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Forebrain circuits and control of feeding by learned cues

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ABSTRACT

Professor Richard F. Thompson and his highly influential work on the brain substrates of associative learning and memory have critically shaped my research interests and scientific approach. I am tremendously grateful and thank Professor Thompson for the support and influence on my research and career. The focus of my research program is on associative learning and its role in the control of fundamental, motivated behaviors. My long-term research goal is to understand how learning enables environmental cues to control feeding behavior. We use a combination of behavioral studies and neural systems analysis approach in two well-defined rodent models to study how learned cues are integrated with homeostatic signals within functional forebrain networks, and how these networks are modulated by experience. Here, I will provide an overview of the two behavioral models and the critical neural network components mapped thus far, which include areas in the forebrain, the amygdala and prefrontal cortex, critical for associative learning and decision-making, and the lateral hypothalamus, which is an integrator for feeding, reward and motivation.

1. Introduction

In the early 1990s, while I was a graduate student at the University of Southern California (USC) conducting neuroanatomical studies to delineate the organization of amygdalar projections, under mentorship of Professor Larry W. Swanson (Swanson & Petrovich, 1998), I was very fortunate to be exposed to Professor Richard Thompson's large, and very active research group. During that time, Professor Thompson was an invaluable member of my PhD committee, and later a postdoctoral mentor along with Professor Swanson. The postdoctoral project examined conditioned fear circuitry in terms of immediate early gene and neuropeptides expression to characterize the critical amygdalar subsystems, in collaboration with Andrea Scicli (Petrovich, Scicli, Thompson, & Swanson, 2000); (Scicli, Petrovich, Swanson, & Thompson, 2004). Professor Thompson's critical influence on my research and career extends beyond the USC years. In fact, my exposure to Professor Thompson's elegant, multidisciplinary approach in understanding the brain substrates of learning and memory steered me towards my current research questions. Indeed, Professor Thompson's thoughtful, and methodical research approach in defining the circuitry and plasticity underlying classical eye blink conditioning continues to teach and inspire as one of the pivotal models in the field of behavioral neuroscience. I am tremendously grateful for the support and influence Professor Thompson has had on my research and career.

My current research program examines the control of feeding by learned cues, and it builds on my graduate and postdoctoral work. Many of the studies reviewed here were conducted in the laboratory of Professor Michela Gallagher, my postdoctoral mentor, and in collaboration with Professor Peter Holland at the Johns Hopkins University.

Appetite and eating are not only regulated by energy needs, but also by extrinsic—environmental and social—factors unrelated to homeostasis. Environmental signals such as learned cues can override homeostatic signals to stimulate eating in sated states, or inhibit eating in states of hunger (Cornell, Rodin, & Weingarten, 1989; Petrovich & Gallagher, 2007; Petrovich, Ross, Mody, Holland, & Gallagher, 2009; Weingarten, 1983). Such influences are important, as environmental rather than metabolic changes are believed to underlie the increased susceptibility to overeating, and the rise of obesity in Western, and other developed countries (Berthoud, 2007; Berthoud & Morrison, 2008; Levitsky, 2005; Popkin, Duffey, & Gordon-Larsen, 2005; Schachter, 1968).

Environmental and social factors that could lead to dysregulation of eating are multifaceted (Hill, Wyatt, Reed, & Peters, 2003; Kaye, 2008; Klein & Walsh, 2004; Popkin et al., 2005). Nevertheless, the prevalence of food-associated cues is important, and persistent priming with images and messages with cues for food in our world of food abundance could provide a setting for overeating. Indeed, studies in both laboratory animals and humans show that food cues, including learned cues, powerfully promote eating (Birch, McPhee, Sullivan, & Johnson, 1989; Cornell et al., 1989; Weingarten, 1983).

Similarly, environmental and social factors critically contribute to the development of anorexia nervosa and other eating disorders

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via complex interactions with the genetic background (Bulik, 2005; Kaye, 2008; Klein & Walsh, 2004; Treasure, Claudino, & Zucker, 2010). Yet, how learning enables signals form the environment to control feeding, and the underlying brain mechanisms are poorly understood.

