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Contributions of the Hippocampus and Medial Prefrontal Cortex to Energy and Body Weight Regulation

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Abstract

The effects of selective ibotenate lesions of the complete hippocampus (CHip), the hippocampal ventral pole (VP), or the medial prefrontal cortex (mPFC) in male rats were assessed on several measures related to energy regulation (i.e., body weight gain, food intake, body adiposity, metabolic activity general behavioral activity, conditioned appetitive responding). The testing conditions were designed to minimize the nonspecific debilitating effects of these surgeries on intake and body weight. Rats with CHip and VP lesions exhibited significantly greater weight gain and food intake compared to controls. Furthermore, CHip-lesioned rats, but not rats with VP lesions, showed elevated metabolic activity, general activity in the dark phase of the light-dark cycle, and greater conditioned appetitive behavior, compared to control rats without these brain lesions. In contrast, rats with mPFC lesions were not different from controls on any of these measures. These results indicate that hippocampal damage interferes with energy and body weight regulation, perhaps by disrupting higher-order learning and memory processes that contribute to the control of appetitive and consummatory behavior.

Much research on the causes of overeating and excessive weight gain has been directed at identifying the brain regions where metabolic and hormonal signals that stimulate or suppress intake are detected and utilized (Benoit et al., 2004; Cummings and Overduin, 2007; Leibowitz and Wortley, 2004; Seeley et al., 2004). Although specification of these physiological substrates will be central to any comprehensive account of food intake regulation, it is now clear that such accounts must also consider the role of learning and memory in the control of eating and appetitive behavior (Davidson et al., 2005; Higgs, 2005; Petrovich and Gallagher, 2007; Sclafani, 1997; Woods and Ramsay, 2000). In recent years, the hippocampus, a brain structure long considered critical to the performance of a number of learning and memory functions (Eichenbaum, 2006; Squire, 2004), has received increasing attention related to its potential involvement in energy regulation.

This increased interest in possible involvement of hippocampus in energy regulation is based, in part, on findings that neurohormonal signals involved with meal termination (e.g., cholecystokinin), meal initiation, (e.g., ghrelin) and signaling the status of bodily energy

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stores (e.g., leptin, insulin) have receptors in the hippocampus (Lathe, 2001) and also appear to modulate the operation of hippocampal-dependent learning and memory processes (Diano et al., 2006; Harvey et al., 2006; Matsushita et al., 2003; Zhao et al., 2004). Other data also indicate that the hippocampus is part of the neural circuitry involved with energy regulation. For example, functional magnetic resonance imagery (fMRI) identified the hippocampus and prefrontal cortex as the sites of greatest activation in obese people, following gastric stimulation known to have effects on intake, stomach distention, hormonal and vagal activity similar to those produced by eating a large meal (Wang et al., 2006). Another fMRI study showed that after consuming a liquid meal to satiation, obese and formerly obese people exhibited decreased hippocampal blood flow relative to lean people (DelParigi et al., 2004). Anatomically, direct neural projections from the ventral pole of the hippocampal CA1 cell field to the lateral hypothalamus, along with disynaptic connections from the CA1 field (e.g., via the subiculum) to other hypothalamic loci known to be involved with the control of feeding, have been identified (Cenquizca and Swanson, 2006; Cenquizca and Swanson, 2007).

Furthermore, densely amnesic humans with brain damage that includes the hippocampus have been reported to show reduced sensitivity to interoceptive signals of hunger and satiety (Hebben et al., 1985; Rozin et al., 1998), an effect that has also been observed in rats with highly selective lesions that are confined to the hippocampus (Davidson and Jarrard, 1993; Hirsh, 1974; Hock and Bunsey, 1998). In addition, relative to intact controls, rats with selective lesions of the hippocampus exhibit increased appetitive responding for food (Clifton et al., 1998; Davidson and Jarrard, 1993; Schmelzeis and Mittleman, 1996)), including reduced ability to inhibit responding elicited by food associated stimuli when those responses are no longer reinforced (Chan et al., 2001; Tracy et al., 2001) and reduced ability to use energy state cues as inhibitory signals (Davidson and Jarrard, 1993; Davidson et al., 2005).

The above findings suggest that (a) the hippocampus is sensitive to signals involved with energy regulation; (b) some of these signals induce changes in hippocampal activity that are thought to facilitate learning and memory; (c) information provided by satiety signals may be transmitted via neural pathways from the gut to the hippocampus and from the hippocampus to forebrain circuits involved with energy regulation; (d) hippocampal responses to these signals appear to be altered for people who have a history of obesity.

Surprisingly, only a limited number of studies have attempted to assess the effects of hippocampal damage on body weight. For example, King et al (King et al., 1993) reported that rats with hippocampal lesions ate significantly more but did not gain more weight compared to intact control rats. In an earlier study by Forloni et al., (1986), hippocampal lesions were accompanied by increased food intake and body weight gain when measured over a much longer period, but this effect was found only with female rats. Unfortunately, both of these studies used nonselective lesion techniques that produced damage to extrahippocampal structures and to fibers of passage. In the present experiment, we attempted to avoid this complication by using a highly selective ibotenate lesioning technique to produce hippocampal damage (Jarrard, 1989).

Furthermore, previous studies have typically not assessed or accounted for the nonspecific behavioral suppressive effects of surgery per se, when evaluating the effects of hippocampal damage on food intake and body weight. Specifically, many types of surgeries, including hippocampal surgery, are accompanied by reductions in food intake and body weight during the post-operative recovery period. Indeed, in our experience, body weight of lesioned rats may stay below that of intact controls for several weeks. Ideally, food intake and body weight gain should be compared among lesioned and non- or sham-lesioned controls only

after lesioned animals have completely recovered from such nonspecific after-effects of surgery. To decrease the likelihood that the specific effects of hippocampal lesions on intake and body weight gain would be confounded with any nonspecific effects of the surgical procedure involved with producing those lesions, the present study defined post-operative recovery as complete when lesioned rats achieved a level of body weight that matched the level of a group of ad lib fed control rats that had not undergone surgery.

The present study also employed an additional control condition. Unlike previous studies, we used a pair-feeding procedure to insure that control rats (half sham-lesioned and half unoperated) experienced reductions in food intake and body weight similar to those experienced by lesioned rats in the aftermath of surgery. Thus, these pair-fed control and lesioned rats were equated with respect to intake and body weight during the period prior to achieving the criterion for post-operative recovery mentioned above. With this procedure, it would be difficult to attribute any effects of lesions on energy intake and body weight gain after post-operative recovery to any residual effects of the effects of reduced eating and body weight loss during the pre-recovery period.

In addition to examining the effects of destruction of the complete hippocampus (CHip) on energy and body weight regulation, the present experiment also assessed the effects of damage limited, respectively, to the hippocampal ventral pole (VP) and the medial prefrontal cortex (mPFC). Recent research has identified direct neuroanatomical projections from the ventral pole of the hippocampal CA1 cell field (Cenquizca and Swanson, 2006), which comprises approximately 10% of the cells of the entire CA1 region, to a number of hypothalamic nuclei (e.g., ventromedial and lateral hypothalamic nuclei) that have long been implicated in the regulation of food intake and body weight (Grill, 2006; King et al., 1994; Stellar, 1994). This suggests that mechanisms related to memory and energy regulation might be integrated within a ventral hippocampal pole-hypothalamic circuit. Accordingly, lesions confined to the hippocampal ventral pole could impair the control of food intake and body weight by disrupting the operation of this circuit.

Neuroanatomical studies also show that the ventral CA1 cell field projects strongly to the medial prefrontal cortex which has, in turn, dense projections to the lateral hypothalamus (Cenquizca and Swanson, 2006; Swanson, 1981). Functionally, rats with medial prefrontal cortex lesions are like rats with the hippocampus removed in that they exhibit normal acquisition of simple discriminative contingencies but are impaired in inhibiting previously reinforced responses when the discriminative contingencies are reversed (Salazar et al., 2004). Another recent study found that rats maintained for 90 days on a diet high in saturated fat showed impaired reversal learning and reduced levels of brain-derived neurotrophic factor (BDNF) in both the ventral (but not dorsal) hippocampus and the medial prefrontal cortex (Kanoski et al., 2007). Several reports have linked reductions in BDNF and/or exposure to high-fat diets to interference with hippocampal learning and memory processes (e.g., Liu et al., 2004; Molteni et al., 2002; Monteggia et al., 2004; Wu et al., 2003; Yamada and Nabeshima, 2003). The present experiment included rats with lesions confined to the medial prefrontal cortex to assess the possibility that damage to the medial prefrontal cortex might have effects on food intake and body weight that are similar to those produced by hippocampal lesions in chow-fed rats.

We also assessed the effects of each of these lesions on learning and performance of appetitive conditioned responses. As noted above, previous research indicates that, compared to controls, rats with hippocampus removed exhibit increased conditioned appetitive behavior to cues that have history of excitatory and inhibitory training (Davidson and Jarrard, 1993; Schmelzeis and Mittleman, 1996). However, the effects of lesions limited to the hippocampal ventral pole are not known. Furthermore, the performance of

conditioned appetitive responses across a wide variety of training conditions is known to depend on level of food deprivation. Although some research with rats indicates that lesions of the medial prefrontal cortex can alter the effects of satiation on the performance of food-reinforced conditioned responses (Petrovich and Gallagher, 2007), the effects of complete hippocampal or hippocampal ventral pole lesions on the sensitivity of appetitive conditioned performance to deprivation/satiation manipulations are largely unexplored. Also important, the effects of CHip, VP, and mPFC lesions on the sensitivity of body weight to deprivation/satiation manipulations have not been reported. The present experiment attempted to help fill each of these gaps in knowledge. Finally, the effects of each type of lesion on energy expenditure, general behavioral activity, and on ability to regulate body weight in response to variations in level of food deprivation were also assessed.

In summary, previous findings suggest that extra-hypothalamic circuits involving the hippocampus and medial prefrontal cortex may contribute to the regulation of food intake and body weight. Recent anatomical studies demonstrate that the ventral pole of the hippocampus projects directly and indirectly, via the mPFC, to the LH. Furthermore, dietary factors which also promote obesity, have similar effects on neurotrophic activity in the hippocampal ventral pole and mPFC. The present studies further assessed mPFC, CHip, and VP lesions on energy balance and on the performance of learned appetitive responses.

