13

Cingulothalamic and Prefrontal Control of Autonomic Function

SHIRLEY L. BUCHANAN AND DONALD A. POWELL

Overview of Autonomic Connections and Training Paradigms

Well before the turn of the century, it was demonstrated that electrical stimulation of the cerebral cortex could elicit changes in autonomic systems (Eulenburg and Landois, 1876; Spencer, 1894). In the intervening years, many studies have suggested that dorsal anterior cingulate (area 24) and medial prefrontal cortices participate in such autonomic adjustments. This review begins with the background evidence that these areas mediate autonomic responses, the pathways that underlie such responses, and methodologies by which their role in learning may be studied. In subsequent sections, the contributions of cingulate and prefrontal cortices, and their related thalamic nuclei, to specific autonomic responses in the rabbit are reported as are their role in learned autonomic responses. Finally, specific connections and neurotransmitter mechanisms of these responses are considered in addition to their general biological relevance.

Types of Electrically Evoked Responses

Virtually every class of autonomic response has been elicited by stimulation of anterior cingulate cortex (ACC, i.e., area 24) and medial prefrontal cortex (PFC). Gastrointestinal motility (e.g., Bailey and Sweet, 1940; Kaada, 1951; Hurley-Guis and Neafsey, 1986), pupillary dilatation (Kaada, 1951; Smith, 1945; Ward, 1948) and constriction (Hodes and Magoun, 1942a,b; Kaada, 1951), thermoregulatory responses (Delgado and Livingston, 1948; Livingston et al., 1948; Blass, 1969; Kaada, 1951), and skin conductance changes (Darrow, 1937; Wilcott, 1968; Isamat, 1961; Langworthy and Richter, 1930) have been reported after such stimulation (see also Hoff et al., 1963; Delgado, 1960; Kaada, 1960; LeDoux, 1987). (This literature was reviewed in detail by Neafsey, 1990; Chapter 6 of this volume.) For the most part, these responses have not been explored in detail, and no consistent pattern has emerged regarding differential ACC and PFC control of them. However, cardiovascular responses (i.e., changes in heart rate and blood pressure) and respiratory changes have been more thoroughly explored and these data are discussed in detail later. The weight of the evidence, although not unequivocal, suggests that responses resembling those that are parasympathetic, with accompanying respiratory inhibition, are elicited from anterior cingulate cortex, while responses resembling those that are sympathetic, with concomitant respiratory increases, are elicited from subcallosal and orbital cortex (e.g., Kaada, 1960). This

Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook
Brent A. Vogt and Michael Gabriel, Editors
© 1993 Birkhäuser Boston

latter pattern of changes also can be elicited by stimulation of midline and mediodorsal (MD) thalamic nuclei (Buchanan and Powell, 1986).

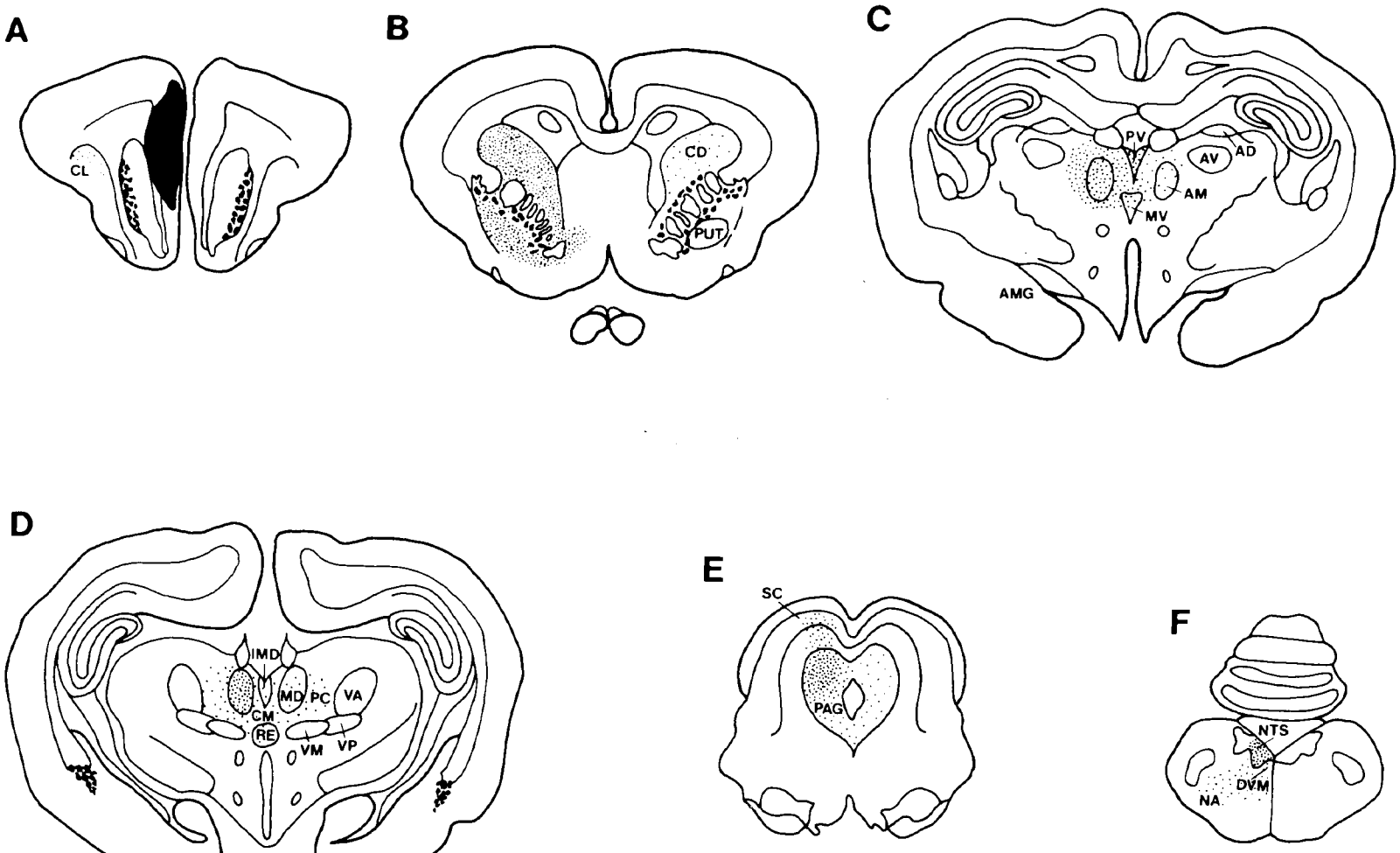
Cortical-Brainstem Connections

For some time it was thought that the pathways for producing visceral changes via stimulation of the cingulofrontal system were routed through the hypothalamus. For example, Lofving (1961) elicited depressor responses from ACC and pressor responses from the ventral subcallosal region (i.e., area 25) in the cat and reported that lesions of the lateral hypothalamus abolished these and other stimulation-evoked visceral changes. There is good reason to believe, as described in detail later, that Lofving's results may have been due to damage to fibers of passage rather than to intrinsic hypothalamic cells, although connections between the frontal cortex and the hypothalamus have been demonstrated in a number of species (e.g., Reep, 1984). Spencer's (1894) early research suggested a pathway between orbital cortex and the upper border of the pons, and Newman (1974), based on electrophysiological analysis, further suggested that there was perhaps a direct connection between PFC and the autonomic regulatory nuclei in the medulla.

The use of more refined tract tracing techniques of recent years has demonstrated that there are indeed direct projections of cingulate cortex and both the medial and lateral (i.e., insular) subdivisions of PFC of the rat to the dorsal motor nucleus of the vagus (DMV), solitary nucleus (SN), and the nucleus ambiguus (NA) of the medulla (Saper, 1982; Shipley, 1982; Terreberry and Neafsey, 1983; Van Der Kooy et al., 1982, 1984; Neafsey et al., 1986; Hurley et al., 1991). These connections have been demonstrated in the rabbit and are shown in Figures 13.1 and 13.2. Figure 13.1 shows anterograde labeling after an injection of wheat germ agglutinin-horseradish peroxidase (HRP) in ACC and PFC. In this case, there are anterogradely labeled terminals in the DMV, SN, and NA. Thus, ACC and PFC projections reach the dorsal as well as ventrolateral medulla in the rabbit. This figure also indicates a strong bilateral projection to the caudate nucleus, globus pallidus, ventral pallidum, and claustrum. In addition, there are strong projections to the MD, midline, and intralaminar nuclei of the thalamus. These ACC and PFC efferents to the thalamus are for the most part reciprocal (e.g., Buchanan et al., 1989; Groenewegen, 1988; Benjamin et al., 1978). Figure 13.1 also confirms earlier reports in the rat (Van Der Kooy et al., 1984; Hurley et al., 1991) of ACC and PFC efferents to the superior colliculus and periaqueductal gray.

Figure 13.2 shows retrogradely labeled cells in areas 25, 8, and 32 of ACC and medial PFC and in insula PFC after HRP injections centered on either the nucleus of the solitary tract and DMV or NA regions of the medulla. Few cells were observed in area 24 after these injections. These findings suggest that anterograde labeling of medullary structures with HRP injections in the ACC are probably due to transport via fibers of passage. Studies in the rat support the con-

FIGURE 13.1. Efferent projections of dorsomedial cortex in the rabbit as demonstrated by anterograde labeling subsequent to HRP injection. Sections in A–F are progressively caudal levels of the rabbit brain. The solid area is the injection site, and dots represent fields of terminal axon labeling. Anterodorsal, AD; anteromedial, AM; amygdala, AMG; anteroventral, AV; caudate, CD; claustrum, CL; centromedial, CM; dorsal motor nucleus of the vagus, DVM; intermediodorsal, IMD; mediodorsal, MD; medioventral, MV; nucleus ambiguus, NA; nucleus of the solitary tract, NTS; periaqueductal gray, PAG; paracentral, PC; putamen, PUT; paraventricular, PV; nucleus reuniens, Re; superior colliculus, SC; ventroanterior, VA; ventromedial, VM; ventroposterior, VP.


A
CL
B
CD
PUT
C
PV
AV
AD
AM
MV
AMG
D
IMD
MD
PC
VA
CM
RE
VM
VP
E
SC
PAG
F
NTS
DVM
NA

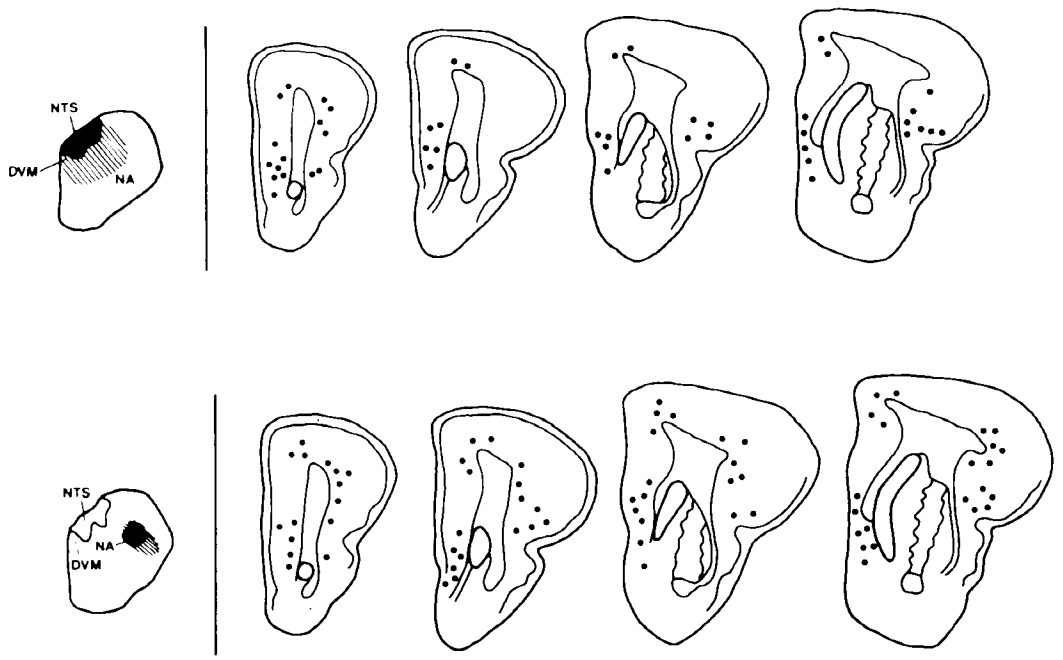


FIGURE 13.2. Retrograde labeling of neurons in the cingulate and prefrontal cortices subsequent to HRP injections in the dorsal *(top)* and ventral *(bottom)* medulla. The injections sites are solid, and retrogradely labeled neurons are represented with dots. Dorsal motor nucleus of the vagus, DVM; nucleus ambiguus, NA; nucleus of the solitary tract, NTS.

clusion that area 24 projections do not reach the medulla (Neafsey et al., 1986; Hurley et al., 1991).

Although the direct connections demonstrated between area 25 and PFC and the medulla may be responsible for its autonomic involvement, this area of the brain also has connections with the periaqueductal gray and thalamus which are known to be also involved in autonomic adjustments. In addition, there are connections between ACC and PFC and the amygdala (Beckstead, 1979; Cassell and Wright, 1986; McDonald, 1987), as well as the insula (Saper, 1985). The amygdala and insula each have monosynaptic connections with the dorsomedial medulla (Schwaber et al., 1982; Kapp et al., 1985b). Thus, the autonomic changes evoked by ACC and PFC electrical stimulation may involve these oligosynaptic pathways rather than the direct connections illustrated in Figures 13.1 and 13.2. Finally, definite topographical relationships between the cytoarchitectural divisions of ACC and PFC and subcortical projection sites have been established in some cases (Neafsey et al., 1986; Hurley et al., 1991). The extent to which these topographical relationships are related to the functional properties of the ACC and PFC, however, remains to be determined. The participation of the ACC and PFC in various aspects of learning and memory is suggested by a variety of different kinds of data (Fuster, 1989; Goldman-Rakic, 1987, 1990). In this chapter we present evidence suggesting that anterior cingulate and prefrontal cortices might mediate the plasticity associated with the autonomic components of associative learning.

Training-Induced Modulation of Autonomic Responses

Autonomic adjustments are sensitive to a variety of learning and conditioning manip-

ulations including both classical and operant conditioning. Classical (Pavlovian) conditioning occurs whenever a neutral stimulus acts as a signal for an important forthcoming but nonneutral event. In most nonhuman animal experiments this latter nonneutral event is of biological relevance, such as food or an aversive stimulus, and elicits an unconditioned reflex (Pavlov, 1927). In Pavlov's (1927) experiments, the neutral stimulus was termed the *conditioned stimulus* (CS) and the food the *unconditioned stimulus* (US). The US elicits what Pavlov referred to as the unconditioned response (UR; i.e., salivation in response to the food). The response of most interest, however, was not the UR but a new, learned response, also consisting of salivation, but in this case salivation to the initially neutral CS. Such learned responses resulted from the CS consistently preceding the food over many CS/US presentations. This learned response was referred to as the conditioned response (CR). It should be noted that the CR does not always resemble the UR, as is the case here. Indeed, often the CR appears to be opposite of the UR. For example, the autonomic changes in response to contextual cues that signal drug administration are often opposite in direction to those produced by the drug itself (Siegel, 1979). Moreover, the heart rate (HR) CRs to CSs signaling aversive USs in restrained rats and rabbits consist of bradycardia, whereas the URs to the USs alone consist of tachycardia (Kazis et al., 1973; Fitzgerald et al., 1973; Fitzgerald, 1976).

Note that during classical conditioning, the US (or reinforcer) is presented regardless of the behavior of the organism. During operant or instrumental conditioning, however, the reinforcer is contingent on a specific behavior that the organism must exhibit. The organism may, for example, press a bar, run down a runway, or, as in Thorndike's (1911) original experiments, open a cage. Thus, the emphasis in classical conditioning is on whatever new behaviors occur as a result of the association between the occurrence of the CS and the reinforcer, while in operant conditioning the emphasis is on behaviors that are necessary for the occurrence of the reinforcer.