Recently, we began to examine how cues from the environment are integrated with homeostatic signals within functional forebrain networks. We use a combination of behavioral studies and neural systems analysis in two well-defined rodent models (Section 2). Here we provide an overview of our recent findings and other evidence that the learned cues modulate food consumption, and that the telencephalon–hypothalamic circuitry is critical. These findings in animals are informative for control of appetite in humans including maladaptive environmental influences that could contribute to eating disorders.

2. Behavioral models for control of feeding by learned cues

We use behavioral models that rely on learning, Pavlovian conditioning, to enable initially neutral environmental signals to modulate food intake based on prior associations with either rewarding or aversive events. In these preparations learned cues override homeostatic signals to stimulate feeding in sated states, or inhibit intake in states of hunger. In one setting, a cue previously paired with food consumption when an animal was hungry, stimulates feeding in sated rats (*cue-induced feeding*). In the other setting, a cue that signals danger, such as a tone previously paired with foot-shocks inhibits feeding in food-deprived rats (*cue-induced inhibition of feeding*).

2.1. Cue-induced feeding

2.1.1. The behavioral model for appetitive learned cue-induced feeding

We use a paradigm based on the protocol by Weingarten (1983), and work of Zamble (1973)—conditioned stimulus potentiation of feeding. The behavioral aspects of this model were described recently (for reviews see Holland and Petrovich (2005) and Petrovich and Gallagher (2007)). The enhanced eating in this preparation is a consequence of motivational properties acquired by an otherwise neutral environmental signal through associative learning.

In a typical experiment food-deprived rats are trained in a Pavlovian conditioning procedure with presentations of a tone (conditioned stimulus, CS+) immediately prior to food (unconditioned stimulus, US) delivery in behavioral chambers distinct from the home cages. An additional control stimulus (CS−) that is not followed by food delivery is also presented during training. It is well established that after repeated parings with food the conditioned stimulus becomes a signal for food, and it brings animals to the site of food delivery (the food cup). The amount of time spent at the food cup (conditioned response, CR) is characterized measure of associative learning. Thus, during training rats learn to approach the food cup during the cue that predicts food (CS+), but not during the presentation of the control cue (CS−).

After training, sated rats are tested for food consumption during tests with CS presentations. The cue-induced feeding is evident in such tests; rats consume more food in the presence of the CS+ compared to tests with CS− presentations. The effect has an associative basis and is not merely due to non-specific activation by a sensory stimulus, because only the cue paired with food (CS+) but not an unpaired cue (CS−) enhances eating. Furthermore, cue-induced eating is not simply a byproduct of the CRs that bring the rats to the food cup. Enhanced eating also occurs in tests when food is presented in a receptacle that is different in appearance and location from the food cup used in training (Holland, Petrovich, & Gallagher, 2002; Petrovich, Ross, Gallagher, & Holland, 2007). Thus, cue-induced eating is a consequence of conditioned motivational properties acquired by the CS through pairings with food.

We have typically used explicit CSs, such as discrete auditory or visual cues in our preparations. Recently, we examined whether the environment in which food is consumed during training can also serve as a CS to promote eating (Petrovich, Ross, Gallagher, et al., 2007). We trained one group of food-deprived rats to consume food pellets in a distinct environment (context), while another control group of food-deprived rats were exposed to the same context, but received food pellets in their home cages. Then we tested sated rats for food pellet consumption in the conditioning context. Rats that were previously fed in the conditioning context when hungry consumed more food pellets in the conditioning context during tests compared to the rats in the control group that were never fed in that context. These results showed that contextual CSs, similar to explicit CSs, could promote food consumption, in agreement with a study in mice (Le Merrer & Stephens, 2006).

