obesity Research, 10*(2), 107–114. http://dx.doi.org/10.1038/oby.2002.17.

Williamson, D. A., Martin, C. K., York-Crowe, E., Anton, S. D., Redman, L. M., Han, H., et al. (2007). Measurement of dietary restraint: Validity tests of four questionnaires. *Appetite, 48*(2), 183–192.

Wing, R. R. (2014). Behavioral approaches to the treatment of obesity. In , *Clinical applications: Vol. 2. Handbook of obesity* (p. 131).

Wing, R. R., & Hill, J. O. (2001). Successful weight loss maintenance. *Annual Review of Nutrition, 21*(1), 323–341.

Wing, R. R., & Phelan, S. (2005). Long-term weight loss maintenance. *The American Journal of Clinical Nutrition, 82*(1), 222S–225S.

Woods, S. C., Seeley, R. J., Porte, D., & Schwartz, M. W. (1998). Signals that regulate food intake and energy homeostasis. *Science, 280*(5368), 1378–1383.

Yeomans, M. R., Gould, N. J., Leitch, M., & Mobini, S. (2009). Effects of energy density and portion size on development of acquired flavour liking and learned satiety. *Appetite, 52*(2), 469–478.

Yokum, S., & Stice, E. (2013). Cognitive regulation of food craving: Effects of three cognitive reappraisal strategies on neural response to palatable foods. *International journal of obesity(London), 37*(12), 1565–1570. http://dx.doi.org/10.1038/ijo.2013.39.

Zellner, M. R., & Ranaldi, R. (2010). How conditioned stimuli acquire the ability to activate VTA dopamine cells: A proposed neurobiological component of reward-related learning. *Neuroscience & Biobehavioral Reviews, 34*(5), 769–780.