Both operant and classical conditioning techniques can modify autonomic responses in a variety of ways. For example, operant conditioning principles can be applied to autonomic responses directly. Thus, the use of biofeedback techniques to change skin temperature or blood pressure (BP) responses in patients suffering from migraine headaches or essential hypertension, respectively, operate by providing a reinforcing signal to the subject whenever an effective change in the appropriate autonomic response occurs (Shapiro and Schwartz, 1972). Organisms can learn to change their autonomic responses as a result of feedback from the external environment either to aversive stimuli or to the presentation of a rewarding stimulus (Miller, 1983; Joseph and Engle, 1981). Animals maintained on operant reinforcement schedules also exhibit a variety of autonomic and endocrinological changes (Murray, 1967; Brady, 1967). Thus, it is clear that autonomic responses can be modified in a variety of ways by operant as well as classical conditioning principles.

Among the most widely used classical conditioning models is that developed by Gormezano and associates (Gormezano, 1966; Gormezano et al., 1983) utilizing the classically conditioned nictitating membrane (NM) response. This learned response and its closely associated eyeblink (EB) CR has proved useful in a number of laboratories focusing on the neuroanatomical substrates of learning (e.g., Thompson, 1988; Lavond et al., 1990; Disterhoft et al., 1988; Moore et al., 1982; Harvey et al., 1988). However, as has been noted by others (e.g., Gantt, 1960; Konorski, 1967; Thompson, 1986; Weinberger and Diamond, 1987; Prokasy, 1984; Schneiderman, 1972), animals exposed to classical conditioning contingencies that elicit specific somatomotor responses, such as the EB, NM, or leg flexion response, also manifest a number of concomitant nonspe-

cific responses that are not usually assessed. Although nonspecific CRs may consist of somatomotor behaviors (Dykman et al., 1965), nonspecific learned visceral changes have been most often studied and include HR, systemic BP, skin conductance, changes in pupillary diameter, and so on (e.g., see Obrist, 1981; Cohen and Randall, 1984; Smith and DeVito, 1984; Weinberger and Diamond, 1987; Bykov, 1957; Stern, 1972; Dykman, 1967).

For the most part we have assumed that the autonomic responses acquired during typical classical conditioning tasks represent an early aspect of learning associated with the attachment of emotional significance to the CS/US contingency. Others have made similar assumptions (e.g., Konorski, 1967; Gantt, 1960). Moreover, there is convincing evidence to suggest that the cingulothalamic system and certain of the structures with which it has afferent and efferent connections provide an essential neural substrate for the operation of this process. The later-occurring acquisition of classically conditioned somatomotor responses, however, does not depend to any great extent on this substrate. Instead, there is good evidence to suggest that an extrapyramidal substrate, including primarily the cerebellum and associated nigrostriatal system, is essential in the conditioning of somatomotor responses. These data are reviewed by Thompson et al. (1988).

Control of Reflexive Autonomic Responses by Cingulate-Prefrontal Systems

Cingulate-Prefrontal Cortical Stimulation

The early experiments of Spencer (1894) demonstrated that arterial pressure changes could be elicited by stimulation of orbital cortex. Increases and decreases in BP have since been obtained from the cat, dog, and monkey by stimulation of ACC as well as orbital PFC (Kaada, 1960; Hoff et al., 1963; Delgado, 1960; Neafsey, 1990). In general, depressor responses are obtained from pregenual anterior cingulate cortex and PFC, and pressor responses from posterior orbital cortex (Kaada, 1951; Buchanan and Powell, 1982a; Lofving, 1961; Burns and Wyss, 1985). However, pressor responses have also been obtained from ACC and especially from area 25 (Kaada, 1951; Lofving, 1961; Burns and Wyss, 1985). In general, HR slowing also occurs. In some cases this may be secondary to BP increases such as that produced by baroreceptor activation, whereas in other cases this appears to be a primary bradycardia produced principally by vagal activation. There are indications that the level of anesthesia also influences the direction of the cardiovascular change (Kaada, 1951; Burns and Wyss, 1985). However, Anand and Dua (1956) reported mainly pressor responses, whereas Hall et al. (1977) reported primarily depressor responses in conscious monkeys with chronically implanted electrodes in orbital PFC. Nevertheless, there are strong indications that the direction of the response is related to the area of ACC or PFC stimulated.

We have focused on the changes elicited by electrical stimulation of ACC and PFC of the rabbit and have attempted to differentiate responses from architectonic subdivisions of these areas. The stimulation studies to be described were all done in conscious animals with chronically implanted bipolar stimulating electrodes. Electrical stimulation of ACC and PFC throughout their anterior-posterior extent produced dramatic bradycardia and depressor responses (Buchanan and Powell, 1982a; Buchanan et al., 1985). Examples of responses evoked by electrical stimulation of dorsomedial cortex are shown in Figure 13.3. Similar stimulation of posterior cingulate cortex, or of lateral isocortical areas, produced only small and variable HR and BP changes and then only at higher stimulus intensities (100 to 200 μA versus 1 mA). As shown in the second series of traces in Figure 13.3, stimulation of insular PFC also produced dramatic inhibitory cardio-

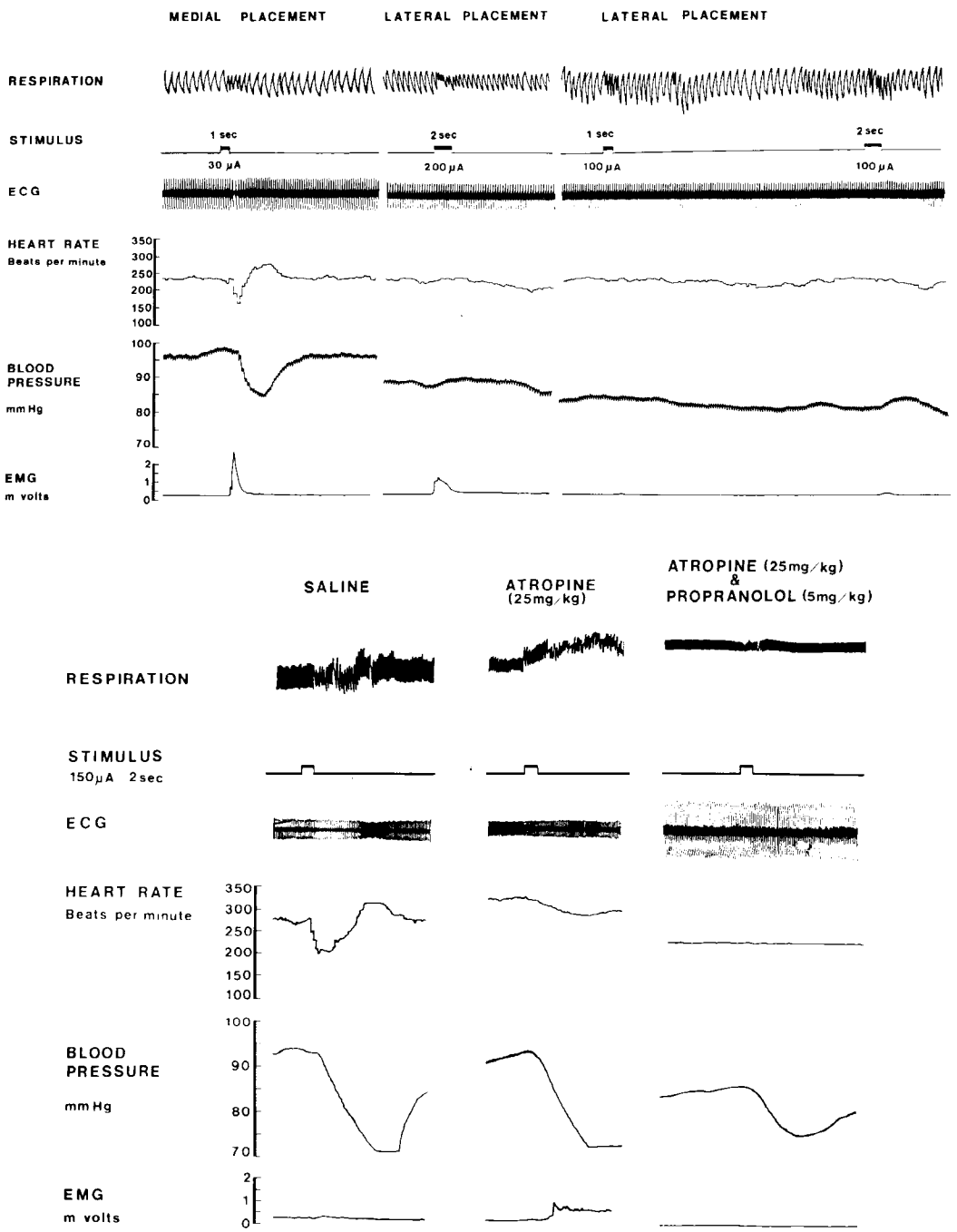


FIGURE 13.3. *Top:* Autonomic changes elicited by electrical stimulation in dorsomedial and lateral isocortical somatomotor cortices in the rabbit. Data are shown for changes in respiration, heart rate, blood pressure, and nuchal electromyographic activity.

Bottom: Autonomic changes elicited by electrical stimulation of agranular insular cortex. Data are also shown subsequent to administration of methylatropine (middle tracings) and methylatropine plus propranolol hydrochloride (tracing on extreme right). Electrocardiogram ECG; electromyogram, EMG. Reprinted from Powell et al. (1985).

vascular changes, which in many cases were much larger in magnitude and longer in duration than those produced by midline stimulation (Powell et al., 1985). With either ACC/PFC or insula stimulation, acetylcholine receptor or β-adrenoceptor blockades were found to produce an attenuation of the response and a double blockade completely abolished stimulation-evoked responses. The blockade with atropine (25 mg/kg) is shown in Figure 13.3 as is a response following combined administration of atropine and propranolol (5 mg/kg). These findings suggest that both ACC/PFC and insular PFC are intimately involved in the cortical integration of visceral activities. Data from other studies support this conclusion (Saper, 1982; Cechetto and Saper, 1987; Neafsey et al., 1986; Yasui et al., 1991). In fact, Krushel and Van Der Kooy (1988) suggested that insular PFC provides a core integrating area for visceral changes mediated by ACC and PFC.

We have attempted to determine if there is a difference in the evoked cardiovascular and respiratory changes elicited from different architectonic subareas of anterior cingulate and prefrontal cortices. Thus, chronic stimulating electrodes were implanted in areas 8, 24, 32, or 25 in different groups of rabbits, and autonomic responses were assessed during electrical stimulation. Although bradycardia and depressor responses were elicited from dorsal areas 8, 24, and 32, pressor responses, accompanied by either bradycardia or tachycardia, were obtained from stimulation of area 25. The administration of the α-receptor antagonist phentolamine to animals receiving area 25 stimulation resulted in a significant reduction in the magnitude of the bradycardia and abolished the pressor response in these animals. This suggests that this bradycardia was most likely secondary to baroreceptor activation. The administration of phentolamine to animals receiving stimulation in areas 24 or 32, however, resulted in an exaggeration of the response. These findings support those of Lofving (1961), who reported that electrical stimulation of dorsal ACC produced depressor responses and bradycardia in the cat, whereas stimulation of area 25 resulted in pressor responses and tachycardia. Similar findings have been obtained in primates, although some inconsistencies have also been reported (cf. Anand and Dua, 1956; Kaada, 1951; Hall et al., 1977).

In earlier experiments in rabbits, increases in respiratory rate and decreases in respiratory depth were usually observed (Fig. 13.3; Buchanan and Powell, 1982a). However, studies in other species have reported different patterns of respiratory changes depending on the area stimulated. Smith (1938) and Kaada (1951), for example, reported distinctive excitatory and inhibitory areas for respiration in primates and cats. For the most part, respiratory inhibition was obtained from area 24 and respiratory increases from area 25 and the medial orbital area. However, the direction of respiratory changes obtained with stimulation of ACC and PFC has also been shown to vary with the depth of anesthesia. As other investigators have noted (e.g., Kaada, 1960), lower doses of anesthesia are more likely to increase respiratory rates. It may be important that in our experiments all animals were unanesthetized. However, stimulation of area 25 sometimes elicited respiratory inhibition. Thus, ACC and PFC in the rabbit appear to be topographically arranged with regard to stimulus-evoked changes in respiration; dorsal areas 8, 24, and 32 are associated with increases in respiration rate and the ventral area 25 with decreases.

Limbic Thalamic Stimulation

Stimulation of various nuclei of the limbic thalamus also produces cardiovascular changes, although the response topography of these changes is quite different from that elicited from ACC or PFC, and they appear to be similar to those elicited from area 25 stimulation. As with ACC and PFC stimulation, HR slowing is obtained subsequent to stimulation of the MD nucleus in almost all cases. West and Benjamin (1983) reported

HR decreases after MD or midline thalamic nuclei stimulation in the rabbit. However, bradycardia elicited from the thalamus is almost always accompanied by pressor responses, rather than depressor responses (Buchanan and Powell, 1986). An example of the cardiovascular adjustments elicited by stimulation of the lateral portion of the MD nucleus can be seen in the left panel of Figure 13.4 including a reduced HR and elevated BP. The right panel shows that administration of phentolamine abolished the effects of stimulation on both BP and HR responses. This figure also shows increases in respiration, and in most cases an increase in a nuchal electromyogram was also obtained. Similar changes were elicited from sites in the anteromedial nucleus and in the midline nuclei including the paraventricular, mediodorsal, intermediodorsal nuclei, and nucleus reuniens. Chemical stimulation of the MD nucleus with either carbachol or glutamate also elicited bradycardia and pressor responses (Powell and Buchanan, 1986), suggesting that the changes were not due to stimulation of fibers of passage, but to stimulation of neurons within the MD nucleus.

Studies by Varner et al. (1988) and Huang et al. (1988) also suggest the participation of medial thalamic nuclei in the sympathetic control of autonomic activity. These investigators demonstrated correlations between the spontaneous and evoked activity of individual thalamic cells and peripheral sympathetic (inferior cardiac) nerve discharge in cats. Areas showing such correlations were the midline, MD, and intralaminar nuclei as well as the hypothalamus. Moreover, lesions that included these diencephalic areas greatly attenuated the reduction in BP and inferior cardiac nerve discharge produced by midbrain transection (Huang et al., 1988). These data support the notion that thalamic neurons participate directly in reflexive sympathetic activity.

Neuronal Correlates of Autonomic Adjustments in Cingulo prefrontal Cortex and Limbic Thalamus

Although it is clear from the previous discussion that a variety of visceral changes can be elicited by stimulation of ACC, PFC and

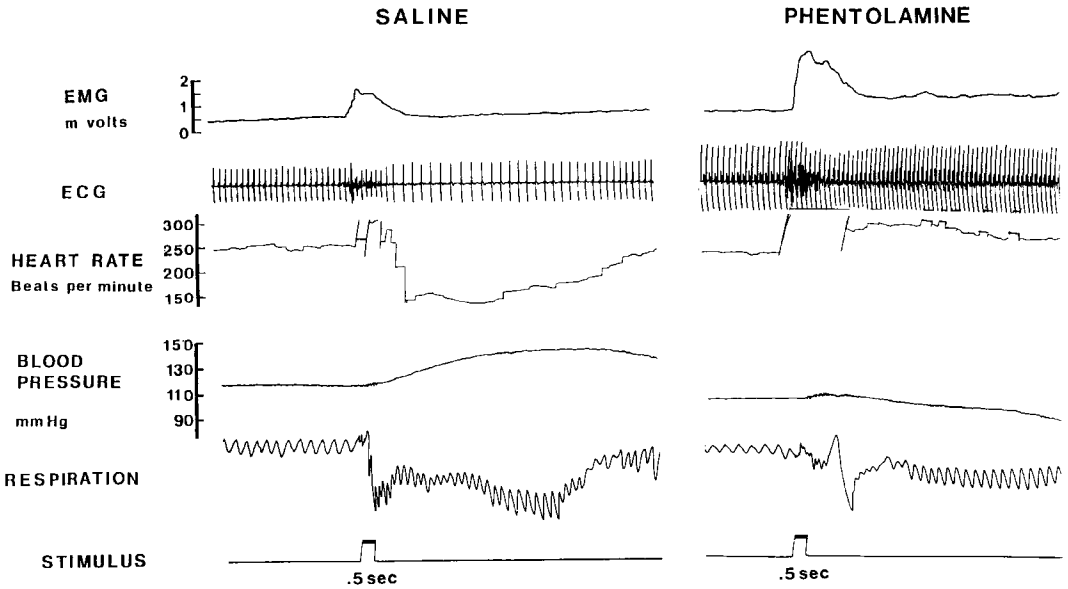


FIGURE 13.4. Autonomic changes elicited by electrical stimulation of the mediodorsal nucleus of the thalamus. Data are shown for changes in respiration, heart rate, blood pressure, and nuchal electromyographic activity. Electrocardiogram, ECG; electromyogram, EMG.

limbic thalamus, no studies have recorded activity from these areas of the brain during "spontaneous" visceral changes (i.e., those associated with homeostatic adjustments). However, studies involving lesions of ACC and PFC suggest that damage to this area of the brain produces little or no effect on baseline activity of the autonomic changes elicited by electrical stimulation (Kaada, 1960). Minor exceptions to this conclusion are the data reported by Delgado and Livingston (1948) and Showers and Crosby (1958) regarding changes in body temperature that result from ACC lesions in primates.

