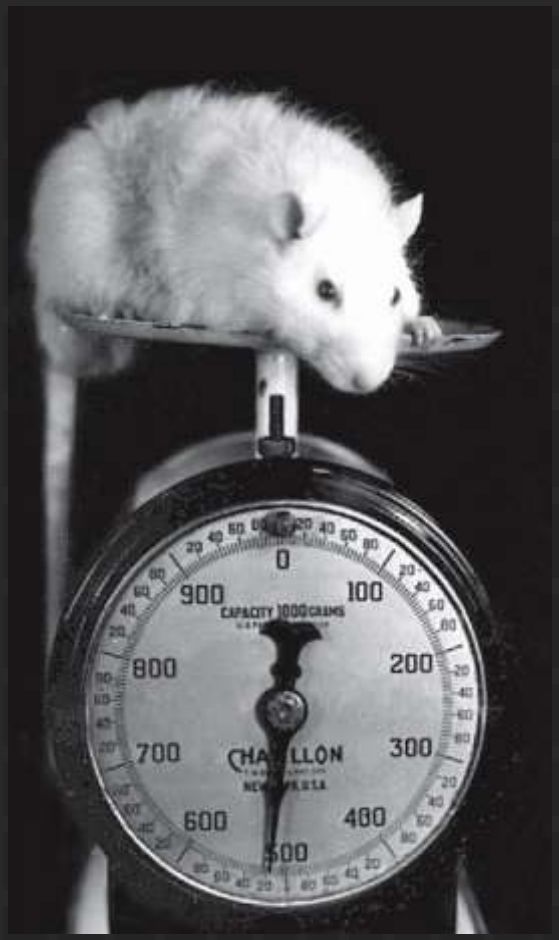
Mohr, Wchnschr ges Heilk 1840: 565



HYPOTHALAMIC CONTROL OF FOOD INTAKE IN RATS AND CATS*

BAL K. ANAND† AND JOHN R. BROBECK

Marked variations in food intake have been described in various species following injury to certain parts of the hypothalamus, including an increased food intake or hyperphagia caused by lesions in the medial hypothalamus, especially lesions in or ventrolateral to the ventromedial nucleus; this hyperphagia leads to obesity.[1-5, 11-13, 17, 18] A decrease or complete inhibition of food intake has also been reported as an incidental finding in animals with hypothalamic lesions, by Hetherington and Ranson[10] in rats, and by Clark, Magoun, and Ranson[14] during their study of temperature regulation in cats. Similar observations were also made in cats by Ingram, Barris, and Ranson,[9] by Ranson[15] in monkeys, and by Anand and Brobeck[1] in certain rats which were being prepared for studies of food intake and activity. The present investigation, therefore, was undertaken as an attempt to localize in the hypothalamus the areas the destruction of which leads to diminution or failure of eating with emaciation, as destruction of certain other areas leads to overeating and obesity. As a result of these studies a small, well-localized area has been found in the lateral hypothalamus; the bilateral destruction of this area is followed by a complete absence of spontaneous eating.[1] This area has been tentatively designated as a "feeding center." An attempt has also been made to discover whether there is any correlation between different areas of the hypothalamus in the regulation of food intake.

MATERIALS AND METHODS

In a series of 94 female albino rats of the Sprague-Dawley strain, electrolytic lesions were placed in different areas of the hypothalamus with the aid of the Horsley-Clarke instrument as adapted by Clark[6] for use on the rat. Evipal was used for anesthesia (12 mg./100 g. body weight). The lesions were made with a unipolar electrode, by a direct current for 15 seconds, its intensity ranging from 0.8 to 2 milliamperes depending upon the size of the lesion desired. It should be noted here that after the milliammeter had been calibrated properly, the lesions produced with a current of 2 milliamperes were invariably found to be much larger than those reported by Brobeck, *et al.*,[2] and by Hetherington and Ranson[10, 11] with the same current.

For placing small, well-localized lesions, the hypothalamus was divided according to the Horsley-Clarke coördinates into discrete points which were separated from each other by 1 mm. in the rostro-caudal planes, and by ½ mm. in the lateral or parasagittal planes (See Figure 18 and Table 2, below). The area between the level of the para-

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Hypothalamic Obesity: The Myth of the Ventromedial Nucleus

Abstract. Lesions restricted to the ventromedial nucleus of the hypothalamus were neither necessary nor sufficient for, and did not contribute to, the production of hypothalamic obesity. Hypothalamic lesions and knife cuts that do produce obesity damage the nearby ventral noradrenergic bundle or its terminals.

For over 30 years the ventromedial nucleus of the hypothalamus (VMN) has been linked in theory to the suppression of eating. There have been many reports of hyperphagia and obesity after destruction of the VMN (*1*). Both neurophysiological and anatomical evidence for connections between a presumed VMN satiety center and a lateral hypothalamic feeding center have been reported (*2*).

However, there is evidence that the overeating and obesity that once seemed associated with destruction of the VMN is not due to VMN damage per se, but rather to destruction of the nearby ventral noradrenergic bundle (*3*). The ventral noradrenergic bundle ascends from brainstem nuclei to innervate limbic areas, including several hypothalamic loci, but sends relatively few terminals to the VMN (*4*).

That VMN damage itself contributes to hypothalamic obesity is open to question. Lesions of the VMN that are produced by radio-frequency currents fail to produce obesity (*5*). Closer examination of the literature reveals that the few lesions caudal or lateral to the VMN, parasagittal knife cuts rostrolateral to the VMN, and midbrain lesions can all produce obesity even though the VMN is left intact (*1, 6*).

I now report that even under optimal testing conditions lesions restricted to the VMN, even iron depositing lesions (*5*), produce neither overeating nor obesity. The VMN lesions cause obesity only when they overflow the VMN, and the magnitude of the obesity is proportional to the amount of overflow.

Female albino rats ($N = 119$) were allowed free access to a highly palatable high fat diet (*7*) and tap water. Lesions were produced by passing an anodal direct current through platinum-iridium, stainless steel, or iron wire electrodes. The lesions were all aimed at the rostral tip of the VMN, with the use of stereotaxic coordinates that had previously been associated with rapid weight gains (*8*).

For the initial series of rats the bilateral lesions were produced by a current of 2 ma for 20 seconds (40 milli-

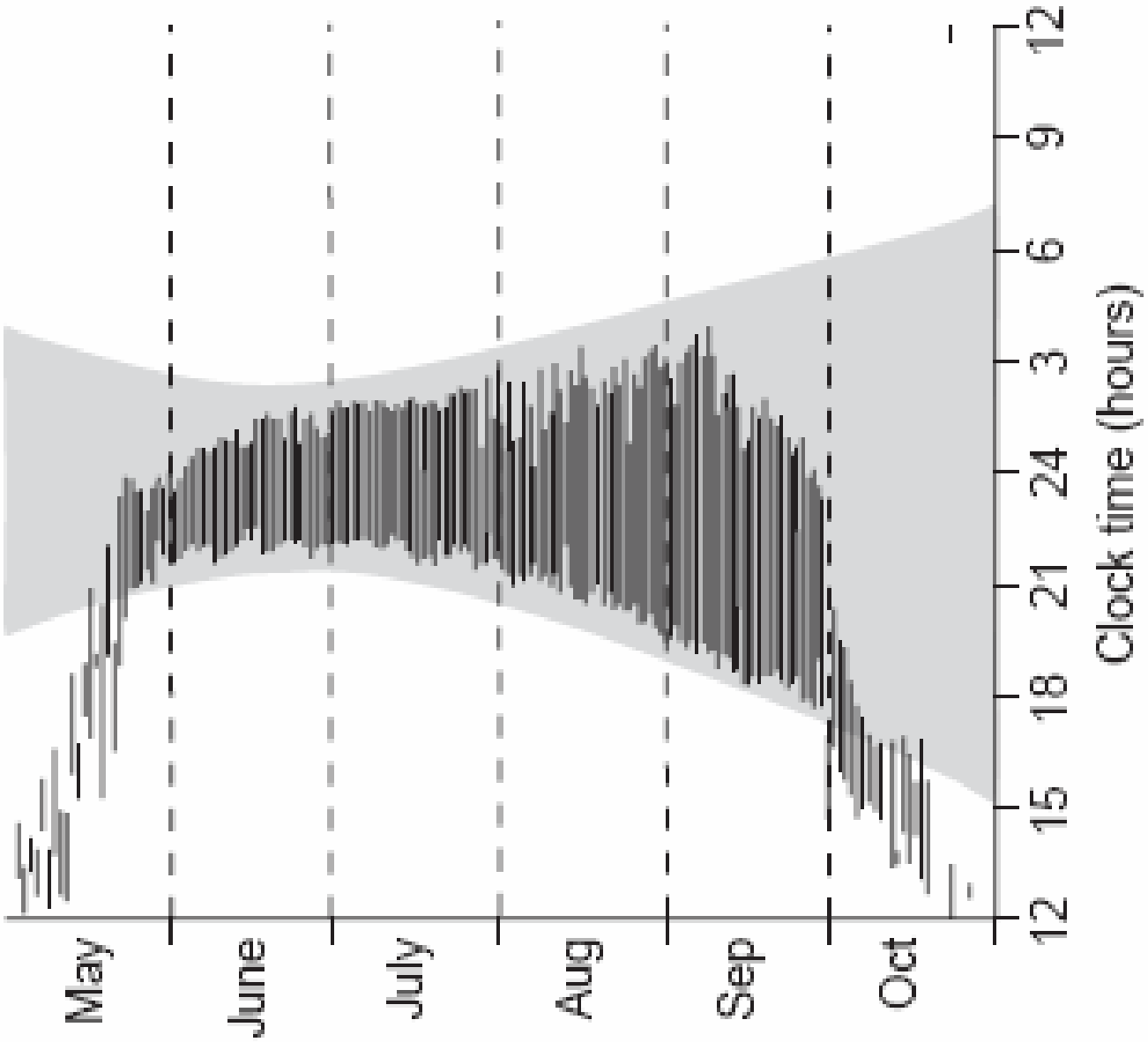
The failure to produce obesity with lesions completely restricted to the VMN occurred despite the use of all of the parameters that maximize postlesion weight gains, that is, female rats (*7*), heavy iron deposits from anodal current delivered through iron or steel electrodes (*5*), and a palatable high fat diet (*7*).

