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Review

Fear and power-dominance drive motivation: neural representations and pathways mediating sensory and mnemonic inputs, and outputs to premotor structures

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Abstract

Based on the available literature on activation of brain structures by fear- and anger-inducing stimuli, on the effects of electrical and chemical stimulation and lesions of candidate structures, and on connectional data, we propose that both the fear and power-dominance drives are represented in four distinct locations: the medial hypothalamus, lateral/dorsolateral periaqueductal gray, midline thalamic nuclei, and medial prefrontal cortex. The hypothalamic fear representation is located in the dorsomedial and posterior hypothalamic nuclei, the midbrain representation in the caudal part of the lateral/dorsolateral periaqueductal gray, the thalamic representation primarily in parts of the paraventricular and reuniens thalamic nuclei, and the cortical representation in prelimbic cortex. The hypothalamic power-dominance representation is located in the anterior hypothalamic nucleus, dorsomedial aspect of the ventromedial nucleus, and in adjacent parts of the medial preoptic area. The corresponding midbrain representation occurs in rostral part of the lateral/dorsolateral periaqueductal gray, and the thalamic representation in parts of the paraventricular, parataenial, and reuniens thalamic nuclei. We discuss sensory/mnemonic inputs to these representations, and outputs to premotor structures in the medulla, caudate-putamen, and cortex, and their differential contributions to involuntary, learned sequential, and voluntary motor acts. We examine potential contributions of neuronal activities in these representations to the subjective awareness of fear and anger.

Keywords: Fear; Aggression; Dominance hierarchies; Periaqueductal gray matter; Hypothalamus; Medial prefrontal cortex

Contents

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1. Introduction

Motivational drives such as hunger, thirst, fear and anger are experienced subjectively as needs or urges that motivate behaviors. Generally speaking the behaviors generated by these drives are designed to protect and preserve the individual human or animal, and to ensure the continuance of the species he or it belongs to. These drives are activated by both internal and external factors; hunger and thirst are due primarily to signals detected within the body, but they are also affected by external visual, auditory and olfactory stimuli. Fear and anger are due mostly to external stimuli, and the sexual drive in mammalian species is due to both hormonal and sensory (olfactory, visual) stimuli [123,230].

Fear motivates behaviors that are intended to reduce potential dangers to the individual. These include escape locomotion and jumping, freezing ('fear paralysis'), alarm vocalizations, and piloerection. In addition, fear inducing stimuli activate autonomic responses, such as increased arterial pressure and heart rate. In the laboratory, degrees of fear or anxiety can be determined by measuring the amount of time spent on the open arms of the elevated maze, the number of grid line crossings in a novel open field, and freezing behavior duration after forced swimming. We note here that we use the term anxiety in essentially the same sense as fear, with the proviso that anxiety connotes lesser fear, and often does not have a specific object, while fear is always directed at a specific stimulus. By panic, we mean extreme fear.

In both animals and humans many behaviors are motivated by what Maslow [188] termed the 'dominance' drive, Adler [3] referred to as 'striving for superiority', and Harding [129] termed the 'power' drive. The earliest reference to this form of motivation is probably that of Nietzsche [216], who spoke of a 'will to power'. In both social and solitary animals, this drive motivates aggressive, defensive, and other behaviors that establish dominance hierarchies, as well as behaviors involved in establishing and guarding territorial domains [96,237]. Maslow argued that what enables one individual (human or animal) to dominate another was its attitude of confidence or superiority, and this is backed up by the individual's fighting ability [189]. In humans the reward due to the achievement of dominance status is experienced as increased self esteem or 'dominance feeling' [129,188]. In contemporary western human societies outright physical aggression is rarely tolerated, and behaviors that are motivated by the power-dominance drive are mostly restricted to those that we attribute to 'ambition' or 'drive', which include competition in the workplace and athletic events, as well as behaviors that lead to the acquisition of material objects such as houses, automobiles and money that might increase one's social status (i.e. behaviors that are commonly assumed to be motivated by material greed). However, verbal and other forms of emotional aggression are still commonplace, and are presumably motivated by the power-dominance drive. In gregarious animal societies, behaviors used to establish dominance hierarchies include physical aggression and scent marking of objects in the territory occupied by a group [96,100]. Humans experience the power-dominance drive subjectively as a need to excel, to overcome obstacles, and in its extreme form, as anger.

In human sensory systems there are neural representations of sensory stimuli present in the proximal environment. In the mammalian visual system, for example, there are several retinotopically organized areas—both cortical and subcortical—where the activities of large numbers of neurons map particular features of the visual scene, and the subjective awareness of this scene is produced by the activities of neurons in some (but not all) of these representations [90,108,308,309]. Stimulation of sites within the lower order visuotopically organized representations in human visual cortex evokes phosphenes. For example, microstimulation of striate cortex of both normal subjects and subjects who are blind due to retinal damage produces punctate phosphenes located in points within the visual field which correspond to the point in the visuotopic map which is stimulated [44,78,256]. Phosphenes can be produced using bipolar electrodes with currents as low as 1.9 μA, and average thresholds around 25 μA, and these currents produce percepts reported as small spots of light [256]. Stimulation of the human superior colliculus also produces phosphenes, but the threshold currents necessary to produce these phenomena are probably much higher [214]. This is in accordance with the fact that activities in striate cortex contribute to visual awareness, but those in the superior colliculus do not [261,276].

The subjective awareness of emotions such as hunger, sexual desire, fear and power-dominance must also be due to neuronal activities in the central nervous system, and by analogy with sensory systems, it may be expected that activities of a large number of neurons grouped in one or more areas of the brain produce this form of awareness. In a fear representation neurons should be specifically activated by the presentation of stimuli that evoke this form of motivation, but not to irrelevant stimuli, or stimuli which evoke drives other than fear. Also by analogy with sensory systems it may be inferred that there may be multiple representations of fear or power-dominance, and not all of these need contribute to the subjective awareness of these emotions. In human subjects, electrical stimulation of sites within the dorsal (but not ventral) periaqueductal gray matter (PAG) elicits intense anxiety, distress, panic, terror, and feelings of imminent death [147,213], while stimulation of sites within the medial hypothalamus elicits anxiety and fear (Fig. 1) [131]. Stimulation of a site within Brodmann area 32 of anterior cingulate cortex (probably homologous to prelimbic cortex of rodents and primates) of a surgery patient elicited a verbal report that "I was afraid and my heart started to beat" [19]. Although subjective experiences of fear can also be elicited by stimulation of sites within the amygdaloid complex [61,119,120], stimulation currents

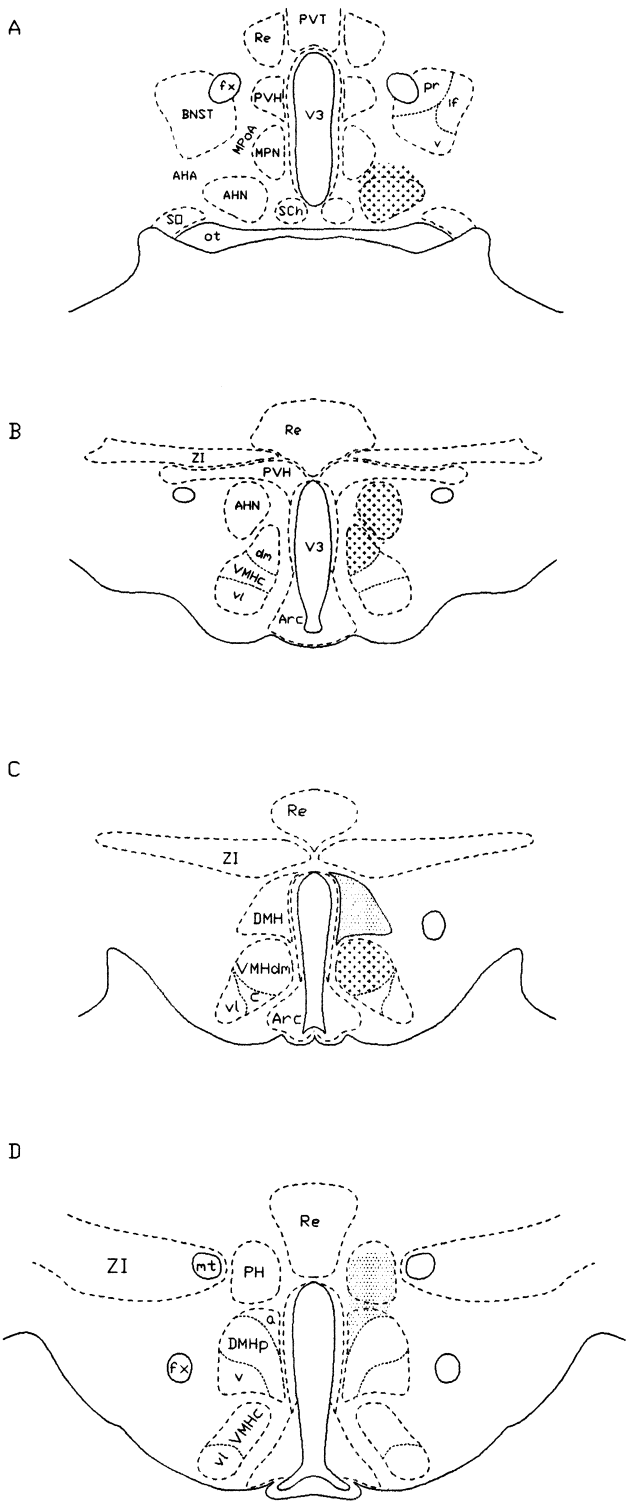

Fig. 1. Locations of the fear and power-dominance representations in the medial hypothalamus of the rat. Stippled areas indicate the fear representation, plus the power-dominance representation. Representations are bilateral, but only indicated unilaterally for clarity. Top section is the most anterior. Abbreviations: AHN, anterior hypothalamic nucleus; Arc, arcuate nucleus; BNST, bed nucleus of the stria terminalis (if, pr, v interfascicular, principal, ventral subnuclei); DMH, dorsomedial hypothalamic nucleus (a, p, v anterior, posterior and ventral subdivisions); fx, fornix; MPoA, medial preoptic area; MPN, medial preoptic nucleus; ot, optic tract; PH, posterior hypothalamic nucleus; PVH, paraventricular hypothalamic nucleus; PVT, paraventricular thalamic nucleus; Re, reuniens thalamic nucleus; Sch, suprachiasmatic nucleus; SO, supraoptic nucleus; V3, third ventricle; VMH, ventromedial hypothalamic nucleus (c, dm, vl central, dorsomedial, ventrolateral divisions); ZI, zona incerta.

used in these studies were quite large, ranging from about 5000 μa to 9000 μA, and afterdischarges often occurred. In addition to fear, these stimulations evoked memory-like hallucinations, and Gloor [119] has argued that the experiential phenomena evoked by stimulation within the amygdaloid complex are due to spreading of afterdischarges to surrounding structures. Thus in the search for areas or structures in which the fear drive is represented, one might expect to find such representations in the hypothalamus, PAG, and medial prefrontal/anterior cingulate cortex, but probably not in the amygdala.