Although the body of data is small, some studies have assessed neuronal activity in other brain regions during stimulation in ACC/PFC or limbic thalamus. It is generally accepted that stimulation of brain structures producing autonomic changes results in electrocortical arousal (e.g., Jasper, 1960; Kaada, 1960). Thus, stimulation in either anterior or posterior orbital cortices or in ACC elicits electroencephalographic changes indicative of arousal. Sloan and Jasper (1950) reported that electrical stimulation of ACC produced a desynchronization of the electroencephalogram in all cortical regions that was similar to that following stimulation of the brainstem reticular formation. Kaada (1951) reported similar effects of stimulation of ACC; subcallosal, orbitoinsular, temporal pole cortices; and the amygdala in cats, monkeys, and chimpanzees. In conscious animals, stimulation of these limbic cortical areas produced not only the typical electroencephalographic arousal response, but also behavioral arousal (Kaada, 1960). Kaada (1951) suggested that electroencephalographic arousal induced by ACC stimulation is not secondary to the accompanying respiratory or autonomic changes. Cessation of motor activity in animals stimulated in these areas indicates that such arousal may be associated with increased attention (Kaada, 1960).

There is some information regarding neuronal electrical changes that occur during stimulation of the limbic thalamus. Data reported by Ferron et al. (1984) suggest that stimulation of the limbic thalamus results in increases in PFC neuronal activity. These investigators also reported inhibition of MD-evoked responses after stimulation of presumably dopamine-containing neurons in the ventral tegmental area. Sikes and DeFrance (1985) showed that most ACC neurons are reliably driven with electrical stimulation of MD in the theta range (i.e., 6 to 8 Hz). We have also found that MD stimulation results in increases in PFC single cell activity; however, spontaneous activity in some cells was inhibited by MD stimulation. Thus, while the data are limited, it appears that PFC and thalamic activity may not be associated with reflexive, homeostatic autonomic adjustments, but, rather, with autonomic changes that are associated with complex behaviors. As described in the next section, considerable evidence suggests that ACC and PFC and their thalamic connections may mediate at least part of the autonomic adjustments that accompany associative learning.

Control of Learned Autonomic Changes

This section reviews evidence that suggests quite strongly that ACC and PFC provide a neural substrate for the integration of autonomic adjustments elicited by classical conditioning contingencies. It is likely that all autonomic adjustments learned through classical and operant conditioning techniques also depend on this neural substrate. For the most part, however, the following evidence is limited to studies of cardiovascular changes in either the rat or rabbit.

Classical Conditioning of Autonomic Adjustments

Classically conditioned cardiovascular responses may represent an early component of information processing that is probably related to initial sensory registration and attention mechanisms (Powell and Kazis,

1976; Powell et al., 1990a; Putnam et al., 1974; Lacey and Lacey, 1980; Pribram and McGuiness, 1975). The later-occurring somatomotor NM and EB responses, as described earlier, however, represent the acquisition of a skeletal behavior that is an adaptation to external environmental contingencies. There is a great deal of information suggesting that autonomic and somatomotor response systems not only depend on different and nonoverlapping neuroanatomical substrates but also represent different aspects of learning (Powell and Levine-Bryce, 1988).

Figure 13.5 shows the dramatic differences between these two response systems in rabbits exposed to classical conditioning contingencies. This figure shows the results of an experiment in which a 1 sec tone was the CS and a 250 msec paraorbital electric shock train was the US. The top panel shows the percentage of EB CRs over five acquisition sessions consisting of 60 CS and US presentations each (namely, conditioning group). A pseudoconditioning control group received a random sequence of unpaired CS/US presentations (namely, explicitly unpaired CS/US group). Eyeblink CRs increased from a low, near-zero rate during session 1 to approximately 80% by session 5 in the conditioning group, while the explicitly unpaired group showed virtually no EB responses.

The bottom panel of Figure 13.5 shows the mean change in duration from the pre-CS baseline of the third interbeat interval of the electrocardiogram following tone onset as a function of acquisition sessions. This interbeat interval usually represents the largest change from the pre-CS baseline that occurs during the CS. The duration of this interbeat interval, known as *heart period*

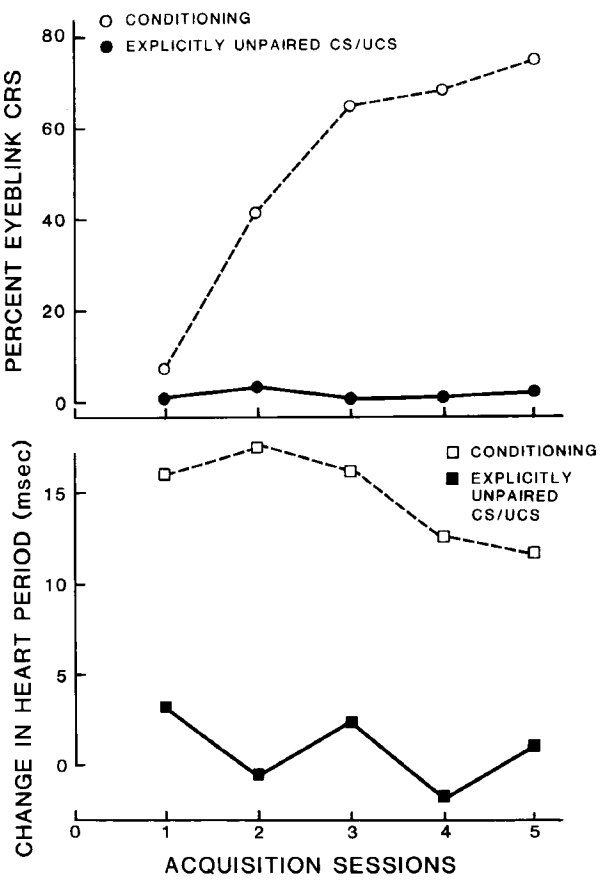


FIGURE 13.5. *Top:* Percentage of eyeblink-conditioned responses (CRs) of rabbits that received paired CS/US presentations (conditioning group) and rabbits that received unpaired CS/US presentations (explicitly unpaired CS/US group) as a function of five acquisition sessions. The CS was a 1.0 sec, 75 dB, 1216 Hz tone that was followed by a 250 msec, 3.0 mA paraorbital shock train as the US.

Bottom: Mean change in heart period (HP) from the pre-CS baseline of the third post-CS interbeat interval of the same rabbits that received conditioning and explicitly unpaired CS/US presentations over acquisition sessions. The third interbeat interval is shown because it was the last one available for analysis in all animals prior to CS offset and is thus usually associated with the largest HP change from pre-CS baseline. Reprinted from Powell et al. (1990b).

(HP), is the reciprocal of HR. Figure 13.5 indicates that HP was lengthened by 10 to 15 msec as a result of training. Thus, HR CRs consisted of decreases from the pre-CS baseline. The HP changes in the unpaired group were much smaller and more variable. Note, however, that no acquisition function is apparent in the conditioning group, as for the EB data earlier. The reason for this can be seen in Figure 13.6, which shows a mean change in the third interbeat interval over blocks of two trials each during the initial session. In this figure the acquisition function for HP is clearly apparent. Change in HP decreased in both groups across the first 5 to 10 trials, representing habituation of the cardiac component of the orienting reflex (OR). The OR is the initial response to novel stimulation and normally also consists of bradycardia (Powell and Kazis, 1976). After habituation of the OR, the conditioning group demonstrated a second bradycardiac response longer than 15 to 20 msec, whereas the unpaired group continued to show small and variable responses. Thus, the decelerative HR CR appeared by trial 10 and reached its maximum magnitude by trial 20, well before EB CRs began to occur in any animal.

These experiments demonstrate that the initial HR response to tone CSs in the rabbit is in a parasympathetic direction. However, an important sympathetic component is also observed when EB conditioning is concomitantly elicited. This finding is illustrated in Figure 13.7 which shows HR and BP conditioning in rabbits using a 1 sec CS/US interval that allows for somatomotor as well as autonomic conditioning. In experiments utilizing this short CS/US interval, the accompanying autonomic changes are typically assessed after CS offset, as well as during the CS proper, to determine the full magnitude of these changes in response to the relatively short signal involved. It is thus

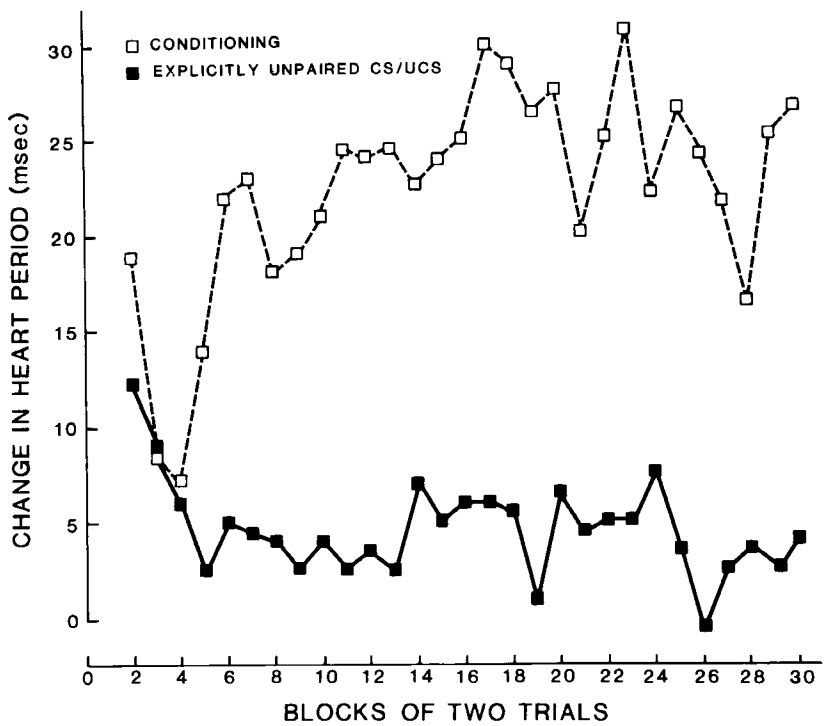


FIGURE 13.6. Change in heart period as a function of blocks of two trials each for the conditioning and explicitly unpaired CS/US groups illustrated in Figure 13.5, for the third interbeat interval during the first session of training. Reprinted from Powell et al. (1990b).

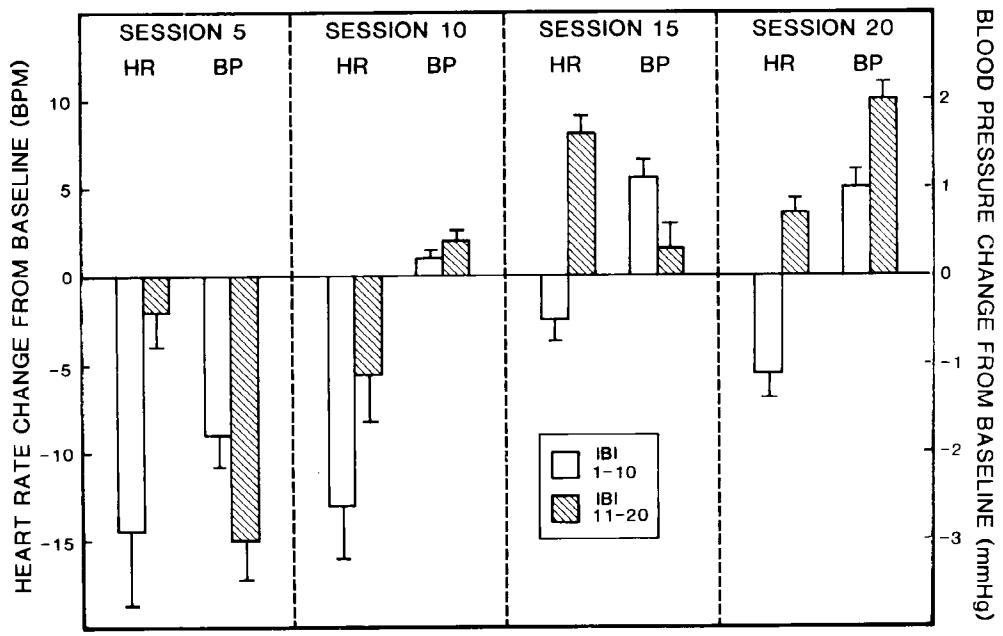


FIGURE 13.7. Heart rate (HR) change (beats per minute, BPM) and blood pressure (BP) change (mmHg) from pre-conditioned-stimulus (CS) baseline of groups of rabbits that received 5, 10, 15, or 20 consecutive daily sessions of eyeblink conditioning in which a 1 sec duration CS was employed. Eyeblink-conditioned responses are not illustrated. The data shown are conditioned responses (CR) to the 1 sec duration CS+ that was consistently paired with paraorbital shock; responding to the CS− is not shown. The data are shown separately for the first block of 10 interbeat intervals (IBI) and the second block of 10 IBI after CS onset. The first block of 10 IBI thus includes the initial HR CR that occurred during the CS, while the second 10 intervals represent HR changes that occurred after CS offset on test trials when the unconditioned stimulus was omitted. Reprinted from Powell et al. (1990b).

necessary to assess HR on "test" or "probe" trials on which the US is not presented; otherwise the presentation of the US interferes with the full expression of the CR. It is after CS offset that the HR accelerations that accompany EB conditioning are observed. Note that the HR changes associated with EB conditioning described in Figures 13.5 and 13.6 were assessed only during the CS. Figure 13.7 shows HR and BP changes separately in groups of animals that received 5, 10, 15, or 20 consecutive daily sessions of training for the first two blocks of 10 beats each after CS onset. Thus, the cardiovascular changes after and during CS presentation are shown. The EB response was also assessed but is not shown in this figure (Powell and Kazis, 1976). It is apparent from Figure 13.7 that early during training (i.e., after 5 sessions) conditioned bradycardia and depressor responses were obtained. However, after longer training in 10, 15, and 20 sessions, when EB acquisition was complete, the initial HR response remained a cardiac deceleration, but the later response consisted of cardiac accelerations. Moreover, the depressor response changed to a pressor response.

Although this discussion has emphasized conditioned cardiac inhibition, the kinds of cardiovascular changes that occur in anticipation of forthcoming USs are many and varied and depend on a variety of factors (Bykov, 1957; Konorski, 1967; Gantt, 1960; Powell et al., 1990a; Lacey and Lacey, 1980; Obrist, 1981). Thus, the direction (namely, bradycardia or tachycardia) of the conditioned HR change is subject to both organ-

ismic and contextual variables (Katcher et al., 1969; Smith and DeVito, 1984; Gantt, 1960; Sutterer and Obrist, 1972; Washton, 1978; Brown et al., 1990; deToledo and Black, 1966; Fitzgerald and Teyler, 1970; Iwata and LeDoux, 1988; Neafsey, 1990; Duncan, 1972; LeDoux et al., 1984; Teyler, 1971; Powell et al., 1971; Cohen and Obrist, 1975; Ginn et al., 1983; Schneiderman et al., 1974). There appears, however, to be overwhelming evidence that a basic underlying cardiovascular response pattern consisting of cardiac inhibition (i.e., HR decelerations) is associated with the initial processing of sensory information, especially that associated with either novelty or aversive classical conditioning contingencies (Graham and Clifton, 1966; Lacey and Lacey, 1980; Powell and Levine-Bryce, 1988; Pribram and McGuiness, 1975; Sokolov, 1963). Other changes such as somatomotor responses that occur in response to CS presentation (e.g., the EB CR) may represent a behavioral bias of this basic cardiovascular response pattern (Obrist, 1981; Black and deToledo, 1972; Schneiderman, 1972; Elliot, 1974; Sherrington, 1900; Cannon, 1929; Cohen and Obrist, 1975; Schneiderman et al., 1974). This would be especially true if simultaneous somatomotor activity is elicited by the CS, as is the case with the cardiovascular changes that accompany skeletal conditioning (Black, 1972; Bruner, 1969; Ginn et al., 1983; Powell and Joseph, 1974; Powell and Kazis, 1976; Smith and DeVito, 1984). Our experiments suggest that ACC and PFC participate in and possibly provide an essential substrate for the early bradycardiac response, whereas its thalamic projection nucleus (i.e., the MD and perhaps the adjacent midline and intralaminar nuclei) are involved in the sympathetic component of these responses.