The brain areas destroyed by the 55 smallest lesions were compared. There was a common area for the lesions of the five rats with the greatest weight gains (9.0 to 12.6 g/day). These most effective of the smallest lesions all destroyed an area immediately rostral to the rostral tip of the VMN (Fig. 1A). It is precisely across this area that a group of noradrenergic fibers crosses the midline within the suprachiasmatic decussation. These noradrenergic fibers are thought to derive from the ventral ascending noradrenergic bundle (*4*). Small lesions located more dorsally or more caudally were less effective (Fig. 1, B and D) (*12*).

Larger lesions produced far greater weight gains. If the thalamus and the nigro-striatal dopamine pathway at the extreme lateral edge of the hypothalamus (*4*) were spared, then the bigger the lesion, the greater the initial rate of weight gain. For example, a large platinum electrode lesion spared the VMN but produced rapid weight gains

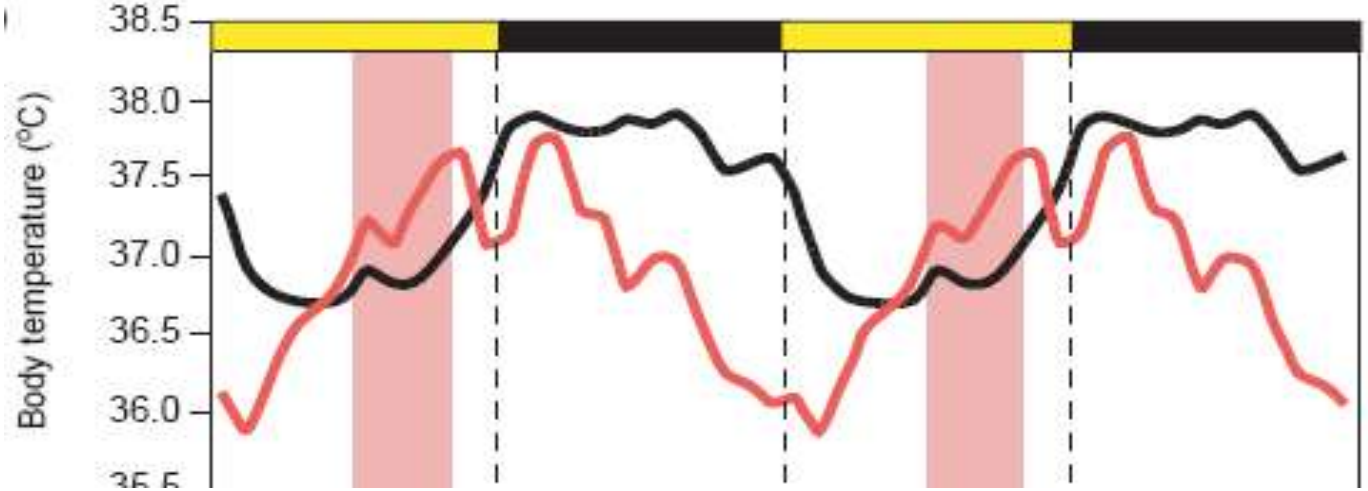
Food as *Zeitgeber*

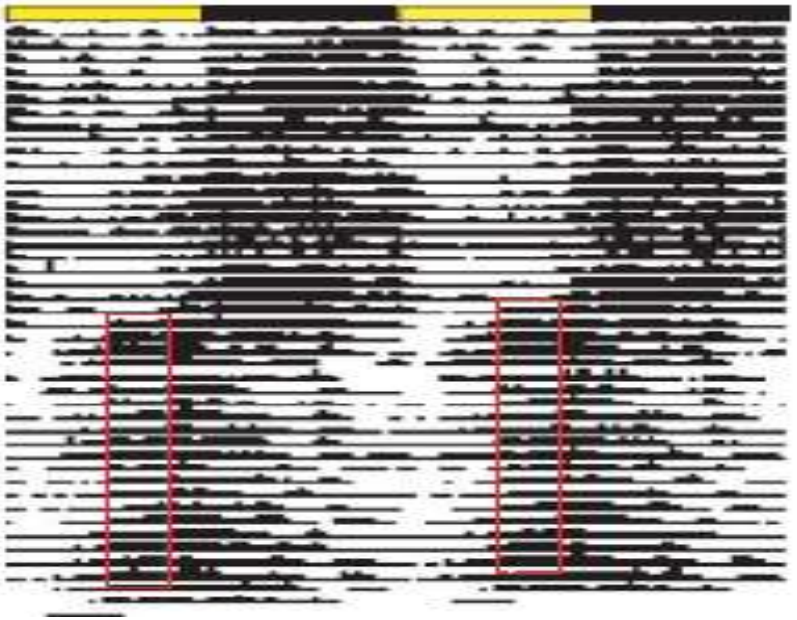
Circadian rhythms in Finnish bats are responsive to environmental stimuli



Nyholm H, Ann.Zool.Fenn. 2, 77–123 1955

Phase shift in food-seeking activities in response to restricted feeding: Where is this FEO?





The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms

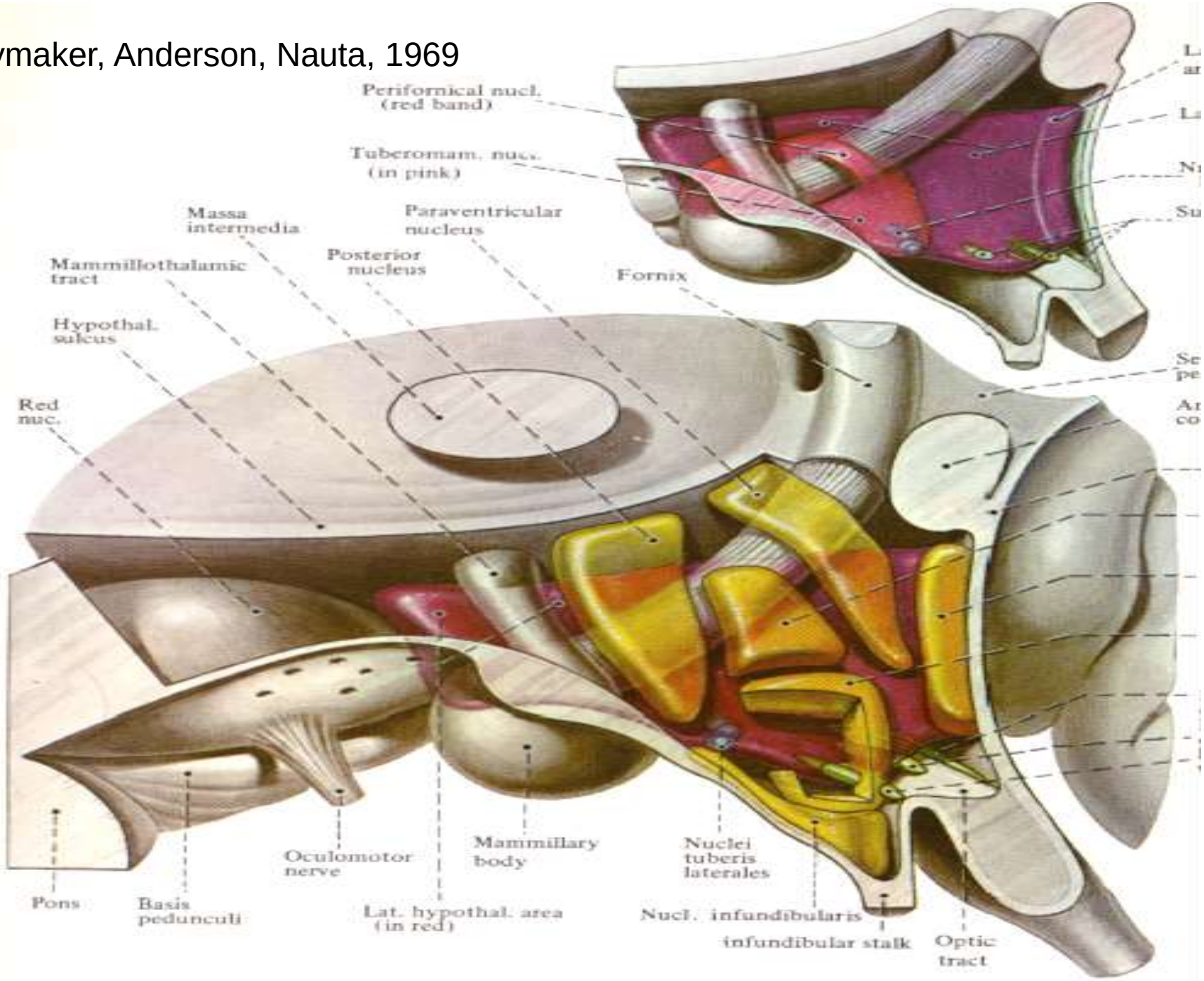
Joshua J Gooley, Aschley Schomer, Clifford B Saper

Volume 9 Number 3 March 2006 Nature Neuroscience , 398 - 407

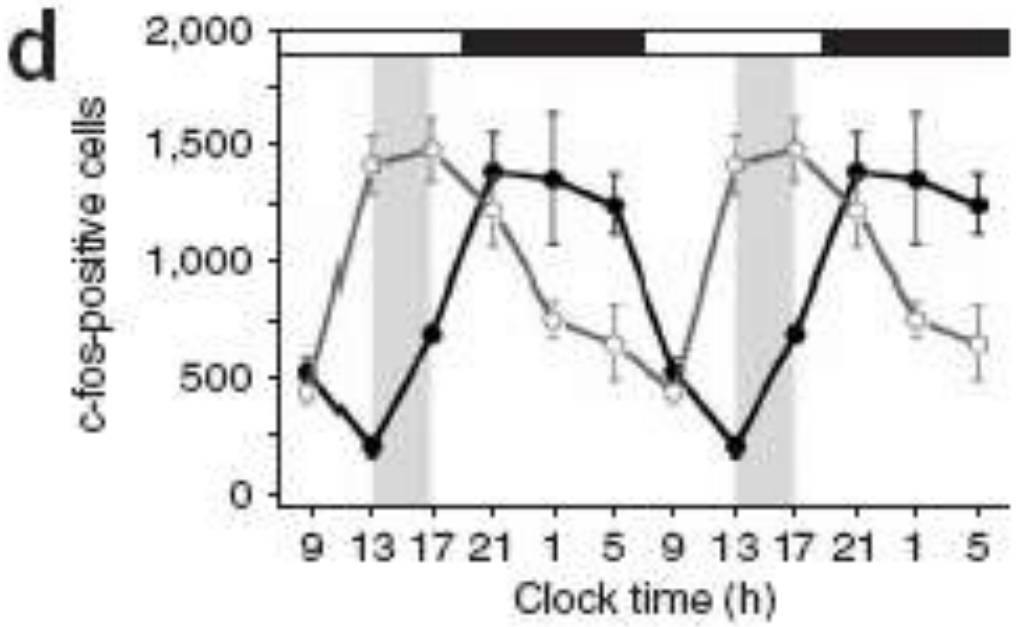
Monell Neuroscience Journal Club March 24, 2006