The rodent cue-induced feeding model allows for examination of the functional neural circuitry, and is relevant to human eating. Notably, classical conditioning supports cue-driven eating in preschool children. Sated children begin eating faster, and consume lager amounts when presented with a distinct song and a flashing light that were previously paired with snacks compared to their consumption in the presence of another song and light that were not paired with food (Birch et al., 1989). Other studies in humans show that the cues associated with the sensory properties of the food itself could also manipulate eating. For example, a brief sight, smell, or taste of a food prior to eating will encourage otherwise sated individuals to eat (Cornell et al., 1989) Interestingly, the cue-enhanced eating is exaggerated in restrained eaters (dieters) (Feodoroff, Polivy, & Herman, 2003; Herman & Polivy, 2005), and in obese children (Jansen et al., 2003), suggesting heightened vulnerability in these populations to cue-triggered overeating. Similarly, obese children show bias for food-associated cues (words) (Braet & Crombez, 2003), while obese women show exaggerated brain response (fMRI) to pictures of high-calorie foods compared to controls (Stoeckel et al., 2008).

2.1.2. The nature of CS-driven eating: selective appetite for the training food

Recently, we began to examine the motivational basis for feeding under the learned cue, and found evidence that it involves a specific drive for the training food, rather than a general drive to eat (Petrovich, Ross, Holland, et al., 2007; Petrovich, Ross, Holland, & Gallagher, 2007). Sated rats showed enhanced food consumption in the conditioning context (CS) only when presented with the training pellets, but not when presented with other familiar, or novel foods (Petrovich, Ross, Holland, et al., 2007; Petrovich, Ross, Holland, et al., 2007). These findings suggest that through conditioning the CS becomes a signal for the training food (US) specifically, rather than a signal for feeding. Other recent studies that used explicit CSs corroborate these findings (Delamater & Holland, 2008; Galarce, Crombarg, & Holland, 2007).

In these studies rats were first trained with two different CSs (tone or noise) that were each paired with a distinct US (sucrose or maltodextrine). Then rats were tested for food consumption during tests with presentations of either the CS that was previously paired with the test food, presentations of the CS for different food, or no CS. In agreement with our findings with contextual CSs, both studies showed that cue-driven feeding is highly specific in that it occurred only in the presence of the CS for the test food US, but not when the CS signaled the other food.

The specificity implies the CS's ability to evoke a sensory-specific representation of the food US that is acquired through parings with food through highly specific associations. In turn, the

motivation underlying selective consumption of the training food (US) that is signaled by the CS, might share similarities with appetite, or craving rather than induction of huger. Similarly, human desire to eat is specific to the food the subject was primed with, and the appetite is correlated with the amounts consumed (Cornell et al., 1989; Feodoroff et al., 2003; Herman & Polivy, 2005).

There are other parallels between cue-induced consumption and food cravings, although food cravings are difficult to define, especially in animal models (Weingarten & Elston, 1990). For example, in restrained eaters (chronic dieters), food-related cues elicited a specific appetite or craving, rather than a general desire to eat, and such appetite was correlated with increased intake of the target food (Feodoroff et al., 2003). Thus, both are food selective and can be elicited by exposure to cues associated with food (Jansen, 1998; Weingarten & Elston, 1990). Similar to binge eating associated with cue-elicited cravings (Jansen, 1998; Sobik, Hutchison, & Craighead, 2005) animals can also consume a large amount in a very short time in the context associated with food (Petrovich, Ross, Gallagher, et al., 2007; Petrovich, Ross, Holland, et al., 2007).