The purpose of this paper is to determine the location and extent of cortical and subcortical fear and power-dominance representations and their interrelationships. In order to accomplish this objective, we will specifically address forms of behaviors that are motivated by these drives. Behaviors motivated by the fear drive in rodents, carnivores and primates include freezing (defined here as reactive, fear-evoked involuntary behavioral immobility), as well as flight and other forms of escape. In rodents, two forms of behavior which are motivated by the power-dominance drive have been extensively studied, and have been shown to have common neural substrates: aggressive ('affective defense') behaviors, and scent marking in hamsters. In carnivores the only form of behavior motivated by the power-dominance drive that has been studied in any detail is aggression. In non-human primates, studies of the effects of lesions and electrical stimulation of central structures on fear- and power-dominance-motivated behaviors are few. However, there are several studies of brain areas activated by fear- and anger-inducing stimuli in human subjects, and these will be examined.

In many species of rodents, when a male intruder is introduced into the home cage of a 'resident' male the resident will attack the intruder. In rats these attacks are characterized by lateral attacks, boxing and biting, and usually the larger animal will defeat the smaller one [38]. Thereafter the defeated rat will become submissive in the presence of the larger (now dominant) rat. In situations in which several animals share a restricted territory, dominant/subordinate relationships are initially determined by overt aggression [99,237], but once the hierarchy is established other behaviors may be used to communicate dominant/subordinate relationships. One such behavior is scent marking, a behavior that is observed in numerous mammalian species, including mice, hamsters, rats, deer, cats, dogs and black rhinoceri [237]. In social animals scent marking of objects in the environment is always observed when a dominance hierarchy is present. In most species in

which this behavior is observed there is a striking correlation between a high rate of marking and high social status or dominance. For this reason, it has been proposed that scent marking behavior communicates dominance status [94,96,143,156]. Hamsters, for example, use their flank glands (darkly pigmented sebaceous glands located on the dorsolateral region of the flanks) to mark objects in their environment by arching their backs and vigorously rubbing their flank glands against vertical objects while moving forward. This behavior occurs in response to the presence of conspecifics or of their odors, and most probably serves to communicate dominance status [96]. The most aggressive, dominant hamsters mark significantly more than subordinates [82].

Cats are territorial animals, and defend their territory with threat displays, which include piloerection, hissing, growling, back arching, and overt attack behaviors. In natural situations these behaviors occur in the presence of a strange animal of the same or different species, or when a cat's territory or its kittens are threatened [124]. Cats also mark the boundaries of their territories using cheek gland excretions and urine [293].

Stimuli that elicit fear often also elicit anger or some other component of the power-dominance drive. For example, agonistic encounters between resident and intruder rodents elicit both fear and anger in both animals, and behavioral acts in the dominant animal will be primarily motivated by anger, while those of the submissive one will be mostly due to fear. Other stimuli that elicit fear and/or power-dominance (mostly anger) include exposure to a predator, inescapable footshock, loud auditory signals (audiogenic stress), restraint (immobilization), and auditory and visual stimuli repeatedly paired with unconditioned nociceptive stimuli such as footshock. Inescapable pain elicits fear, anger and the affective/motivational aspect of pain [13,142,173,239], so it is probable that stimuli conditioned to electrical shock also elicit all three of these forms of motivation. Restraint stress, particularly when it is repeated, produces both freezing and struggling behaviors, and the latter are probably motivated at least in part by anger. Although the behavioral responses of rats to loud noise are characteristic of fear [49], in human subjects this form of stress also produces anger. The behavioral responses due to stimuli that produce both fear and power-dominance will presumably be determined by the relative activation of these two drives (e.g. fight or flight responses).

In order to determine the existence and location of fear and power-dominance representations it is necessary to establish criteria that serve to differentiate areas or structures in which neuronal activities represent these drives, and other areas where activities represent either sensory, mnemonic, or other processes, or in which they represent other emotions. A first and important criterion is that low current electrical stimulation and/or low dose chemical stimulation of a candidate structure should either elicit or facilitate behaviors characteristic of either fear or power-dominance. While this is a necessary criterion, it is by no means sufficient, since stimulation of sensory structures that provide inputs to motivational representations may also elicit such behaviors, as may stimulation of premotor structures. Most importantly, electrical stimulation of sites within fear and power-dominance representations in human subjects should elicit verbal reports of the subjective experience of these drives, and it is to be hoped that stimulation of the homologous structures in animals would elicit behaviors and autonomic responses that are characteristic of those drives. It should be noted, however, that problems can arise with the interpretation of the results of these studies, particularly in the case of electrical stimulation, since fibers of passage can be excited, or after discharges can spread to surrounding structures. In addition, stimulation of structures adjacent to candidate drive representations can potentially elicit behaviors characteristic of those drives by transynaptic activation of a drive representation, and chemical stimulation of a given structure may not reveal the whole behavioral repertoire, since the substances used often activate only one type of receptor.

The second criterion involves the interpretation of the effects of lesions to candidate areas on behaviors motivated by the fear or power-dominance drive: lesions to areas containing putative representations of these drives should result in deficits in behaviors motivated by these drives. As in the case of stimulation studies, this criterion is not a sufficient one, since lesions to sensory, mnemonic, premotor and motor structures may also produce deficits in fear-motivated behaviors. A third criterion is that fear- or power-dominance-evoking stimuli, both innate and conditioned, should activate neurons in the corresponding representations, and studies of regional brain activation should reveal this. This criterion is clearly not a necessary one, since if there are multiple representations of each of these drives, one or more of these representations might not be activated, and the corresponding behavior could still occur. In addition stimuli that elicit fear may also simultaneously activate the power-dominance drive (e.g. the resident-intruder paradigm), and structures activated by such stimuli will include both fear and power-dominance representations, as well as sensory, mnemonic, premotor and motor structures. Below we cite several studies of structures activated by stressful stimuli in which the immediate-early gene c-Fos method was used. We note here that it is not really possible to demonstrate that neurons that are activated by this method are necessarily activated by the stressful stimulus itself, since it is necessary to wait for a considerable period of time between exposure to the stimuli and decapitation. Often, in fact, numerous olfactory structures are found to be 'activated' by stressors, whereas in fact their activation is probably due to olfactory processing after the stimulus has been removed. On the other hand, studies of structures activated by stressful

stimuli in human subjects employ magnetic resonance imaging, or the detection of regional cerebral brain flow using positron emission tomography, and these methods are instantaneous and consequently do not introduce the problems involved in the c-Fos method.

In addition to the above specific criteria, certain more general considerations pertain to motivational representations. Since the subjective experience of emotions such as fear or power-dominance is unitary, if there is more than one representation, and more than one representation contributes to subjective awareness, then some form of binding between separate representations must take place. This form of binding is presumably mediated by interconnections between the representations [76], so it is to be expected that motivational representations will be strongly and reciprocally interconnected.

2. Neural representations of the fear and power-dominance drives

2.1. Hypothalamus

The involvement of the diencephalon in emotion has been evident since the time of Cannon [52,53], who observed that emotional reactions in animals persisted after removal of the cortex, while removal of the thalamus and hypothalamus as well as the cortex abolished all signs of emotional reactivity. Lesion experiments by Bard [22–24] localized the area of the diencephalon responsible for emotional expression to the hypothalamus. Subsequently, Hess and Brügger [138] demonstrated that electrical stimulation of sites within the hypothalamus evoked an aggressive behavior pattern termed the 'defense reaction'. Heath [131] reported that stimulation of sites within the human medial hypothalamus evoked subjective fear and anxiety.

The neural substrates of 'affective defense' behaviors in cats have been extensively studied by Siegel and coworkers [124,268]. In the laboratory, electric stimulation of hypothalamic sites elicits hissing, growling, threat postures and aggressive paw swipes at moving objects [111,112,124, 267,268]. The area in which stimulating electrodes produce these behaviors includes the anterior hypothalamic nucleus, adjacent part of the medial preoptic area, and the dorsomedial division of the ventromedial hypothalamic nucleus. In rats, electrical stimulation of sites in the anterior hypothalamic nucleus and adjacent parts of the ventromedial nucleus produces vigorous affective attack behaviors on cage partners [34,167,171]. Microinjections of arginine-vasopressin into the anterior hypothalamic nucleus and adjacent parts of the medial preoptic area of resident golden hamsters significantly shortens the latency biting attacks on intruders placed in their home cages [18,93,100]. Blockade of the V1 receptor for arginine-vasopressin using the antagonist d(CH2)5Tyr(Me)AVP into the anterior hypothalamic nucleus reduces the number of biting attacks, and also causes an increase in the resident hamster's latencies to attack the intruder [97]. Another form of aggressive behavior, termed 'predatory attack', can be elicited by stimulation of sites within the lateral hypothalamic area [97]. In the laboratory, a cat placed in an experimental cage with a rat will, upon stimulation, become alert, then stealthily circle and attack the rat with a well-directed bite aimed at the rat's neck. If stimulation is continued, the cat will repeatedly bite the rat, or pick it up and shake it. Similar behaviors have been obtained in rats after stimulation of sites in the lateral hypothalamic area, although these attacks were directed at conspecifics [167,171]. This form of behavior is presumably not motivated by the power-dominance drive, since the animals show no signs of anger.

Vasopressin injected into sites located within the anterior hypothalamic nucleus and adjacent parts of the medial preoptic area of hamsters also elicits flank marking, while injections of other neuropeptides, including oxytocin, angiotensin II and neurotensin have essentially no effect [5,94]. Injection of V1 vasopressin receptor antagonists into the anterior hypothalamic nucleus significantly inhibits flank marking in response to arginine-vasopressin [6]. In addition, microinjections of V1 antagonists into the anterior hypothalamic nucleus of dominant hamsters greatly reduces flank marking in the presence of subordinate hamsters, and increases flank marking in the untreated subordinates, thereby reversing the major behavioral component reflecting dominance status [95]. These results, and those of the previous paragraph, suggest that a power-dominance drive representation is located in the anterior hypothalamic nucleus, extending into adjacent parts of the medial preoptic area and the dorsomedial division of the ventromedial nucleus.

In both rodents and cats, defensive responses, including escape jumps and flight, but not freezing, are evoked by electrical or chemical stimulation of sites within the dorsomedial hypothalamic nucleus [35,110,170,201], and posterior hypothalamic area [42,110,264,269]. In marmoset monkeys, escape behaviors have been obtained by electrical stimulation of the posterior hypothalamic area [179]. Hence a fear representation is presumably located in the dorsomedial hypothalamic nucleus, extending caudally into the posterior hypothalamic area.

Exposure of rats to a predator (cat) causes substantial increases in c-Fos immunoreactive neurons in the dorsomedial aspect of the ventromedial nucleus, anterior sector of the dorsomedial nucleus, in the region between the ventromedial and dorsomedial nuclei, and in the lateral aspect of the anterior hypothalamic nucleus [57]. Exposure of rats to the odor of a predator activates essentially the same structures [77]. Both swim stress and immobilization strongly activate the anterior, dorsomedial and posterior nuclei [70]. An auditory stimulus previously paired with footshock, and contextual cues related to the site where the footshock was delivered, activate the anterior, ventromedial

and dorsomedial hypothalamic nuclei [27,51]. Intermittent inescapable footshock activates the anterior hypothalamic nucleus and adjacent medial preoptic area and the dorsomedial nucleus [178]. Audiogenic stress activates the anterior hypothalamic nucleus, and the dorsomedial and ventromedial nuclei [50]. Exposure to a novel open field activates the dorsomedial nucleus and part of the medial preoptic area [89]. Agonistic encounters between dominant and submissive hamsters activate the anterior, dorsomedial and ventromedial hypothalamic nuclei of both dominant and submissive animals [162,163]. The results of these studies suggest that these stimuli induce both fear and anger, and hence hypothalamic representations of both these drives are activated.