Methods

Subjects

Subjects were adult, male, Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 275 – 325 g at the outset of the study. Animals were housed individually in hanging wire cages with laboratory chow (Lab Diets 5001) and water available ad lib except during testing as described below. The colony room was maintained on a 12:12 light:dark cycle (lights off at 1600 hrs), with temperature maintained at 21 -23 C. All procedures for the care and treatment of the rats during this experiment were approved by the Purdue Animal Care and Use Committee.

Apparatus

All appetitive training and testing procedures were conducted in eight identical conditioning chambers constructed of aluminum end walls and clear Plexiglas side walls, measuring 21.6 × 21.6 × 27.9 cm. The floors of each conditioning chamber consisted of stainless steel bars spaced 1.9 cm apart, measuring 0.48 cm in diameter. A recessed food magazine was located in the center of one end wall of each chamber. A computer-controlled infrared monitoring system was used to record food magazine approaches and entries. One infrared photo transmitter and one receiver were located on each side wall of the recessed food magazine, situated so that a rat could not gain access to sucrose pellet reinforcers without interrupting the photobeam.

Procedures

Surgical and histological procedures—The rats were assigned to seven groups matched on pre-operative body weight calculated two days prior to the beginning of surgery. Rats in the complete hippocampus (CHip), hippocampal ventral pole (VP), and medial prefrontal cortex (mPFC) groups were lesioned at these sites by the use of multiple, focal injections of small amounts of the axon-sparing neurotoxin, ibotenic acid (IBO: Biosearch Technologies). The IBO was dissolved in phosphate buffered saline (pH 7.4) at a concentration of 10 mg/ml. The rats were anesthetized with intraperitoneal injections of a combination of sodium pentobarbital and chloral hydrate, and were placed in a Kopf stereotaxic apparatus with the skull level. Following the procedure described in detail by

Jarrard (1989), an incision was made in the scalp, and the bone overlying the area to be damaged was removed. Injections of IBO were made with a 5-μl Hamilton syringe mounted on the stereotaxic frame and held in a Kopf microinjector unit (Model 5000). A small diameter glass micropipette was glued onto the end of the needle of the syringe in order to minimize damage to the cortex overlying the area to be lesioned. Injections were made over ~ 1 min at each site and the pipette was left in place for ~ 1 min to prevent spread of the neurotoxin up the tract.

Rats in the VP Group (n = 12) received injections of IBO (0.05 μl) at two sites in each hemisphere using the following stereotaxic coordinates: anteriorposterior (AP) - 3.8 mm; mediolateral (ML), +/- 4.3 mm; dorsoventral (DV) − 7.1 mm (taken from dura at the site of injection); and AP -4.3 mm, ML +/- 4.8 mm, DV -6.5 mm (taken from dura as above).

Each rat in the mPFC Group (n = 8) received a total of 12 injections (0.05 μl per site) of IBO at the following coordinates: AP + 2.7 mm, ML +/- 0.8 mm, DV − 3.0 and -1.5 mm from dura; AP + 3.5 mm, ML +/- 0.8 mm, DV − 3.0 and -1.5 mm; and AP + 4.2 mm, ML +/- 0.8 mm, and DV − 3.0 and -1.5 mm. Injections of IBO at 30 sites (0.05 to 0.12 μl per site; for stereotaxic coordinates see (Jarrard, 1989; Jarrard, 2002) were made in each rat in the CHip Group (n = 8).

Each of these lesioned groups had their own corresponding pair-fed control group (n = 8 each). Food rationing was used to match these control groups with respect to the amount of weight lost by the lesioned groups at the outset of the postoperative recovery period. Half of the rats in each control group received sham-lesions, which were produced using the same procedures as described for their respective lesion group with the exception that no IBO was administered. The remaining rats in each pair-fed control group were unoperated controls. The final group of rats (n = 6) were ad lib fed controls. This group received neither food deprivation nor food rationing during the study. All surgeries were conducted over a three-day period. The number of rats that received surgery on each day was equated for each surgical and corresponding pair-fed control condition.

Following testing, all rats were administered an overdose of the anesthetic and were perfused transcardially with a mixture of buffered physiological saline followed by 10% formaldehyde solution. The brains were removed, embedded in egg yolk, cryoprotected in a 30% solution of sucrose-formalin, and subsequently cut on a cryostat into 40-μm sections. Every fifth section from rats in the CHip and mPFC Groups was saved for histology, while every second section from VP rats was saved and stained. A cresyl violet stain was used to determine cell loss and gliosis resulting from the lesions.

Food intake and body weight—The rats were weighed daily beginning on the first day of surgery until each rat in each lesioned group had returned to their respective pre-operative body weighs. Food intake was also monitored daily for each rat during this period. Each rat in each lesioned group had a corresponding weight-matched, pair-fed control. Food rationing was used to maintain each pair-fed control at the same body weight as its corresponding lesioned rat until the body weights of lesioned rats recovered to their preoperative level. When this recovery was achieved the rats were given ad libitum lab chow. Body weight and amount of food consumed was recorded every 48 hrs for each rat throughout the remainder of the study. Amount consumed was calculated by weighing the amount of food given at the beginning of each measurement period and subtracting from that number the amount of food remaining in the food hopper plus crumbs collected from papers placed beneath each cage.

Analysis of conditioned appetitive behavior—The acquisition and extinction of appetitive conditioned responses and potential differences in behavioral sensitivity to low and relatively high levels of food deprivation was assessed by using a type of latent discrimination procedure (e.g., Davidson et al, 1992). With this technique, rats are exposed to a small numbers of acquisition trials followed immediately by extinction training, though learning is not evident until the extinction phase.

Prior to the beginning of training, the rats in each lesion group and their pair-fed controls (ad libitum-fed controls were not included) were assigned to squads and conditioning chambers such that equal numbers of rats from each surgical condition were trained in each of the 8 chambers, with one exception. Because there were 12 rats with VP lesions, eight of the rats in this group were assigned to each of the 8 conditioning chambers and the remaining four rats were randomly assigned to four of these chambers.

Adapting procedures used in longer-term studies of similar design (Davidson et al., 2005a; Kanoski et al., 2007b), the rats in the present study received single daily training sessions under alternating levels of 24-hr and 0-hr food deprivation. On each session the rats were placed into the conditioning chambers for 4 minutes, without discreet stimuli. When the rats were placed in the conditioning chambers after they had been food deprived for 24 hrs, this four-minute trial period terminated with the delivery of five sucrose pellets (45 mg sucrose pellets, P.J. Noyes Company, Inc. Lancaster, NH). When rats were placed into the conditioning chambers after they had been given ad libitum lab chow in the home cage for approximately 24 hrs, (i.e., under 0-hr food deprivation, meaning that the rats were not food deprived), the feeder mechanisms operated, but no pellets were delivered, Thus, during training for all rats, trials that took place under 24-hr food deprivation were reinforced whereas trials that took place under 0-hr food deprivation were not reinforced. Throughout the experiment, each 4-min trial was divided into twenty-four 10-s bins, the last of which terminated with the operation of the feeder mechanism. The percentage of these 10-s periods in which the photobeam inside the recessed food cup was interrupted served as the index of conditioned appetitive behavior. On both 24-hr and 0-hr deprived trials, the rats remained in the conditioning chambers for an additional two minutes before being returned to their home cages.

The rats received six training sessions under 24-hr food deprivation and 6 under 0-hr food deprivation. The rats received only one such four-min trial on each training session and they received no more than one training session per day. Training sessions were always held at the same time of day (1430 hrs). Although food deprivation levels alternated each day between 0- and 24-hrs, sessions did not occur every day to prevent the pellets from being delivered according to a single-alternating schedule. The schedule of training sessions conducted under 24- and 0-hr food deprivation was: 24, 24, 0, 24, 0, 0, 24, 24, 0, 0, 24, 0.

When six trials under each level of food deprivation had been completed, pellet deliveries were suspended and all rats were tested in extinction for 10 additional sessions, five under 0-hr and five under 24-hr food deprivation, according to the following sequence: 0, 24, 0, 0, 24, 24, 0, 24, 24, 0. The procedures for extinction testing were identical to those used during training except that no sucrose pellets were delivered on any trial. The rats were weighed immediately prior to each training and extinction session.

Indirect calorimetry—Indirect calorimetry was performed using the Columbus Instruments Oxymax 5.41 system to measure oxygen (O2) consumption. Rats were placed in individual metabolic chambers 2 hours prior to the onset of the dark cycle. They remained in the chambers for 24 hours with ad libitum access to chow and water. Samples were collected approximately every 15 minutes. For each time point, the samples for each group were

averaged. Average kcal/h values were compared during the light and dark cycles for all groups. The flow rate to the individual chambers was set at 0.6 liters per minute, with room air as the reference. The system measuring time was set for 60 seconds and represents the amount of time during which the indirect calorimeter monitors the gas concentrations. The indirect calorimeter takes as many readings as possible during this interval and derives a mean value. The system settling time was set at 120 seconds and represents the amount of time between the opening of the intake valve and the onset of the measuring time. This time allows for the complete purging of any residual gas in the system.

Body composition analysis—Body composition was analyzed with a custom-designed rodent quantitative NMR apparatus (Echo MRI Whole Body Composition Analyzer; Echo Medical Systems). Briefly, each rat was transported into a room that housed the NMR and placed (without anesthesia) in a Plexiglas tube that was then inserted into the NMR for body composition analysis. Body fat and lean tissue were measured during the test, which took less than 60 seconds per rat to perform.

Homecage behavioral activity analysis—Behavioral activity was determined using the SmartFrame stainless steel cage rack frame (Hamilton-Kinder Scientific Company, Poway, CA) which was placed around each animal's shoebox homecage. Infrared photobeam interruption sensors (7X and 15Y) mounted in the frame detected movement which was recorded and analyzed using the HMM100 MotorMonitor software. Vertical and horizontal activity within the homecage was recorded for 48 hours, and the events were collapsed into 60 min bins. The data were analyzed as the average number of beam interruptions per group per hour. Additional analyses were conducted to analyze the location of the rat (measured by beam interruptions) across time to produce percent time spent in the half of the cage containing the food hopper and percent time in the opposite half of the cage.