2.1.3. The forebrain circuitry for cue-driven feeding

Our work has been driven by the hypothesis that the lateral hypothalamus (LHA) is an integrative site for the "intrinsic" (physiological signals from the body), and "extrinsic" (environmental, emotional, cognitive) signals underlying the motivation to eat (Fig. 1). Furthermore, it builds on the functional and anatomical evidence for the LHA role in initiation of feeding, reward and motivation (Elmquist, Elias, & Saper, 1999; Wise, 1974). Anatomical literature supports the view that the LHA functions under the influence of the physiological signals from the body related to energy needs, which are relayed via the arcuate nucleus of the hypothalamus (ARH), and other hypothalamic and brainstem areas, and telencephalic afferents related to motivation, emotion, and cognition (Elmquist et al., 1999; Grill & Kaplan, 2002; Risold, Thompson, & Swanson, 1997; Swanson, 2000). Notably, substantial telencephalic input to the LHA originates in the amygdala and medial prefrontal cortex, areas well known for their roles in associative learning and decision-making.

Our behavioral model provides a framework in which these functions can be probed within defined anatomical circuits. To that end, we showed that cue-driven food consumption critically depends on an intact basolateral area of the amygdala (BLA, includes basolateral, basomedial, and lateral nuclei), and the BLA–LHA system (Holland et al., 2002; Petrovich, Setlow, Holland, & Gallagher, 2002) (Fig. 1). In these studies, the impairments in rats did not produce general deficits in learning or food consumption, rather it produced a more selective impairment in the ability of the CS to stimulate food consumption during the tests (Holland et al., 2002; Petrovich et al., 2002).

The BLA can communicate with the LHA via direct, and indirect pathways. One of the areas well positioned to relay the information between the BLA and LHA is the ventral medial prefrontal cortex (vmPFC) (Floyd, Price, Ferry, Keay, & Bandler, 2001; Gabbott, Warner, Jays, Salway, & Busby, 2005; Hurley, Herbert, Moga, & Saper, 1991; Risold et al., 1997; Sesack, Deutch, Roth, & Bunney, 1989; Swanson & Petrovich, 1998). Our two recent studies provide evidence that the vmPFC is a critical component of the BLA–LHA system (Fig. 1). In the first study, we found that the BLA and vmPFC neurons that send direct pathways to the LHA are functionally activated (immediate early gene induction) selectively by the tests with the CS that stimulates eating (Petrovich, Holland, & Gallagher, 2005). Then in the second study, we targeted that region of the vmPFC with bilateral, neurotoxic lesions, and found an impairment in feeding under the CS (Petrovich, Ross, Holland, et al., 2007). The vmPFC lesions abolished conditioned context-driven food consumption (Petrovich, Ross, Holland, et al., 2007). Interestingly,

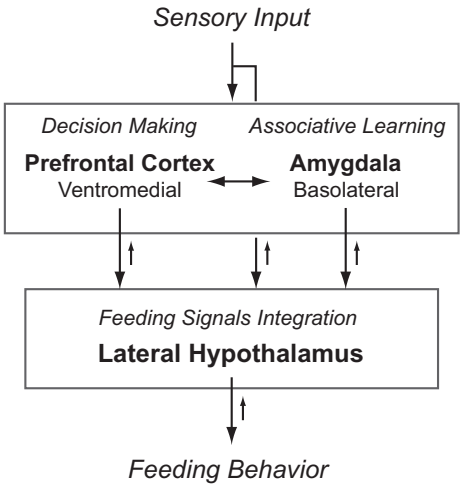

Fig. 1. Diagram illustrates the basic circuitry for learned cue-induced feeding. The circuitry is based on recent findings using neural systems analysis of a behavioral model that relies on learning (Pavlovian conditioning) to override homeostatic signals and stimulate eating in sated states. The basolateral amygdala, and ventral medial prefrontal cortex are critical for cue-driven feeding as shown by lesions of each of these areas. The lateral hypothalamus is an integrative site for feeding signals, including physiological signals from the body and environmental and learned cues, and its communication with the basolateral amygdala is necessary for cue-driven feeding. Sensory information, such as taste associated with food (US) and an auditory cue (CS), can reach all three areas of the circuitry via direct or indirect pathways.

these lesions also produced changes in food consumption in novel settings. The vmPFC-lesioned rats consumed less than controls when fed in a novel environment, or when a novel food was first presented in a familiar environment. These effects were specific to food consumption during tests, and the lesions did not impact food intake in the home cage or body weight. This is in agreement with a recent study that found no changes in body weight after vmPFC lesions (Davidson et al., 2009). Thus, the vmPFC might not be necessary for maintenance of food intake and body weight under homeostatic control. Rather it might be critically recruited when evaluation of environmental signals based on prior experience is required, such as eating under the learned cue, or in a novel, or ambiguous setting.