Rats with lesions to the medial hypothalamic nuclei, which damaged the rostral two-thirds of the ventromedial nucleus, a portion of the anterior hypothalamic nucleus, and the ventral portion of the dorsomedial nucleus, are more aggressive than controls [8]. Lesions restricted to the anterior hypothalamus of adult male Wezob rats, which damaged most of the anterior hypothalamic nucleus, rostral parts of the ventromedial nucleus, and part of the medial preoptic area, result in significant reductions in aggressive behaviors towards subordinate intruder rats placed in their home cages [221].

Thus the electrical and chemical stimulation data, lesion data, and results of brain activation studies all suggest that a fear representation is located in the anterior part of the dorsomedial hypothalamic nucleus, extending caudally into the posterior hypothalamic area, while power-dominance motivation is represented in the anterior hypothalamic nucleus, dorsomedial sector of the ventromedial hypothalamic nucleus, and adjacent parts of the medial preoptic area (Fig. 1).

2.2. Periaqueductal gray matter

As mentioned above, electrical stimulation of sites within the human periaqueductal gray matter elicits verbal reports of intense fear or anxiety [131,147,213]. Chemical stimulation of the feline subtentorial (caudal one-third, situated ventral to inferior colliculus) part of the lateral/dorsolateral PAG using D,L homocysteic acid produces strong flight responses, increased arterial pressure, and extracranial vasoconstriction [21,59,311], while stimulation of the pretentorial (rostral two-thirds, ventral to the superior colliculus) of the lateral/dorsolateral PAG produces strong threat ('affective defense') displays (piloerection, hissing and growling, etc.), increased arterial pressure, and extracranial vasodilation [20,21,144,268]. These results suggest that a fear representation is located in the subtentorial part of the lateral/dorsolateral column of the feline PAG, while the power-dominance representations is found in the pretentorial part (Fig. 2).

Low current electrical stimulation of sites within the lateral/dorsolateral PAG of rodents elicits intense emotional and motor responses such as periods of intense freezing, followed by explosive, undirected running and vertical jumping, which are similar to responses seen when rats are placed in close proximity to a predator [2,152,164,278,291]. Chemical stimulation of neurons located in the intermediate third of the rat PAG produces backward defensive behavior, characterized by upright postures and retrograde locomotion, and ultrasonic vocalizations [75]. Chemical stimulation of the sites within the lateral/dorsolateral PAG of rats paired with non-treated conspecifics elicits aggressive behaviors, including biting, vocalizations, sideways and backward escape behaviors, and escape jumps [74]. In these studies, a differential location of sites eliciting escape or aggressive behaviors was not reported. Hence, at least in rats, the situation is not as clear cut as in carnivores, where an evident segregation between fear and power-dominance representations has been demonstrated [21].

As mentioned above, stimulation of sites within the anterior hypothalamic nucleus and adjacent part of the medial preoptic area using microinjections of arginine-vasopressin elicits flank marking. In addition, this form of stimulation produces elevated numbers of Fos-labeled neurons in the rostral lateral/dorsolateral PAG [18]. More importantly, microinjections of arginine-vasopressin into sites located within the rostral part of the lateral/dorsolateral column of the PAG of Syrian hamsters elicits flank marking [7,134].

The areas in the medial hypothalamus where the fear and power-dominance drives are represented, including the dorsomedial sector of the ventromedial nucleus, anterior nucleus, dorsomedial nucleus and posterior hypothalamic area extend dense projections to the PAG, and these projections terminate in the entire rostrocaudal extent of the dorsolateral column [55,242, 285,296].

c-Fos studies of brain areas activated by stimuli which evoke either the fear or power-dominance drives (or both) have revealed that the dorsolateral PAG of rats is consistently activated. For example, intermittent inescapable footshock activates the lateral/dorsolateral column [178]. Agonistic encounters between dominant and submissive hamsters produce Fos immunolabeled neurons in the dorsolateral PAG of both dominant and submissive animals [162,163]. The dorsolateral PAG is also activated by audiogenic stress [50]. The entire rostrocaudal extent of the rat lateral/dorsolateral column is activated by an encounter with a predator (cat) [57,58], and by exposure to predator odor [77]. Presentation of an auditory stimulus previously paired with footshock elicits substantially increased numbers of Fos-labeled neurons in the dorsolateral PAG, as does exposure to the context in which the footshock was applied [51]. Both swim and immobilization stress activate the lateral/dorsolateral parts of the PAG [70]. Exposure to a novel open field elicits Fos immunoreactivity in the dorsal PAG [211]. In addition, an rCBF/PET study of brain areas of humans activated by anticipatory anxiety (expectation of an unpredictable pain stimulus) has

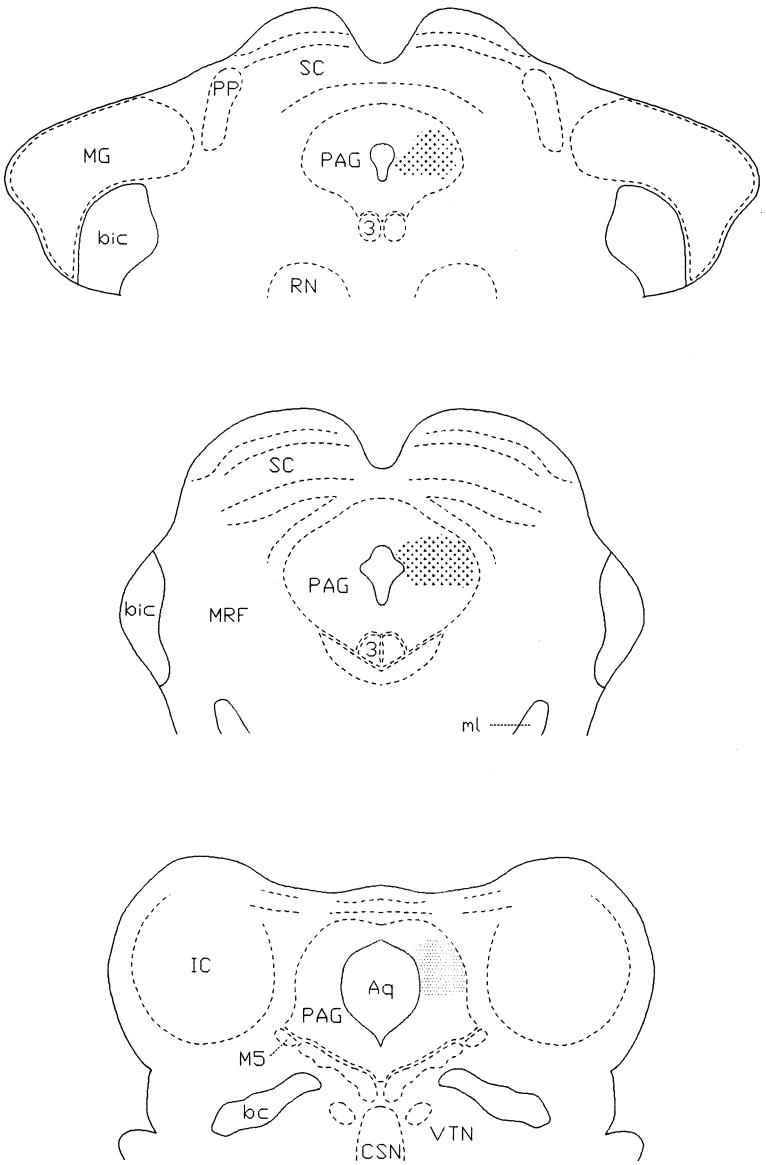

Fig. 2. Locations of the fear and power-dominance representations in the feline periaqueductal gray matter. Stippled area indicates the fear representation; pluses the power-dominance representation. Abbreviations: 3, oculomotor nucleus; Aq, aqueduct; bc, brachium conjunctivum; bic, brachium of the inferior colliculus; CSN, central superior nucleus; IC, inferior colliculus; M5, motor nucleus of the trigeminal nerve; ML, medial lemniscus; MRF, mesencephalic reticular formation; PAG, periaqueductal gray matter; PP, peripeduncular nucleus; RN, red nucleus; SC, superior colliculus; VTN, ventral tegmental nucleus.

demonstrated significantly increased rCBF in the PAG [142], and competitive arousal due to autobiographical scripts which describe athletic success also activates the PAG [238].

The hierarchical relationship between the drive representations in the medial hypothalamus and lateral/dorsolateral PAG was established by Hunsperger [144], who found that hissing responses elicited by stimulation of sites in the medial hypothalamus were abolished by bilateral lesions to the PAG, but hissing elicited by PAG stimulation was not affected by hypothalamic lesions. Flight elicited by stimulation of the medial hypothalamus was suppressed by PAG lesions, but it could still be obtained by increasing the stimulation current. These results indicate that the representations in the PAG are higher order motivational entities than those in the medial hypothalamus. The lateral/dorsolateral PAG column extends a substantial projection to areas of the medulla where premotor circuits for involuntary motor acts, including locomotion and other components of the 'defense reaction' are located [1,135,247], while anterograde tracing experiments indicate that the anterior, dorsomedial and ventromedial hypothalamic nuclei do not project to those areas [55,242,285]. However, the posterior hypothalamic nucleus does extend a moderate projection to the nucleus gigantocellularis [296]. This latter projection may mediate the flight responses obtained by Hunsperger [144] by medial hypothalamic stimulation after PAG lesions.

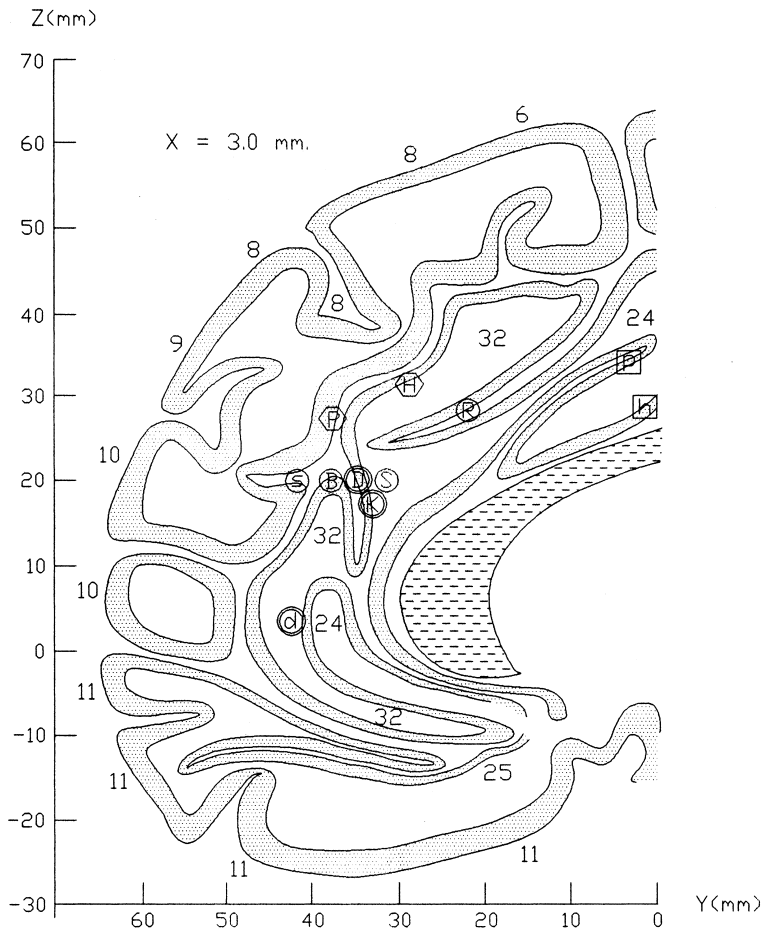

Fig. 3. Reported centers of activations within medial prefrontal cortex due to fear- and anger-inducing stimuli, and due to the motivational aspect of pain, shown in saggital section. Letters in hexagons indicate activations due to anticipatory anxiety, those in double circles activations due to script-driven anger and anger produced by mental imagery. Letters in squares indicate activations due to the motivational aspect of pain. Letters with single circles indicate activations due to other stimuli, discussed in text. Talairach stereotaxic coordinates (*Y*,*Z*) are indicated on the horizontal and vertical scales. *X* coordinate is 3.0 mm, chosen to show locations of cortical areas. B, Bremner et al. [43]; D, Dougherty et al. [80]; d, Drexler et al. [81]; H,h, Hsieh et al. [142]; K, Kilts et al. [158]; P,p, Ploghaus et al. [233]; R, Rauch et al. [238]; S,s, Shin et al. [265].