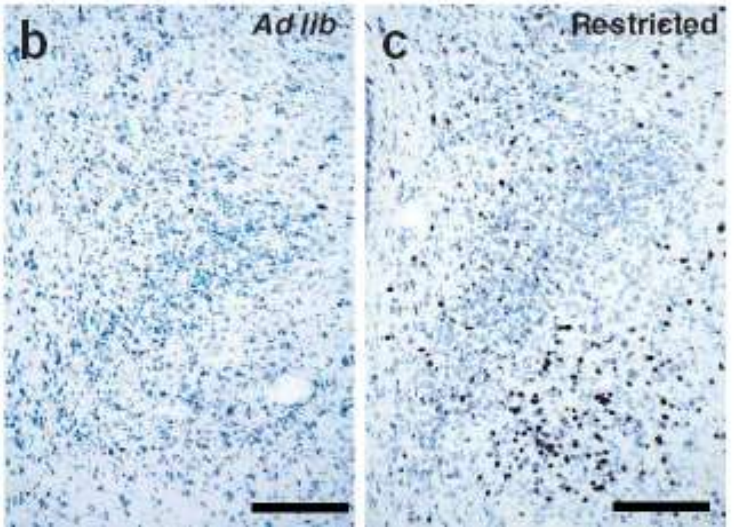
Discussion: Dr. Arun Chaudhury

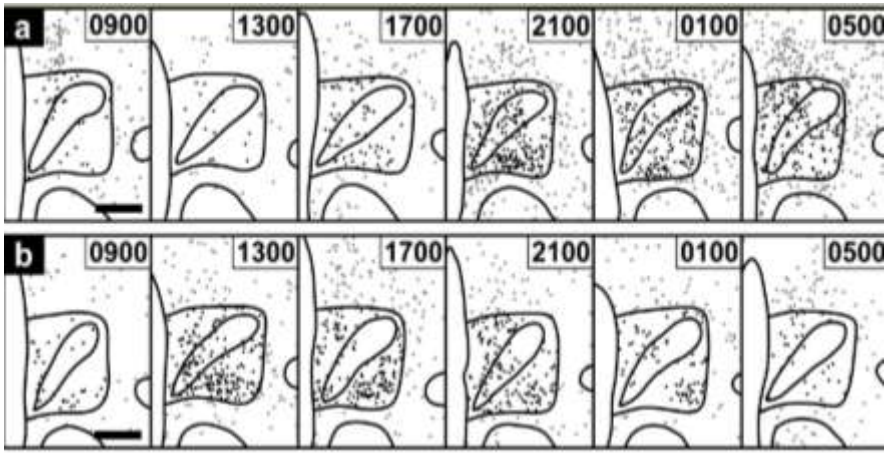
Haymaker, Anderson, Nauta, 1969

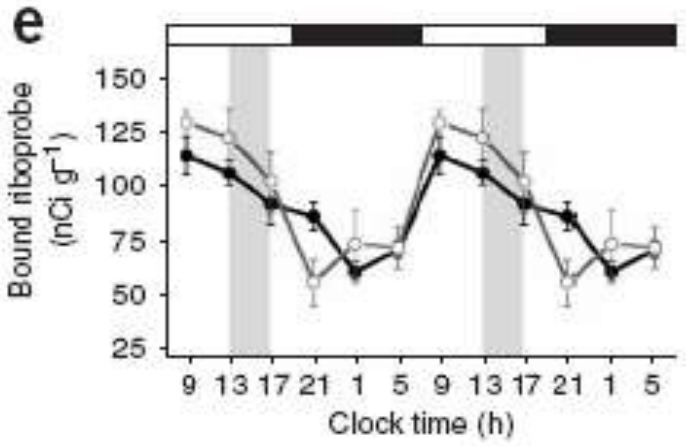


Restricted daytime food availability shifts daily rhythm of neuronal activity in DMH