Much remains unknown, however, about the specific roles of the BLA, vmPFC, and their interactions. In addition to their ability to influence the LHA independently via direct pathways, the BLA and vmPFC share extensive bidirectional connections (Hoover & Vertes, 2007; Hurley et al., 1991; Kita & Kitai, 1990; Krettek & Price, 1977; Sesack et al., 1989; Swanson & Petrovich, 1998). Furthermore, the vmPFC includes several distinct regions, the infralimbic (ILA), ventral prelimbic (PL), and ventral medial orbitofrontal (vmOFC) areas (Dalley, Cardinal, & Robbins, 2004; Swanson, 2004), and there is evidence they might serve different functions in appetitive processing, and associated motivation for food and drugs.

The PL is thought to mediate the initial choice to explore novel food (Burns, Annett, Kelley, Everitt, & Robbins, 1996), and is necessary for responding to conflicting information guided by context (Marquis, Killcross, & Haddon, 2007). The ILA, which is critical in extinction of aversive CSs (Quirk, Garcia, & Gonzalez-Lima, 2006), plays a role in functions associated with extinction of appetitive CSs. The ILA lesions enhance recovery and reinstatement of conditioned responses (Rhodes & Killcross, 2004), and similarly this region is critical for inhibition of previously extinguished cocaine seeking behavior (Peters, LaLumiere, & Kalivas, 2008). Accordingly, both areas were activated (Fos induction) by contextual cues for

chocolate or nicotine (Schroeder, Binzak, & Kelley, 2001), but likely for different reasons, the PL due to contextual nature of the cue and ILA due to extinction. In humans food cues and cue-induced cravings for food and drugs are attributed to the medial OFC (Hinton et al., 2004) (Arana et al., 2003; Brody et al., 2002; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001), a region that appears somewhat homologous to the vmOFC in rats (Petrovich, Ross, Holland, et al., 2007). Nevertheless, whether the vmOFC might be necessary for CS memory recall and subsequent induction of the drive to eat remains to be determined.

Our prior study that showed impairments with vmPFC lesions used a conditioning chamber (context) as a CS, and less is know about the vmPFC's role in a cue-induced feeding task with explicit CSs (such as discrete auditory or visual). We found immediate early gene induction in the vmPFC in response to a tone, CS (Petrovich et al., 2005) that suggests its role in the cue-induced feeding regardless whether the CS is explicit or contextual. Nevertheless, evidence from another associative learning paradigm, fear conditioning, shows dissociable circuitry for processing of explicit and contextual CSs. The amygdala is necessary for explicit and contextual CSs while the hippocampus is recruited only for contextual CSs (Kim & Fanselow, 1992; Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008). Notably, the vmPFC is connected with the hippocampal formation (Condé, Maire-Lepoivre, Audinat, & Crépel, 1995; Swanson, Köhler, & Björklund, 1987; Van Groen & Wyss, 1990), relevant for contextual information, and its integration with motivational processing associated with appetitive learning and the control of feeding behavior (Davidson, Kanoski, Walls, & Jarrard, 2005; Davidson et al., 2009; Ito, Everitt, & Robbins, 2005). Thus, the vmPFC or its regions might be differentially recruited for cue-induced feeding depending on the complexity of the CS (simple/discrete vs. complex/contextual).