2.3. Medial prefrontal cortex

Laitinen [169] stimulated the rostral cingulum of prospective surgical patients and found that in about half of the cases subjective emotional experiences were obtained. In most cases, the reported experience was one of anxiety and tension. The rostral cingulum carries fibers that terminate in the medial prefrontal cortex [205]. As mentioned above, Bancaud and Talairach [19] reported that electrical microstimulation of a site within Brodmann area 32 of medial prefrontal cortex (homologous to prelimbic cortex of rodents and carnivores) of a surgery patient elicited a verbal report of subjective fear. Stimulation of sites within the anterior part of Brodmann area 24 of the macaque (which corresponds in part to area 32 of Vogt et al. [299]) elicits alarm vocalizations, piloerection and other components of the 'defense reaction' [275].

Functional magnetic resonance imaging and rCBF/PET studies have demonstrated that the inferior part of the human anterior cingulate gyrus is activated by anticipatory anxiety (the expectation of painful electric shocks) [142, 233]. The anticipation of pain will inevitably cause anxiety, but it is unlikely to elicit anger or any other aspect of the power-dominance drive. In the study of Ploghaus et al. [233] the center of activation is located in the dorsal part of Brodmann area 32, while the painful stimulus (which presumably activates representations of the affective/motivational aspect of pain) activated a region centered some 25 mm posterior to the area activated by anticipatory anxiety (Fig. 3). In Hsieh et al. [142] study the centers of activation due to anxiety and pain in areas 32 and 24 lie close to the corresponding centers in the Ploghaus et al. study (Fig. 3). These results, along with those of the stimulation studies cited in the previous paragraph, suggest that in primate species there is a cortical representation of the fear drive, located in area 32 of human medial prefrontal cortex, and in the corresponding part of medial prefrontal cortex of non-human primates.

There are no reports of the experience of subjective anger due to stimulation of sites within human prefrontal cortex.

However, two recent studies have investigated human brain areas activated during the subjective experience of anger, using script-driven imagery [80,158]. In both studies, a region located within Brodmann area 32 was activated. The centers of activation in both these studies lie ventral to the centers activated by fear (Fig. 3). Drexler et al. [81] also found significantly increased rCBF in the neighborhood of area 32 due to cue-induced anger, located ventral to the areas activated in the studies of Dougherty et al. [80] and Kilts et al. [158] (Fig. 3). Recall of childhood sexual abuse events in normal (but not in PTSD) women, which probably elicits more anger than fear, activates two regions within Brodmann area 32, whose centers lie close to those in the Dougherty et al. [80] and Kilts et al. [158] studies [265]. Bremner et al. [43] reported the activation of a site within area 32 of non-PTSD combat veterans exposed to combat-related traumatic pictures and sounds which lies between the two sites activated in Shin et al. [265] study (Fig. 3). An rCBF/PET study of areas activated by scripts of auto-biographical events characterized by athletic success (e.g. a game-winning goal) also revealed activation of a region within area 32 [238] (Fig. 3). The centers of activation in the two anticipatory anxiety studies are located dorsal to the sites activated by anger and recall of traumatic events (Fig. 3), and all lie within area 32. It may be inferred from these data that a power-dominance drive representation lies in area 32 of the human medial prefrontal cortex, ventral to the fear representation.

c-Fos and 2-deoxyglucose brain activation studies have demonstrated that an area within the rodent and carnivore medial prefrontal cortex is activated by unconditioned and conditioned stimuli that evoke the fear and/or power-dominance drives. Intermittent inescapable footshock activates the infralimbic, prelimbic and rostral anterior cingulate cortices [178]. Activities in the rostral anterior cingulate cortex (macaque area 24) probably represent the affective/motivational aspect of pain [141,142,236], so that neuronal activities in the activated area within prelimbic and/or infralimbic cortex presumably represent fear and/or anger. Stress due to the elevated maze activates the prelimbic and infralimbic cortices [85]. Audiogenic stress activates all three of the above mentioned medial prefrontal areas [50]. Exposure to a predator activates the prelimbic and infralimbic cortices [57], and predator odor activates the prelimbic cortex alone [77]. Swim and immobilization stress also activate all three components [70], and it is likely that the activation of the rostral anterior cingulate cortex is due to the physical discomfort caused by these forms of stimulation. Elevated c-Fos mRNA is observed in the prelimbic and infralimbic cortices of submissive rats after a fight with a dominant animal, and in the dominant animals the infralimbic cortex is selectively activated [163]. Exposure to a novel open field activates prelimbic, but not infralimbic, cortex [211]. Baeg et al. [15] recorded from single units in prelimbic and infralimbic cortex of rats in response to an auditory stimulus previously paired with footshock and found that the majority of units sampled changed their activities significantly during the delay period between the presentation of the conditioned stimulus and the delivery of footshock. Similar activation was obtained by exposing the rats to contextual stimuli. Maxwell et al. [191] recorded multi- and single-unit activities in prelimbic cortex of rabbits during Pavlovian heart rate conditioning. Activities in both superficial and deep layers of prelimbic cortex increased systematically in response to the presentation of an auditory stimulus that had been previously paired with paraorbital electric shock.

As discussed above, in humans fear and anger representations are located in area 32 of medial prefrontal cortex, and these representations are separate. In rodent species the c-Fos and unit activity studies suggest that fear and power-dominance representations are also located in medial prefrontal cortex, specifically in the prelimbic and infralimbic areas. The single unit study of Baeg et al. [15] shows that neurons in the prelimbic and infralimbic cortices are activated during the delay period after the conditioned stimulus is presented, when one would expect the animals to experience fear and/or anger. The selective activation of a region within infralimbic cortex in dominant rats in the resident/intruder study of Kollack-Walker et al. [163], and the selective activation of prelimbic cortex by exposure to an open field (which is unlikely to evoke anger), suggests that the power-dominance representation in rodents is located primarily in infralimbic cortex, and the fear representation in prelimbic cortex.

Bilateral lesions of the medial prefrontal cortex result in the loss of both fear and aggression in monkeys [310]. In rodents, lesions to the medial prefrontal cortex that damaged parts of prelimbic, infralimbic and anterior cingulate cortex have been found to have no effect on, or increase, freezing responses to conditioned and unconditioned stimuli [117, 204]. These results are not particularly surprising, since freezing responses are involuntary, and motivated primarily by the fear representations in the hypothalamus and PAG (see below). It is to be expected that learned behavioral responses to fear-inducing stimuli would be more significantly affected by lesions to medial prefrontal cortex, and this possibility is discussed more fully in the section on outputs from fear and power-dominance representations to premotor structures.

The rat prelimbic and infralimbic cortices extend substantial projections to the medial hypothalamic nuclei, with terminations principally in the anterior, dorsomedial and posterior nuclei [105,145,282]. In monkeys, prelimbic and infralimbic projections terminate most densely in the anterior hypothalamic nucleus and ventromedial nucleus [223]. Retrograde tracers placed into the middle third of the rostrocaudal extent of the rat and rabbit dorsolateral PAG column label cells primarily in the prelimbic cortex, but cells in infralimbic and anterior cingulate cortex are also labeled [104,197]. The projection from the monkey medial

prefrontal cortex to the dorsolateral PAG in the monkey is similar [11].

2.4. Thalamus

The cortical fear and power-dominance representations located in medial prefrontal cortex must receive fear-related information from subcortical structures, and since non-thalamic projections to the medial prefrontal cortex from subcortical structures are fairly modest, it is reasonable to expect that this input should arrive via a relay in the thalamus. The principal thalamic nuclei that project to the medial prefrontal cortex (other than the intralaminar nuclei whose projection is essentially restricted to lamina I) are the mediodorsal, paraventricular, parataenial and reuniens nuclei. Prelimbic cortex of rodent species receives thalamic afferents primarily from the paraventricular nucleus [32,126], but also from the dorsal part of the mediodorsal nucleus and from the reuniens nucleus [32,67]. In the macaque, injections of retrograde tracers into prelimbic cortex label cells in the paraventricular and central densocellular thalamic nuclei, and a few cells in the dorsomedial part of the parvicellular division of the mediodorsal nucleus [299]. The dorsal part of the macaque central densocellular nucleus (of Olszewski [222]), which is located between the paraventricular and mediodorsal nuclei, is probably homologous to part of the rodent paraventricular thalamic nucleus. The projections from the paraventricular, parataenial, reuniens and dorsal mediodorsal thalamic nuclei to the medial prefrontal cortex are reciprocated by corticothalamic projections [63,64,145,260,297].

These four thalamic nuclei receive afferent projections from the hypothalamic nuclei in which fear and power-dominance motivation are represented. The power-dominance representation located in the anterior hypothalamic nucleus and dorsomedial division of the ventromedial nucleus project to the rostral paraventricular, parataenial, rostral reuniens and dorsal mediodorsal nuclei [55,225,242]. The fear representation located in the dorsomedial hypothalamic nucleus and adjacent posterior hypothalamic area projects to the dorsal paraventricular and reuniens thalamic nuclei [284,285,295]. In addition, neurons in the lateral/dorsolateral PAG project to the paraventricular, parataenial, reuniens and mediodorsal nuclei [63,166,198].

Neurons in the paraventricular thalamic nucleus are activated by both unconditioned and conditioned fear- and anger-evoking stimuli such as intermittent inescapable footshock [178], the elevated maze [270], audiogenic stress [50], open field exposure [89], immobilization [36,62], predator exposure [57], presentation of an auditory stimulus previously paired with footshock [51], and exposure to the context where footshock was experienced [27,51]. The mediodorsal nucleus is activated by audiogenic stress [50], and by swim stress and immobilization [70]. The reuniens nucleus is also activated by swim stress and immobilization [70], and by predator exposure [57]. The parataenial nucleus is activated by inescapable footshock [178].