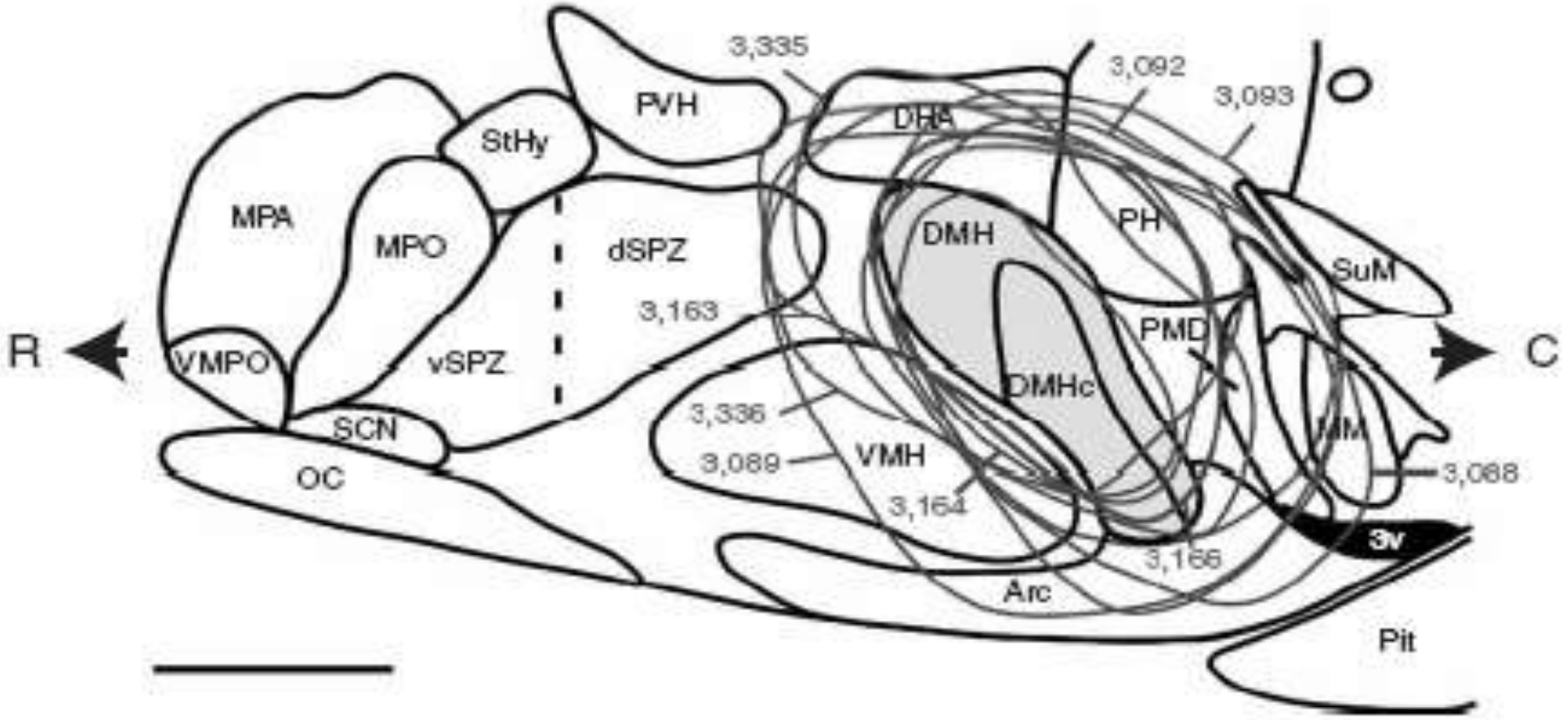




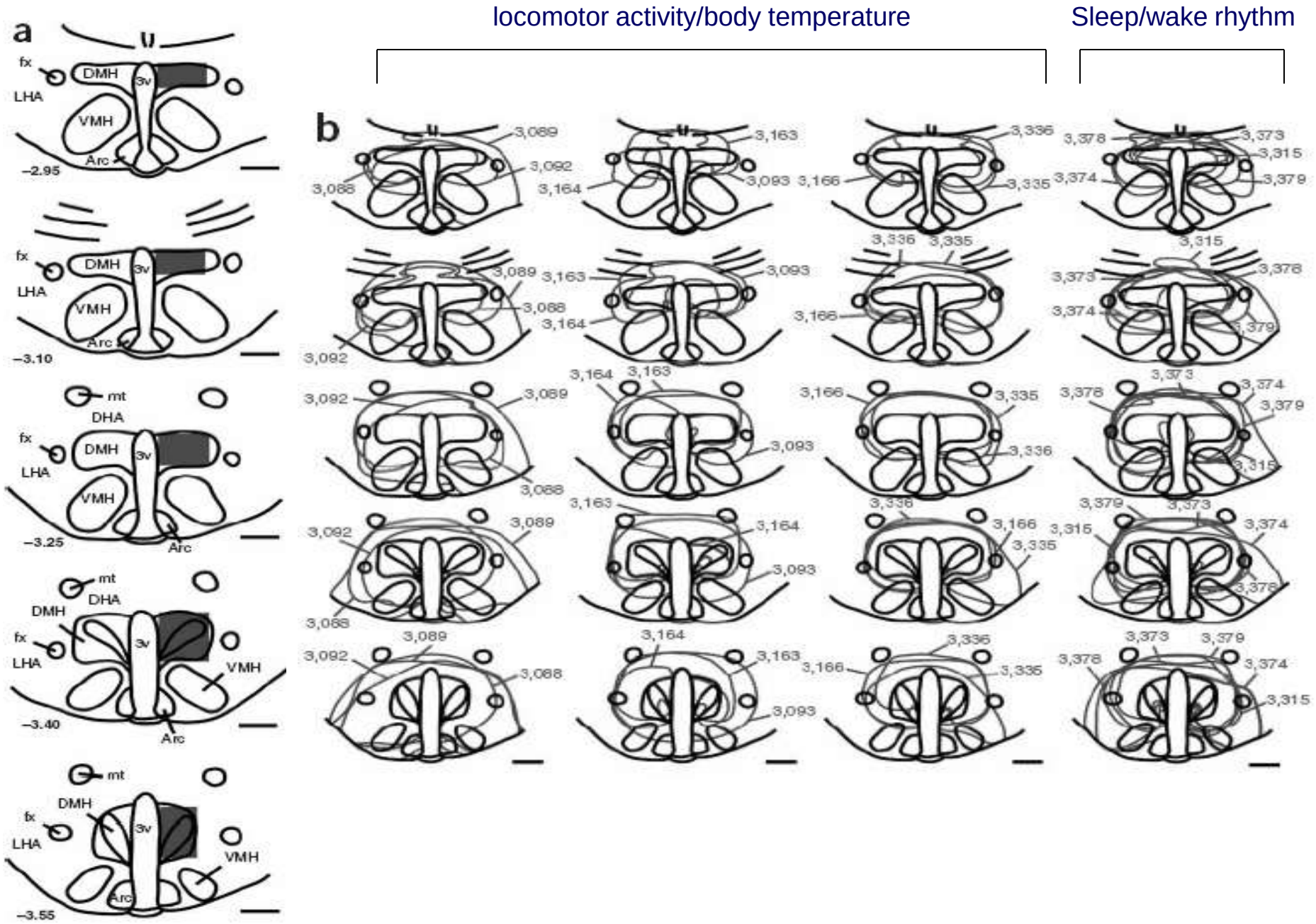




Sagittal reconstruction of rat hypothalamus



Ibotenic acid-induced DMH lesion (>75% cell loss)



How does a lesioned DMH look like?

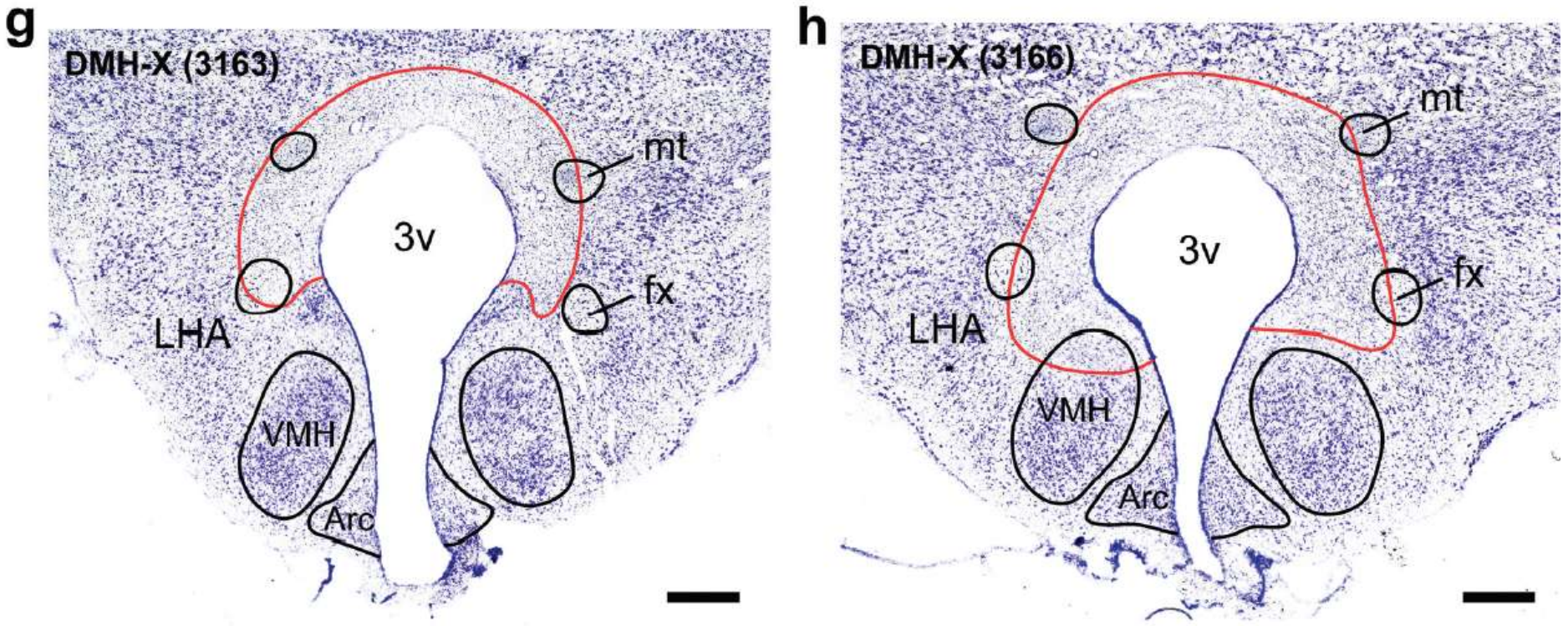
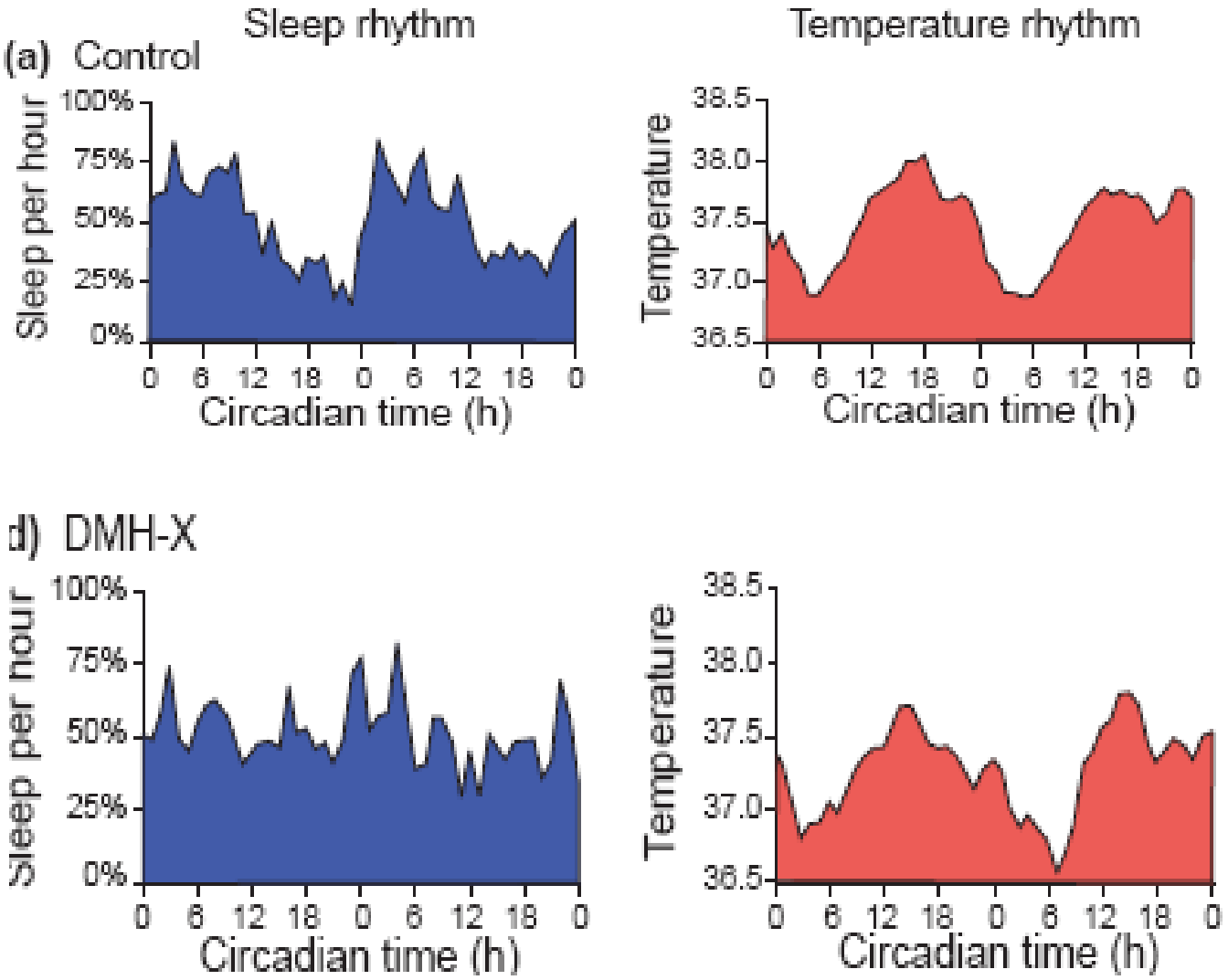