Data analysis—Analysis of variance (ANOVA) with Groups (i.e., surgical condition) as between-subjects factors and Days or Sessions as within-subjects factors were used to evaluate the effect of lesions on body weight, food intake, and appetitive behavior. Analysis of simple main effects and post-hoc Newman-Keuls tests were used to identify specific patterns of differences on which findings of significant main effects and interactions were based. ANOVAs with only Groups as a (between-subjects) factor were also used to assess the effects of lesions on metabolic and general behavioral activity and body composition. Dunnett tests were used to assess the basis of significant main effects in these analyses. Alpha level was set at 0.05 for all statistical tests. In addition, separate analyses of the type described above were used to compare each of the respective control groups that were used for the CHip-, VP-, and mPFC-lesioned groups. When these analyses failed to reveal significant main effects or interactions involving the different control conditions, the controls were combined for comparison with the lesioned groups.

Results

Histology

The nature and extent of the brain damage resulting from the surgical procedures is described in the following paragraphs. Microphotographs of sections from rats with VP and mPFC lesions are shown in Figures 1 and 2, respectively.

Complete Hippocampus (CHip) lesion—All animals in the CHip lesion Group had extensive loss of the cells that comprise the hippocampus including the CA1-CA3 pyramidal, dentate granule cells, and the cells within the hilar region of the dentate gyrus. Further, there was minimal involvement of adjacent structures. The brain damage was

generally similar to that reported in a number of other studies where focal injections of IBO have been employed as a lesion procedure (Jarrard, 1989; Jarrard, 2002; Jarrard and Davidson, 1990; Jarrard et al., 2004). Since microphotographs of the resulting lesions are shown in these and other published papers, photographs of the complete hippocampus lesion will not be included here.

Atrophy of the hippocampus was present in all rats in the CHip Group, and as a result the ventricles appeared enlarged with slight distortion of the remaining adjacent structures. The only sparing of hippocampus was some remaining, normal looking cells in a limited unilateral area of dorsal CA1 in 2 rats and in ventral CA3 and CA1 in several other rats; however, these small 'islands' of normal looking cells were few in number and were generally unilateral. While it is not known if these remaining neurons were functional, given the isolation of the cells and the limited number, one would guess they were nonfunctional.

Hippocampal ventral pole (VP) lesion—The CA1 and CA3 cells in the ventral hippocampus that comprise the ventral pole are shown in the coronal section in Figure 1A for an unoperated rat. The area of interest is the area of the hippocampus within the square. The images in Figure 1B are from a rat with similar bilateral injections and a 3-day survival. The cell loss shown in the figure is representative of that in most rats included in the ventral pole Group. As can be seen in Figure 1B, there was an extensive loss of CA3 and CA1 cells in the area of interest together with a proliferation of glial cells.

In several rats the cell loss included adjacent neurons in the subiculum but this extra damage was not great in amount and was unilateral. Of special concern was possible loss of cells in the amygdala but careful examination of the brains did not indicate that this structure was damaged.

Medial prefrontal (mPFC) lesion—There was clear, bilateral loss of neurons in the prelimbic, medial orbital cortex, and infralimbic cortical areas in 6 of the 8 rats in the mPFC Group. The cell loss in the 2 other rats was similar to that of the 6 rats in one hemisphere but there was less damage to the area of interest on the contralateral side. Statistical analyses of results for the mPFC group did not differ whether or not these two rats were included. Therefore, the data for these 2 rats were included in the overall analyses. As shown in Figure 2 (B) at three A-P levels, the mPFC lesion (identified with arrows) included considerable bilateral damage to the three main divisions of the medial prefrontal cortical area.

Body weight gain

Pre-surgical baseline—Rats were assigned to groups matched on mean ad libitum body weight (i.e. baseline) calculated two days prior to the beginning of surgery. Mean baseline body weights (gms) for each group were: CHip 318.56g, SEM = 3.38; CHip pair-fed controls 319.63g, SEM = 3.31; VP 319.21g, SEM = 2.17; VP pair-fed controls 319.00g, SEM = 2.63; mPFC 318.75g, SEM = 2.90; mPFC pair-fed controls, 318.94g, SEM = 2.94; Ad-lib fed controls 317.58g, 4.73. None of these differences were statistically significance ($F(6,51) < 1$).

Weight changes during post-operative recovery—Figure 3 shows mean body weight gain for each group compared to baseline on the day of surgery (Day 0) and at the end of each two-day period post-surgery until the lesioned groups achieved the same mean body weight (+/- 1 g) as the ad-lib fed controls—the point at which we considered post-operative recovery to be complete. As can be seen in that figure, the CHip,(left panel) VP (center panel) and mPFC (right panel) groups, and their pair fed controls, all exhibited weight loss on postoperative Day 2, with the largest weight loss being observed for the rats

with CHip lesions and the smallest weight loss exhibited by the VP-lesioned group. An ANOVA evaluating the decrease in body weight for each of the lesioned groups from the day of surgery (Day 0) to post-operative Day 2, obtained significant main effects of Group, Day, and a significant Group × Day interaction smallest $F(2,25) = 16.68$, $p < .01$ for the main effect of Group). Analyses of simple main effects found no significant differences among the groups on Day 0 ($F(2,25) < 1$); However, the main effect of Group was highly significant on post-operative Day 2 ($F(2,25) = 23.12$, $p < .01$). Post-hoc Newman-Keuls test confirmed that significantly greater weight loss was sustained on Day 2 by the CHip-lesioned compared to both the mPFC- and VP lesioned groups (ps < .01), whereas the mPFC-lesioned group also showed greater weight loss than the VP-lesioned group on Day 2 ($p < .05$).

Figure 3 shows that the lesioned groups differed not only with respect to the amount of weight loss after surgery, but also with respect to the number of days that were needed for each group to complete post-operative recovery as defined by achieving a mean body weight that matched (+/- 1 g) the Ad lib-fed controls. The criterion was achieved on (postoperative) Day 20 for Group CHip, on Day 16 for Group VP and on Day 30 for the mPFC-lesioned group. Furthermore, pair-fed groups were returned to free access to food when the post-operative body weights of their corresponding lesioned rats returned to or exceeded the presurgical body weight recorded on Day 0. Based on this criterion, all of the Pair-fed controls for CHip group were given ad lib food beginning on post-operative Day 8, whereas ad lib feeding began on postoperative Day 4 and postoperative Day 6, for the pair-fed controls of the VP- and mPFC-lesioned, respectively. Because of these differences in the apparent nonspecific effects of lesions on post-operative body weight loss and recovery, subsequent analyses focused on comparing body weight changes for each lesion group with its Pair-fed and Ad lib Fed controls after post-operative recovery was deemed complete for each lesioned group.

An ANOVA comparing pre–recovery weight gain for the CHip-lesioned rats with that of their Pair-fed and the Ad lib-fed controls on Days 2-20 following surgery yielded significant main effects of Group ($F(2,19) = 18.4$, $p < .01$), Day ($F(10, 190) = 263.84$, $p < .01$) as well as a significant Group × Day interaction ($F(20,190) = 12.21$, $p < .01$). Post hoc analyses comparing the CHip-lesioned with their Pair-fed control groups during the same period obtained a significant main effect of Day ($F(9.126) = 233.72$, $p < .01$), indicating that both groups exhibited significant weight gain and also a significant Group × Days interaction ($F(9,126) = 1.96$, $p < .05$). Analyses of simple main effects showed that these two groups differed significantly only on post-operative Day 2, with weight loss greater for the lesioned group. The same type of analysis comparing Group CHip with the Ad lib-fed controls found that the main effects of Group ($F(1,12) = 24.10$, $p < .01$) Day ($F(9,12) = 199.28$, $p < .01$) and the Group × Day interaction ($F(9,108) = 25.70$, $p < .01$) were significant. Analyses of simple main effects revealed significant differences in mean body weight between the CHip group and the Ad-lib fed control group on post-operative Days 2-14 (largest $F(1,12) = 5.49$, $p < .05$ on Day 14) whereas these differences were not significant on post-operative Days 16-20.

ANOVA comparing VP-lesioned rats and controls from post-operative Days 2 -16 obtained significant main effects of Group and Day (smallest $F(2, 23) = 8.25$, $p < .01$ for Group) and a significant interaction between these two factors ($F(14,161) = 8.47$, $p < .01$). Analysis of simple main effects revealed that mean body weight gain for VP-lesioned rats was significantly higher than their Pair-fed controls on post-operative Days 12-16 (smallest $F(1,18) = 4.55$, $p < .05$ on Day 12). No differences between these groups on other days were significant. The same type of analysis showed that VP-lesioned rats weighed significantly less than Ad lib-fed controls on Days 2-8 (smallest $F(1,16) = 4.85$, $p < .05$ on Day 8), with no significance differences on postoperative Days 10-16.

Statistical evaluation of differences between mPFC-lesioned rats and controls obtained a significant effect of Day ($F(14,266) = 238.29$, $p < .01$) and a significant Group × Day interaction ($F(28,266) = 4.20$, $p < .01$), but no significant main effect of Group ($F(2,19) = 2.15$, $p < .01$). Subsequent analysis comparing only the mPFC group with their Pair-fed controls failed to yield either a significant main effect of Group ($F(1,14) < 1$) or a significant Group × Day interaction ($F(14,196) <1$). In contrast, when this analysis compared only the mPFC and Ad lib fed groups, the main effect of Days ($F(14,168) = 132.78$, $p <.01$) and the Group × Day interaction ($F(14,168) = 5.54$, $p < .01$) were significant. Analyses of simple main effects showed that mPFC groups weighed significantly less than the Ad lib-fed control on post-operative Days 2-14 (smallest $F(1,12) = 4.95$, $p < .05$, Day 14). Differences on Days 16-30 were not significant.