The activation of the rodent paraventricular thalamic nucleus, and to a lesser extent, the reuniens, parataenial, and dorsal mediodorsal nuclei, by stimuli that elicit fear and anger, in conjunction with the relationship of these nuclei with the prelimbic cortex, suggest that both fear and power-dominance representations exist in this thalamic area. Since fear and power-dominance representations are segregated in the hypothalamus, PAG, and medial prefrontal cortex, it is logical to assume that these two drives are also represented separately in the midline thalamus. It is not possible to determine the locations of the two thalamic representations based on the brain activation data, but connectional data may serve to establish the approximate locations of the representations. The hypothalamic power-dominance drive representation is preferentially connected with the rostral paraventricular, rostral reuniens, parataenial and dorsal mediodorsal nuclei. The hypothalamic fear representation is preferentially connected with the dorsocaudal part of the paraventricular nucleus and reuniens nuclei. From these data it is possible to infer that the fear representation may be located (at least in part) in the posterior part of the paraventricular nucleus and part of the reuniens nucleus, and the power-dominance representation in the anterior paraventricular, rostral reuniens, parataenial and dorsal mediodorsal nuclei.

2.5. Additional areas activated by fear and power-dominance eliciting stimuli

In the c-Fos brain activation studies cited above, stimuli that activate the fear or power-dominance representations in the hypothalamus, periaqueductal gray, midline thalamus and medial prefrontal cortex also activate several other structures, and neuronal activities in any one of these could potentially represent either of the two drives in question. In addition, it has been demonstrated that lesions to some of these structures cause deficits in behaviors motivated by the two drives. Some of the structures activated in these studies include components of auditory and visual sensory pathways, including the inferior and superior colliculus, medial geniculate complex, dorsal lateral geniculate nucleus, and areas within auditory and visual cortex. Similarly, components of the vomeronasal pathway, including the posteromedial cortical and medial amygdaloid nuclei and the vomeronasal subnuclei of the bed nucleus of the stria terminalis (i.e. the principal, transverse and interfascicular subnuclei, which are reciprocally connected with the medial amygdaloid nucleus [56]) are activated by fear- and anger-inducing stimuli, as are components of the main olfactory pathway, including the piriform cortex and endopiriform nucleus. Needless to say, activities in these structures do not represent motivational drives.

In the hypothalamus, in addition to the nuclei discussed above, the paraventricular hypothalamic nucleus is activated

by agonistic encounters between dominant and submissive rats and hamsters [163], audiogenic stress [50]; exposure to a novel open field [89], inescapable footshock [178], and swim and immobilization stress [70]. However, chemical or electrical stimulation of sites within the paraventricular nucleus elicits yawning and self-grooming, but not aggressive or fear motivated behaviors [170,171,248], and axon sparing lesions to this nucleus have essentially no effect on these behaviors in rats [220].

In brain activation studies on human areas activated by fear- and/or power-dominance eliciting stimuli, it has been reported that additional cortical areas are activated by these stimuli. These include insular cortex, the superior temporal sulcus, temporopolar cortex, and orbitofrontal cortex [80, 233,265]. Electrical stimulation of sites within the human insular cortex elicit verbal reports of gustatory, somatic and visceral sensations, but not fear or anger [226], so it is unlikely that a fear representation is located there. The activation the superior temporal sulcus in these studies was presumably due to attentional processing of auditory stimuli associated with the experimental situation. Temporopolar cortex is also activated by autobiographic memory retrieval [186], and lesions to this area cause marked retrograde memory deficits [165], so it is evident that temporopolar neurons process mnemonic information, but not fear- or anger-related signals. Activities in medial orbitofrontal cortex also process mnemonic information [262], and lesions to this area in humans result in anterograde memory deficits [4,257]. Neurons in the caudolateral part of orbitofrontal cortex process information related to the reward or punishment value of gustatory, visual, auditory and somatosensory stimuli [218,251].

In addition to these sensory and mnemonic structures, brain activation and lesion studies have implicated the dorsal premammillary nucleus, supramammillary nucleus, hippocampal formation, and basolateral and central amygdaloid nuclei in behaviors motivated by fear and/or power-dominance. The function of these structures is discussed in detail below.

3. Sensory and mnemonic inputs to fear and power-dominance representations

In order that behaviors motivated by fear and/or power-dominance occur in response to specific stimuli or classes of stimuli, it is usually necessary that either the individual stimulus or the class of stimuli that an individual stimulus belongs to be recognized. Fear and anger responses that occur due to exposure to a natural predator, for example, require the recognition of the class of object the individual predator belongs to, or at the very least, recognition that the object is a predator. However, recognition of the stimulus object is not always necessary, and frankly noxious stimuli such as footshock will presumably elicit fear and anger responses with no need for identification of the nature of the object providing the nociceptive input. Recognition of stimulus objects requires sensory processing, and this usually involves hierarchical processing in several separate sensory structures. Rodents rely primarily on olfaction for object recognition [146,228,229], and we will restrict our discussion here to this sensory modality.

Rodents are able to recognize objects through two distinct olfactory pathways and mechanisms. The first of these is the vomeronasal pathway, which mediates innate recognition of classes of stimuli [84]. Aggressive behaviors exhibited by male rodents are usually provoked by other males [9], and this implies that the animals are able to recognize the gender of individuals of their own species. Gender recognition is also evidently necessary for behaviors related to reproduction. Although recognition of this characteristic in rodents may also be possible using either visual or auditory cues, it is most probably mediated primarily by distinct chemical (pheromonal) cues emitted by individuals of either gender [228]. The cues necessary for this form of recognition are detected in the vomeronasal organ, and it has been demonstrated that removal of this organ virtually eliminates a male mouse's sexual responsiveness to females [305]. Lesions to the medial amygdaloid nucleus, a component of the vomeronasal pathway, cause deficits in gender recognition but spare discrimination of individual odors in golden hamsters [228]. In addition, it is likely that the recognition of classes of prey and predators in rodents is mediated by pheromonal cues, since for example exposure of a rat to a predator strongly activates components of the vomeronasal pathway, including the medial amygdaloid nucleus and interfascicular and transverse subnuclei of the bed nucleus of the stria terminalis [57]. Learned recognition of individual conspecifics is mediated by the main olfactory system, and nasal irrigations of zinc sulfate which deafferent the main olfactory system result in the complete loss of individual conspecific recognition in mice [190], while removal of the vomeronasal organ has no effect on this form of recognition in hamsters [229].

Since gender recognition is an important factor in intermale aggression, it may be expected that removal of the vomeronasal organ will affect aggressive behaviors. It has been demonstrated that mice lacking a vomeronasal organ, but with a fully operative main olfactory system, exhibit significant deficits in aggressive behaviors [26,65, 187]. The involvement of the vomeronasal system in flank marking in hamsters has been investigated recently [157, 229]. These studies have shown that removal of the vomeronasal organ reduces overall investigation of flank gland odors, and produces abnormal patterns of flank marking. Overall levels of flank marking are not affected by the removal [229], and this is to be expected, since this behavior occurs after a dominance hierarchy has been established, and thus depends primarily on the recognition of individual conspecifics. Hence it is not surprising that deafferentiation of the main olfactory system using zinc

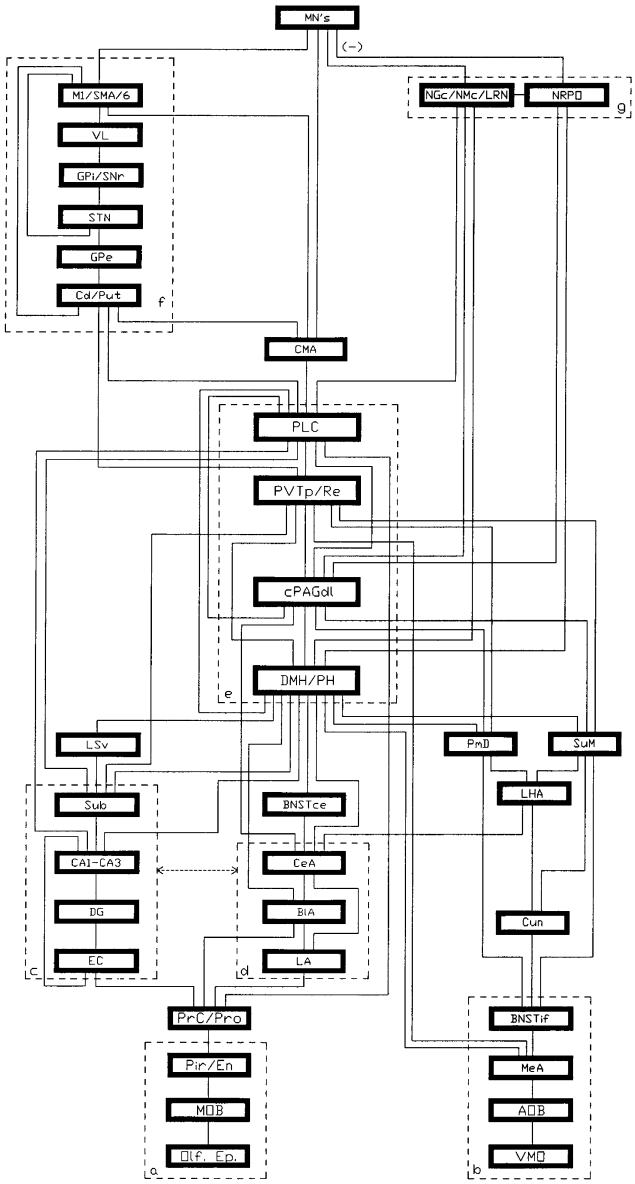

Fig. 4. Schematic showing rodent hypothalamic, midbrain, thalamic and cortical fear representations, sensory/mnemonic structures that provide inputs to these representations, and outputs to premotor and motor structures. Dashed arrow between amygdaloid complex and hippocampal formation indicates amygdalo-hippocampal and hippocampo-amygdaloid connections which are not shown. Also not shown are sensory, mnemonic and proprioceptive inputs to premotor structures, nor inputs from cognitive areas of the dorsolateral prefrontal cortex. Function is discussed in the text: (a) Main olfactory system. (b) Vomeronasal system. (c) Hippocampal formation. (d) Amygdaloid complex. (e) Fear representations. Abbreviations: AOB, accessory olfactory bulb; BlA, basolateral amygdaloid nucleus; BNSTce, central (non-vomeronasal) subnuclei of the bed nucleus of the stria terminalis; BNSTif, interfascicular subnucleus of the bed nucleus of the stria terminalis; CA1–CA3, hippocampal fields; CeA, central amygdaloid nucleus; Cd/Put, caudate-putamen; CMA, cingulate motor area; cPAGdl, caudal dorsolateral periaqueductal gray; Cun, cuneiform nucleus; DG, dentate gyrus; DMH, dorsomedial hypothalamic nucleus; EC, entorhinal cortex; GPe, external globus pallidus; LA, lateral nucleus of the amygdala; LHA, lateral hypothalamic area; LSv, ventral lateral septal nucleus; M1, motor cortex; MeA, medial nucleus of the amygdala; MN's, motoneurons; MOB, main olfactory bulb; NGc, nucleus reticularis gigantocellularis; NMc, nucleus reticularis magnocellularis; NRPO, nucleus reticularis pontis oralis; Olf. Ep., olfactory epithelium; Pir, piriform cortex; PH, posterior hypothalamic nucleus; PLC, prelimbic cortex; PmD, dorsal premammillary nucleus; PrC, perirhinal cortex; Pro, prorhinal (parahippocampal) cortex; PVTp, posterior paraventricular thalamic nucleus; Re, reuniens nucleus; Sub, subiculum; SuM, supramammillary nucleus; VL, ventral lateral thalamic nucleus; VMO, vomeronasal organ; 6, premotor cortex.

sulfate substantially reduces flank marking behaviors in female golden hamsters [157].