Cingulate, Prefrontal, and Hypothalamic Lesion Studies

An early study of the role of ACC and PFC in classical conditioning established that ablation of midline, but not lateral, isocortex dramatically attenuated conditioned bradycardia (Buchanan and Powell, 1982b). In a later experiment (Buchanan and Powell, 1982a), lesions were made in more anterior portions of the midline prefrontal region including the anterior limbic and agranular precentral areas 8, 24, and 32 without damage to area 25. These lesions were compared with midline damage restricted to posterior cingulate cortex. As Figure 13.8 indicates, the area of midline cortex responsible for the lesion-induced attenuation of conditioned bradycardia was ACC and anterior PFC.

Lesions of anterior or posterior cingulate cortex did not attenuate the cardiac component of the OR. As noted earlier, the OR also involves a cardiac deceleration that is the normal cardiac response to novel stimulation. Unless reinforced with an appetitive or aversive US, this response habituates rapidly in 10 to 15 presentations (Powell and Kazis, 1976). It is thus significant that the OR was not attenuated by ACC or PFC lesions, since this is basically part of the unconditioned cardiac response to the CS. In a subsequent experiment, there were no differences between animals with anterior or posterior cingulate lesions or sham lesions on EB conditioning (Buchanan and Powell, 1982a), thus demonstrating that the effects of medial cingulate lesions on classical conditioning were limited to HR CRs. A series of control experiments also suggested that the effects of ACC and PFC lesions were specific to an associative process, since URs to neither the CS (i.e., the OR) nor the US were adversely affected by ACC and PFC lesions. Lesions of insular PFC had only minimal effects on conditioned bradycardia, which suggests that associative HR changes were unaffected by such lesions (Powell et al., 1985).

Another series of experiments investigated Pavlovian conditioning in rabbits with hypothalamic knife cuts (Powell and Levine-Bryce, 1989). The rationale for these experiments was as follows. First, Kapp et al. (1979) reported that lesions of the central nucleus of the amygdala produced a severe attenuation of conditioned bradycardia in

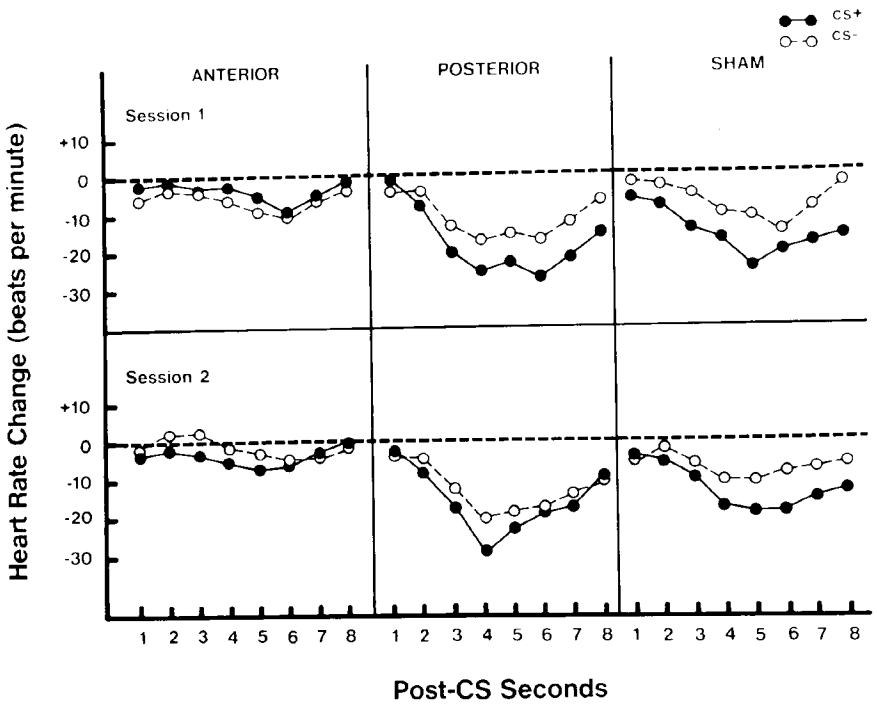


FIGURE 13.8. Heart rate changes (beats per minute) from pre-conditioned-stimulus (CS) baseline in response to CS+ and CS− of rabbits that received aspiration lesions of anterior or posterior midline cortex or sham lesions. Data are shown for 4 test trials that occurred during two consecutive daily sessions of 60 trials each as a function of 8 sec after CS onset. Reprinted from Buchanan and Powell (1982a).

the rabbit. Moreover, there is a direct pathway from the central nucleus to the autonomic regulatory nuclei in the dorsal medulla (Schwaber et al., 1982). As described earlier, there are also monosynaptic connections between ACC and PFC and the dorsal and ventral medulla. It thus may be important that neither the central nucleus nor cingulate cortex lesions appeared to completely abolish conditioned bradycardia, although severe attenuations were produced by both types of lesions (Kapp et al., 1979; Buchanan and Powell, 1982a). Since ACC and PFC and central nucleus efferents to the medulla pass through the ventral diencephalon, it was reasoned that either coronal or parasagittal knife cuts should interrupt activity in both systems. Second, previous studies had shown that lateral hypothalamus lesions interfere with associative learning of visceral response systems in several species including primates (Smith et al., 1968), pigeons (Cohen and Macdonald, 1976), rabbits (Francis et al., 1981), and rats (Iwata et al., 1986). It was unclear, however, whether the disruption of associative responding in these studies was due to the destruction of neurons within the lateral hypothalamus or to interruption of fibers passing through this area connecting brainstem and forebrain structures. Thus, this series of studies utilized either coronal or parasagittal knife cuts at the level of the lateral preoptic area and lateral hypothalamus in order to do the following:

1. To determine if such cuts, interrupting efferents to the medulla from both the central nucleus of the amygdala and PFC, would completely abolish conditioned bradycardia

2. To compare the effects of such knife cuts with those of ibotenic acid lesions of the lateral hypothalamus that would destroy hy-

pothalamic neurons and leave the fibers of passage intact.

The coronal knife cuts that interrupt efferents from lateral hypothalamic neurons anterior to the cuts and also damage many lateral hypothalamic cells in the region of the cuts greatly disrupted the cardiac OR as well as the conditioned bradycardia. Parasagittal knife cuts that left these lateral hypothalamic cells intact affected only the learned response (i.e., conditioned bradycardia). Ibotenic acid lesions in the same area of the lateral hypothalamus in which the coronal knife cuts were made also attenuated the OR, but left the conditioned bradycardia intact. Thus, lateral hypothalamic cells may mediate the cardiac component of the OR, but not the development of the decelerative HR CR. In contrast, structures rostral to lateral hypothalamus, presumably including both the central nucleus of the amygdala and ACC and PFC are instrumental in producing conditioned bradycardia, but are not necessary for occurrence of the OR (Powell and Levine-Bryce, 1989).

The architectonic subareas of the ACC and PFC were ablated with multiple injections of ibotenic acid in areas 24, 32, or 25 in separate groups of rabbits (Powell and Watson, 1990). Each group was then compared with a group of sham control animals during differential classical conditioning. The magnitude of the HR CR was impaired only in animals with area 32 damage, and these animals showed virtually no bradycardia in response to either CS+ or CS−. Thus, these data support brain stimulation and neuroanatomical observations regarding the ACC and PFC subareas and strongly suggest that area 32 is the critical area for mediation of conditioned bradycardia in the rabbit. Although parasympathetic HR decreases and BP depressor responses are obtained from stimulation of both areas 24 and 8, it is only from areas 32 and 25 that a direct pathway exists from this part of the PFC to the autonomic regulatory nuclei in the medulla. It is significant that lesions of area 25, which has a strong projection to the dorsal medulla in both the rabbit and rat, had no effect on conditioned bradycardia. However, stimulation of this area elicits sympathetic changes, as opposed to parasympathetic changes (S. L. Buchanan and D. A. Powell, unpublished observations), suggesting that it would not be involved in conditioned HR slowing.

Other studies in both primates and rats also suggest that ACC and PFC are involved in autonomic conditioning. Grueninger et al. (1965) reported that rhesus monkeys with dorsolateral prefrontal lesions failed to exhibit skin resistance changes to either a novel unreinforced tone or to a tone that was paired with electric shock as a US. However, unconditioned and movement-related skin resistance changes occurred in the ablated animals. In an earlier study Smith et al. (1968) also found that PFC lesions in monkeys abolished learned sympathetic cardiovascular changes, but these lesion-induced effects were transient unless accompanied by lateral hypothalamic lesions. Frysztak and Neafsey (1987) reported that ACC and PFC lesions in rats had no effect on a classically conditioned pressor response, but converted the conditioned tachycardia normally observed in the free-moving animal to pronounced bradycardia. However, the lesions of Frysztak and Neafsey (1987) were centered on area 25, which appears to mediate sympathetic mechanisms as discussed earlier. Moreover, the rats in these studies were free moving, whereas in the studies on rabbits described earlier the animals were always restrained. Nevertheless, this study and those of Grueninger et al. (1965) and Smith et al. (1968) suggest that medial ACC and PFC may be involved in autonomic learning of a variety of different kinds, and is thus not specific to conditioned bradycardia in the rabbit.

Neuronal Changes in the Cingulate and Prefrontal Cortices During Training

Electrophysiological recording studies support the contention that ACC and PFC participate in autonomic conditioning. For

example, multiunit activity in ACC and PFC of conscious rabbits exhibits tone-evoked increases during both orienting and classical HR conditioning (Gibbs and Powell, 1988). Increases in neuronal output from the pre-CS baseline occur during initial nonreinforced trials (namely, during OR assessment), but decline over further nonreinforced trials. During conditioning training, a considerable increase in neuronal activity from this pretraining level occurs. Moreover, this activity is trial-related and reaches its maximum during conditioning trials 11 to 30. Peak activity during the CS occurs with a latency of between 40 and 180 msec (Gibbs and Powell, 1988).

Subsequent studies (Gibbs et al., 1992) have compared tone-evoked changes in multiunit activity in dorsomedial cortex with those in ventrolateral insular PFC. In these studies multiunit activity at either site was recorded from chronically implanted electrodes during a two-day training period. Figure 13.9 summarizes the day 1 results of these studies. The initial, unconditioned tone-evoked multiunit activity increases recorded from insular PFC showed a gradual onset, and were of considerably smaller magnitude, than those recorded from ACC and PFC. Moreover, tone-evoked multiunit activity in ACC and PFC was systematically enhanced by paired training, but progressively attenuated by unpaired CS/US presentations. Changes in the group with insular placements, however, were not significantly different from those in animals receiving unpaired CS/US presentations and were not systematically trial-related. Correlations between tone-evoked multiunit activity and HR CR magnitude were significant only for animals with dorsomedial electrode placements and only during conditioning. These data are consistent with previous lesion findings: Electrical activity recorded from neuronal populations in dorsomedial cortex is correlated with concomitantly occurring conditioned bradycardia, whereas activity in insular PFC is not.

Extracellular single-unit recordings also suggest that ACC and PFC are involved in conditioned autonomic adjustments. In one study (Gibbs and Powell, 1991), six types of neurons were located in ACC and PFC that showed changes in firing frequency in response to tone-eyeshock contingencies. Table 13.1 summarizes the response characteristics for each of the six types of responses. The mean changes in evoked discharge during a 4 sec CS+ and CS− of type I–IV cells, which were the most frequent cells encountered, are shown in Figure 13.10. As this figure indicates, each of these neuronal subpopulations exhibited differential responsivity to the two CSs, since significantly greater responses were elicited on CS+ trials irrespective of the direction of the evoked change. Moreover, 52% of these cells, including 70% of the type I cells, exhibited tone-evoked activity changes that were reliably correlated with concomitant HR changes on a trial-by-trial basis. It should also be noted that the largest number of neurons were those that had increases in activity comparable to those that were observed during the multiunit experiments. These data indicate quite conclusively that neuronal activity of cells in ACC and PFC is significantly related to Pavlovian conditioned changes in HR activity, whereas the multiunit data suggest that activity of cells in insular PFC is not.

Limbic Thalamic Lesion Studies

There is substantial evidence relating limbic thalamic structures to learning and memory processes (e.g., Markowitsch, 1982; Chapters 15 to 17 of this volume). However, these structures have been little investigated with regard to their involvement in classical conditioning or in learned autonomic changes. An early study in the monkey (Nathan and Smith, 1971) suggested that, although damage of the MD nucleus had little effect on learned cardiac increases, learned somatomotor inhibition (conditioned suppression) was eliminated by damage of the MD nucleus. Skinner and associates (e.g., Skinner and Reed, 1978) reported, however, that PFC afferent connections from the tha-

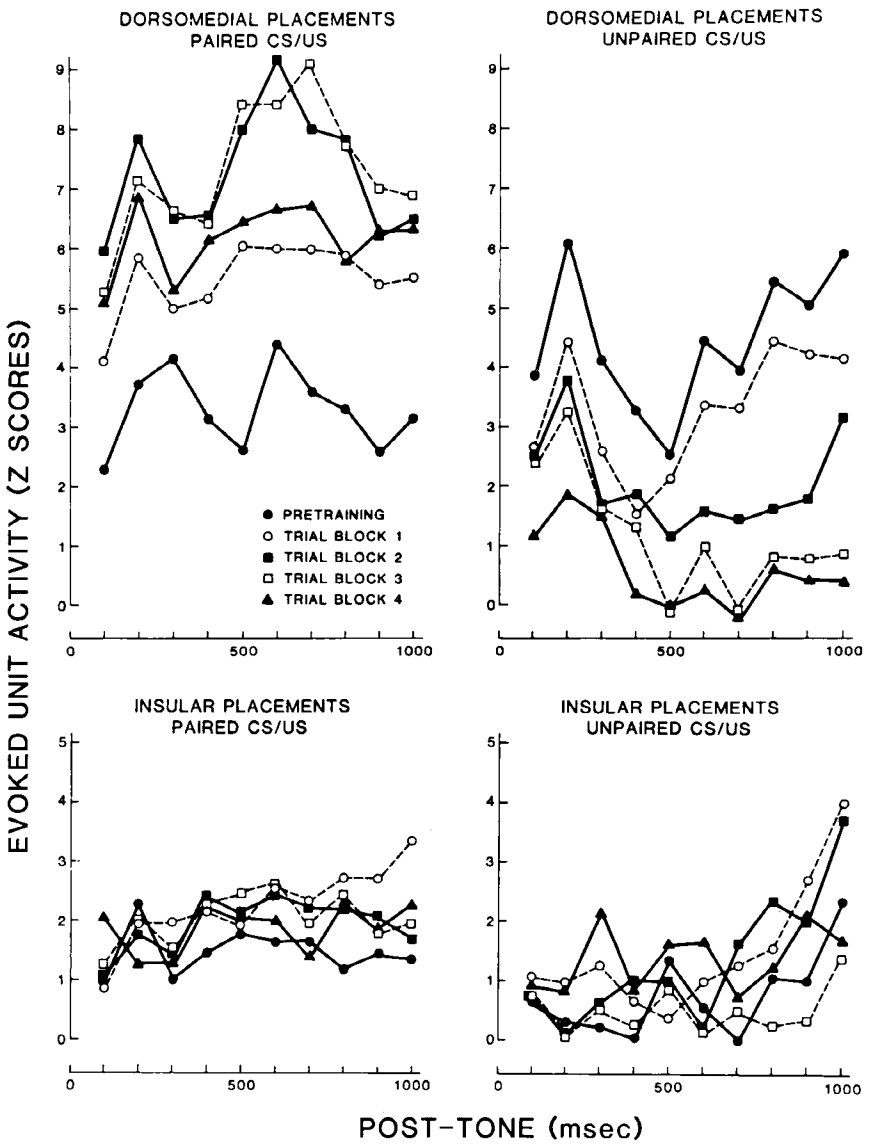


FIGURE 13.9. Mean conditioned-stimulus-evoked (CS) multiunit activity elicited by classical conditioning contingencies in dorsomedial cortex and agranular insular cortex of animals that received paired CS/US and explicitly unpaired CS/US presentations. Data are shown for the last block of 3 trials during pretraining in which tones alone were presented and for four 10 trial blocks in which CS tone and paraorbital shock US were presented. The data are shown for 10 bins of 100 msec each in Z-score units that were normalized with respect to pre-CS baseline discharge. Reprinted from Gibbs et al. (1992).