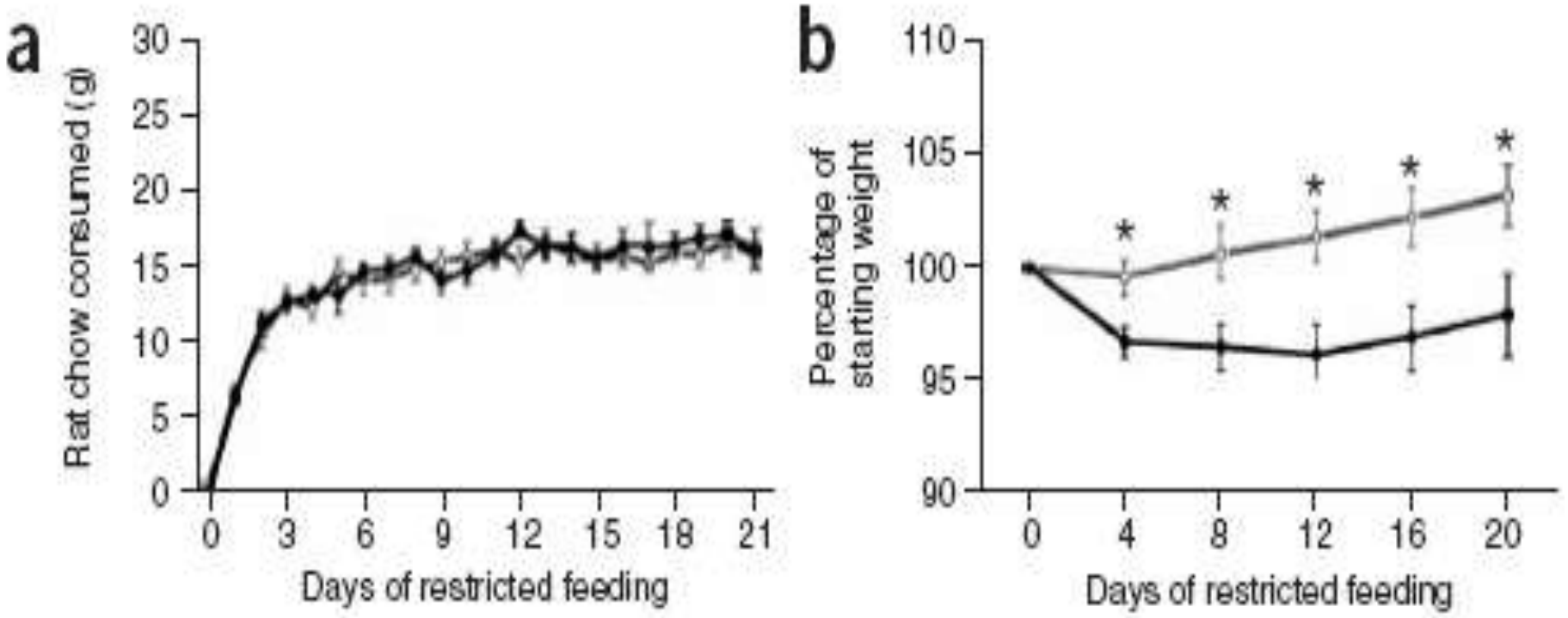
Table 1 Comparison of behavior and physiology in unlesioned and DMH-lesioned rats during *ad lib* feeding and restricted feeding

Measurement	Feeding	Unlesioned	DMH Lesions	*t*-test, *P* value
Daily locomotor activity counts	*ad lib*	927.0 ± 76.7	469.1 ± 48.8	1.5×10^{-4}
	restricted	635.2 ± 49.7	417.6 ± 44.2	4.5×10^{-3}
	t-test, P value	3.8×10^{-4}	0.023	
Preprandial locomotor activity counts (10:00 a.m. to 1:00 p.m.)	*ad lib*	43.4 ± 5.2	32.9 ± 4.6	0.15
	restricted	74.1 ± 6.7	40.8 ± 5.9	3.5×10^{-3}
	t-test, P value	5.2×10^{-5}	0.050	1.7×10^{-3}
Percent daily locomotor activity occurring during daytime	*ad lib*	32.3 ± 1.8	36.8 ± 1.5	0.074
	restricted	65.1 ± 2.2	44.5 ± 2.3	6.0×10^{-6}
	T-test, P value	3.6×10^{-6}	6.4×10^{-3}	
Mean daily body temperature	*ad lib*	37.50 ± 0.039	37.26 ± 0.031	1.9×10^{-4}
	restricted	37.07 ± 0.040	36.97 ± 0.030	0.054
	t-test, P value	3.1×10^{-6}	1.0×10^{-6}	
Body temperature rhythm magnitude (peak minus trough)	*ad lib*	1.24 ± 0.064	1.33 ± 0.067	0.34
	restricted	1.66 ± 0.060	1.67 ± 0.070	0.92
	t-test, P value	1.3×10^{-3}	2.0×10^{-3}	
Preprandial body temperature magnitude, °C above the nadir	*ad lib*	0.064 ± 0.017	0.078 ± 0.023	0.648
	restricted	0.62 ± 0.043	0.032 ± 0.022	2.3×10^{-7}
	t-test, P value	1.4×10^{-6}	0.21	
Body temperature rhythm acrophase	*ad lib*	12:01 a.m. ± 0:10	12:47 a.m. ± 0:09	4.4×10^{-3}
	restricted	7:25 p.m. ± 0:08	11:28 p.m. ± 0:14	3.7×10^{-9}
	t-test, P value	5.6×10^{-10}	2.9×10^{-9}	
Daily wakefulness (min)	*ad lib*	684.8 ± 20.5	672.3 ± 19.7	0.67
	restricted	685.6 ± 17.2	629.2 ± 27.3	0.13
	t-test, P value	0.97	0.23	
Preprandial wakefulness (min; 10:00 a.m. to 1:00 p.m.)	*ad lib*	39.9 ± 3.2	59.5 ± 2.2	1.4×10^{-3}
	restricted	101.6 ± 4.5	70.3 ± 5.6	2.7×10^{-3}
	t-test, P value	1.7×10^{-4}	0.085	
Percent daily wakefulness occurring during daytime	*ad lib*	31.2 ± 0.76	41.8 ± 0.47	1.0×10^{-5}
	restricted	52.1 ± 1.6	40.9 ± 1.9	2.3×10^{-3}
	t-test, P value	5.7×10^{-4}	0.66	
Rat chow consumed (g)	*ad lib*	22.2 ± 0.57	19.0 ± 0.91	0.019
	restricted	15.9 ± 0.56	15.5 ± 0.73	0.70
	t-test, P value	1.9×10^{-5}	0.14	

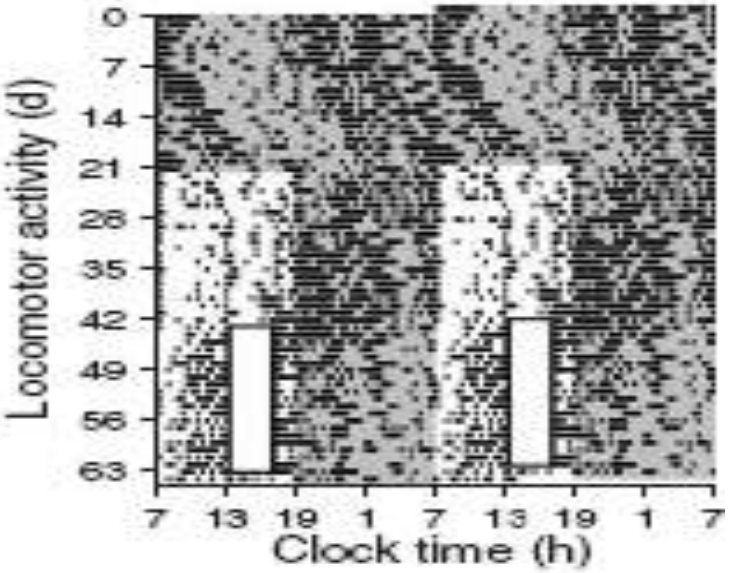
Differential regulation by hypothalamic circadian integrator



Rats (Unlesioned/DMH-X) show stable maintenance of body weight during restricted feeding