Chemosensory signals detected and transduced in the vomeronasal organ must reach one or more of the fear and power-dominance representations located in the hypothalamus, periaqueductal gray, thalamus and medial prefrontal cortex in order that appropriate behaviors in response to pheromonal cues be motivated. The vomeronasal pathway includes the accessory olfactory bulb, cortical and medial amygdaloid nuclei and principal, transverse and interfascicular subnuclei of the bed nucleus of the stria terminalis. Only the posterodorsal sector of the medial amygdaloid nucleus extends substantial direct projections to the hypothalamic nuclei involved in fear and power-dominance motivated behaviors, with terminations primarily in the dorsomedial sector of the ventromedial nucleus, anterior hypothalamic nucleus, and dorsomedial nucleus [56,121]. This sector of the medial nucleus also projects strongly to the bed nucleus of the stria terminalis, with terminations in the transverse and interfascicular subnuclei [56]. However, projections from the medial amygdaloid nucleus to the PAG are very meager [56]. Projections from the vomeronasal subnuclei of the bed nucleus of the stria terminalis do not reach the hypothalamic representations of fear and power-dominance, but they do extend to the dorsal premammillary and supramammillary nuclei [66,217]. The dorsal premammillary nucleus (PMd), in turn, projects to the fear and power-dominance representations in the hypothalamic area, with substantial terminations in the anterior hypothalamic nucleus, and fewer fibers entering the dorsomedial division of the ventromedial nucleus, posterior hypothalamic area, and dorsomedial nucleus [54]. The dorsal premammillary nucleus also extends a massive projection to the representations in the lateral/dorsolateral column of the PAG [54]. It receives afferents from the interfascicular subnucleus of the bed nucleus of the stria terminalis, ventral tegmental nucleus, and the cortical fear and power-dominance representations in the prelimbic and infralimbic cortices [66]. The supramammillary nucleus also projects to the dorsomedial hypothalamic nucleus, anterior hypothalamic nucleus, medial preoptic area, and to the lateral/dorsolateral column of the PAG [294]. It receives afferents from the pontine central superior and ventral tegmental nuclei [130], and vomeronasal subnuclei of the bed nucleus of the stria terminalis [217]. It is reciprocally connected with infralimbic cortex [14,130,145,282]. The connections of the dorsal premammillary and supramammillary nuclei are evidently similar, as shown in Figs. 4 and 5.

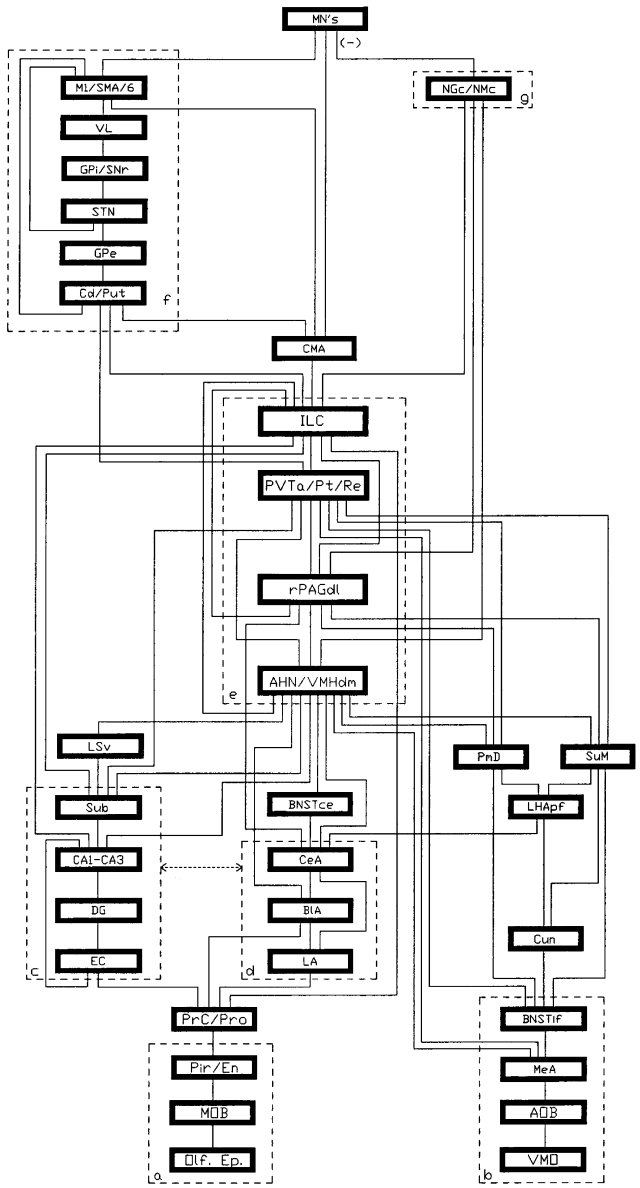

Fig. 5. Schematic showing rodent hypothalamic, midbrain, thalamic and cortical power-dominance representations, sensory/mnemonic inputs and outputs to premotor structures. Abbreviations as in Fig. 4, except for: AHN, anterior hypothalamic nucleus, ILC, infralimbic cortex; Pt, parataenial thalamic nucleus; PVTa, anterior paraventricular thalamic nucleus; rPAGdl, rostral part of the dorsolateral periaqueductal gray matter; VMHdm, dorsomedial sector of the ventromedial hypothalamic nucleus.

The fear and power-dominance representations in the paraventricular, reuniens and parataenial thalamic nuclei receive inputs which convey information processed in the vomeronasal pathway through direct projections originating in the medial amygdaloid nucleus [56,63] and bed nucleus of the stria terminalis [217], and through lesser projections from the dorsal premammillary and supramammillary nuclei [54,294]. The prelimbic and infralimbic representations may also receive vomeronasal information through modest direct projection from the supramammillary nucleus [14], and through the relays in the midline thalamic nuclei.

Exposure of rats to a predator strongly activates the dorsal premammillary nucleus and the supramammillary nucleus to a lesser degree [57], and these nuclei are also activated by swim and immobilization stress [70], while only the supramammillary nucleus is activated by audiogenic stress [50], exposure to a novel open field [304], and conditioned auditory and contextual stimuli [27,51]. Lesions to the dorsal premammillary nucleus virtually eliminate freezing and escape responses to predator exposure [57]. These data suggest that neuronal activities in the dorsal premammillary nucleus might represent fear. However, low-current electrical stimulation of this nucleus produces exploratory behaviors such as scanning, rearing and walking, and significantly higher currents are required to elicit escape jumps [60,255], which suggests that the latter behaviors may be due to transsynaptic activation of a projection target of this nucleus. The authors of these studies have suggested that the dorsal premammillary nucleus may be involved in the assessment of the degree of risk or danger due to threatening stimuli.

The above hodological and brain activation data suggest that conspecific gender recognition necessary to elicit aggressive behaviors between male rodents, and the recognition of predators that produces freezing and flight, are mediated by the vomeronasal system, and information related to this recognition reaches the fear and power-dominance drive representations in the anterior hypothalamus, dorsolateral PAG, and midline thalamic nuclei via a variety of pathways involving the medial amygdaloid nucleus, bed nucleus of the stria terminalis, dorsal premammillary nucleus and associated structures, including the cuneiform nucleus and lateral hypothalamic area (Figs. 4 and 5).

As mentioned above, the recognition of individual conspecifics in rodents is mediated primarily by olfactory cues detected and processed in the main olfactory system. This system originates in the main olfactory bulb, which recent studies indicate is actually the primary olfactory cortex [128,155]. Projections from the main olfactory bulb reach secondary cortical olfactory areas such as the piriform cortex, the underlying endopiriform nucleus, and associated areas [266], and these in turn project to the perirhinal, postrhinal and entorhinal cortices [29,46,155]. Direct projections from perirhinal cortex reaches the fear and power-dominance representations in medial prefrontal cortex [196,290]. Lesions to perirhinal cortex cause severe deficits in stimulus recognition in the visual, somatosensory and olfactory modalities [115,199,200,206,207,208,280]. Herzog and Otto [136,137] reported that pretraining electrolytic and excitotoxin lesions to perirhinal cortex cause an attenuation in fear-motivated behaviors due to explicit olfactory stimuli conditioned to footshock, but no attenuation to the training context. However, Bucci et al. [45] found that lesions to perirhinal or postrhinal cortex also cause deficits in contextual fear conditioning, but not to an explicit auditory conditioned stimulus. It has been suggested that activities of neurons in perirhinal cortex represent engrams for stimulus object recognition [16,262,283].

The perirhinal and postrhinal cortices are reciprocally connected, and both project to the amygdaloid formation, with terminations in the basolateral complex and central nucleus [47,194,232]. The involvement of the basolateral complex and central nucleus of the amygdala in fear-motivated behaviors that occur in response to explicit conditioned auditory and visual cues is now well established [210], and it is now clear that the function of the basolateral complex is mnemonic, in that activities there mediate the association between the unconditioned and previously neutral conditioned stimuli [176,181,182,250,254]. The involvement of the amygdala in behavioral responses to olfactory stimuli paired with unconditioned noxious somatosensory stimuli and to the context in which the unconditioned stimuli were presented has been further examined in a recent lesion study [69]. These forms of learning obviously require recognition of the conditioned stimulus odor, and of contextual stimuli (which probably include odors of objects in the contextual setting), and this requires cortical processing through the main olfactory pathway. Cousens and Otto [69] reported that both pretraining and posttraining axon-sparing lesions of the basolateral amygdaloid complex abolish freezing responses to the olfactory conditioned stimulus, and to the context. Other than serving as an output station for signals related to the associations computed in the basolateral complex, the role of the central amygdaloid nucleus in olfactory fear conditioning is not clear.

Information about learned explicit and contextual stimuli processed in the basolateral complex and central nucleus of the amygdala may reach the hypothalamic fear and power-dominance representations via relatively sparse direct projections from the amygdaloid nuclei to the dorsomedial division of the ventromedial hypothalamic nucleus and the dorsomedial and posterior nuclei [40,180,224], but a more substantial pathway involves a relay in the non-vomeronasal subnuclei of the bed nucleus of the stria terminalis (i.e. components of the central extended amygdala, including the juxtacapsular, oval, fusiform, and several other subnuclei). The central amygdaloid nucleus project to the lateral and dorsolateral aspect of the bed nucleus of the stria terminalis [40,192,279,302]. In turn, the non-vomeronasal subnuclei of the bed nucleus project to the dorsomedial and ventromedial hypothalamic nuclei, anterior hypothalamic nucleus, and medial preoptic area [73,79,160,274,286]. The bed nucleus of the stria terminalis is moderately activated by an auditory tone conditioned to footshock [51], and strongly activated by exposure to contextual stimuli where footshock was previously delivered [27]. LeDoux et al. [175] found that lesions to this structure had no effect on conditioned freezing to an auditory tone, and Davis and Shi [71] have argued that the bed nucleus is differentially involved in contextual conditioning. The lateral/dorsolateral PAG receives a moderate direct projection from the central amygdaloid nucleus [30,197,246], and it has been proposed that freezing responses due to fear-conditioned stimuli are mediated by this pathway [175,249]. There is, in addition, a considerably stronger indirect pathway from the central nucleus to the dorsolateral PAG through the lateral hypothalamic area and dorsal premammillary nucleus (Fig. 4). The bed nucleus of the stria terminalis does not project to the lateral/dorsolateral PAG [30,197].