lamic reticular nucleus were intimately involved in learned sympathetic changes in swine. However, the MD nucleus, despite its strong interconnections with ACC and PFC in the rabbit, does not appear to play a direct role in mediating learned bradycardia or the bradycardia associated with orienting in this species. For example, parasagittal knife cuts lateral to the MD nucleus that interrupt fibers going to, as well as arising from, medial PFC affected neither the cardiac component of the OR nor acquisition of con-

TABLE 13.1. Functional characteristics of six subpopulations of cells in dorsomedial cortex in response to a positive conditioned tone stimulus reinforced with paraorbital shock[a]

Cell classification	Number of cells	Maintained activity (Hz)	Tone-Evoked Activity[b]
Type I	37	6.6±1.3	+/+ or +/0
Type II	5	1.1±0.4	0/+
Type III	14	10.1±2.1	+/−
Type IV	16	5.8±1.7	−/−
Type V	2	17.2±6.8	−/+ or −/+/−
Type VI	26	2.3±0.6	0/0

[a]Data shown are for an initial (1st or 2nd sec) or later (3rd or 4th sec) phase of a 4 sec tone.
[b]+ = increase from pre-conditioned-stimulus (CS) baseline; − = decrease from pre-CS baseline; and 0 = no significant change from pre-CS baseline.

ditioned bradycardia (Buchanan and Powell, 1989). However, acquisition of differential HR conditioning was impaired in animals with ibotenic acid lesions of the MD nucleus because of an inability of these animals to suppress responding to the CS−. Moreover, this finding was accompanied by a lesion-induced exaggeration of the cardiac OR (Buchanan, 1988). Since both the OR and the CR are parasympathetically mediated, these results suggest that damage to MD cells leads to an enhanced parasympathetic response.

As noted earlier, the autonomic response constellation elicited by stimulation of the MD nucleus is similar to that which occurs relatively late during EB conditioning, when skeletal responding has become maximal and

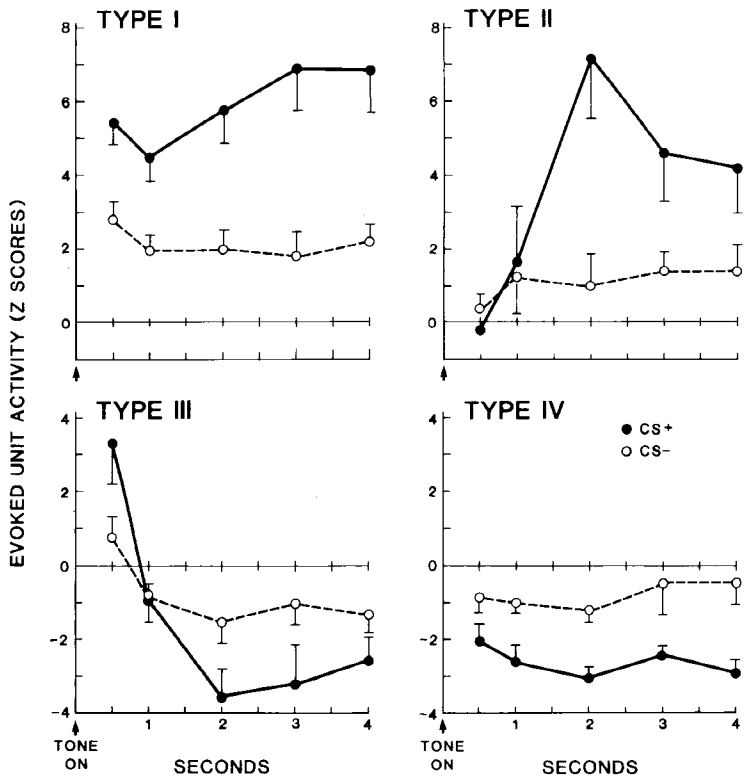


FIGURE 13.10. Evoked unit activity (Z scores) of individual units that showed different types of evoked discharge (see also Table 13.1) in response to a positive conditioned stimulus (CS+), which was paired with paraorbital shock (solid lines) and a CS−, which was not paired with shock (dashed lines). The data are shown for 4 sec after tone onset in Z-score units that were normalized with respect to pre-CS baseline discharge. All cells were located in the dorsomedial cortex. Reprinted from Gibbs and Powell (1991).

a sympathetic component to the HR CR appears. It is possible, then, that the MD nucleus plays a role in skeletal response selection and in the concomitant engaging of sympathetic systems to support these responses during learning tasks. Lesion studies provide support for this interpretation. For example, Figures 13.11 and 13.12 illustrate the results from an experiment in which EB and HR conditioning were assessed in animals with ibotenic acid lesions of the MD nucleus or sham lesions (Buchanan and Thompson, 1990). Animals with lesions showed delayed acquisition of the EB response, along with enhanced bradycardiac CRs throughout four sessions of training. Further, by the last acquisition session, animals with sham lesions showed the typical biphasic HR response including a later-occurring tachycardia. However, ablated animals continued to show bradycardia throughout training. Although the impaired EB acquisition and decreased conditioned tachycardia of the ablated animals may have been unrelated, it is possible that the inability of animals with damaged MD nucleus function to recruit sympathetic mechanisms in support of somatomotor response acquisition may have resulted in the retarded EB conditioning observed. Thus, it appears that, although lesions of the MD nucleus may have little effect on initial HR conditioning, concomitant EB conditioning is impaired possibly through elimination of important sympathetic mechanisms that facilitate somatomotor learning.

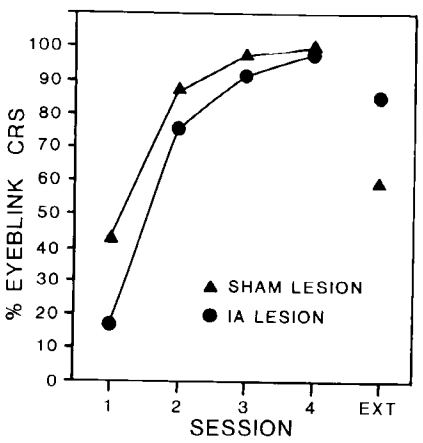


FIGURE 13.11. Percentage of conditioned eyeblink responses (CRs) in animals with ibotenic acid (IA) or sham lesions of the mediodorsal nucleus of the thalamus. Data are shown for four acquisition sessions (1 to 4) and one extinction session (EXT). Reprinted from Buchanan and Thompson (1990).

One experiment studied EB and HR discrimination and reversal conditioning (Buchanan, 1991). Animals were trained to respond to a preestablished criterion and then the CS+ and CS− were reversed; that is, the previously nonreinforced tone (CS−) was followed by eyeshock, whereas the previously reinforced CS+ was not. Virtually no lesion effects were seen on original acquisition of the discrimination; however, a severe deficit was obtained during reversal in the ablated animals. During reversal only two of eight ablated animals met the reversal criterion, whereas all sham control animals met this criterion. In addition, the magnitude of the OR was exaggerated, which occurred in previous studies, and those animals with the MD nucleus ablated also showed evidence of impaired HR discrimination during both acquisition and reversal.

These findings taken as a whole support our previous suggestion that a deficient response selection mechanism may result from damage of the MD nucleus. These results are also consistent with a model proposed by Gabriel (1990) in which the MD nucleus and its projection cortex constitute a *recency* memory system active in encoding events early in the learning process. However, it is superseded by another *primacy* system that maintains well-learned behaviors and is mediated by the anterior thalamic nuclei and posterior cingulate cortex. This model predicts the impaired EB reversal, since damage of the MD nucleus would result in reversal responding being controlled by the undamaged primacy system that retains the original discrimination. This model, however, also predicts impaired acquisition of the original discrimination, which would be consistent with our earlier findings of slightly impaired acquisition of simple conditioning tasks. As noted earlier, acquisition of the original discrimination was not significantly impaired in this study. Other investigators have, how-

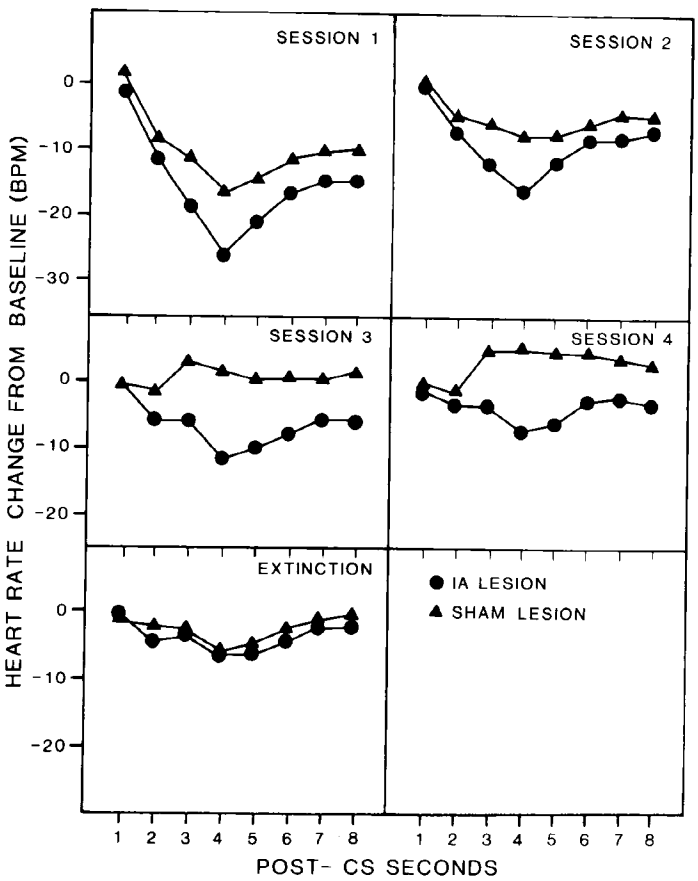


FIGURE 13.12. Mean heart rate change (beats per minute, BPM) from baseline during four acquisition sessions and one extinction session for ibotenic acid (IA) and animals with sham lesions as described in Figure 13.11. Data represent the first 8 sec after conditioned stimulus (CS) onset during nonshock test trials. Reprinted from Buchanan and Thompson (1990).

ever, reported impairments on discrimination tasks involving damage of the MD nucleus (Slotnick and Kaneko, 1981; Staubli et al., 1987; Waring and Means, 1976; Weis and Means, 1980; Gabriel et al., 1989). Differences in the results of this study and those reported by these investigators are probably due to the type of task employed, since the previously described studies all used operant conditioning.

Neuronal Changes in Limbic Thalamus during Training

In a series of preliminary experiments we assessed CS-evoked multiunit activity from MD nucleus during classical HR conditioning (Powell et al., 1990b). The results of these experiments indicate that CS-evoked neuronal activity in the MD nucleus has a short latency increase within 40 to 120 msec that was trial related. A group of animals that received explicitly unpaired CS/US presentations, however, showed trial-related decreases in multiunit activity. These data are shown in Figure 13.13 and suggest that there were two major differences between tone-evoked PFC multiunit activity, as described earlier, and multiunit activity recorded from the MD nucleus. First, the overall magnitude of multiunit activity was initially greater in the unpaired MD group than it was in the paired group, which was not the case for PFC placements. Second, the peak increase in multiunit activity of the MD nucleus occurred between 200

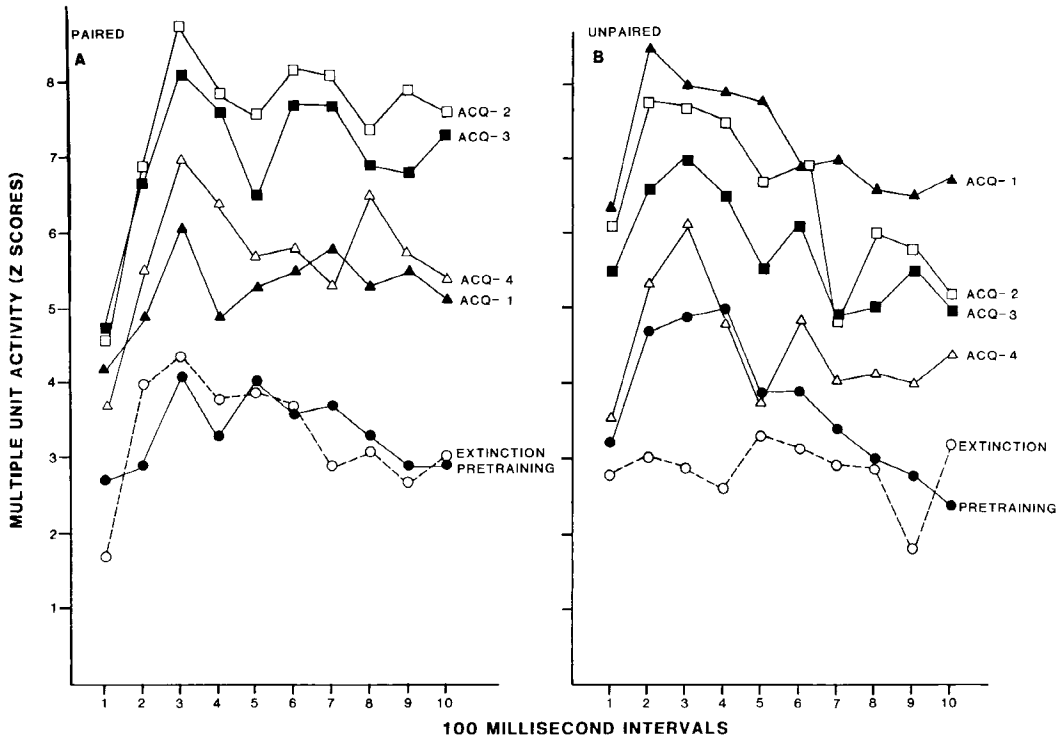


FIGURE 13.13. Mean conditioned-stimulus (CS) evoked multiunit discharge associated with mediodorsal thalamic placements plotted as a function of 100 msec intervals after CS onset in z-score units that were normalized with respect to pre-CS baseline discharge. *A* shows changes associated with the paired CS/US group and *B* shows similar changes associated with the unpaired CS/US group. Mean change in multiunit activity is shown for each of the four blocks of 10 training trials on day 1 (ACQ-1 to -4), for the last 4 trials of pretraining, and for the last 10 trial blocks of extinction. Reprinted from Powell et al. (1990b).

and 300 msec after tone onset, whereas peak latency was somewhat shorter at 100 to 200 msec in animals with dorsomedial cortex electrode placements. These differences are no doubt related to the relative roles that these two structures play in associative learning, but further research will be required to relate them to specific aspects of learned behavior.