In our prior studies, all manipulations were made before any behavioral training, and thus could have interfered with the learning acquisition, memory recall, or behavioral expression phase of the cue-induced feeding. In that regard, the BLA and prefrontal cortex are differentially engaged in other tasks that are similar to our paradigm in that they also rely on CS properties acquired through associative learning to modulate behavior. In the devaluation task, and in the second order conditioning, the BLA is needed during the acquisition phase, but not when the flexible use of the CS acquired value is used to modulate behavior (Setlow, Gallagher, & Holland, 2002). On the other hand, a region of the prefrontal cortex (the lateral OFC) is needed during both the acquisition, and expression phase in the devaluation task (Pickens et al., 2003). Furthermore, OFC encoding, and updating of the acquired associative value of the CS depends on communications with the BLA (Schoenbaum, Setlow, Saddoris, & Gallagher, 2003; Stalnaker, Franz, Dingh, & Schoenbaum, 2007).

Similar relationship has been shown for the BLA and vmPFC in aversive conditioning. The vmPFC's responses to aversive CSs (Laviolette, Lipski, & Grace, 2005), and cannabinoid potentiation of learning plasticity within the vmPFC requires BLA input during the acquisition, but not once the association has been formed (Laviolette & Grace, 2006). Thus, the BLA plays a role in guiding prefrontal cortical responses during the learning acquisition based on the incentive value acquired through the association between environmental signals and rewards or punishments. We hypothesize this general framework also underlies the BLA-vmPFC interactions in cue-induced feeding, and our current studies are testing the premise.

2.1.3.1. Learned cue integration with the hypothalamic homeostatic system. Learning and associated anticipatory motivation are critical for homeostatic control and function in preparing the body for the incoming meal (Berridge, 2004; Woods, 1991; Woods & Ramsay, 2000). The classic example is control of insulin, a critical peptide-hormone released from the pancreas that peripherally regulates glucose metabolism, and acts directly on the brain feeding systems as an adiposity signal (Woods, 2005). Insulin release is not only initiated by meal-related physiological signals (e.g., increase in blood glucose), but also by cues that predict a meal (Woods, 1991) including arbitrary cues that gain control through conditioning (Woods et al., 1977). The anticipatory ("cephalic") insulin is regulated by the brain signals via the vagus nerve, and this mechanism helps prevent hyperglycemia that would otherwise occur because of the delay in meal-induced insulin cascade (Berthoud, Bereiter, Trimble, Siegel, & Jeanrenaud, 1981; Woods, 1991).

Similarly, hypothalamic mechanisms can be conditioned independent from physiological signals, as demonstrated recently with exogenous manipulation of the neuropeptide Y (NPY) (Drazen, Wortman, Seeley, & Woods, 2005), a potent feeding stimulant (Leibowitz, 1994). This evidence for the NPY role in conditioned anticipatory mechanisms, together with its role in the motivation to eat (Flood & Morley, 1991), and the ability to initiate feeding in satiated rats via the LHA (Stanley, Chin, & Leibowitz, 1985) make it a suitable candidate for the cue-driven feeding mechanism. The NPY neurons from the ARH send input to the LHA where they end on neurons that express the neuropeptides that stimulate feeding, melanin concentrating hormone (MCH) and orexin/hypocretin (ORX) (Elias et al., 1998).

Our data provide support that the telencephalon–lateral hypothalamic system is critical for cue-induced eating; however, the exact hypothalamic mechanisms remain unknown. Anatomical evidence supports a possibility that the CS acts via the orexigenic systems in the LHA and other hypothalamic areas. The BLA, and vmPFC send direct pathways to the LHA (Floyd et al., 2001; Gabbott et al., 2005; Hurley et al., 1991; Petrovich, Canteras, & Swanson, 2001; Sesack et al., 1989; Swanson & Petrovich, 1998), however, they reach topographically distinct regions, and the vmPFC innervates the area with neurons that express the orexigenic peptide regulators (MCH, and ORX) (Elias et al., 1998; Elmquist et al., 1999; Floyd et al., 2001; Petrovich et al., 2001; Schwartz, Woods, Porte, Seeley, & Baskin, 2000; Swanson, Sanchez-Watts, & Watts, 2005). On the other hand, neither the BLA nor vmPFC send direct pathways to the ARH, which is a critical component of the feeding circuitry, and considered a primary sensory area for the physiological signals from the body (Schwartz et al., 2000). However, a polysynaptic pathway was revealed with a viral labeling technique that links the BLA with the NPY neurons in the ARH (DeFalco et al., 2001). Finally, there are no direct inputs from the BLA or vmPFC to the paraventricular nucleus of the hypothalamus, another critical node of the hypothalamic feeding circuitry (Elmquist et al., 1999; Schwartz et al., 2000; Swanson, 2000), however indirect pathways could allow their influence on this region (Dong, Petrovich, & Swanson, 2001; Petrovich et al., 2001; Risold et al., 1997; Swanson & Petrovich, 1998).