The perirhinal and postrhinal cortices are also an essential gateway to the hippocampal formation, and project strongly to the entorhinal cortex [47,148,209]. The dorsal and ventral divisions of the rodent hippocampal formation and the lateral septal nucleus are activated by the presentation of an auditory stimulus previously paired with footshock, and by contextual cues [27,51]. Lesions to the rat hippocampal formation cause deficits in behavioral responses to contextual stimuli related to the site where footshock was administered [231,253]. It has been reported that lesions to the hippocampal formation cause deficits in behavioral responses to auditory stimuli conditioned to footshock [183,184,303]. Within the hippocampus the dorsal and ventral divisions contribute differentially to contextual conditioning. Lesions to the ventral division essentially mimic complete hippocampal lesions, causing significant anterograde deficits in conditioned freezing, while lesions to the dorsal division cause only mild deficits [241]. It has been observed that while the processing of an auditory CS is relatively simple because of its unimodal and discrete nature, the processing of contextual stimuli is more complex because they are multimodal and temporally diffuse, so the role of the hippocampus in contextual conditioning may be to provide a unified representation of the context [12]. The differential contributions of the amygdala and hippocampus in conditioning to explicit and contextual cues remains controversial [12,48,91,118,241], and it is possible that both structures participate in both forms of conditioning.

The information related to explicit and contextual stimuli that is processed in the hippocampal formation reaches the hypothalamic representations via substantial direct projections from the subiculum and adjacent parts of the CA1 field to the ventromedial and dorsomedial nuclei, anterior nucleus, medial preoptic area and posterior hypothalamic area [54]. They terminate most densely in the dorsomedial division of the ventromedial nucleus and medial parts of the anterior nucleus. In addition, there is a massive projection from the CA1-CA3 fields and subiculum to the lateral septal nucleus [54,243,281], and the latter entity projects to the medial parts of the anterior hypothalamic nucleus, ventromedial nucleus, dorsomedial nucleus, ventral parts of the posterior hypothalamic area, and medial preoptic area [244]. Only a few fibers from neurons in the subiculum and lateral septal nucleus reach the PAG, and the paraventricular thalamic nucleus receives a modest projection from the subiculum [54,244]. The representations in the prelimbic and infralimbic cortex of rats receive moderate direct projections from the subiculum and CA1/CA2 fields, and from the entorhinal cortex [14,67,150,151]. The macaque

medial prefrontal areas 25 and 32 receive projections of similar density from the subiculum and the CA1 field [252].

Lesions to the lateral septum potentiate freezing responses to contextual stimuli associated with footshock [300]. Bilateral electrolytic lesions of the hamster lateral septum result in a reduction in intraspecific aggression and social dominance status in rats, mice and guinea pigs [39,68, 117,234,273]. However, rats with these lesions are hyper-irritable, and respond to noxious somatosensory stimuli with overt rage [41,87]. Flank marking behaviors in hamsters, which depends on the recognition of the odors of individual conspecifics and of physical objects in the natural environment of these animals, is significantly reduced by ibotenic acid lesions of the lateral septum [98]. These observations indicate that the function of the lateral septal nuclei in learned recognition of stimuli that elicit fear- and power-dominance drive motivated behaviors is complex, and poorly understood at present.

The excitatory and/or inhibitory nature of the projections from the amygdaloid complex to the medial hypothalamus and PAG, and the neurotransmitters involved, have recently been reviewed by Gregg and Siegel [124]. Those of the bed nucleus of the stria terminalis, ventral hippocampus, and lateral septum have been reviewed by Graeff [122].

4. Motivational inputs from fear and power-dominance representations to premotor structures

Motivational inputs are necessary for premotor structures to program and execute behavioral responses, so we would expect that one or more of the four fear representations will project to each of these structures. Primitive 'automatic' fear-motivated behaviors such as wild flight and vertical leaping are mediated by premotor circuits located in the nuclei gigantocellularis and magnocellularis of the medulla [116, 259]. Freezing responses (behavioral arrest) are mediated by circuits located in the pontine reticular formation, specifically the nucleus reticularis pontis oralis [88,202]. Learned (procedural) motor sequences are mediated by the basal ganglia-thalamocortical 'motor' circuit [10,139], and the programming of these sequential motor acts is probably achieved in the caudate-putamen [159,185]. It has been demonstrated that the caudate-putamen is activated during learned two-way shuttle-box avoidance responses [277]. Voluntary motor acts are executed by cortical premotor and motor structures, including the cingulate premotor areas, the supplementary motor area, premotor cortex and primary motor cortex [17,72].

The nuclei magnocellularis and gigantocellularis receive substantial projections from the lateral/dorsolateral PAG [1,133,135,247]. Only a few cells in the anterior and dorsomedial hypothalamic nuclei project to these nuclei [247], but the posterior hypothalamic nucleus extends a more substantial projection [296]. There is, in addition, a light projection from the medial prefrontal cortex [215]. Sensory/mnemonic inputs also reach these nuclei from the central amygdaloid nucleus, and bed nucleus of the stria terminalis [247]. Of all these inputs, those originating in the periaqueductal gray and central amygdaloid nucleus are by far the strongest. Thus the primary source of motivational input for involuntary behavioral acts due to fear and/or anger inducing stimuli is the periaqueductal gray.

Freezing responses are also involuntary, and obtained by electrical stimulation or microinjections of carbachol into an inhibitory zone located in the nuclei reticularis pontis oralis. The cessation of movement is probably produced by inhibition of motoneurons in the brainstem and spinal cord through projections from the nucleus pontis oralis to these motoneurons [140]. The nucleus pontis oralis receives a substantial projection from the periaqueductal gray [263], and weaker projections from the fear representation in the dorsomedial and posterior hypothalamic nuclei [284,296]. As in the case of inputs to the premotor circuits in the nuclei gigantocellularis and magnocellularis, the primary source of motivational input governing freezing responses is the periaqueductal gray.

The caudate-putamen receives direct substantial projections from the prelimbic and infralimbic cortices [33,86,101, 258]. In the rat, this projection spares only the lateral part of the caudate-putamen. The paraventricular nucleus projects to the caudate-putamen, with terminations primarily in the ventral, medial and caudal parts of the complex [28,31], and the reuniens nucleus extends a lighter projection [31,219]. In monkeys, thalamic projections reach the caudate-putamen from the parataenial, paraventricular, central densocellular, and reuniens nuclei [83,212]. Sensory/mnemonic inputs reach the caudate-putamen from the basolateral amygdaloid nuclei and subiculum [125,193], and perirhinal and entorhinal cortices [287,289]. Cognitive inputs reach this structure from the dorsolateral prefrontal cortex, with terminations primarily in the caudate nucleus [289]. Since programming of learned sequential motor acts is organized in the caudate-putamen, and motivational inputs to this structure originate almost exclusively in the fear and power-dominance representations in medial prefrontal cortex and midline thalamic nuclei, it is to expected that stimulation of sites within the midline thalamic nuclei or medial prefrontal cortex (prelimbic and infralimbic cortices of rodents) should facilitate learned sequential (operant) behaviors, but should have no effect on involuntary freezing and flight behaviors, since the latter are organized by premotor circuits in the pons and medulla, and receive their motivational input primarily from the PAG and hypothalamus.

The macaque cingulate premotor areas receive direct projections from the prelimbic and infralimbic cortices [290]. However, medial prefrontal areas do not project to the premotor structures located in cortical area 6. Hence motivational input to the cingulate premotor areas must be sufficient to initiate and execute voluntary motor acts. The fear and power dominance representations in the hypothalamus, PAG and midline thalamic nuclei do not project

to the cingulate premotor areas [290]. The macaque cingulate premotor areas receive sensory/mnemonic inputs from the parahippocampal, perirhinal and entorhinal cortical areas [203,290]. Cognitive inputs from dorsolateral prefrontal cortical areas 46 and 8a also reach the cingulate premotor areas [25].

In rodents, cingulate premotor areas as such have not been described, but Zeng and Stuesse [310] have observed that rat cingulate areas Cg1 and Cg2 (of Zilles [312], which correspond to areas 24b and 24a of Vogt and Miller [298]) have extensive connections with cortical motor areas, and with the ventrolateral thalamic nucleus, and Sinnamon and Galer [272] obtained motor responses through electrical stimulation of sites in the dorsal part of anterior cingulate cortex (area 24b) of rats. Given the relationships between the anterior cingulate motor area in the macaque (area 24c) and adjacent parts of cingulate cortex (areas 24a and 24b) and macaque premotor and motor cortices and the corresponding relationships between rat areas 24a and 24b, and the premotor area located in the medial agranular cortex (area 8), it is reasonable to assume that in the rat, area 24b is homologous to the macaque anterior cingulate premotor area. Perirhinal cortex extends only minor projections to area 24b [196], as does the entorhinal cortex [148], and neither the nuclei of the amygdaloid complex or components of the hippocampal formation project to this area. Area 24b of the rat receives substantial projections from infralimbic and prelimbic cortices [103,145]. All of the outputs from the fear and power-dominance representations to premotor structures are shown in Figs. 4 and 5.