Weight gain following post-operative recovery—Weight gain for the CHip, VP, and mPFC lesion groups were compared to their controls during the 20-day period beginning, for each group, immediately after their postoperative recovery was deemed complete (i.e., after the post-surgical body weight of the group matched that of the ad lib fed control). Figure 4 shows weight gain for each lesion group, relative to their pre-operative baseline, on the day that postoperative recovery was deemed complete (PR) and for the 20-days thereafter. Within each lesion condition, there were no significant differences between the body weights of the pair-fed and ad lib fed controls at the end of the recovery period. In, addition, ANOVA revealed no significant main effects of Group or Group × Day interactions for any comparison of pair-fed and ad lib-fed controls groups during the 20 days after recovery from surgery. Therefore, these data for the control groups were combined for the remaining analyses of body weight gain.

The left panel of Figure 4 indicates that rats with CHip lesions exhibited a faster rate of weight gain following post-operative recovery compared to their combined controls. Although the difference in mean weight gain for the two groups over all of the 20-day post recovery period did not achieve significance (main effect of Group, $F(1,20) < 1$), a significant main effect of Day showed that both groups exhibited significant weight gain during the post-recovery period and a significant Group × Day interaction ($F(10,200) = 2.58$, $p < .01$) confirmed that the rate of weight gain across days was significantly higher for Group CHip than for controls.

The middle panel of Figure 4 shows that rats with VP lesions gained more weight and gained weight faster than their combined controls. ANOVA confirmed these impressions by obtaining significant main effects of Group ($F(1,24) = 10.68$, $p < .01$) and Day $F(10,240) = 188.80$, $p< .01$) and also a significant Group × Day interaction ($F(10,240) = 7.57$, $p < .01$).

Little difference in either rate or amount of weight gain was observed when Group mPFC was compared with their combined controls (see right panel of Figure 4). ANOVA yielded a significant main effect of Day ($F(10,200) = 176.87$, $p < .01$) confirming that both groups gained weight across the 20-day period following recovery from surgery. However, the failure to obtain a significant main effect of Group ($F(1,20) < 1$) or a significant Group × Days interaction ($F(10,200) <1$) provides no evidence that mPFC lesions had effects on body weight that were different from the control treatments.

Food Intake

Amount eaten (in kcals) was recorded at the end of each 2-day block during the 20 days following post-operative recovery for each group. Comparisons of the Pair-fed and Ad lib-fed controls for each respective surgical treatment yielded no significant main effects of Group or Group × Day interactions. Thus, the control groups for each respective lesion

group were combined for the analyses of the effects of CHip, VP, and mPFC lesions on food intake.

Figure 5 shows mean amount of food consumed by the lesioned groups and the combined control group on each 2-day block that took place over the first 20-days following post-operative recovery. Both CHip and VP lesioned rats ate more than their respective controls. Little difference was observed for mPFC lesioned rats relative to their controls. An ANOVA comparing CHip rats with their controls yielded a significant main effect of Group ($F(1,20) = 16.54$, $p < .01$), whereas the Group × Block interaction was not significant ($F(10,200) = 1.11$, $p > .35$). Similarly, a significant main effect of Group ($F(1,23) = 6.76$, $p < .01$) but no Group × Block interaction ($F(10,230) < 1$) was found when the VP-lesioned group was compared to their controls. In contrast, when the mPFC-lesioned rats and their controls were compared, neither the main effect of Group nor the Group × Block interaction achieved significance ($Fs < 1$).

Conditioned Appetitive Behavior

ANOVA comparing the previously pair-fed control groups for each lesion condition obtained no significant main effects or interactions involving Group. Thus, these controls were combined for subsequent comparison with the lesioned groups.

The results depicted in the left portion of each panel in Figure 6 show that conditioned appetitive responding was elevated at the outset of training under 0-hr and throughout training under 24-hr food deprivation for rats with CHip lesions compared to controls and to rats with VP and mPFC lesions. In addition, only CHip lesioned rats responded more under 24-hr than under 0-hr food deprivation by the end of reinforced training. ANOVA of these data obtained a significant main effect of Group ($F(3,48) = 7.9$, $p < .01$) and significant Group × Deprivation level ($F(3,48) = 4.3$, $p < .01$) and Group × Deprivation level × Sessions ($F(15,240) = 2.6$, $p < .01$) interactions. Newman-Keuls tests found that rats in Group CHip showed significantly more conditioned appetitive responding overall (all $ps < .01$) and significantly more responding under both the 0-hr (all $ps < .05$) and the 24-hr (all $ps < .05$) food deprivation levels compared to each of the groups VP, mPFC, and controls and that none of these latter three groups differed significantly from one another. Post-hoc analysis of discriminative responding revealed that on the first two sessions of training under each deprivation level Groups VP, mPFC, and controls responded significantly more on nonreinforced trials under 0-hr food deprivation than on reinforced trials under 24-hr food deprivation, whereas this pattern of responding was obtained for Group CHip only when the first session under each deprivation level was compared. Responding more on nonreinforced compared to reinforced trials is common at the outset of discrimination training when overall response strength is increasing and rats have not differentiated among the discriminative stimuli. In contrast, significantly greater responding on reinforced (24-hr food deprivation) compared to nonreinforced (0-hr food deprivation) trials emerged for Group CHip ($ps < .05$ for sessions 3, 5 and 6).

The purpose of extinction was to assess whether tendencies to respond more under 24- compared to 0-hr food deprivation, that were not apparent (i.e., were latent) at the conclusion of reinforced training would emerge on nonreinforced trials during extinction. The right portion of each panel in Figure 6 shows that response strength decreased for all groups under each deprivation level across extinction trials, an effect that was confirmed statistically by a significant main effect of sessions ($F(4,192) = 37.50$, $p < .01$). Furthermore, the higher level of responding exhibited by Group CHip on trials under 24-hr compared to 0-hr food deprivation at the end of training, was largely maintained across extinction testing. Each of the remaining groups that did not respond differentially based on deprivation level at the end of training, did exhibit some tendency for latent discrimination, by coming to

respond more on sessions under the previously reinforced 24-hr food deprivation level, compared to sessions under 0-hr deprivation.

ANOVA for the extinction test data obtained a significant Group × Deprivation level interaction ($F(3,48) = 6.82$, $p < .01$). Newman-Keuls tests showed that Groups CHip and mPFC responded significantly more during extinction under 24-hr compared to 0-hre food deprivation (ps <.05), whereas this difference was not significant for either Group VP or the controls. However, separate ANOVAs comparing each lesioned group with controls yielded a significant Group × Deprivation level interaction only for the comparison of Group CHip with controls ($F(1,30) = 16.41$, $p< .01$). This indicates that the magnitude of the difference between responding on 24-hr versus 0-hr deprivation was significantly larger compared to controls only for CHip lesioned rats. Although Group CHip showed significant differential responding during extinction, this can't be termed latent discrimination as it was also apparent at the end of training.

Body weight under 0-hr and 24-hr food deprivation

During appetitive conditioning, the body weights of the rats in each group were recorded immediately prior to the beginning of each training (sessions 1-6) and extinction (sessions 7-11) session under 0- and 24-hr food deprivation. Although the rats received 0- and 24-hr deprivation sessions in a irregular order. Figure 7 segregates mean body weights recorded for each group on 0-hr deprivation sessions (left panel) from those recorded on 24-hr food deprivation sessions (right panel).The left panel of Figure 7 shows that mean body weight prior to sessions under 0-hr food deprivation remained relatively stable for rats in the CHip group, but decreased across session for the rats in the VP, mPFC, and control conditions. The rate of decrease in body weight appeared to be largest for rats in the control group. On the last 0-hr session, mean weight was highest for the rats with CHip lesions, followed respectively by the VP, the mPFC, and Control groups.

ANOVA obtained significant main effects of Group ($F(3,48) = 3.05$, $p < .01$), Session ($F(10,480) = 71.64$, $p < .01$) and a significant Group × Sessions interaction ($F(30,480) = 6.83$, $p < .01$). Subsequent analyses comparing CHip-lesioned rats with controls obtained a significant Group × Sessions interaction ($F(1,30) = 24.24$, $p < .01$.). Analyses of simple main effects found that mean body weight for CHip-lesioned rats did not differ from controls on the first session under 0-hr food deprivation ($F(1,30) = 1.21$, $p > .28$), but that this difference was highly significant on the last 0-hr food deprivation session ($F(1,30) = 14.26$, $p < .01$). In contrast, the same comparison between VP-lesioned and control rats yielded a significant main effect of Group ($F(1,34) = 5.90$, $p < .05$), but lacked a significant Group × Sessions interaction indicating that the magnitude of the this difference was about the same across sessions. Neither the main effect of Group nor the Group × Session interaction achieved significance when the mPFC and control rats were compared across the first and last 0-hr food deprivation session.

The right panel of Figure 7 shows mean body weight for each group prior to each session under 24-hr food deprivation. Rats in Group VP weighed more than each of the other groups, which did not differ, on the first session under 24-hr food deprivation. Although all groups lost weight with repeated 24-hr deprivation sessions, the amount of weight reduction appeared to be less for the rats with CHip lesions, than for the rats in the VP, mPFC, and Control conditions, such that by the last of these sessions, the highest mean body weight was shown by the CHip group. An overall ANOVA obtained a significant main effect of Sessions ($F(10,480) = 141.32$, $p < .01$) and a significant Group × Sessions interaction ($F(30,480) = 5.34$, $p < .01$). A separate analysis comparing the CHip and control rats also yielded a significant Group × Sessions interaction ($F(10,300) = 12.05$, $p < .01$). Simple main effects analysis showed that mean weight for these groups did not differ on the first session

of 24-hr food deprivation ($F(1,30) < 1$), but differed significantly on the last session under 24-hr food deprivation ($F(1,30) = 4.18$, $p < .05$). The same analysis comparing the VP lesioned group with controls obtained significant main effects of Group and Session (smallest $F(1,34) = 5.32$, $p < .05$, for Group), and no significant interaction. An ANOVA comparing the mPFC and control groups obtained only a significant main effect of sessions ($F(10,300) = 89.98$, $p < .01$).