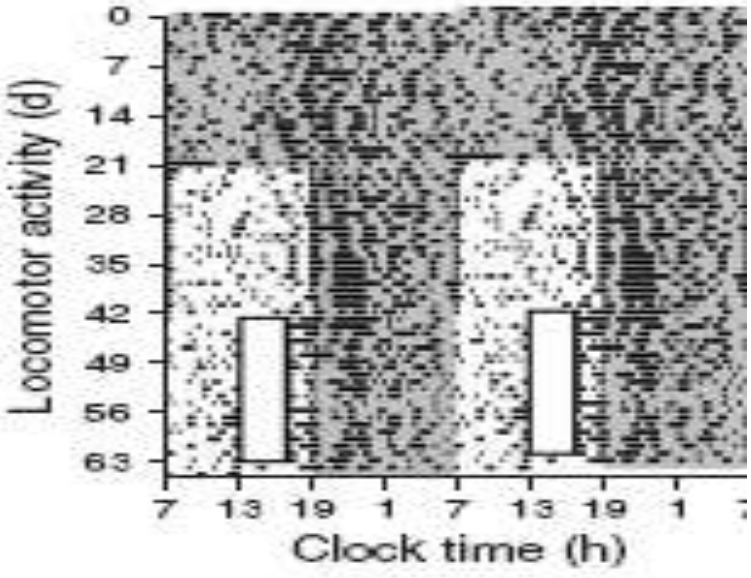


Raster double-plot of locomotor activity

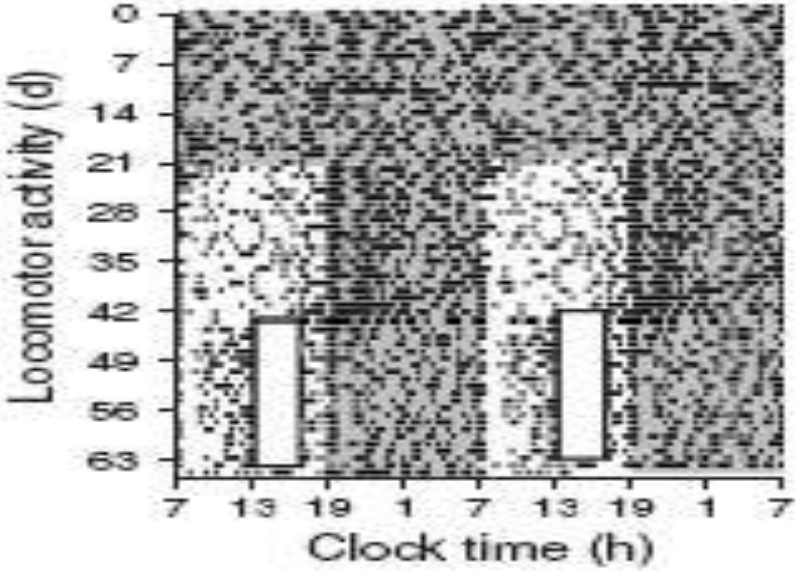


C/3,165,
Unlesioned

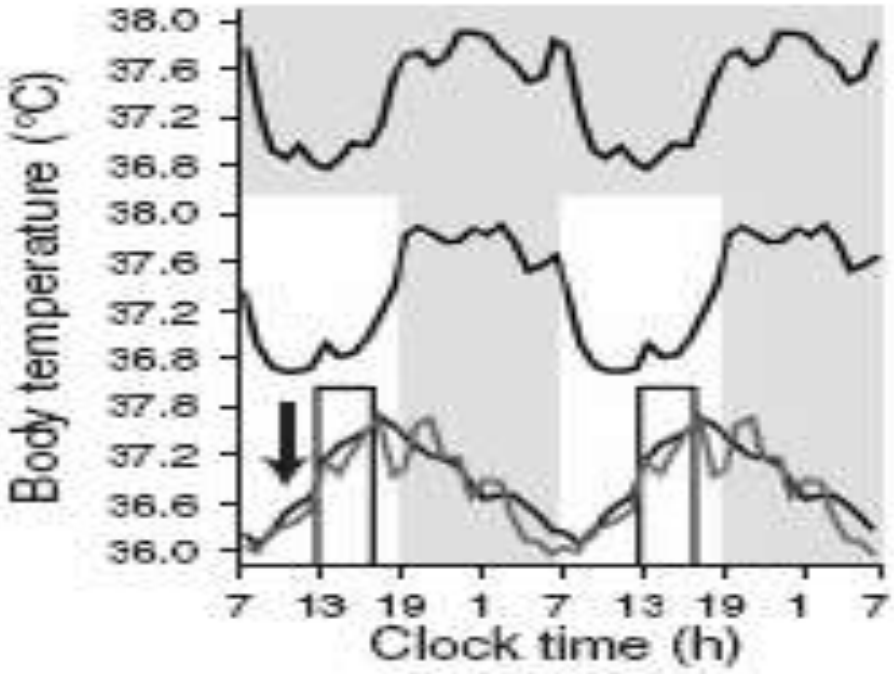
C/3,163, DMH-X



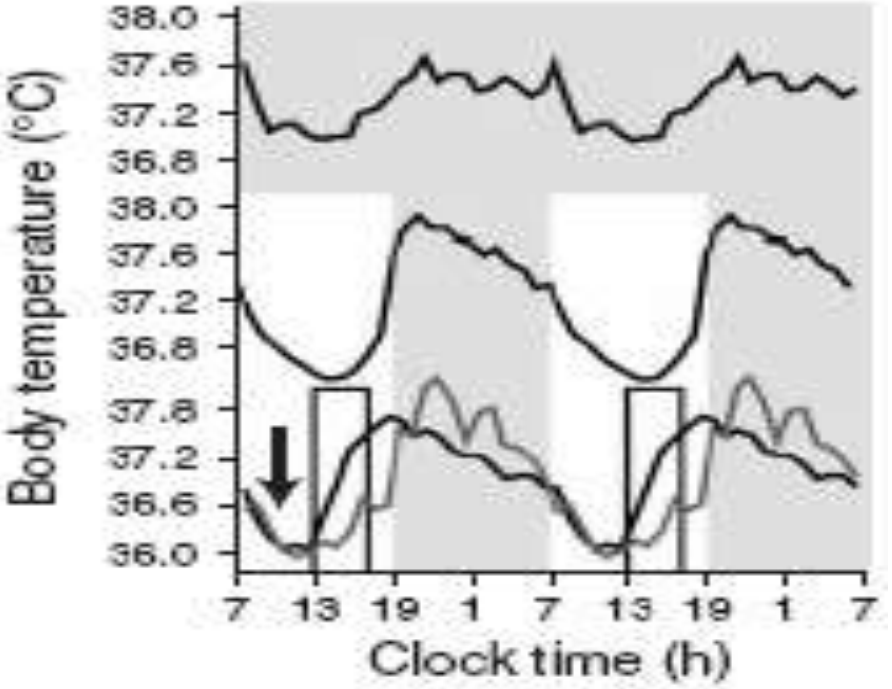
C/3,166, DMH-X



DMH-X block preprandial rise in body temperature



C/3,165, Unlesioned

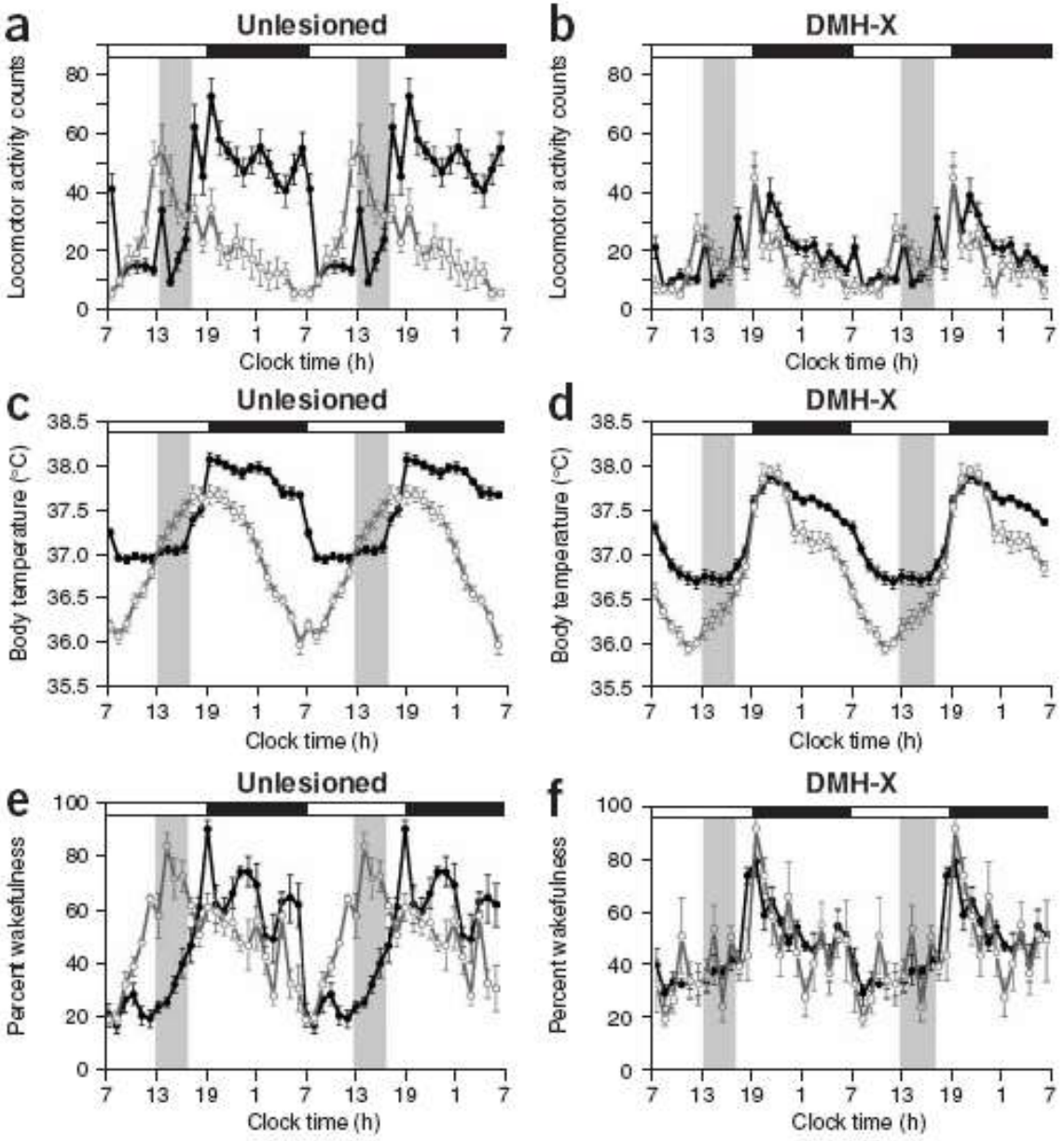


C/3,166, DMH-X

Learning component in DMH-induced entrainment of food anticipatory behavior

3 wks restricted feeding