In separate groups of animals, similar multiunit recordings were made from the intralaminar thalamic nuclei. The pattern of tone-evoked change in multiunit activity in the intralaminar group was different from that observed in animals with MD nucleus placements. Increases in intralaminar neuronal activity occurred later during the CS/US interval (i.e., approximately 400 to 500 msec) and persisted throughout the duration of the CS. As in the MD group, these differences were trial related; no such trial-related changes were observed in animals that received unpaired CS/US training. These data suggest that the tone-evoked increases in multiunit activity in the intralaminar group were also due to an associative process. Although the increase in CS-evoked multiunit activity in the MD nucleus was correlated with HR CR magnitude, the increase in intralaminar activity was not. An important question concerns the functional significance of the differences in CS-evoked activity in the intralaminar nuclei versus the MD nucleus. As noted earlier, although both the intralaminar and MD nuclei project to anterior cingulate and prefrontal cortices, a projec-

tion from the intralaminar nuclei to the neostriatum has been demonstrated in a variety of species (Scheibel and Scheibel, 1967). The caudate nucleus and other extrapyramidal structures are involved in the elaboration of classically conditioned somatomotor responses (Kao and Powell, 1988; Powell et al., 1978; Thompson, 1986). Thus, it is possible that the intralaminar nuclei are also involved in somatomotor response selection.

In general, these results are compatible with earlier studies in which neuronal activity was recorded from the thalamus in rats and rabbits during learning tasks. Delacour (1984), for example, reported increases in unit activity in both the MD and the intralaminar centromedian nuclei during differential classical conditioning in the rat. Differential increases in unit activity to the reinforced CS+ compared with a nonreinforced CS−, however, occurred only in MD nucleus. Although centromedian activity increased over a 60-trial session, these responses occurred equally often to the CS+ and CS−. Orona and Gabriel (1983a,b) also reported CS-evoked differential short latency increases in multiunit activity in both PFC and MD nucleus in rabbits during a CS+ tone that signaled footshock in an instrumental running wheel avoidance task. Such increases occurred during both pretraining and conditioning sessions and were significantly greater than changes recorded during a similar tone that never signaled footshock (i.e., the CS−). Earlier studies in the rat reported by Disterhoft and Olds (1972) also showed significant differential increases in multiunit activity in a variety of thalamic and cortical structures in response to a CS+ tone that predicted food as compared with a second tone that was never paired with food. Taken as a whole, these results suggest that significant changes in discriminative unit activity may occur in both PFC and medial thalamic structures as a result of conditioning tasks. Our data, however, as well as that of Delacour (1984), suggest that the occurrence of a learned specific somatomotor response is not required for this increase in neuronal discharge to occur, although, of course, such neuronal changes may be different when such a response is required.

In summary, these lesion and electrophysiological recording data suggest that the MD nucleus is responsible for mediating sympathetic mechanisms in support of somatomotor response acquisition during learning tasks. In this regard it appears to function in an opposite manner to its projection cortex in the anterior cingulate and prefrontal regions. It is thus tempting to speculate that normally ACC and PFC and their thalamic projection nuclei function in an antagonistic but balanced fashion. Thus, the cortical region might be active during the early stages of learning when stimuli are being processed for information, while thalamic nuclei, as originally suggested by Vanderwolf (1971), are active during a response selection process in which skeletal responses, designed to deal adaptively with environmental contingencies, are selected and executed.

Corticothalamic Control of Autonomic Regulation and Behavior

Commonalities of Cingulate and Prefrontal Contributions

The MD nucleus projects to both anterior cingulate and prefrontal cortices. Thus, according to an often-used definition of prefrontal cortex (i.e., that the PFC has reciprocal connections with the MD nucleus) ACC is itself part of PFC (e.g., Rose and Woolsey, 1948). However, this definition has been criticized on several grounds (e.g., Ulyings and Van Eden, 1990; Reep, 1984; Goldman-Rakic and Porrino, 1985; Fuster, 1989). A major problem is that a variety of other medial thalamic nuclei also have reciprocal projections to the prefrontal area that overlap with MD projections to various degrees. Accordingly, Uylings and Van Eden (1990) suggested that PFC be defined as those regions of frontal cortex for which the reciprocal connections with the MD nucleus

are stronger than those of any other thalamic nuclei. Again, however, both ACC and PFC would be defined as prefrontal cortex (Uylings and Van Eden, 1990).

It is clear that some areas of ACC and PFC play a role in associative learning, especially that aspect of classical conditioning in which visceral responses are acquired. As detailed earlier, it appears that the specific architectonic region which may be responsible for mediating the plasticity associated with autonomic responses is centered in area 32 of PFC. However, since large portions of area 24 were also involved in several of these lesions, it is possible that the combination of damage to both areas 32 and 24 is necessary for impaired visceral learning. In any case, the fact that lesions of ACC and PFC produce deficits in acquisition of visceral responses is compatible with the general conception of this area of the brain as mediating emotional responses, alertness, and attention (Neafsey, 1990; Chapter 6 of this volume; Kaada, 1960; LeDoux, 1987).

Electrical stimulation studies, however, suggest differences between the kinds of responses elicited from ACC and PFC. Thus, in the primate and cat posterior orbital PFC is more often associated with sympathetic responses, whereas ACC appears to be frequently associated with parasympathetic responding (Kaada, 1960). Our work with the rabbit suggests that both ACC and PFC produce responses resembling those that are parasympathetic, whereas area 25 produces responses resembling those that are sympathetic. Although insular PFC has been mapped for electrically evoked visceral changes in the rabbit (Powell et al., 1985), orbital PFC has not. There are, of course, differences as well as commonalities in the connections of ACC and PFC that might account for their relationship to behavior, as discussed in the next section.

Connectional and Neurotransmitter Mechanisms

The common projections from the medial thalamus to ACC and PFC suggest functional commonalities for the two areas. As outlined earlier, much evidence suggests the involvement of the MD nucleus in somatomotor response initiation. The large projection of ACC and PFC to the neostriatum also suggests that this circuit may be important for somatomotor function (Fuster, 1989). That the MD nucleus receives afferents from the ventral pallidal region, which in turn receives caudate projections (Groenewegen, 1988; Groenewegen et al., 1990), completes a loop involving the MD nucleus and ACC and PFC with brain structures that have historically been associated with movement and skeletal behaviors.

The reciprocal connections of both ACC and PFC and the MD nucleus with the basolateral nucleus of the amygdala suggests that another possible behavioral function of this loop may be to assign affective value to motivational stimulation so that appropriate somatomotor behaviors can occur. Obviously such behavior would be for the most part learned. This possibility is discussed in more detail later. In any case, the interconnections between historically motor and limbic systems in this area of the brain suggest that it may be a major interface for the control of learned somatomotor behaviors by motivating circumstances such as CSs associated with either rewarding or aversive stimuli.

Neurotransmitter mechanisms that might be involved in these kinds of changes are for the most part unknown. As mentioned earlier, stimulation of both MD and ventral tegmental area evokes single-unit activity in PFC of the rat (Ferron et al., 1984). The ventral tegmental area inputs are presumably dopaminergic. Serotonergic and nonadrenergic inputs to dorsomedial cortex may play an equally important role in controlling the activity of individual cells in this structure (Thierry et al., 1990). Other studies have demonstrated that dopamine turnover and utilization is affected by various kinds of motivational conditions such as exposing rats to footshock or other kinds of stressful situations such as restraint (Deutch and Roth, 1990). The motivational significance

of dopamine processes is also illustrated by the implication of such processes in the affective states associated with drugs of abuse such as cocaine (e.g., Goeders and Smith, 1983; Chapter 15 of this volume), although the exact role that dopamine afferents might play in such complex behaviors is unknown. It is equally clear that addictive behaviors involve classical conditioning principles (O'Brien et al., 1988; Siegel, 1979). Autonomic adjustments would clearly be a part of these processes, and much data suggest a major role of ACC and PFC in the plasticity associated with such processes.

A related question of some importance concerns the extent to which the plasticity associated with ACC and PFC function is intrinsic to this cortex or is carried into ACC and PFC from afferent projections such as those from the ventral tegmental area and the MD nucleus. Although this question cannot be answered unequivocally, the finding by Laroche et al. (1990) that PFC synaptic efficacy could be increased by stimulation of its hippocampal and subicular inputs suggests a possible mechanism by which such plasticity is mediated. Other structures possibly involved in producing increased synaptic efficacy obviously include the basolateral nucleus of the amygdala and the MD nucleus. It would appear from the lesion studies described earlier, however, that the MD-prefrontal axis does not mediate the learning associated with conditioned bradycardia. The amygdala-cingulate-prefrontal axis has not been studied in this regard. Since it has been demonstrated that the central nucleus of the amygdala also plays a primary role in conditioned bradycardia (Kapp et al., 1979), one would suspect that this is also a possible mechanism by which PFC plasticity takes place. However, there are neither afferent nor efferent connections between the central nucleus and ACC and PFC (Kapp et al., 1985a). Rather, amygdala-prefrontal fibers arise primarily from the basolateral nucleus (McDonald, 1987, 1991; Chapter 8 of this volume).

LeDoux and coworkers demonstrated a medial geniculate projection to the lateral nucleus of the amygdala in the rat that projects to both the central nucleus and the basolateral nucleus (Clugnet et al., 1990; LeDoux et al., 1990, Clugnet and LeDoux, 1990). Other investigators (e.g., Jarrell et al., 1986) showed that lesions of the medial geniculate cells projecting to the amygdala abolish discriminative, classically conditioned cardiovascular responding in rabbits. Although no conditioning studies have been done in which the basolateral projection area to the MD nucleus and PFC has been ablated, it is an obvious connectional mechanism for mediating the plasticity associated with ACC and PFC control of conditioned autonomic responding.

The functional implications associated with these different forebrain and hindbrain controls of learned cardiovascular adjustments is unclear. It should be noted, however, that Bard and Mountcastle (1948) much earlier suggested that there was differential control of autonomic activity by the mediocortical and anterior temporal areas including the amygdala, and, further, that the amygdala served as a funnel through which activity from the temporal and medial cortical areas mediating emotional reactivity could be routed to lower brainstem centers. Thus, there appear to be ample findings suggesting independent control of autonomic activity by the amygdala subnuclei and ACC and PFC areas. One obvious interpretation of such findings is that the "higher level" ACC and PFC regions provide for interpretation of emotional processes that are expressed at subcortical levels by amygdala activity. Another interpretation, however, is that ACC and PFC integrate autonomic adjustments with adaptive skeletal behaviors through its extensive connections with the neostriatum, whereas amygdala control of autonomic activity is more direct and devoid of such integration. Although there is still little evidence to support this hypothesis, it is compatible with the larger role postulated for ACC and PFC in complicated behavioral processes such as planning, intention, and timing of behaviors (e.g., see Fuster, 1989).

Cardiac-Behavior Relationships: Biological Relevance of Conditioned Bradycardia

Of concern in the present context is whether conditioned bradycardia, which we can tentatively conclude is controlled by neurons in the amygdala and ACC and PFC, can be related to skeletal behaviors. As discussed earlier, much research has demonstrated that the cardiac CR in the rabbit always contains an initial cardioinhibitory component (Powell and Levine-Bryce, 1988). It has been suggested elsewhere (Powell et al., 1990b) that this early-occurring bradycardia is specifically related to CNS processing of the CS, whereas the later-occurring tachycardia is not. Other manipulations that decrease stimulus certainty (e.g., decreased discriminability between CS+ and CS− during differential conditioning or partial reinforcement schedules) also enhance the magnitude of the bradycardiac CR (Powell and Milligan, 1975; Powell et al., 1974). These findings strongly suggest that the learned bradycardiac response is sensory related and that its form is not a function of either the later-occurring somatomotor CR or UR. Thus, activity in forebrain systems that normally produce bradycardia may be invariant when significant stimuli occur, but the actual occurrence of this cardiac response may be masked or biased by an excitatory cardiac system if somatomotor behaviors are simultaneously triggered (Powell et al., 1990b). Data reviewed earlier suggest that medial thalamic structures may participate in such a process by counteracting the parasympathetic changes mediated by ACC and PFC through the engagement of sympathetic mechanisms.

Lacey and Lacey (1974) suggested that the cardiovascular system serves as a negative feedback system to the CNS. According to this hypothesis, inhibitory cardiac changes would facilitate the intake and processing of sensory information. An inference from this generalization is that manipulations that affect cardiovascular activity might have nonspecific effects on the acquisition of new somatomotor responses. In several earlier experiments we found that pharmacological interventions that only indirectly affect somatomotor response systems, but directly influence autonomic mechanisms, also affect the acquisition of Pavlovian conditioned somatomotor responses. For example, peripheral acetylcholine receptor blockade with the quatenary analogues methylscopolamine or methylatropine, which do not cross the blood-brain barrier, significantly impairs the rate of acquisition of the EB response (Albiniak and Powell, 1980; Kazis et al., 1973; Powell, 1979). Methylatropine prevents a major source of cardiac inhibition from occurring, since it is an effective vagal blockade, but has only minimal effects on the central structures that mediate somatomotor learning. Thus, in these studies, the HR decelerations associated with the early stages of EB conditioning were prevented from occurring, even though central cholinergic systems were minimally, if at all, affected. More importantly, EB acquisition itself was retarded. An obvious interpretation of these findings is that the damping of HR CR magnitude by peripheral vagal blockade prevents normal afferent feedback and interferes with efficient CNS processing of the CS, which adversely affects EB CR acquisition (Lacey and Lacey, 1974).

The role that afferent feedback from peripheral autonomic systems plays in controlling behavior has a long but controversial history in the psychological literature (e.g., Fehr and Stern, 1970). However, other investigators have also emphasized that peripheral hormonal and autonomic changes may play a significant role in learning and memory (e.g., De Wied, 1980; Gold and McGaugh, 1977; Leshner et al., 1981; Martinez, 1986; McGaugh, 1990). Thus, environmental contingencies that elicit strong peripheral autonomic and hormonal responses, such as those employed in Pavlovian conditioning studies, may produce their effects by virtue of the feedback to the CNS that such peripherally occurring events produce. Martinez (1986) refers to this kind of modulation of learning and memory by

peripheral events as a "James-Lange" model of learning and memory and suggests that the importance of environmental events are established via these physiological changes. Moreover, this author further suggests that these peripherally occurring changes provide a physiological basis for what Brown and Kulik (1977) refer to as "flashbulb" memories.

> In analogy with the James-Lange theory of emotion, we can suggest a James-Lange view of memory; we meet a bear, run, and most likely remember in vivid detail many aspects of the encounter. In this view, hormonal responses, which are massive following the bear encounter, modify some brain process to help store information on the size of the bear, its particularly bad smell, its large, glistening sharp teeth, and so on. . . . most remember the circumstances in which one first heard of John Kennedy's assassination. Most not only remember the fact that he was assassinated, but also many details surrounding one's particular circumstance, such as where you were, who was with you, and so on. Thus, the similarity between the bear encounter and John Kennedy's death is massive autonomic and hormonal activation, which serves to mark the importance of the event for the individual organism. Importantly, flashbulb memories (strongly stored memories) should only represent one end of a continuum of hormonal modulation of learning and memory. (Martinez, 1986, pp. 139–140)

Such modulation must consist of peripheral events that affect CNS structures via either afferent nervous feedback or direct hormonal stimulation. For the most part, previous descriptions of the impact of these peripherally occurring hormonal and autonomic events on learning and memory processes have referred to sympathetic mechanisms (e.g., Martinez, 1986). However, the data obtained from the classical conditioning model with the rabbit described earlier, suggest that parasympathetic mechanisms may also play a role. Specifically we suggest that cardiac inhibition is part of a sensory registration mechanism that plays a role in all instances in which stimuli are processed for informational value (i.e., significance). Others also emphasized that parasympathetic mechanisms may play an important role in the early stages of information processing (Lacey and Lacey, 1974; Gray, 1982). Gray (1982) described in detail a behavioral inhibition system that is operative during exposure to signals predicting aversive circumstances. Behavioral inhibition would no doubt be accompanied by cardiac inhibition. Conditioned bradycardia is thus but one example of a variety of peripherally occurring events that may produce afferent feedback that could influence learning and memory. It is an important one, however, in the sense that its CNS substrate is beginning to be understood. The fact that such a CNS substrate has been identified suggests a possible central site for the reception of the peripheral afferent events that give rise to flashbulb memories or otherwise influence learning and memory processes. Anterior cingulate and prefrontal cortices and limbic thalamus are almost certainly a part of such a CNS substrate.

Acknowledgments

The research of both authors is supported by Veterans Administration Institutional Research Funds awarded to the Wm. Jennings Bryan Dorn Department of Veteran Affairs Medical Center, Columbia, SC 29201. The authors also thank Dianne Levine, Karen Watson, and Richard Thompson for assistance in data collection and analysis. We also thank Elizabeth Hamel for secretarial assistance and Judy Burris and the Medical Media Service of the Wm. Jennings Bryan Dorn VA Medical Center for assistance with the illustrations.