Indirect calorimetery

We assessed differences in energy expenditure in the CHip-, VP-, mPFC-lesioned and controls. Because of equipment limitations, the control group for this and all remaining analyses were composed of two rats from the Pair-fed control of each lesion group and two rats from the Ad lib-fed control condition. The two rats selected from each control group were the rats that were closest to the mean body weight of all rats in each respective control condition.

We found that CHip-lesioned rats exhibited significantly increased rates of energy expenditure (as measured by O2 consumption) relative to other groups (See Figure 8). The left panel of Figure 9 shows cumulative energy expenditure during the 12 hour dark period. The right panel depicts cumulative energy expenditure across the 24-hr light/dark cycle. Specifically, rats in Group CHip had higher levels of O2 consumption during the dark phase of the diurnal cycle, when rats are most active. On dark-phase energy expenditure, Dunnett's individual comparisons yielded a significant difference between CHip and CON groups ($q = 2.57$, $p < .05$). Neither VP nor PF rats were significantly different than CON rats. There were no significant differences during light-phase for total energy expenditure.

Body composition analysis

Figure 9 shows the final body weight (left panel) and final total body adiposity (right panel) for each group. This weight was recorded approximately 150 days following surgery. As seen in that figure, rats in Groups VP and CHip had higher body weights relative to rats in the mPFC and control groups. One-way ANOVA on final body weight confirmed a significant main effect of Group ($F(3,35) = 3.46$, $p < .05$) and follow-up Dunnett's tests revealed that both VP and CHip lesioned rats weighed significantly more than control rats. Additionally, there was a trend for increased body adiposity in each of these two lesioned groups, relative to control rats. However, these differences were not confirmed statistically by ANOVA or by individual comparisons (ps > .05).

Behavioral activity in the homecage

Rats with CHip lesions exhibited increased levels of home cage activity, relative to all other groups. The left panel of Figure 10 depicts mean cumulative (24-hr) photobeam breaks. As seen in that figure, rats in group CHip exhibited an approximate doubling of locomotor activity relative to groups CON, VP and PF. These difference were confirmed statistically by one-way ANOVA ($F(3,35) = 8.16$, $p < .05$). Dunnett's individual comparisons showed that activity levels in group CHip were significantly greater than the mPFC, VP, or controls.

We have previously hypothesized that increased activity levels in CHip-lesioned rats may be due in part to conditioned responses based on the availability of food (Benoit et al., 1999; Davidson and Jarrard, 2004). It is well-known that rats exhibit increased activity levels in the presence of discrete and contextual stimuli that predict the availability of food. It is also well-known that general activity levels follow a predictable circadian rhythm that can be entrained based on the delivery of food to food-deprived rats. We predicted that at least part of the increased activity levels would be based on contextual cues that predict the availability of food and, further, that hippocampal rats would be impaired at inhibiting such

cue-driven conditioned responses. Consistent with this we observed that rats in Group CHip spent significantly more time near the food cup than controls. The right panel of Figure 10 depicts the amount of time (number of beam breaks across time) rats spent in the front half of the cage containing the food hopper. While rats in all surgical groups exhibited increased percent time in the food-hopper containing side of the cage, this difference was statistically significant only when Group Chip and controls ($t = 2.27$, $p < .05$, one-tailed) were compared.

Discussion

Recent accounts propose that (a) environmental food cues will tend to evoke eating until that behavior is inhibited by biological control mechanisms and (b) obesity may be more prevalent because these biological control mechanisms are failing (Berthoud, 2004b; Prentice, 2005)). What these control mechanisms might be, and why they fail are two questions fundamental to understanding, and ultimately controlling, continuing trends toward increased body weight and obesity in the human population. Much previous work aimed at addressing these questions has focused on hypothalamic control mechanisms and on identifying direct effects of changes in regulatory neuropeptides (e.g., leptin, CCK, ghrelin, etc.) and their receptors. By showing that damage to the hippocampus, a brain structure considered to be an important substrate for learning and memory, interferes with the control of food intake and body weight, the present findings encourage us to think about energy dysregulation, not solely as a deficit in some type of hypothalamic signaling system but, at least in part, as a disorder of higher-order learning and memory functioning (Davidson et al., 2007; Davidson et al., 2005).

There is wide agreement that learned cues can exert strong control over appetitive and consummatory behavior. This control depends, in part, on the formation of simple associations between food-related conditioned stimuli (CSs) and highly salient appetitive unconditioned stimuli (USs) that are produced as a consequence of eating (Berthoud, 2004a; Davidson et al., 2005; Davidson and Swithers, 2004; Holland and Petrovich, 2005; Sclafani, 1997; Woods and Ramsay, 2000). A food-related CS comes to promote the performance of appetitive and consummatory responses by exciting or activating a representation of its appetitive US in memory (Bouton and Moody, 2004). This type of simple association formation does not appear to depend on the hippocampus as animals with the complete hippocampus removed are not impaired at learning that discrete CSs signal delivery of appetitive USs, or at solving simple discriminations where an event always signals reinforcement and another event is always nonreinforced (Benoit et al., 1999; Han et al., 1995; Squire, 1992).

Although not necessary for the formation of simple associations, the hippocampus appears to be involved with the performance of certain higher-order learning and memory operations. Morris (2006) noted that several modern accounts converge on the idea that one function of the hippocampus is to solve problems that involve “predictable ambiguity”. These problems often require animals to learn that the relationship between an event and a particular outcome varies depending upon the presence or absence of other events or conditions. For example, animals with the hippocampus removed often show deficits in appetitive problems (e.g., extinction, discrimination-reversal, feature-negative discrimination, working memory) where performance depends on learning to refrain from responding to cues that are, under some conditions, reliable signals for reinforcement (Berger and Orr, 1983; Chan et al., 2003; Holland and Bouton, 1999; Jarrard et al., 2004). In these cases, it may be that hippocampal damage reduces the ability of animals to inhibit their appetitive behavior by impairing their ability to learn or remember when events will not be followed by reinforcing outcomes.

In the present experiment, damage to the complete hippocampus was not only accompanied by greater food intake and body weight gain, but also by increased appetitive responding in the conditioning apparatus, especially on trials under 24-hr food deprivation, and elevated behavioral activity in the home cage, especially in the vicinity of the food magazine, when the rats were fed ad libitum. Although heightened appetitive responding could be indicative of stronger simple excitatory appetitive conditioning, elevated appetitive performance can also be a consequence of impaired inhibitory learning. As discussed elsewhere (e.g., Benoit et al., 1999) in Pavlovian conditioning, apparatus cues are both reinforced at the time of US delivery and nonreinforced during periods prior to presentation of the US. This could make apparatus cues ambiguous predictors of reinforcement. Intact rats could use handling or temporal cues to determine when to respond and to inhibit their responding to the apparatus cues. However, if removing the hippocampus interferes with the ability to use such contextual cues as signals that predict the nonreinforcement of apparatus cues, then weaker inhibition of responding to the apparatus cues would be expected. Furthermore, consistent with the training contingencies, if the expectation of receiving the sucrose pellet US was greater under 24-compared to 0-hr food deprivation, the effects of impaired inhibition would be more obvious when the rats were under the higher level of food deprivation—the outcome obtained in the present experiment.

Similarly, background cues in the home cage were presumably associated with a strong appetitive postingestive US when rats were hungry (e.g., prior to a meal) but not when they were food sated (e.g., after eating). Under these circumstances, the rats could use interoceptive cues produced by satiety to signal when food and food-related cues in the apparatus will not be followed by postingestive reinforcement. Increased activity on the part of CHip-lesioned rats, relative to controls, is consistent with the hypothesis that CHip lesions reduced the ability of satiety cues to signal the nonreinforcement of food cues, and thus to inhibit behaviors evoked by those cues. The finding that our CHip-lesioned rats spent significantly more time than controls on the side of the apparatus where food was delivered, indicates that some, if not all, of the increased homecage activity exhibited by CHip-lesioned rats was attributable to heightened appetitive behavior (Tracy et al., 2001).

A general feature of this analysis is the assumption that the decision to eat or refrain from eating may involve higher-order or conditional learning processes that would help animals predict when food CSs are followed by an appetitive (pleasant or satisfying) postingestive US and when they are not (Davidson et al., 2007; Davidson et al., 2005). Given that survival depends on efficiently performing many behaviors (e.g., reproduction, defense, driving in rush hour traffic) in addition to procuring and consuming food, it would be highly adaptive if the ability of food CSs to excite memories of appetitive outcomes which promote food-seeking and eating responses was inhibited during times of food satiation. The present analysis is consistent with the idea that the performance of this adaptive function could depend on the hippocampus.

Could hippocampal dysfunction contribute to current global trends toward increased obesity in humans? Compared to the well-known and dramatic increases in food intake and body weight that accompany other types of experimental manipulations, such as lesioning the hypothalamus or genetic mutations (King, 2006; Lindstrom, 2007; Tschop and Heiman, 2001), the effects of hippocampal lesions on food intake and weight gain that are reported here may seem modest. However, very few humans show dramatic increases in food intake and body weight like those shown by hypothalamic-lesioned or genetically-altered rodents. One could argue that the gradual increase in body weight seen in our rats makes them more similar to the current U.S. human population, which has exhibited about a 10% increase in body weight over the past 10 years (Lewis et al., 2000).

Clear links between the function of the hypothalamus and recent increases in the incidence of obesity in the general population have not yet been identified. For example, there are relatively few cases of overweight or obese humans that can be attributed causally to hypothalamic pathologies or genetic mutations in hypothalamic signaling systems (Eikelis et al., 2007; Pinkney et al., 2002). Thus, although surgical, genetic, and other manipulations of the hypothalamus may have profound effects on energy regulation in laboratory settings, it is not yet clear how these manipulations are related to the reduced regulatory control that is occurring outside of the laboratory.