2.2. Cue-induced inhibition of feeding

2.2.1. The behavioral model for aversive learned cue-induced inhibition of feeding

Recently, we developed a preparation for inhibition of feeding by an aversive learned cue (Petrovich et al., 2009). We showed that a cue that predicts danger, based on prior pairings with an aversive event effectively inhibits food intake in food-deprived rats. Our model builds on well-established fear conditioning paradigms (Davis, 1992; Fendt & Fanselow, 1999; LeDoux, 2000; Maren, 2001) whereby an initially neutral, environmental signal such as a tone (conditioned stimulus, CS) acquires ability to produce behavioral

responses (conditioned responses, CRs) based on pairings with mild, electric, foot-shock (unconditioned stimulus, US).

In our preparation, rats receive tone-shock pairings during the aversive training sessions, and are given food pellets that they consume during the appetitive training sessions. The aversive and appetitive training sessions are conducted in distinct environments (contexts) and occur in alternating order. After training, food-deprived rats are tested for food consumption during tests with tone presentations in the appetitive context. Rats that previously received tone pairings with shocks consume minuscule amounts compared to rats in the control condition that did not receive tone-shock pairings.

Our preparation allows comparisons across multiple behavioral responses produced by the same cue in the same animals. Thus, in addition to food consumption measures we analyze CS-induced freezing behavior. Freezing behavior is a species-typical defense response that has been extensively studied in fear conditioning paradigms, and is characterized by the absence of all movement except that required for breathing (Blanchard & Blanchard, 1969; Fanselow, 1984), In our preparation, the CS induces both behavioral responses—the freezing behavior and the inhibition of feeding. Importantly, the inhibition of feeding is not merely a consequence of immobilization due to CS-induced conditioned freezing behavior.

We observed CS-induced inhibition of feeding in the absence of conditioned freezing. In our study bilateral electrolytic lesions of the ventrolateral region of the periaqueductal gray (PAGvl), an area critical for conditioned freezing (Amorapanth, Nader, & LeDoux, 1999) were made after training in which rats received tone-foot-shock pairings. This lesion abolished conditioned freezing, but left inhibition of feeding intact during a test with tone (CS) presentations (Petrovich, Ross, Holland, & Gallagher, 2006), our unpublished observations). Additionally, our recent study also demonstrated that the CS's influence on feeding is independent of CS-induced freezing, and engages dissociable amygdalar subsystems (Petrovich et al., 2009; see Section 2.2.2.).

The mechanism by which an aversive cue (tone, CS) overrides homeostatic signals triggered by acute food-deprivation to inhibit feeding is currently unknown. Our paradigm provides a behavioral framework for defining the critical brain substrates. The behavioral model is also relevant to human eating and associated disorders. Notably, a core features and a diagnostic criterion of anorexia nervosa is fear of weight gain despite being underweight, and our model allows for preliminary examination of fear cue-induced short–term anorexia.