References

Albiniak BA, Powell DA (1980): Peripheral autonomic mechanisms and Pavlovian conditioning in the rabbit *(Oryctolagus cuniculus). J Comp Physiol Psychol* 94:1101–1113

Anand BK, Dua S (1956): Circulatory and respiratory changes induced by electrical stimulation of limbic system (visceral brain). *J Neurophysiol* 19:393–400

Bailey P, Sweet WH (1940): Effects on respira-

tion, blood pressure and gastric motility of stimulation of orbital surface of frontal lobe. *J Neurophysiol* 3:276–281

Bard P, Mountcastle VB (1948): Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behavior. *Res Publ—Assoc Res Nerv Ment Dis* 27:362–404

Beckstead RM (1979): An autoradiographic examination of corticocortical and subcortical projections of the mediodorsal-projection (prefrontal) cortex in the rat. *J Comp Neurol* 184:43–62

Benjamin RM, Jackson JC, Golden GT (1978): Cortical projections of the thalamic mediodorsal nucleus in the rabbit. *Brain Res* 141:251–265

Black AH (1972): The operant conditioning of central nervous system electrical activity. In: *The Psychology of Learning and Motivation,* Bower GH, ed. New York: Academic Press, Vol 6, pp 47–95

Black AH, DeToledo L (1972): The relationship among classically conditioned responses: Heart rate and skeletal behavior. In: *Classical Conditioning II: Current Theory and Research,* Black AH, Prokasy WF, eds. New York: Appleton-Century-Crofts, pp 290–311

Blass EM (1969): Thermoregulatory adjustments in rats after removal of the frontal poles of the brain. *J Comp Physiol Psychol* 69:83–90

Brady JV (1967): Emotion and the sensitivity of psychoendocrine systems. In: *Neurophysiology and Emotions,* Glass DC, ed. New York: Rockefeller University Press, pp 70–95

Brown DR, Randall DC, Raisch RM (1990): A temporally detailed reanalysis of the conditional heart rate response in dog. *Physiol Behav* 48:333–337

Brown R, Kulik J (1977): Flashbulb memories. *Cognition* 5:73–99

Bruner A (1969): Reinforcement strength in classical conditioning of leg flexion, freezing and heart rate in cats. *Conditional Reflex* 4:24–31

Buchanan SL (1988): Mediodorsal thalamic lesions impair differential Pavlovian heart rate conditioning. *Exp Brain Res* 73:320–328

Buchanan SL (1991): Differential and reversal Pavlovian conditioning in rabbits with mediodorsal thalamic lesions: Assessment of heart rate and eyeblink responses. *Exp Brain Res* 86:174–181

Buchanan SL, Powell DA (1982a): Cingulate cortex: Its role in Pavlovian conditioning. *J Comp Physiol Psychol* 96:755–774

Buchanan SL, Powell DA (1982b): Cingulate damage attenuates conditioned bradycardia. *Neurosci Lett* 29:261–268

Buchanan SL, Powell DA (1986): Electrical stimulation of anteromedial and mediodorsal thalamus elicits differential cardiovascular response patterns from conscious rabbits. *Physiol Psychol* 14:439–452

Buchanan SL, Powell DA (1989): Parasagittal thalamic knife cuts and cardiac changes. *Behav Brain Res* 32:241–253

Buchanan SL, Powell DA, Thompson RH (1989): Prefrontal projections to the medial nuclei of the dorsal thalamus in the rabbit. *Neurosci Lett* 106:55–59

Buchanan SL, Thompson RH (1990): Mediodorsal thalamic lesions and Pavlovian conditioning of heart rate and eyeblink responses in the rabbit. *Behav Neurosci* 104:912–918

Buchanan SL, Valentine JD, Powell DA (1985): Autonomic responses are elicited from medial but not lateral frontal cortex in rabbits. *Behav Brain Res* 18:51–62

Burns SM, Wyss JM (1985): The involvement of the anterior cingulate cortex in blood pressure control. *Brain Res* 340:71–77

Bykov KM (1957): *The Cerebral Cortex and the Internal Organs,* Gantt WH, transl. New York: Chemical Publishing Co

Cannon WB (1929): *Bodily Changes in Pain, Hunger, Fear and Rage.* New York: Appleton-Century

Cassell M, Wright D (1986): Topography of projections from the medial prefrontal cortex to the amygdala in the rat. *Brain Res Bull* 17:321–333

Cechetto DF, Saper CB (1987): Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. *J Comp Neurol* 262:27–45

Clugnet M, LeDoux JE (1990): Synaptic plasticity in fear conditioning circuits: Induction of LTP in the lateral nucleus of the amygdala by stimulation of the medial geniculate body. *J Neurosci* 10:2818–2824

Clugnet M, LeDoux JE, Morrison SF (1990): Unit responses evoked in the amygdala and striatum by electrical stimulation of the medial geniculate body. *J Neurosci* 10:1055–1061

Cohen DH, Macdonald RL (1976): Involvement of the avian hypothalamus in defensively conditioned heart rate change. *J Comp Neurol* 167:465–480

Cohen DH, Obrist PA (1975): Interactions between behavior and the cardiovascular system. *Circ Res* 37:693–706

Cohen DH, Randall DC (1984): Classical conditioning of cardiovascular responses. *Annu Rev Physiol* 46:187–197

Darrow CW (1937): Neural mechanisms controlling the palmar galvanic skin reflex and palmar sweating. *Arch Neurol Psychiatry* 37:641–663

Delacour J (1984): Two neuronal systems are involved in a classical conditioning in the rat. *Neuroscience* 13:705–715

Delgado JMR (1960): Circulatory effects of cortical stimulation. *Physiol Rev* 40:146–178

Delgado JMR, Livingston RB (1948): Some respiratory, vascular and thermal responses to stimulation of orbital surface of frontal lobe. *J Neurophysiol* 11:39–55

DeToledo L, Black AH (1966): Heart rate: Changes during conditioned suppression in rats. *Science* 152:1404–1406

Deutch AY, Roth RH (1990): The determinants of stress-induced activation of the prefrontal cortical dopamine system. *Prog Brain Res* 85:367–403

De Wied D (1980): Behavioral actions of neurohypophysial peptides. In: *Neuroactive Peptides,* Burgen A, Kosterlitz HW, Iversen LL, eds. London: Royal Society, pp 183–194

Disterhoft JF, Coulter DA, Alkon DL (1988): Conditioning-specific biophysical alterations in rabbit hippocampus. In: *Cellular Mechanisms of Conditioning and Behavioral Plasticity,* Woody CD, Alkon DL, McGaugh JL, eds. New York: Plenum, pp 89–104

Disterhoft JF, Olds J (1972): Differential development of conditioned unit changes in thalamus and cortex of rat. *J Neurophysiol* 35:665–679

Duncan PM (1972): Effect of septal area damage and base-line activity levels on conditioned heart-rate response in rats. *J Comp Physiol Psychol* 81:131–142

Dykman RA (1967): On the nature of classical conditioning. In: *Methods in Psychophysiology,* Brown CC, ed. Baltimore, MD: Williams & Wilkins, pp 234–283

Dykman RA, Mack RL, Ackerman PT (1965): The evolution of autonomic and motor components of the non-avoidance conditioned response in the dog. *Psychophysiology* 1:209–230

Elliot R (1974): The motivational significance of heart rate. In: *Cardiovascular Psychophysiology: Current Issues in Response, Mechanisms, Biofeedback and Methodology,* Obrist PA, Black AH, Brener J, Dicara LV, eds. Chicago: Aldine, pp 505–537

Eulenburg A, Landois L (1876): Vasomotor effects from cortex. *C R Hebd Seances Acad Sci* 82:564

Fehr FS, Stern JA (1970): Peripheral physiological variables and emotion: The James-Lange theory revisited. *Psychol Bull* 74:411–424

Ferron A, Thierry AM, Le Douarin C, Glowinski J (1984): Inhibitory influence of the mesocortical dopaminergic system on spontaneous activity or excitatory responses induced from the thalamic mediodorsal nucleus in the rat medial prefrontal cortex. *Brain Res* 302:257–265

Fitzgerald RD (1976): Involvement of vagal activity in the unconditioned heart-rate response of restrained rats. *Physiol Behav* 17:785–788

Fitzgerald RD, Martin GK, O'Brien JH (1973): Influence of vagal activity on classically conditioned heart rate in rats. *J Comp Physiol Psychol* 83:485–491

Fitzgerald RD, Teyler TJ (1970): Trace and delayed heart-rate conditioning in rats as a function of US intensity. *J Comp Physiol Psychol* 70:242–253

Francis J, Hernandez LL, Powell DA (1981): Lateral hypothalamic lesions: Effects on Pavlovian conditioning of eyeblink and heart rate responses in the rabbit. *Brain Res Bull* 6:155–163

Frysztak RJ, Neafsey EJ (1987): Effects of rat medial frontal cortex lesions on conditioned emotional responses. *Soc Neurosci Abstr* 13:1551

Fuster JM (1989): *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe,* 2nd ed. New York: Raven Press

Gabriel M (1990): Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits. *Prog Brain Res* 85:467–483

Gabriel M, Sparenborg S, Kubota Y (1989): Anterior and medial thalamic lesions, discriminative avoidance learning, and cingulate cortical neuronal activity in rabbits. *Exp Brain Res* 76:441–457

Gantt WH (1960): Cardiovascular component of the conditional reflex to pain, food, and other stimuli. *Physiol Rev* 40:266–291

Gibbs CM, Powell DA (1988): Neuronal correlates of classically conditioned bradycardia in the rabbit: Studies of the medial prefrontal cortex. *Brain Res* 442:86–96

Gibbs CM, Powell DA (1991): Single-unit activity in the dorsomedial prefrontal cortex during the expression of discriminative bradycardia in rabbits. *Behav Brain Res* 43:79–92

Gibbs CM, Prescott LB, Powell DA (1992): A comparison of multiple-unit activity in the me-

dial prefrontal and agranular insular cortices during Pavlovian heart rate conditioning in rabbits. *Exp Brain Res,* 89:599–610

Ginn SR, Valentine JD, Powell DA (1983): Concomitant Pavlovian conditioning of heart rate and leg flexion responses in the rat. *Pavlov J Biol Sci* 18:154–160

Goeders NE, Smith JE (1983): Cortical dopaminergic involvement in cocaine reinforcement. *Science* 221:773–775

Gold PE, McGaugh JL (1977): Hormones and memory. In: *Neuropeptide Influences on the Brain and Behavior,* Miller LH, Sandman CA, Kastin AJ, eds. New York: Raven Press, pp 127–143

Goldman-Rakic PS (1987): Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of Physiology, Sec I: The Nervous System, Vol. V: Higher Functions of the Brain, Part 1,* Plum F, Mountcastle V, eds. Bethesda; MD: Am Physiol Soc, pp 373–417

Goldman-Rakic PS (1990): Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. *Prog Brain Res* 85:325–336

Goldman-Rakic PS, Porrino LJ (1985): The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. *J Comp Neurol* 242:535–560

Gormezano I (1966): Classical conditioning. In: *Experimental Methods and Instrumentation in Psychology,* Sidowski JB, ed. New York: McGraw-Hill, pp 385–420

Gormezano I, Kehoe EJ, Marshall BS (1983): Twenty years of classical conditioning research with the rabbit. *Prog Psychobiol Physiol Psychol* 10:197–275

Graham FK, Clifton RK (1966): Heart-rate change as a component of the orienting response. *Psychol Bull* 65:305–320

Gray JA (1982): *The Neuropsychology of Anxiety: An Inquiry into the Functions of the Septo-hippocampal System.* New York: Oxford University Press

Groenewegen H (1988): Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neuroscience* 24:379–431

Groenewegen HJ, Berendse HW, Wolters JG, Lohman AHM (1990): The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: Evidence for a parallel organization. *Prog Brain Res* 85:95–118

Grueninger WE, Kimble DP, Grueninger J, Levine S (1965): GSR and corticosteroid response in monkeys with frontal ablations. *Neuropsychologia* 3:205–216

Hall RE, Livingston RB, Bloor CM (1977): Orbital cortical influences on cardiovascular dynamics and myocardial structure in conscious monkeys. *J Neurosurg* 46:638–647

Harvey JA, Gormezano I, Coolhauser VA, Schindler CW (1988): Effects of LSD on classical conditioning as a function of CS-UCS interval: Relationship to reflex facilitation. *Pharmacol Biochem Behav* 30:433–441

Hodes R, Magoun HW (1942a): Autonomic responses to electrical stimulation of forebrain and midbrain with special reference to pupil. *J Comp Neurol* 76:169–190

Hodes R, Magoun HW (1942b): Pupillary and other responses from stimulation of frontal cortex and basal telencephalon of rat. *J Comp Neurol* 76:461–472

Hoff EC, Kell JF Jr, Carroll MN Jr (1963): Effects of cortical stimulation and lesions on cardiovascular function. *Physiol Rev* 43:68–114

Huang Z, Varner KJ, Barman SM, Gebber GL (1988): Diencephalic regions contributing to sympathetic nerve discharge in anesthetized cats. *Am J Physiol* 254:R249-R256

Hurley KM, Herbert H, Moga MM, Saper CB (1991): Efferent projections of the infralimbic cortex of the rat. *J Comp Neurol* 308:249–276

Hurley-Guis KM, Neafsey EJ (1986): The medial frontal cortex and gastric motility: Microstimulation results and their possible significance for the overall pattern of organization of rat frontal and parietal cortex. *Brain Res* 365:241–248

Isamat F (1961): Galvanic skin responses from stimulation of limbic cortex. *J Neurophysiol* 24:176–181

Iwata J, LeDoux JE (1988): Disassociation of associative and nonassociative concomitants of classical fear conditioning in the freely behaving rat. *Behav Neurosci* 102:66–76

Iwata J, LeDoux JE, Reis DJ (1986): Destruction of intrinsic neurons in the lateral hypothalamus disrupts the classical conditioning of autonomic but not behavioral emotional responses in the rat. *Brain Res* 386:161–166

Jarrell TW, Romanski LM, Gentile CG, McCabe PM, Schneiderman N (1986): Ibotenic acid lesions in the medial geniculate region prevent

the acquisition of differential Pavlovian conditioning of bradycardia to acoustic stimuli in rabbits. *Brain Res* 382:199–203

Jasper HH (1960): Unspecific thalamocortical relations. In: *Handbook of Physiology, Sect 1: Neurophysiology, Vol. II,* Field J, Magoun HW, Hall VE, eds. Washington, DC: Am Physiol Soc, pp 1307–1321

Joseph JA, Engle BT (1981): Instrumental control of cardioacceleration induced by central electrical stimulation. *Science* 214:341–343

Kaada BR (1951): Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat and dog. *Acta Physiol Scand* 23:1–285

Kaada BR (1960): Cingulate, posterior orbital, anterior insular and temporal pole cortex. In: *Handbook of Physiology, Sect 1: Neurophysiology, Vol. II,* Field J, Magoun HW, Hall VE, eds. Washington, DC: Am Physiol Soc, pp 1345–1372

Kao K-T, Powell DA (1988): Lesions of the substantia nigra retard Pavlovian eyeblink but not heart rate conditioning in the rabbit. *Behav Neurosci* 102:515–525

Kapp BS, Frysinger RC, Gallagher M, Haselton JR (1979): Amygdala central nucleus lesions: Effect on heart rate conditioning in the rabbit. *Physiol Behav* 23:1109–1117

Kapp BS, Schwaber JS, Driscoll PA (1985a): Frontal cortex projections to the amygdaloid central nucleus in the rabbit. *Neuroscience* 15:327–346

Kapp BS, Schwaber JS, Driscoll PA (1985b): The organization of insular cortex projections to the amygdaloid central nucleus and autonomic regulatory nuclei of the dorsal medulla. *Brain Res* 360:355–360

Katcher AH, Solomon RL, Turner LH, LoLordo V, Overmier JB, Rescorla RA (1969): Heart rate and blood pressure responses to signaled and unsignaled shocks: Effects of cardiac sympathectomy. *J Comp Physiol Psychol* 68:163–174