A potential link between the hippocampus and energy dysregulation in humans is suggested by evidence that dietary manipulations known to promote excessive food intake and body weight also disrupt hippocampal-dependent learning and memory processes. For example, Molteni et al., (Molteni et al., 2002) reported that rats maintained for 60 days on a diet high in saturated fat and sucrose, showed impaired hippocampal-dependent spatial memory in a Morris water maze compared to rats maintained on normal (low-fat, high-carbohydrate) lab chow. Similarly, Kanoski et al (Kanoski et al., 2007) found that giving rats 90-day ad libitum access to a diet high in saturated fat and dextrose had long-term detrimental effects on performance in Pavlovian conditioning tasks (reversal learning and extinction) that depend on the hippocampus or prefrontal cortex. These same rats did not exhibit performance deficits on a simple discrimination task that does not require an intact hippocampus or prefrontal cortex. Consistent with this general analysis, deficits in performance on hippocampal-dependent spatial learning problems are also observed in rat models of obesity (Matsushita et al., 2003; Nomoto et al., 1999; Winocur et al., 2005).

Furthermore, Molteni (Molteni et al., 2002) reported that spatial memory deficits by rats maintained on the high-fat diets, were accompanied by reduced levels of hippocampal brain-derived neurotrophic factor (BDNF). Kanoski et al (Kanoski et al., 2007)) also found that BDNF was significantly reduced in the ventral hippocampus and medial prefrontal cortex, but not in the dorsal hippocampus, in rats that showed deficits in nonspatial reversal and extinction performance following maintenance on the high-fat diet. BDNF contributes to the survival, growth, and maintenance of many types of neurons (Allen and Dawbarn, 2006; Nottebohm, 2004) and is thought to contribute to hippocampal long-term potentiation (LTP) and neurogenesis ((Bramham and Messaoudi, 2005; Lee et al., 2002; Rossi et al., 2006; Wibrand et al., 2006). Both of these processes have been described as important mechanisms for hippocampal-dependent forms of learning and memory (Dalla et al., 2007; Gruart et al., 2006; Kitabatake et al., 2007; Whitlock et al., 2006). It may be that the ability of high-fat diets to promote increased food intake and body weight gain occurs as a consequence of interfering with the same hippocampal-dependent mechanisms that were disrupted by hippocampal lesions in our present experiment.

Obviously, hippocampal damage could also influence behavior by interfering with processes that do not involve learning and memory. In the present study, indirect calorimetry revealed that metabolic activity during the dark phase of the light-dark cycle was elevated for rats with CHip lesions compared to controls. It may be that this increased energy expenditure was a byproduct, at least in part, of the increased appetitive behavioral activity exhibited by rats with CHip lesions. However, heightened metabolism might have also been induced, in part, by the increased food intake on the part of the CHip-lesioned rats. Several studies have shown that metabolism increases, perhaps as a counterregulatory response, when animals are forced to consume calories in excess of their metabolic needs ((Balkan et al., 1993; Harris et al., 2006; Shibata and Bukowiecki, 1987; Weyer et al., 2001). It may be that increased metabolism is an effect of excess caloric intake that was difficult for rats with CHip lesions to control. However, in the present study increased metabolism was not enough to abolish weight gain on by rats with CHip lesions.

In addition, a relatively unexplored possibility is that the disturbances in energy regulation reported here involve a reduction in direct sensing by the hippocampus of nutrients or peripheral factors that regulate energy balance. As mentioned previously, the hippocampus expresses many of the same receptors (e.g., insulin, leptin, ghrelin and CCK) that are thought to be important for energy balance in the hypothalamus and brainstem. Thus, in our rats with hippocampal lesions, the sensing or relaying of this information may have been damaged contributing to increased food intake and/or body weight gain. Similarly, it is conceivable that intake of diets high in saturated fat could also interfere with this type of hippocampal functioning. An intriguing possibility is that selective genetic deletion of hippocampal nutrient or hormonal receptors might result in changes in energy balance as well. Consistent with this idea, Irani et al., (2007) reported that intake of a high-fat diet is associated with reduced insulin binding in the hippocampal CA1 cell field of rats.

Rats with lesions confined to the hippocampal ventral pole also ate significantly more and gained significantly more weight relative to their controls. However, unlike rats with the complete hippocampus removed, VP lesions were not associated with significant increases in appetitive behavior, general activity, or metabolism. Furthermore, compared to rats with CHip lesions, weight gain for rats with VP lesions appeared to increase faster, relative to their controls, during the post-surgical recovery period and during the first 20 days after complete recovery from surgery. Despite exhibiting greater initial weight gain, the magnitude of the increase in food intake for VP-lesioned rats relative to controls appeared smaller than that observed for rats with CHip lesions. The finding that rats with VP lesions recovered from surgery more rapidly than CHip-lesioned rats could reflect that the debilitating effects VP surgery subsided more rapidly compared to the debilitation produced by much more extensive lesions of the complete hippocampus. These differences in recovery may have allowed the facilitating effects of VP lesions on intake and body weight gain to emerge more quickly compared to CHip lesions.

In the present study the damage produced by the CHip lesion encompassed all of the hippocampus including the ventral pole. The ventral pole lesion was relatively small by comparison (injection of IBO at 30 sites for the CHip lesion compared to 4 sites for the VP lesion). While the intent with the VP lesion was to remove all of the cells that comprise the ventral pole, it is possible that there was some sparing of the relevant cells in this group compared to the damage found in the CHip lesioned rats. Thus, differences in the effects of the two types of lesions on energy and body weight regulation can not be attributed solely to a common disruption of direct connections between the VP and the lateral hypothalamus. Further, It may be that the greater effect of the CHip lesion reflects interference with learned behavioral control processes in addition to those mediated by the hippocampal ventral pole-lateral hypothalamic circuit

On the other hand, it is possible that VP lesions interfered with the same learning and memory mechanisms as did CHip-lesions, but that the magnitude of this interference was smaller for VP-lesioned rats. It is difficult to evaluate the above possibilities since the effects of lesions confined to the VP on learning and memory, including occasion setting and similar hippocampal-dependent processes, have not yet been thoroughly studied.

It is also the case that rats with neurotoxic lesions of the medial prefrontal cortex did not differ from their controls with respect to any of the measures (e.g., intake, appetitive behavior, body weight gain, etc.) that were recorded in the present experiment. These rats required more time than rats with either CHip- or VP-lesions to achieve the criterion for post-operative recovery. However, it is not clear whether this effect was a consequence of greater general behavioral debilitation produced by mPFC lesions or weaker facilitation of eating and appetitive behavior, compared to CHip and VP lesions. The latter possibility

seems likely based on the finding that during the post-recovery period, neither mean food intake nor weight gain for mPFC rats differed significantly relative to their controls.

Our findings that mPFC lesions had no significant effects on intake or weight gain is noteworthy for several reasons: first, the area of the mPFC that was lesioned in this experiment was the same area that showed reduced levels of BDNF following exposure to a maintenance diet high in saturated fat and dextrose (Kanoski et al., 2007). Given that destruction of this area had little impact on energy regulation in the present study, this suggests that the excess intake and weight gain exhibited by rats maintained on the high fat + dextrose diet used in the study by Kanoski et al were not based on the effects of that diet on functions performed by the medial prefrontal cortex or by neural circuits that include this area of the brain. Second, the lack of effects of mPFC lesions on intake and body weight gain that we observed is consistent with another report that rats with lesions of the medial prefrontal cortex, albeit at a site slightly (but perhaps importantly-see below) ventral to the site of the mPFC lesions used in the present experiment, showed no differences in home cage food intake or in body weight relative to controls ((Petrovich and Gallagher, 2007).

However, previous studies have shown that rats with lesions that include the ventral mPFC exhibited less “conditioned stimulus potentiated eating” when either discrete CSs or contextual cues that were trained to predict food when the rats were hungry, are presented when the rats are subsequently food sated (Petrovich and Gallagher, 2007; Petrovich et al., 2007). In the present study, rats with mPFC lesions did not differ significantly from controls with respect to their appetitive responding to contextual cues in the training apparatus, under either food deprived or nondeprived conditions. However, in addition to differences in exact location of medial prefrontal cortex damage, the present experiment also employed different food deprivation manipulations and training procedures compared to the earlier studies. It is possible that the different lesion effects reported in these experiments might be reconciled if rats were tested under more similar lesion or training conditions. In any event, the results of the present study provide no compelling evidence that energy and body weight regulation depends on the structural integrity of the medial prefrontal cortex or on any hippocampal-prefrontocortical neural pathway.

Conclusions

Previous research shows that the hypothalamus, especially the arcuate nucleus, contains receptors that are involved with the detection of a variety of neurohormonal hunger, satiety, and adiposity signals. The identification of these signals and their receptor sites has contributed much to our understanding of the control of food intake and body weight regulation. However, the question of how the detection of these cues is translated into adaptive behavioral outcomes has often been addressed by little more than an arrow in a diagram (e.g.,Berthoud, 2003; Woods and Seeley, 2000). The results of the present study suggest that to more fully understand the mechanisms that underlie energy and body weight regulation it may be necessary to describe how the operation of neurohormonal signaling systems that depend on the hypothalamus are integrated with higher-order learning and memory processes that depend on the hippocampus.

In the present study we found that destruction of the complete hippocampus in the rat is accompanied by increased food intake, body weight gain, appetitive behavior, metabolic, and general behavioral activity, whereas the effects of damaging the hippocampal ventral pole were limited to increased food intake and body weight gain. We suggested that the operation of higher-order, hippocampal-dependent learning and memory processes may underlie the ability of interoceptive satiety signals and perhaps other types of conditional cues to inhibit appetitive and consummatory responding evoked by food and food-related environmental stimuli. Within this model, damage to the hippocampus could therefore

interfere with the inhibition of appetitive and eating behaviors. Thus, the question of "how" physiological satiety signals inhibit food intake and reduce body weight gain may be addressed, in part, with reference to learning and memory mechanisms that depend on the hippocampus. As others have suggested, improved understanding of the functional links between the neural controls of food and drug intake and the operation of higher-order learning and memory processes may be key to developing effective therapeutic interventions that can combat obesity (Berthoud, 2002; Moran and Gao, 2006).