2.2.2. The forebrain circuitry for cue-induced inhibition of feeding

Recently, we began to map the circuitry that mediates the aversive (fear) cue-induced reduction of feeding. We examined the involvement of amygdalar sub-regions, the central nucleus (CEA) and the BLA. These structures have been linked to a range of functions that rely on associative learning to control goal-directed behavior (for reviews see Cardinal, Parkinson, Hall and Everitt (2002), Davis (1992), Fendt and Fanselow (1999), Gallagher (2000), Holland and Gallagher (1999), Kapp, Pascoe and Bixler (1984), LeDoux (2000), Maren (2001). Important for the fear cue-mediated regulation of feeding the BLA and CEA are both necessary components of the conditioned fear circuit (Davis, 1992; Fendt & Fanselow, 1999; Kapp et al., 1984; LeDoux, 2000; Maren, 2001), and could influence hypothalamic and brainstem function via distributed network of direct and indirect connections (Petrovich et al., 2001; Swanson & Petrovich, 1998).

We found that CS-induced short-term anorexia was abolished with bilateral, neurotoxic lesions of the central amygdala, but not with bilateral, neurotoxic lesions of the basolateral amygdala, while lesions of each structure abolished CS-induced freezing behavior (Petrovich et al., 2009). These data suggest that the CS's influence on feeding is independent of CS-induced freezing, and engages dissociable amygdalar subsystems. Both the BLA- and CEA-lesioned rats greatly reduced freezing compared to the Sham-lesioned rats in agreement with prior work, but only the CEA-lesioned rats failed to inhibit feeding in the presence of an aversive CS.

Nevertheless, where the CEA acts within the feeding network to influence food consumption and the exact routes are unknown. The CEA output network allows multiple influence via direct projections to the brainstem, lateral hypothalamus, and bed nuclei of the stria terminalis (Dong et al., 2001; Swanson & Petrovich, 1998), and indirect pathways to the paraventricular nucleus of the hypothalamus (Dong et al., 2001; Prewitt & Herman, 1988). The CEA and its associated network may also be critical for long-term suppression of eating, triggered by repeated stress, fear and anxiety, and as such dysfunction within this system could contribute to anorexia nervosa.

Support for the role of the amygdala in anorexia nervosa has been shown in recent human brain imaging studies. Abnormal amygdalar functioning (Takano et al., 2001), and a decrease in its volume (Giordano et al., 2001) in anorexia nervosa patients have been reported. Others showed greater amygdala activation among anorexia patients in response to their own body image distortion, a provocation that is based on a core feature of the disease involving fear of weight gain (Seeger, Braus, Ruf, Goldberger, & Schmidt, 2002). Interestingly, in another study the amygdala was recruited in non-eating disordered young women when viewing pictures of slim/idealized female bodies, and its activity was correlated with increased anxiety induced by those images (Friederich et al., 2007).

3. Conclusion

In summary, we have developed two behavioral protocols that rely on learning to modulate feeding, and as such allow mapping of the integration between the systems that process associative learning (the amygdala, prefrontal cortex and associated network) and the hypothalamic and brainstem feeding systems. Thus far our work has highlighted several critical nodes of the forebrain circuitry for cue-induced feeding (Fig. 1), but the entire network remains unknown. Even less is known about the system through which aversive cues inhibit feeding. Thus, much work is needed to delineate the exact components of these undoubtedly complex, and highly interconnected brain networks.

Determining the relevant brain circuitry is a necessary first step toward understanding the mechanisms that allow environmental contribution to the homeostatic regulation of food intake and body weight and settings that lead to dysregulation. On a higher level, the functional neuroanatomical work should provide a framework for understanding the role of the telencephalon in control of feeding and more broadly in regulation of goal-directed behaviors in the context of learning and anticipatory motivation. The amygdalo-hypothalamic connections have long been thought to play a role in modulation of basic, motivated behaviors. Referring to the functional neuroanatomy of amygdalo-hypothalamic circuits, Kaada noted that "the amygdala adds plasticity to the basic inborn and more fixed reflex mechanisms" (Kaada, 1972). Indeed, our long-term goal is to elucidate fundamental principles of how the amygdala and its associated network processes biologically relevant sensory stimuli and modulates behavior accordingly.

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