Kazis E, Milligan WL, Powell DA (1973): Autonomic-somatic relationships: Blockade of heart rate and corneoretinal potential. *J Comp Physiol Psychol* 84:98–110

Konorski J (1967): *Integrative Activity of the Brain.* Chicago: University of Chicago Press

Krushel LA, Van Der Kooy D (1988): Visceral cortex: Integration of the mucosal senses with limbic information in the rat agranular insular cortex. *J Comp Neurol* 270:39–54

Lacey BC, Lacey JI (1974): Studies of heart rate and other bodily processes in sensorimotor behavior. In: *Cardiovascular Psychophysiology: Current Issues in Response, Mechanisms, Biofeedback, and Methodology,* Obrist PA, Black AH, Brener J, DiCara LV, eds. Chicago: Aldine, pp 538–564

Lacey BC, Lacey JI (1980): Cognitive modulation of time-dependent primary bradycardia. *Psychophysiology* 17:209–221

Langworthy OR, Richter CP (1930): The influence of efferent cerebral pathways upon the sympathetic nervous system. *Brain* 53:178–193

Laroche S, Jay TM, Thierry A (1990): Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. *Neurosci Lett* 114:184–190

Lavond DG, Logan CG, Sohn JH, Garner WDA, Kansawa SA (1990): Lesions of the cerebellar interpositus nucleus abolish both nictitating membrane and eyelid EMG conditioned responses. *Brain Res* 514:238–248

LeDoux JE (1987): Emotion. In: *Handbook of Physiology, Sect 1: The Nervous System, Vol. V: Higher Functions of the Brain, Part 1,* Plum F, Mountcastle V, eds. Bethesda, MD: Am Physiol Soc, pp 419–459

LeDoux JE, Cicchetti P, Xagoraris A, Romanski LM (1990): The lateral amygdaloid nucleus: Sensory interface of the amygdala in fear conditioning. *J Neurosci* 10:1062–1069

LeDoux JE, Sakaguchi A, Reis DJ (1984): Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. *J Neurosci* 4:683–698

Leshner AI, Merkle DA, Mixon JF (1981): Pituitary-adrenocortical effects on learning and memory in social situations. In: *Endogenous Peptides and Learning and Memory Processes,* Martinez JL Jr, Jensen RA, Messing RB, Rigter H, McGaugh JL, eds. New York: Academic Press, pp 159–179

Livingston RB, Fulton JF, Delgado JMR, Sachs E Jr, Brendler SJ, Davis GD (1948): Stimulation and regional ablation of orbital surface of frontal lobe. *Res Publ—Assoc Res Nerv Ment Dis* 27:405–420

Lofving B (1961): Cardiovascular adjustments induced from the rostral cingulate gyrus with special reference to sympatho-inhibitory mechanisms. *Acta Physiol Scand* 53(Suppl 184):1–82

Markowitsch HJ (1982): Thalamic mediodorsal

nucleus and memory: A critical evaluation of studies in animals and man. *Neurosci Biobehav Rev* 6:351–380

Martinez JL Jr (1986): Memory: Drugs and hormones. In: *Learning and Memory: A Biological View,* Martinez JL Jr, Kesner RP, eds. Orlando, FL: Academic Press, pp 127–163

McDonald A (1987): Organization of amygdaloid projections to the mediodorsal thalamus and prefrontal cortex: A fluorescence retrograde transport study in the rat. *J Comp Neurol* 262:46–58

McDonald A (1991): Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience* 44:1–14

McGaugh JL (1990): Significance and remembrance: The role of neuromodulatory systems. *Psychol Sci* 1:15–25

Miller NE (1983): Biofeedback and visceral learning. *Annu Rev Psychol* 29:373–404

Moore JW, Desmond JE, Berthier NE (1982): The metencephalic basis of the conditioned nictitating membrane response. In: *Representation of Involved Neural Functions,* Woody CD, ed. New York: Plenum, pp 455–478

Murray K (1967): Operant conditioning. In: *Methods in Psychophysiology,* Brown CC, ed. Baltimore, MD: Williams & Wilkins, pp 291–310

Nathan MA, Smith OA (1971): Conditional cardiac and suppression responses after lesions in the dorsomedial thalamus of monkeys. *J Comp Physiol Psychol* 76:66–73

Neafsey EJ (1990): Prefrontal cortical control of the autonomic nervous system: Anatomical and physiological observations. *Prog Brain Res* 85:147–166

Neafsey EJ, Hurley-Guis KM, Arvanitis D (1986): The topographical organization of neurons in the rat medial frontal, insular and olfactory cortex projecting to the solitary nucleus, olfactory bulb, periaqueductal gray and superior colliculus. *Brain Res* 377:261–270

Newman PP (1974): *Visceral Afferent Functions of the Nervous System.* Baltimore, MD: Williams & Wilkins

O'Brien CP, Childress AR, McLellan AT, Ehrman R, Ternes JW (1988): Types of conditioning found in drug-dependent humans. In: *Learning Factors in Drug Abuse,* Ray BA, ed. Washington, DC: US Public Health Service, NIDA Res Monogr 84, pp 44–61

Obrist PA (1981): *Cardiovascular Psychophysiology: A Perspective.* New York: Plenum

Orona E, Gabriel M (1983a): Multiple-unit activity of the prefrontal cortex and mediodorsal thalamic nucleus during acquisition of discriminative avoidance behavior in rabbits. *Brain Res* 263:295–312

Orona E, Gabriel M (1983b): Multiple-unit activity of the prefrontal cortex and mediodorsal thalamic nucleus during reversal learning of discriminative avoidance behavior in rabbits. *Brain Res* 263:313–329

Pavlov I (1927): *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex,* Anrep GV, transl. New York: Oxford University

Powell DA (1979): Peripheral and central muscarinic cholinergic blockade: Effects on Pavlovian conditioning. *Bull Psychon Soc* 14:161–164

Powell DA, Buchanan SL (1986): Chemical stimulation of the mediodorsal nucleus of the thalamus elicits autonomic adjustments. *Pharmacol Biochem Behav* 25:423–430

Powell DA, Buchanan SL, Gibbs CM (1990a): Role of the prefrontal-thalamic axis in classical conditioning. *Prog Brain Res* 85:433–466

Powell DA, Buchanan SL, Hernandez LL (1985): Electrical stimulation of insular cortex elicits cardiovascular adjustments but insular lesions do not abolish conditioned bradycardia. *Behav Brain Res* 17:125–144

Powell DA, Joseph JA (1974): Autonomic-somatic interaction and hippocampal theta activity. *J Comp Physiol Psychol* 87:978–986

Powell DA, Kazis E (1976): Blood pressure and heart rate changes accompanying classical eyeblink conditioning in the rabbit *(Oryctolagus cuniculus). Psychophysiology* 13:441–447

Powell DA, Levine-Bryce D (1988): A comparison of two model systems of associative learning: Heart rate and eyeblink conditioning in the rabbit. *Psychophysiology* 25:672–682

Powell DA, Levine-Bryce D (1989): Conditioned bradycardia in the rabbit: Effects of knife cuts and ibotenic acid lesions in the lateral hypothalamus. *Exp Brain Res* 76:103–121

Powell DA, Lipkin M, Milligan WL (1974): Concomitant changes in classically conditioned heart rate and corneoretinal potential discrimination in the rabbit *(Oryctolagus cuniculus). Learn Motiv* 5:532–547

Powell DA, Mankowski D, Buchanan SL (1978): Concomitant heart rate and corneoretinal potential conditioning in the rabbit *(Oryctolagus cuniculus):* Effects of caudate lesions. *Physiol Behav* 20:143–150

Powell DA, Milligan WL (1975): Effects of par-

tial and continuous reinforcement on conditioned heart rate and corneoretinal potential responses in the rabbit *(Oryctolagus cuniculus). Psychol Rec* 25:419–426

Powell DA, Schneiderman N, Elster AJ, Jacobson A (1971): Differential classical conditioning in rabbits *(Oryctolagus cuniculus)* to tones and change in illumination. *J Comp Physiol Psychol* 76:267–274

Powell DA, Watson K (1990): Ibotenic lesions of the prefrontal cortex in the rabbit: Effects on heart rate conditioning. *Soc Neurosci Abstr* 16:269

Powell DA, Watson K, Buchanan SL (1990b): Neuronal activity in the mediodorsal and intralaminar nuclei of the dorsal thalamus during classical heart rate conditioning. *Brain Res* 532:211–221

Pribram KH, McGuiness D (1975): Arousal, activation and effort in the control of attention. *Psychol Rev* 82:116–149

Prokasy WF (1984): Acquisition of skeletal conditioned responses in Pavlovian conditioning. *Psychophysiology* 21:1–13

Putnam LE, Ross LE, Graham FK (1974): Cardiac orienting during "good" and "poor" differential eyelid conditioning. *J Exp Psychol* 102:563–573

Reep R (1984): Relationship between prefrontal and limbic cortex: A comparative anatomical review. *Brain Behav Evol* 25:5–80

Rose J, Woolsey C (1948): The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. *Res Publ—Assoc Res Nerv Ment Dis* 27:210–232

Saper CB (1982): Convergence of autonomic and limbic connections in the insular cortex of the rat. *J Comp Neurol* 210:163–173

Saper CB (1985): Organization of cerebral cortical afferent systems in the rat. II. Hypothalamocortical projections. *J Comp Neurol* 237:21–46

Scheibel ME, Scheibel AB (1967): Structural organization of nonspecific thalamic nuclei and their projection toward cortex. *Brain Res* 6:60–94

Schneiderman N (1972): Response system divergencies in aversive classical conditioning. In: *Classical Conditioning II: Current Theory and Research,* Black AH, Prokasy WF, eds. New York: Appleton-Century-Crofts, pp 341–376

Schneiderman N, Francis J, Sampson LD, Schwaber JS (1974): CNS integration of learned cardiovascular behavior. In: *Limbic and Autonomic Nervous Systems Research,* Dicara LV, ed. New York: Plenum, pp 277–309

Schwaber JS, Kapp BS, Higgins GA, Rapp PR (1982): Amygdaloid and basal forebrain direct connections with the nucleus of the solitary tract and the dorsal motor nucleus. *J Neurosci* 2:1424–1438

Shapiro D, Schwartz GE (1972): Biofeedback and visceral learning: Clinical applications. *Semin Psychiatry* 4:171–184

Sherrington CS (1900): Experiments on the value of vascular and visceral factor for the genesis of emotion. *Proc R Soc London* 66:390–403

Shipley MT (1982): Insular cortex projection to the nucleus of the solitary tract and brainstem visceromotor regions in the mouse. *Brain Res Bull* 8:138–148

Showers MJC, Crosby EC (1958): Somatic and visceral response from the cingulate gyrus. *Neurology* 8:561–565

Siegel S (1979): The role of conditioning in drug tolerance and addiction. In: *Psychopathology in Animals: Research and Clinical Implications,* Keehn JD, ed. New York: Academic Press, pp 143–168

Sikes RW, DeFrance JF (1985): Cingulate cortex response to electrical stimulation of the mediodorsal nucleus. *Exp Neurol* 89:428–441

Skinner JE, Reed JC (1978): Prevention of ventricular fibrillation in the ischemic myocardium of the conscious pig during cryogenic blockade in the thalamic gating system. In: *Neural Mechanisms in Cardiac Arrhythmias,* Schwartz PJ, Brown AM, Malliani A, Zanchetti A, eds. New York: Raven Press, pp 275–278

Sloan N, Jasper H (1950): Studies of regulatory functions of limbic cortex. *Electroencephalogr Clin Neurophysiol* 2:317–327

Slotnick BM, Kaneko N (1981): Role of mediodorsal thalamic nucleus in olfactory discrimination learning in rats. *Science* 214:91–92

Smith OA, DeVito JL (1984): Central neural integration for the control of autonomic responses associated with emotion. *Annu Rev Neurosci* 7:43–65

Smith OA, Nathan MA, Clarke NP (1968): Central nervous system pathways mediating blood pressure changes. *Hypertension* 16:9–22

Smith WK (1938): The representation of respiratory movements in the cerebral cortex. *J Neurophysiol* 1:55–68

Smith WK (1945): The functional significance of the rostral cingular cortex as revealed by its responses to electrical excitation. *J Neurophysiol* 8:241–255

Sokolov EN (1963): *Perception and the Condi-*

tioned Reflex. New York: Macmillan

Spencer WG (1894): The effect produced upon respiration by faradic excitation of the cerebrum in the monkey, dog, cat and rabbit. *Philos Trans R Soc London, Ser B* 185:609–657

Staubli U, Schottler F, Nejat-Bina D (1987): Role of dorsomedial thalamic nucleus and piriform cortex in processing olfactory information. *Behav Brain Res* 25:117–129

Stern JA (1972): Physiological response measures during classical conditioning. In: *Handbook of Psychophysiology,* Greenfield NS, Steinbach RA, eds. New York: Holt, Rinehart, & Winston, pp 197–227

Sutterer JR, Obrist PA (1972): Heart rate and general activity alterations of dogs during several aversive conditioning procedures. *J Comp Physiol Psychol* 80:314–326

Terreberry RR, Neafsey EJ (1983): Rat medial frontal cortex: A visceral motor region with a direct projection to the solitary nucleus. *Brain Res* 278:245–249

Teyler TJ (1971): Effects of restraint on heart-rate conditioning in rats as a function of US location. *J Comp Physiol Psychol* 77:31–37

Thierry A, Godbout R, Mantz J, Glowinski J (1990): Influence of the ascending monoaminergic systems on the activity of the rat prefrontal cortex. *Prog Brain Res* 85:357–365

Thompson RF (1986): The neurobiology of learning and memory. *Science* 233:941–947

Thompson RF (1988): The neural basis of basic associative learning of discrete behavioral responses. *Trends Neurosci* 11:152–155

Thompson RF, Donegan NH, Lavond DG (1988): The psychobiology of learning and memory. In: *Stevens Handbook of Experimental Psychology,* Atkinson RC, Herrnstein RJ, Lindsey G, Luce RD, eds. New York: Wiley, 2nd ed, Vol 2, pp 245–347

Thorndike EL (1911): *Animal Intelligence.* New York: Macmillan

Uylings HBM, Van Eden CG (1990): Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Prog Brain Res* 85:31–62

Van Der Kooy D, Koda LY, McGinty JF, Gerfen CR, Bloom FE (1984): The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. *J Comp Neurol* 224:1–24

Van Der Kooy D, McGinty JF, Koda LY, Gerfen CR, Bloom FE (1982): Visceral cortex: A direct connection from prefrontal cortex to the solitary nucleus in rat. *Neurosci Lett* 33:123–127

Vanderwolf CH (1971): Limbic-diencephalic mechanisms of voluntary movement. *Psychol Rev* 78:83–113

Varner KJ, Barman SM, Gebber GL (1988): Cat diencephalic neurons with sympathetic nerve-related activity. *Am J Physiol* 254:R257-R267

Ward AA Jr (1948): The anterior cingulate gyrus and personality. *Res Publ—Assoc Res Nerv Ment Dis* 27:438–445

Waring AE, Means LW (1976): The effect of medial thalamic lesions on emotionality, activity, and discrimination learning in the rat. *Physiol Behav* 17:181–186

Washton AM (1978): Pavlovian conditioning of heart rate in *Macaca mulatta:* Autonomic and stimulus control of cardiac responding as a function of CS-US interval. Unpublished Ph.D. dissertation, City University of New York

Weinberger NM, Diamond DM (1987): Physiological plasticity in auditory cortex: Rapid induction by learning. *Prog Neurobiol* 29:1–55

Weis BJ, Means LW (1980): A comparison of the effects of medial frontal, dorsomedial thalamic, and combination lesions on discrimination and spontaneous alteration in the rat. *Physiol Psychol* 8:325–329

West CHK, Benjamin RM (1983): Effects of stimulation of the mediodorsal nucleus and its projection cortex on heart rate in the rabbit. *J Auton Nerv Syst* 9:547–557

Wilcott RC (1968): Cortical control of skin potential, skin resistance and sweating. *Psychophysiology* 4:500

Yasui Y, Breder CD, Saper CB, Cechetto DF (1991): Autonomic responses and efferent pathways from the insular cortex in the rat. *J Comp Neurol* 303:355–374