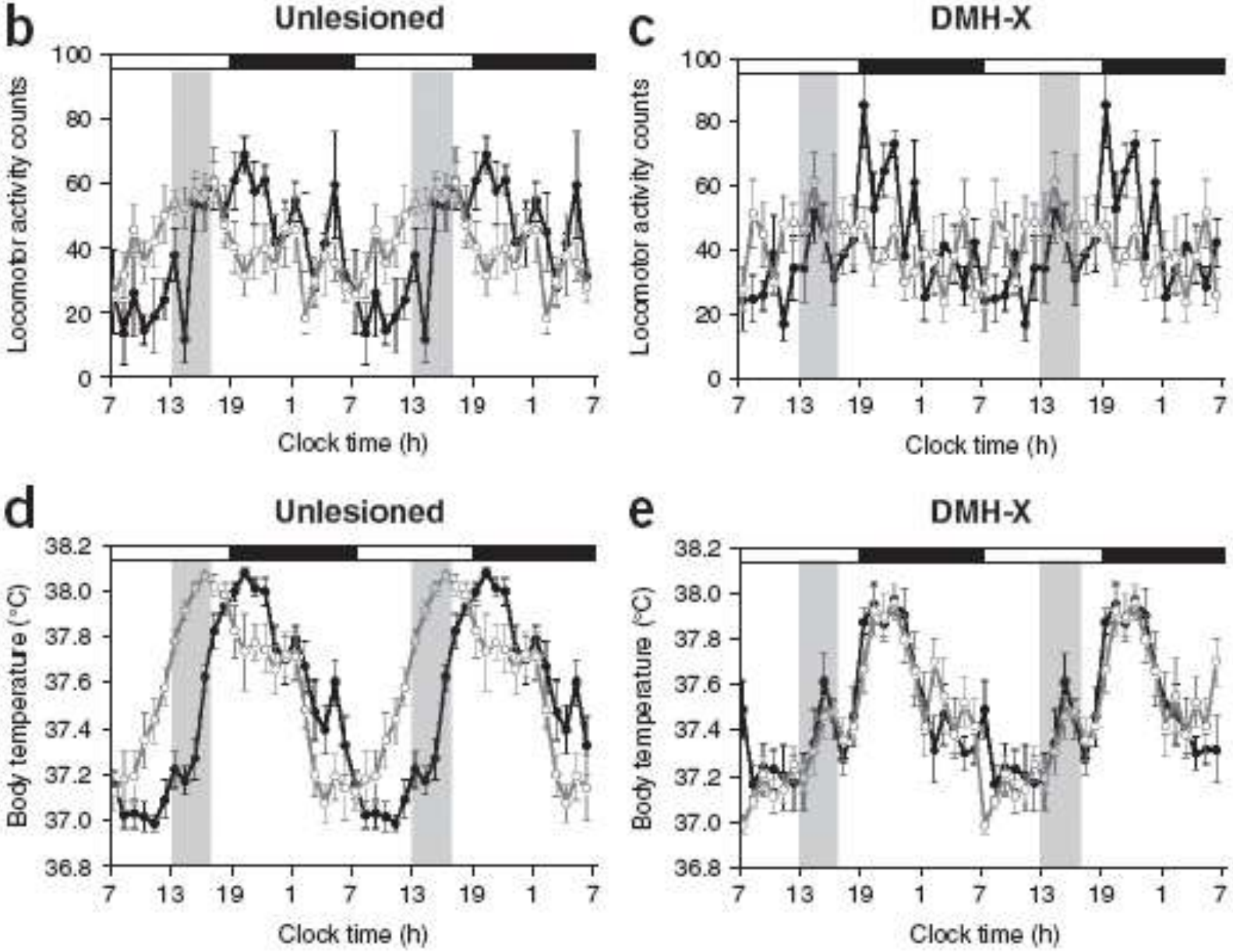
Fd deprivation 2 d



DMH-induced entrainment is light-independent & DMH-X abolishes food entrainment

3 wks restricted feeding

Fd deprivation 2 d **in constant darkness**



Fd entrainment correlates with remaining DM neuronal count

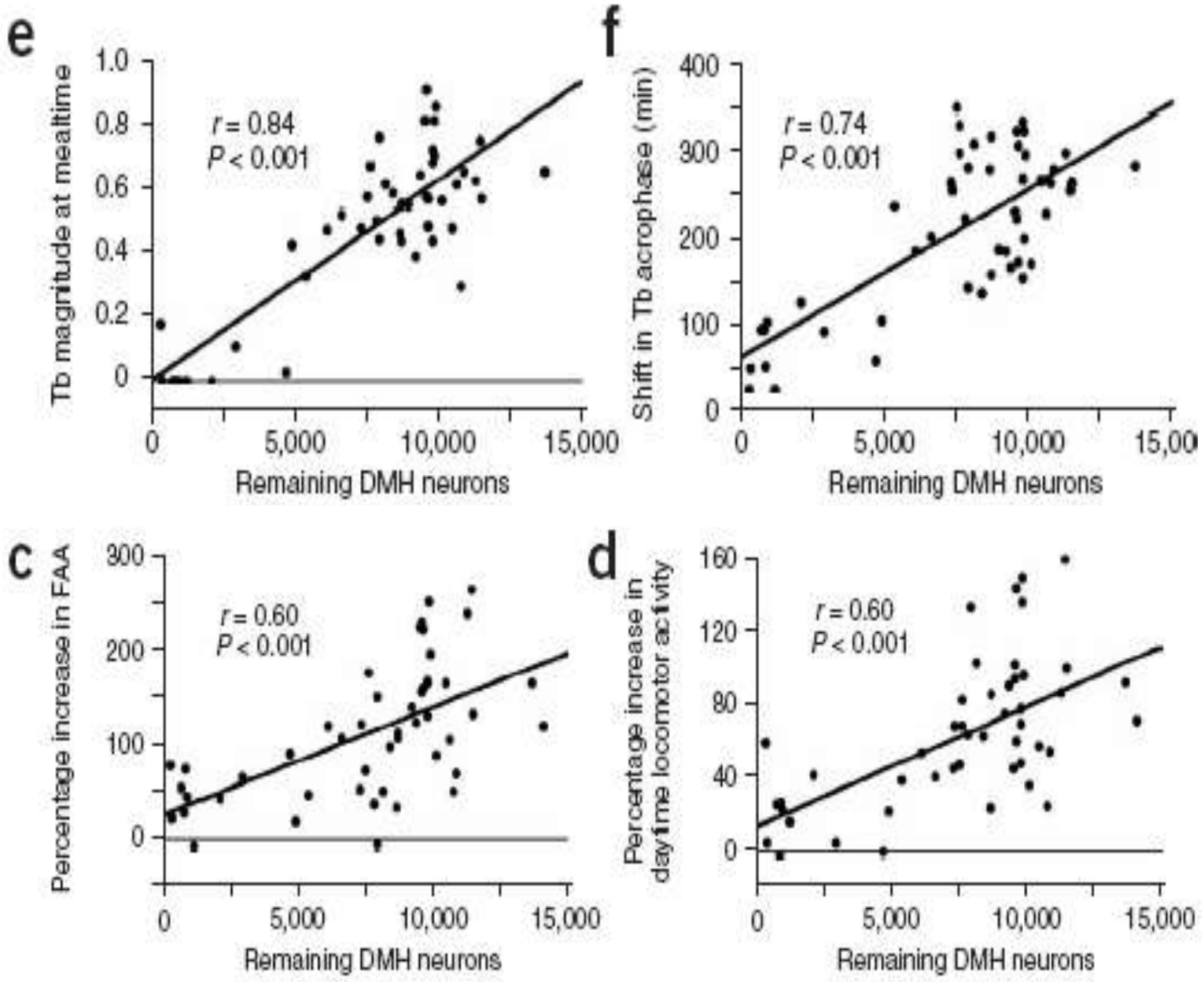
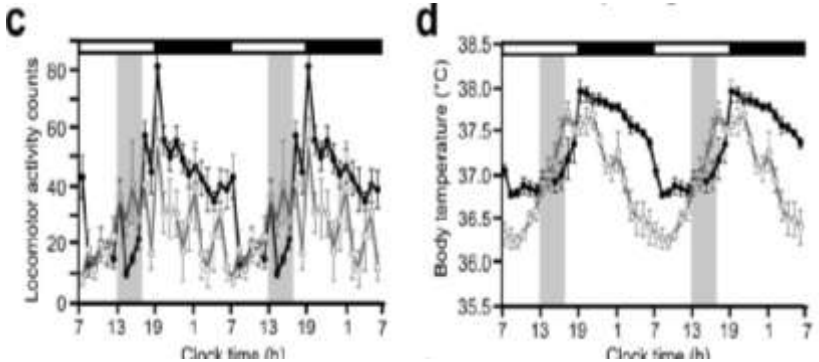
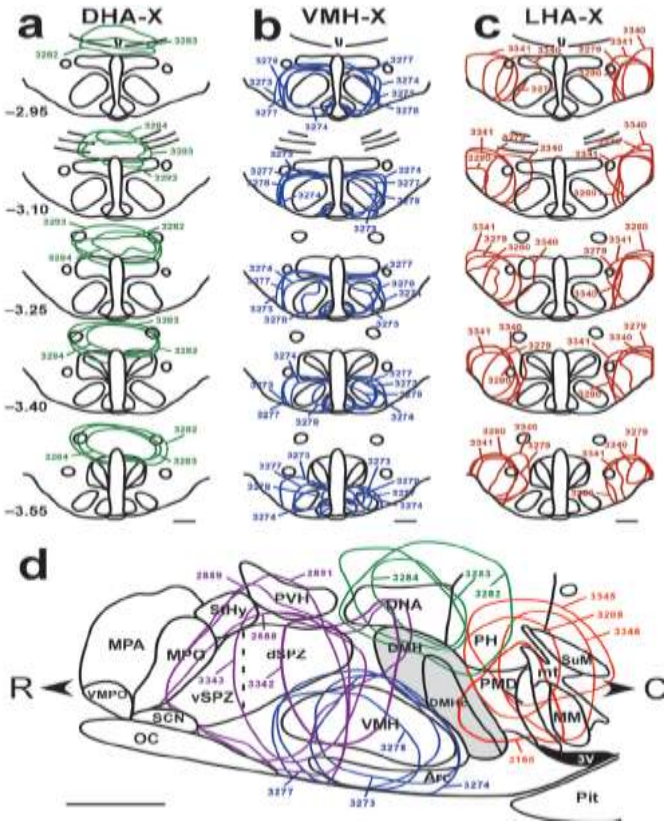


Table 2 Comparison of food entrainment in unlesioned rats, DMH-lesioned rats and control-lesioned rats