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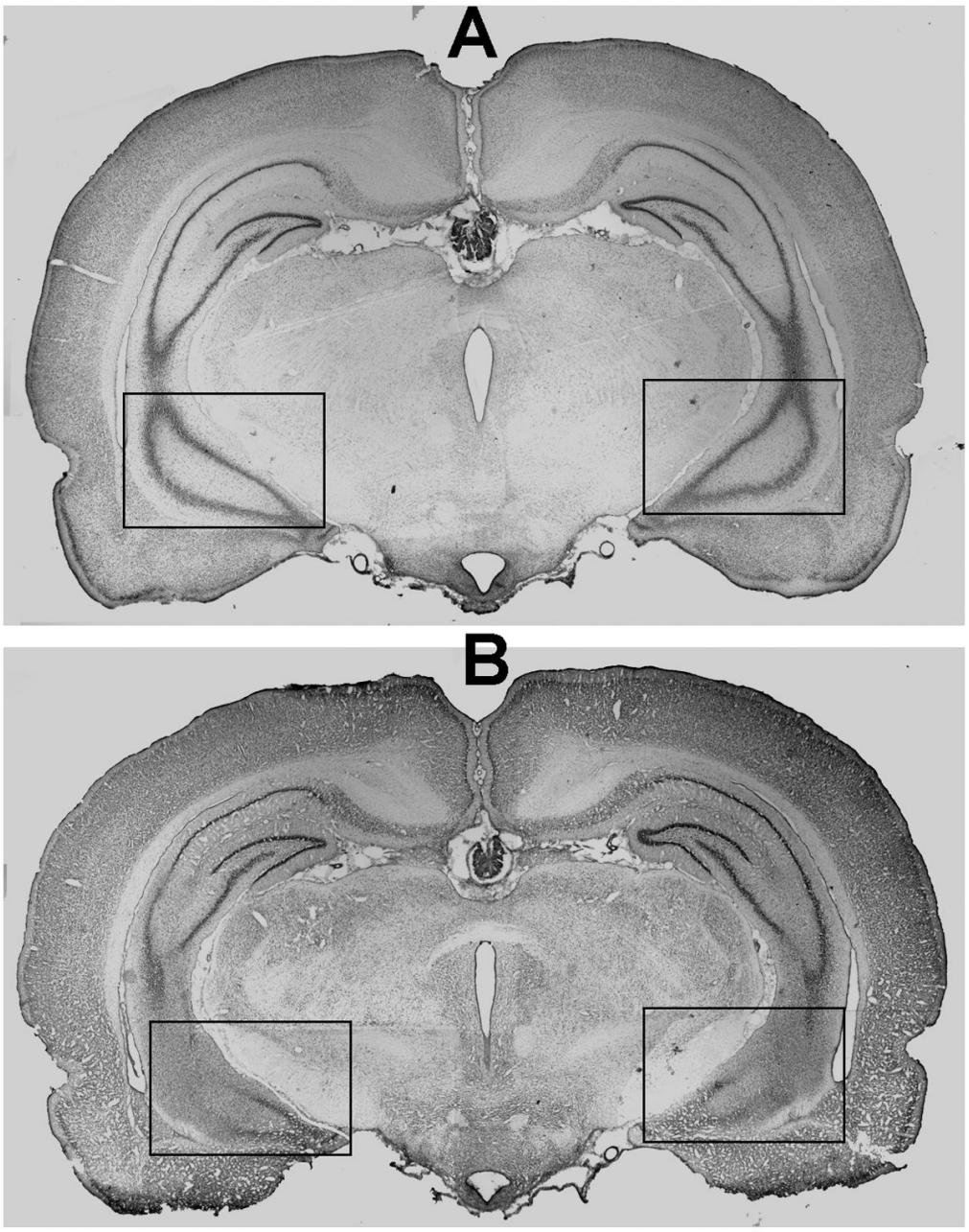

Figure 1.
Photomicrographs of a coronal section from an unoperated rat (A), and the cell loss in a representative rat that received the bilateral ventral pole (VP) hippocampal lesion with a 3-day survival (B). The hippocampal ventral pole is the area outlined with boxes.

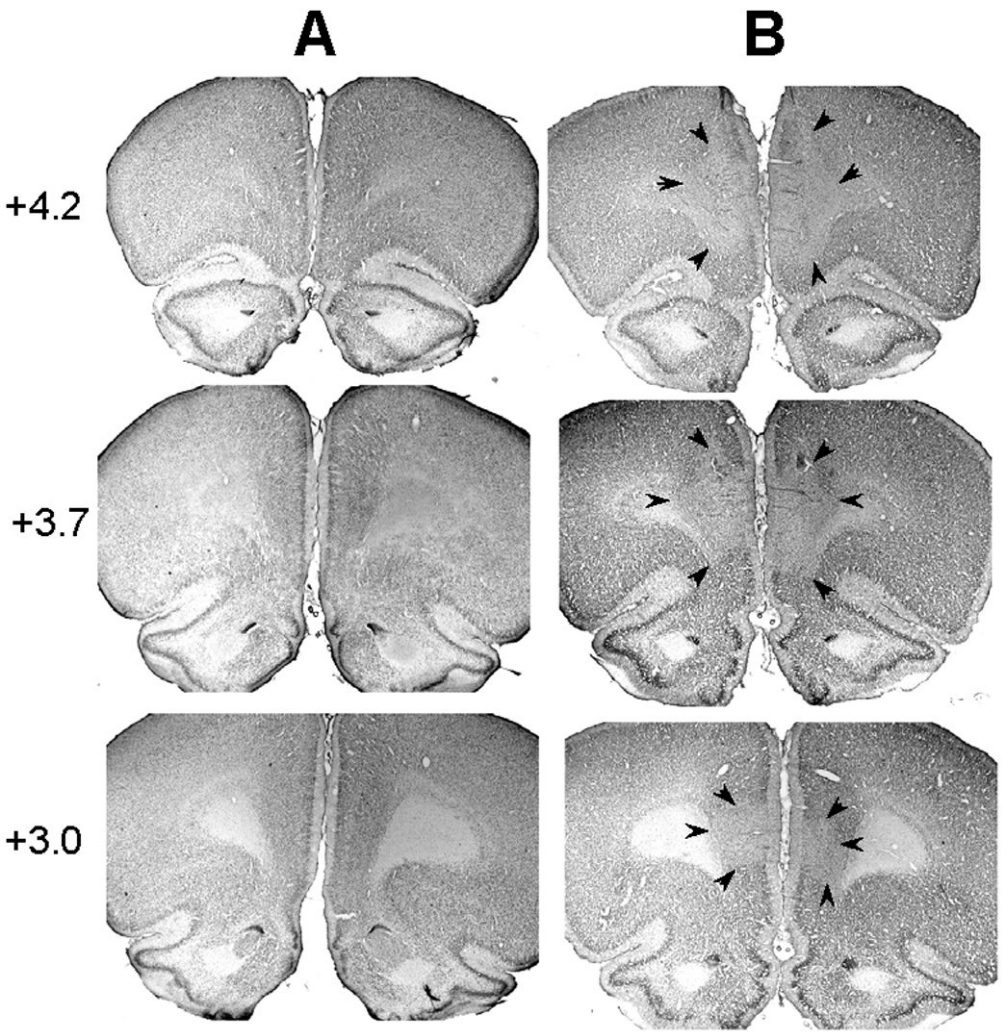

Figure 2.
Photomicrographs showing the medial prefrontal cortex (mPFC) at three anterior-posterior levels from an unoperated rat (A) and a lesioned rat (B). The mPFC and the area of cell loss is identified with arrows in B.

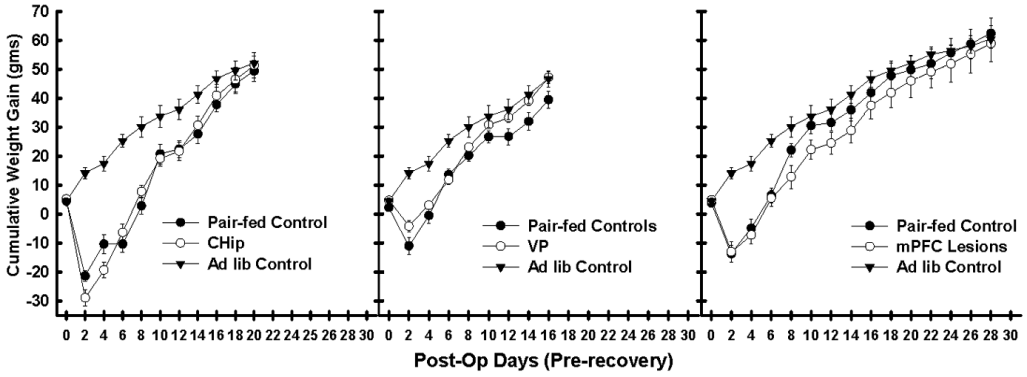

Figure 3.

Mean weight gain by rats with CHip, VP, and mPFC lesions and their pair-fed and adlib controls during pre-recovery period beginning immediately after surgery and ending when mean body weight for the lesioned groups achieved the level of their ad lib controls.

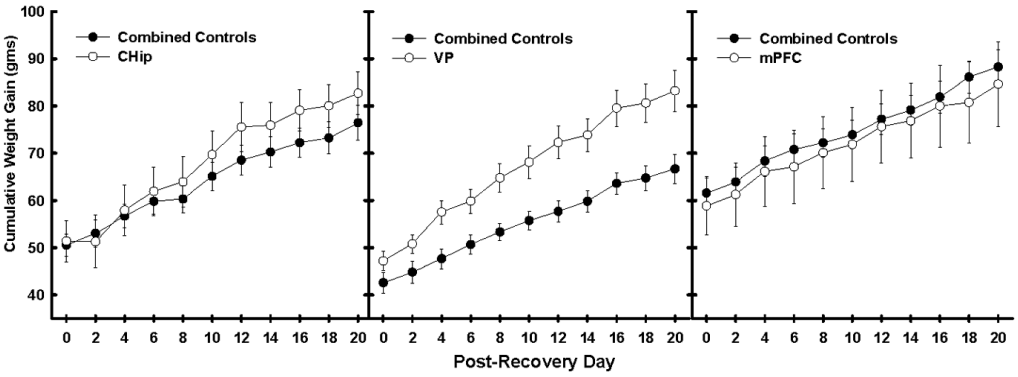

Figure 4.

Mean weight gain by rats with CHip, VP, and mPFC lesions and their combined controls (pair-fed and adlib) during post-recovery period which began after mean body weight for the lesioned groups achieved the level of their ad lib controls.