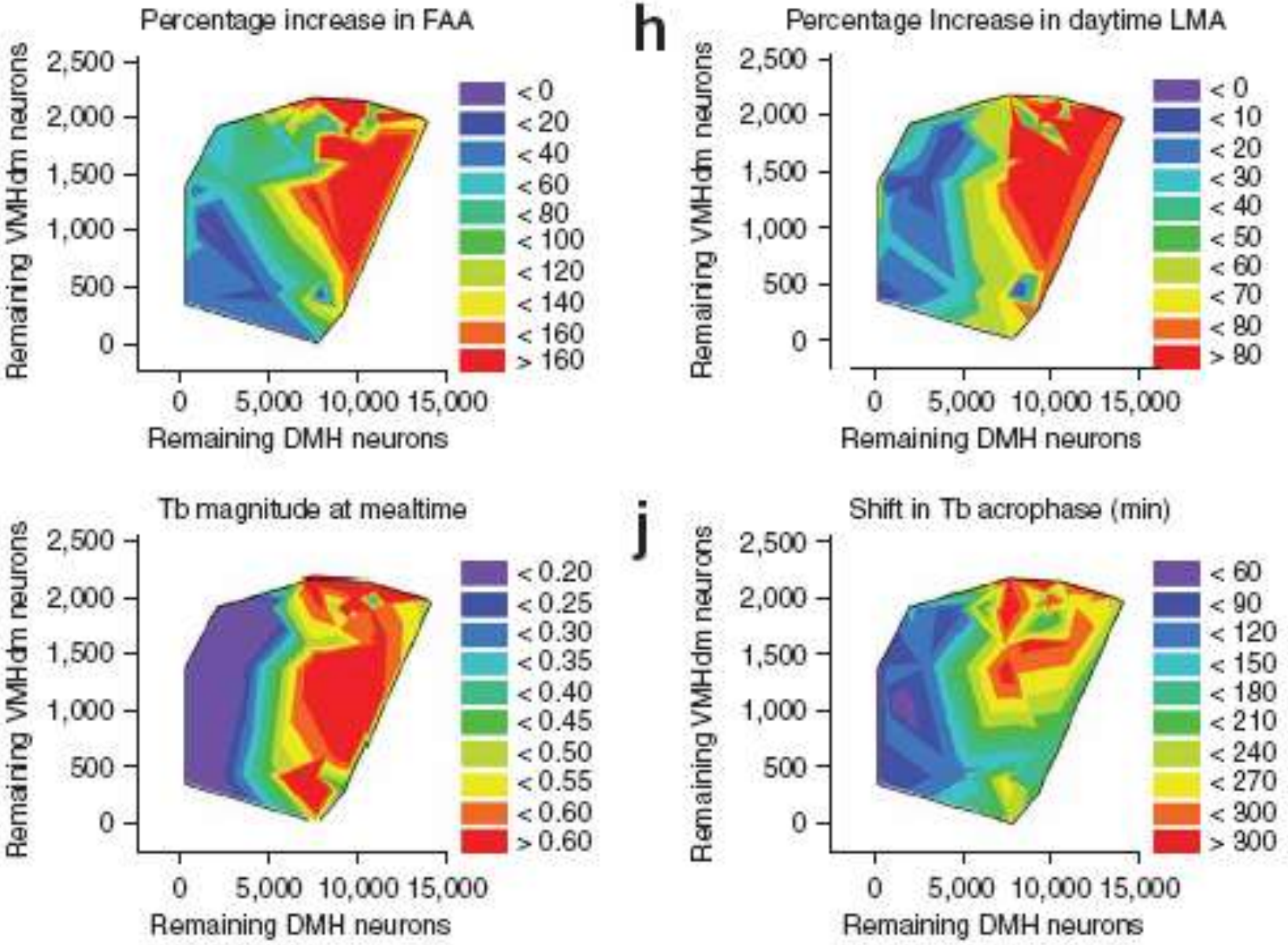
Measurement	Unlesioned	DMH-X	DHA-X	VMHdm-X	LHA-X	PH-X
Rats	10	9	3	6	4	4
Remaining DMH neurons	100 ± 4.2	10.5 ± 2.5	78.3 ± 5.6	74.8 ± 3.4	84.2 ± 1.7	85.9 ± 3.9
Food anticipatory activity	100 ± 12.0	26.5 ± 5.5	93.3 ± 9.6	57.9 ± 16.5	143.2 ± 16.7	77.7 ± 30.7
Preprandial body temperature	100 ± 7.0	5.1 ± 3.5	100.9 ± 5.0	96.0 ± 14.5	112.4 ± 8.9	88.3 ± 19.0
Phase shift in body temperature	100 ± 3.7	28.3 ± 4.3	78.0 ± 15.8	68.8 ± 19.2	99.5 ± 4.2	100.9 ± 0.9



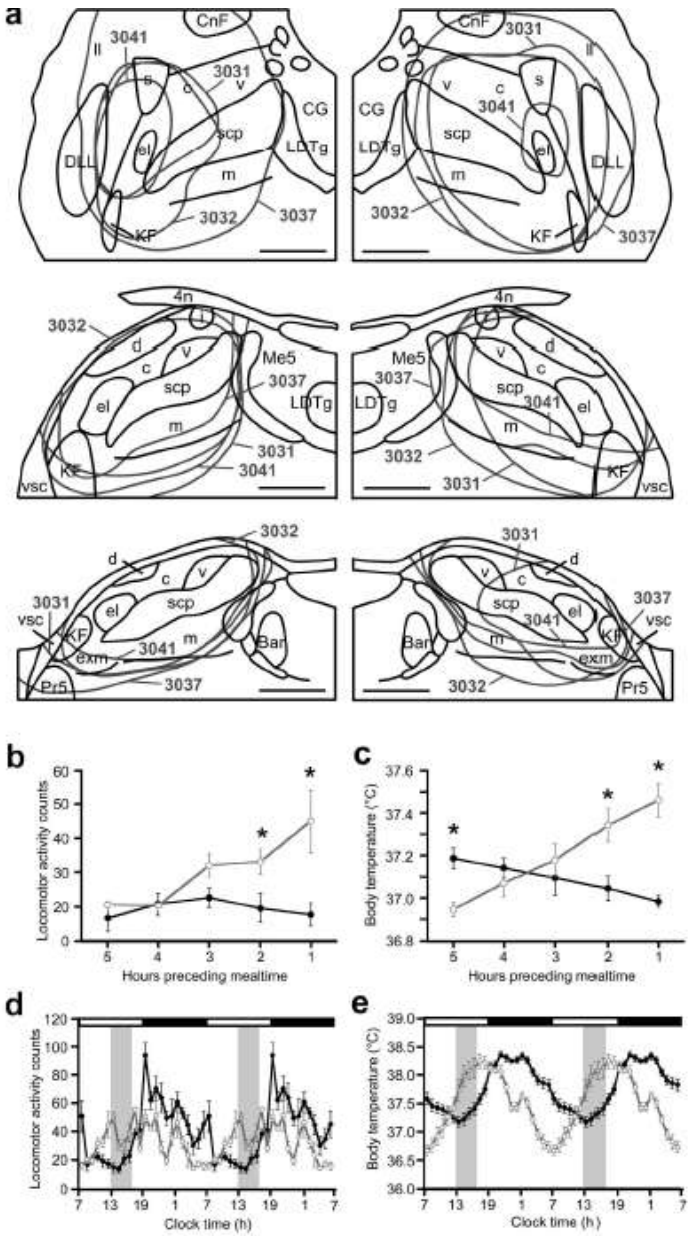
VMHdm-X & fd entrainment



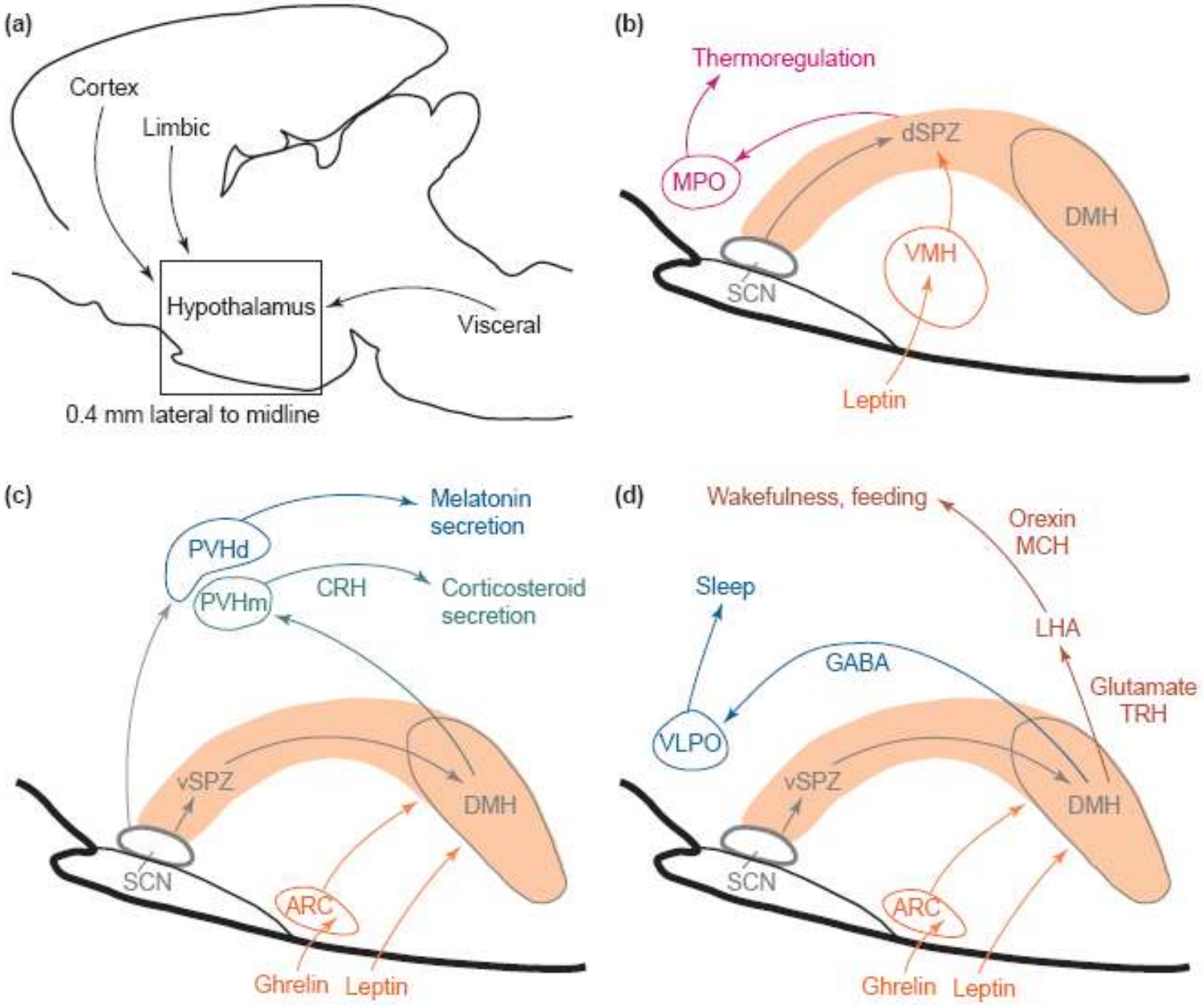
How faithful is the DMH-X?



Parabrachial nucleus-X does not block fd entrainment



Integration pathways for clock signals



The dilemma still hangs around: DMH as a critical player in SCN- and food entrainable rhythms