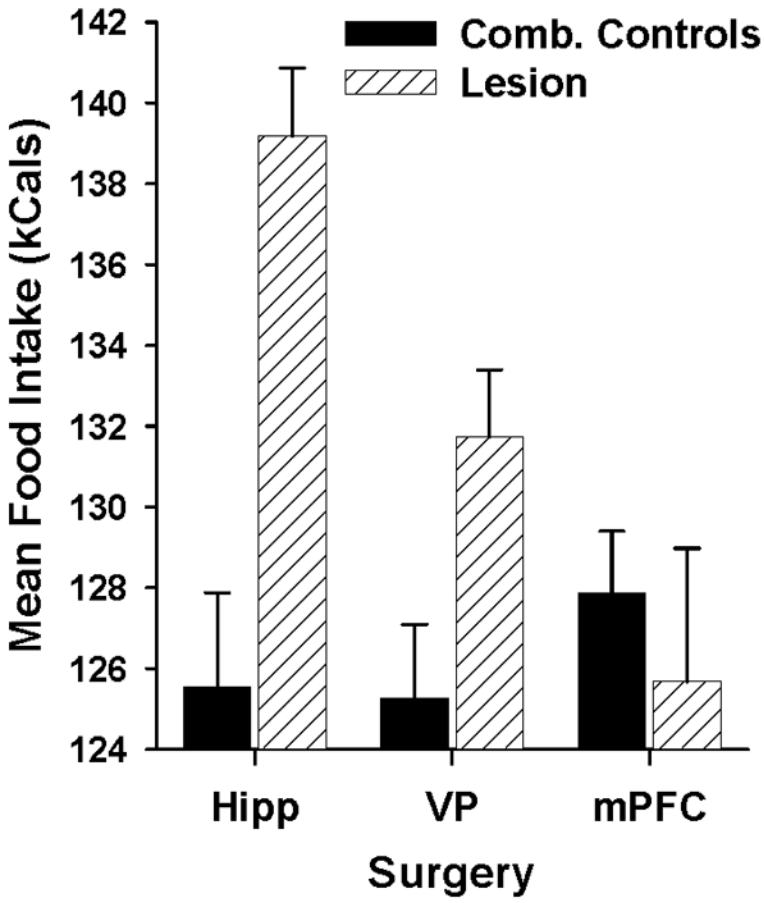

Figure 5.
Mean food intake (in kcals) by rats with CHip, VP, and mPFC lesions and their combined controls (pair-fed and adlib) during post-recovery period which began after mean body weight for the lesioned groups achieved the level of their ad lib controls.

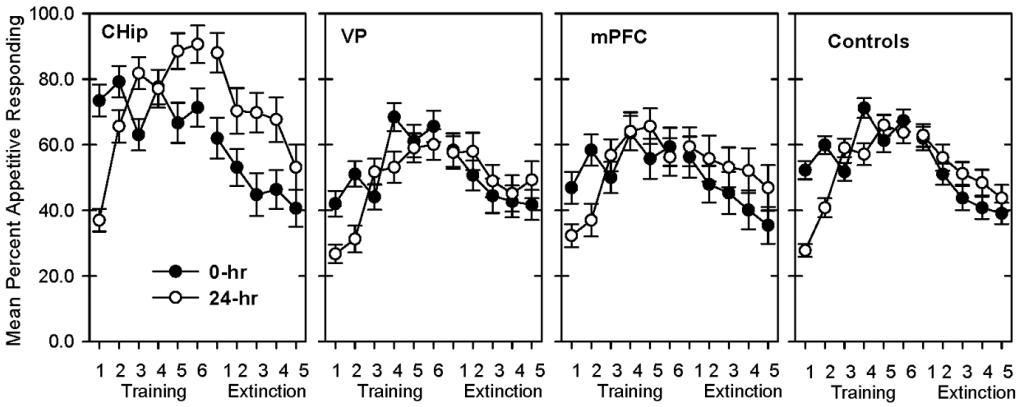

Figure 6.

Mean conditioned appetitive responding during training (data on left of each panel) and extinction (data on the right of each panel) on under 24-hr (reinforced during training and nonreinforced during extinction) and 0-hr (nonreinforced during training and extinction) food deprivation by rats with CHip (leftmost panel), VP (left-center panel), and mPFC (right-center panel) lesions and their combined (pair-fed controls (rightmost panel).

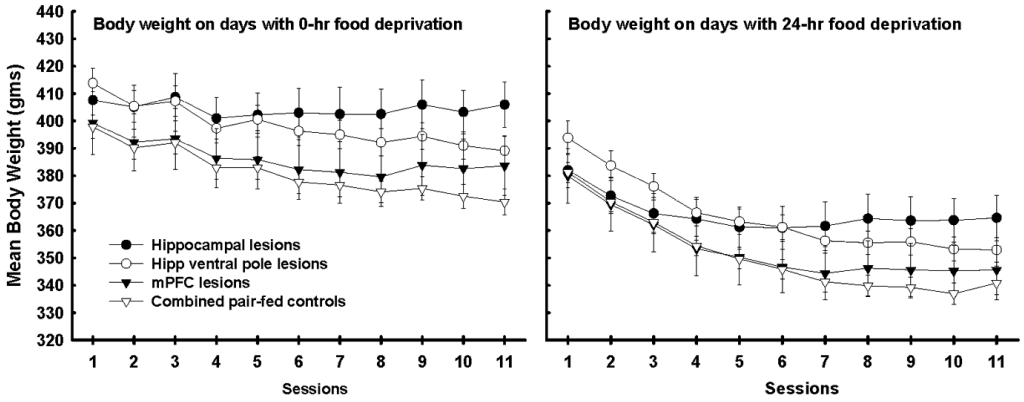

Figure 7.

Mean body weight prior to training (sessions 1-6) and extinction (sessions 7-11) sessions under 0-hr and 24-hr food deprivation for rats with CHip, VP, and mPFC lesions and their combined (pair-fed) controls. Although the rats received 0- and 24-hr deprivation sessions in a irregular order, in the figure mean body weights recorded for each group on 0-hr deprivation sessions (left panel) are segregated from those recorded on 24-hr food deprivation sessions (right panel).

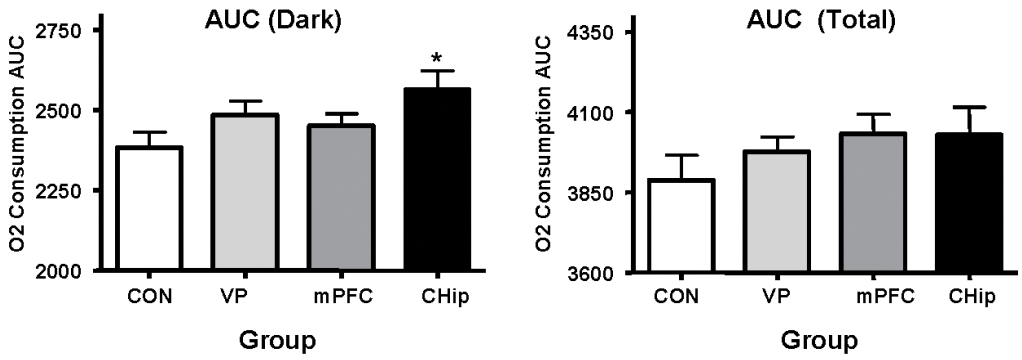

Figure 8.

Mean energy expenditure (O2 consumption, area under the curve (AUC) during the dark phase of the light/dark cycle (left panel) and in total (right panel) by rats with CHip, VP, and mPFC lesions and controls.

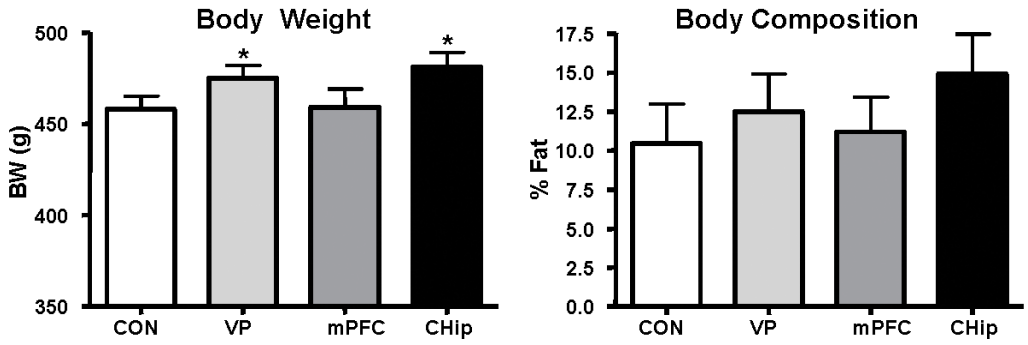

Figure 9.
Mean body weight (left panel) and mean body adiposity (right panel) approximately 150 days post-surgery by rats with CHip, VP, and mPFC lesions and controls.

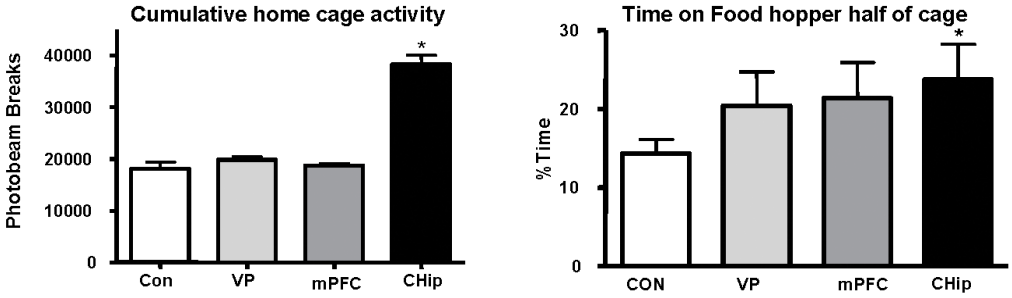

Figure 10.

Mean behavioral activity (left panel) and mean percent time spent on the half of the chamber where the food hopper was located (right panel) during the dark phase of the light/dark cycle by rats with CHip, VP, and mPFC lesions and controls.