5. Discussion

5.1. Functional considerations

While involuntary behaviors are mediated by the premotor circuits located in the medulla, which receive their principal inputs from the periaqueductal gray, the connectional data indicate that both voluntary and learned sequential behavioral acts are motivated primarily by inputs from the cortical fear and power-dominance representations in the medial prefrontal cortex. Thus while lesions to the PAG result in severe deficits in freezing and other involuntary escape responses, it might be expected that lesions to medial prefrontal cortex would cause similar deficits in voluntary and learned escape or avoidance responses. Trafton [288] found that lesions to the rat anterior cingulate cortex, that damaged infralimbic, prelimbic and anterior cingulate cortical areas (areas 25, 32 and 24) completely abolished learned avoidance responses of rats trained to avoid footshock by shuttling back and forth in response to a visual conditioned stimulus. However, Joel et al. [153] found that lesions to the medial prefrontal cortex, sparing anterior cingulate cortex, led to better two-way avoidance performance, and Fritts et al. [109] reported that lesions to medial prefrontal cortex that spared the prelimbic area led to moderate deficits in shuttle-box avoidance, but larger lesions had no effect. Lacroix et al. [168] also found that *N*-methyl-D-aspartate lesions to medial prefrontal cortex that spared anterior cingulate cortex had no effect on this task. Thus it would appear that fear motivation is not necessary for this form of learned avoidance responses. Footshock avoidance in the shuttle-box induces prominent Fos-like immunoreactivity in both the medial prefrontal cortex (areas 25 and 32) and anterior cingulate cortex (area 24) [85]. In Trafton's lesion study [288], the anterior cingulate cortex (area 24) was also lesioned, so the possibility exists that neurons in that area could furnish the necessary motivational input to the basal ganglia-thalamocortical circuits involved in generating these responses. The involvement of neuronal activities in area 24 in avoidance learning in rabbits has been extensively investigated by Gabriel and colleagues [113,106,107]. These authors examined neuronal activities in area 24 during differential avoidance conditioning, in which rabbits learned to prevent footshock by stepping in an activity wheel after an auditory stimulus, and to ignore a different auditory stimulus. Records of neuronal activities showed neuronal discrimination between the two auditory stimuli both during pretraining avoidance and with unpaired presentations of the stimuli. Electrolytic and ibotenic acid lesions to area 24 of cingulate cortex caused significant deficits in shock avoidance learning, and additional lesions to posterior cingulate cortex (area 29) essentially abolish the responses [114]. Johansen et al. [154] also found that anterior cingulate lesions that spared infralimbic and prelimbic cortex significantly reduced formalin-induced conditioned place avoidance behaviors in rats. Since all the avoidance experiments use nociceptive stimuli as the unconditioned stimulus, and activities of neurons in cingulate area 24 represent the motivational aspect of pain, it would appear that the primary motivational input to the basal ganglia-thalamocortical circuits that mediate these learned avoidance responses (both in the shuttle box procedure and in stepping in an activity wheel) is due to pain. The Fos study of Duncan et al. [85] suggests that fear motivation may also contribute to the motivation of these learned behaviors, but the lesion studies indicate that pain motivation is sufficient. Since essentially all avoidance conditioning experiments use nociceptive unconditioned stimuli, there are no extant studies on learned responses that are motivated exclusively by fear. One experimental model that could serve to test the effects of lesions to medial prefrontal cortex on learned inhibitory avoidance behaviors due exclusively to fear-inducing stimuli is the elevated T-maze [307]. In addition, conventional avoidance tasks which require the pressing of a lever to avoid an electrical shock could be modified in such a way as to allow the animals to escape from the presence or proximity of a

predator. The arguments presented above predict that avoidance responses to these types of stimuli would be strongly attenuated by lesions to the fear representation in the medial prefrontal cortex.

The medial prefrontal cortex has been implicated in the inhibition of inappropriate responses to fear inducing stimuli, and lesions to this cortical area cause preservative responding in both animals and humans [161]. It has been demonstrated that rats with lesions to the medial prefrontal cortex can acquire freezing responses to auditory stimuli paired with footshock, but require a longer period to extinguish those responses when the auditory stimulus is presented alone over a period of several days [204]. Thus extinction is a form of learning involving the inhibition of conditioned involuntary responses, rather than the erasure of the association between the unconditioned and conditioned stimuli. Recently, Quirk et al. [235] have examined the effects of lesions involving infralimbic and prelimbic cortices on the acquisition, extinction and spontaneous recovery of conditioned fear responses over a two day period. They found that after the conditioning and extinction procedures on the first day (in which extinction rates of sham and lesioned rats were approximately the same) rats with sham lesions only recovered 27% of their acquired freezing on the second day when the conditioned stimulus was presented alone, while rats with medial prefrontal cortex lesions recovered 86% of acquired freezing responses. The recovery of extinguished fear observed by Quirk et al. [235] could slow the extinction rates in animals in which the extinction procedure takes several days, as in the study of Morgan and LeDoux [204]. These results suggest that fear representation in the medial prefrontal cortex may be necessary for the consolidation of extinction learning. If this is the case, the inhibition of the freezing responses may be mediated by the non-reciprocal projection from prelimbic and infralimbic cortex to the central nucleus of the amygdala [194], or by the projection from these areas of cortex to the dorsolateral PAG [11,104].

It has recently been observed that stimulation of the dorsal PAG matter in rodents produces symptoms and behavioral reactions that are very similar to those that occur during panic attacks in human patients [152,255,292], and the authors of these studies propose that dorsal PAG defence reaction can be considered an animal model of panic anxiety. The arguments are based on the acute signs of autonomic arousal and subjective fear induced by electrical stimulation of the dorsal PAG in humans [213], and comparable physical and behavioral responses in rats undergoing similar stimulation, and the fact that yohimbine and other drugs known to induce panic attacks in humans induce increased Fos expression in the PAG of rats [271]. In addition, Javanmard et al. [149] reported that a panic attack induced by the panicogen CCK4 produced increases in rCBF in the medial hypothalamus, but no concomitant increases in the medial prefrontal cortex. Fischer et al. [102] also found that rCBF in medial prefrontal cortex was not increased during an unexpected panic attack. Since there were rCBF increases in both the hypothalamus and PAG, and no corresponding increases in the fear representation in the medial prefrontal cortex, it appears likely that the extreme fear experienced by these patients is not due to cortical activities, but is produced by neuronal activities in the hypothalamic and PAG representations. This may explain the behavioral symptoms exhibited by these patients in whom an attack may cause flight or freezing behaviors similar to the responses of rodents to fear-eliciting situations, and which can be elicited by electrical or chemical stimulation of the lateral/dorsolateral PAG. These involuntary behaviors are generated by neuronal activities in the pontine inhibitory area and the medullary motor pattern generators, which receive their primary motivational input from the fear representation in the caudal lateral/dorsolateral PAG, and are thus not subject to cognitive control. The lack of activation of the medial prefrontal fear representation in panic disorder patients implies that fear motivation inputs probably do not reach the cingulate and area 6 cortical premotor structures during panic attacks, and thus cognitively regulated behaviors are not supported in these situations.

In Bremner et al. [43] study of brain areas activated by traumatic combat-related pictures and sounds in PTSD and non-PTSD combat veterans it was reported that these stimuli produced activation of area 32 in non-PTSD subjects, but not in PTSD subjects. These types of stimuli should elicit both fear and anger, so the absence of activation of area 32 in PTSD subjects suggests that if these stimuli did indeed elicit fear and/or anger in these subjects, this must have been due to increased activities in the subcortical (hypothalamic, PAG) representations. This effect is similar to that occurring in panic disorder patients, and probably also results in a decrease in cognitively regulated behaviors, and a concomitant increase in involuntary actions.

5.2. Neural correlates of the subjective awareness of fear and power-dominance

Neuronal activities in each of the fear and power-dominance representations need not contribute equally, or at all, to the awareness of these emotions. Studies of the effects of lesions to each structure are potentially useful in determining which representations contribute to awareness, and how strong that contribution is. However, the assessment of the effects of such lesions on conscious awareness is by no means straightforward, since lesions to individual fear representations may partially deafferent other representations. At best, these studies allow certain general inferences about the contributions of individual representations to awareness.

It is natural to expect that at least in primate species activities in the cortical representation located in the cingulate gyrus should contribute to the awareness of

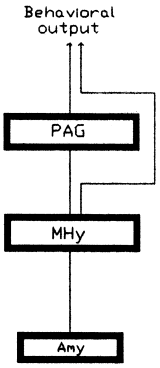

Fig. 6. Model system for defensive responses of Fernandez de Molina and Hunsperger [92]. Behavioral output is mediated by projections from the medial hypothalamus and periaqueductal gray to the medullary motor pattern generators. Abbreviations: MHy, medial hypothalamus, PAG, periaqueductal gray matter; Amy, amygdaloid complex.

anger and fear. Papez [222] proposed that the locus of neuronal activities that produce the awareness of emotion was the cortex of the cingulate gyrus. This proposal has recently received support from the results of Lane and colleagues, who have demonstrated that there is a significant correlation between neural activity in the anterior cingulate cortex and levels of subjective emotional awareness in human subjects presented with emotion inducing films or during recall of emotional experiences [172].

In cats, decerebration sparing the hypothalamus results in extreme responses to aversive stimuli, which include overt rage and wild escape behavior [22]. The intensity of these responses are similar to those in cats with septal lesions [127], and may be due to the removal of inhibitory influences of forebrain structures over the medial hypothalamic nuclei via the hippocampo-septal and septohypothalamic projections [132]. The rage and fear responses to aversive stimulation in the decerebrate animals have been described as being 'sham', because it was thought that subjective emotional experience could only be due to neuronal activities in the cerebral cortex. However, there is no compelling reason why this should be so, and the presence of manifest affective responses suggests that Bard's cats actually experienced extreme fear and rage. This subjective experience must have been due to activities in the representations in the medial hypothalamus and/or caudal and rostral dorsolateral PAG. This does not necessarily mean that activities in these structures contribute to awareness in unlesioned animals, since the inhibitory influence of the septohypothalamic projection (and perhaps also of the projection from medial prefrontal cortex) may reduce or abolish these contributions in unlesioned animals. Nevertheless, there is additional evidence that the PAG and/or hypothalamic representations contribute to fear awareness in human subjects. The reported absence of increases in rCBF in medial prefrontal cortex [102,149] and substantial activations of the hypothalamus and PAG [149,240] during panic attacks suggest that the extreme fear experienced subjectively by the subjects during the attacks may have been due to activities in the subcortical fear representations.

5.3. Comparison with previous models

Based on electrical stimulation studies, Fernandez de Molina and Hunsperger [92] proposed the earliest neural system mediating fight/flight behaviors in the cat. This system was based on studies of the effects of lesions to the feline medial hypothalamus and PAG on behaviors induced by electrical stimulation of sites within the amygdaloid complex, hypothalamus and PAG. As mentioned above, Hunsperger [144] demonstrated that bilateral lesions of the PAG abolished hissing responses elicited by stimulation in the medial hypothalamus, but hissing elicited by PAG stimulation was unaffected by hypothalamic lesions. Large lesions to the medial hypothalamus or dorsal PAG also abolished fear and anger responses, including hissing, piloerection and threat postures, elicited by stimulation of sites within the dorsomedial amygdala [92]. The study of Hunsperger [144] indicates that the PAG is a higher order component of the system than the medial hypothalamus, and that behavioral output is mediated by projections from both the PAG and hypothalamus to the motor pattern generators located in the medulla. Mnemonic input reaches both these structures via projections from the amygdaloid complex (Fig. 6). Comparison with Figs. 4 and 5 shows that the system proposed by Fernandez de Molina and Hunsperger [92] to mediate defensive behaviors is incorporated within the system described in this paper.

Since the time when the model described above was delineated, the function of the various components of the amygdaloid complex (and its extension into the bed nucleus of the stria terminalis) has been greatly clarified, particularly in so far as the medial and central divisions are concerned, and the functions of the basolateral complex in forming associations between unconditioned and conditioned stimuli have been detailed [37,250,254]. This knowledge has led LeDoux and colleagues to propose a neural model for fear conditioning to explicit auditory stimuli in rodents that includes sensory and mnemonic structures, including the auditory pathway and the basolateral complex and central nucleus of the amygdala, with the PAG as the output station for behavioral responses (Fig. 7) [249]. This system does not include any medial hypothalamic structures, and it is argued that the mnemonic inputs to the PAG are mediated by a direct projection from the central amygdaloid nucleus. The hippocampus is only involved in contextual conditioning, and its contribution is mediated via projections from the output stations (subiculum, CA1 field) of the complex to the lateral, basolateral and basomedial amygdaloid nuclei. All the components (except the structures of the auditory pathway) of the system proposed by Rogan and LeDoux to mediate conditioned fear responses are incorporated in the system proposed here, with the significant difference that

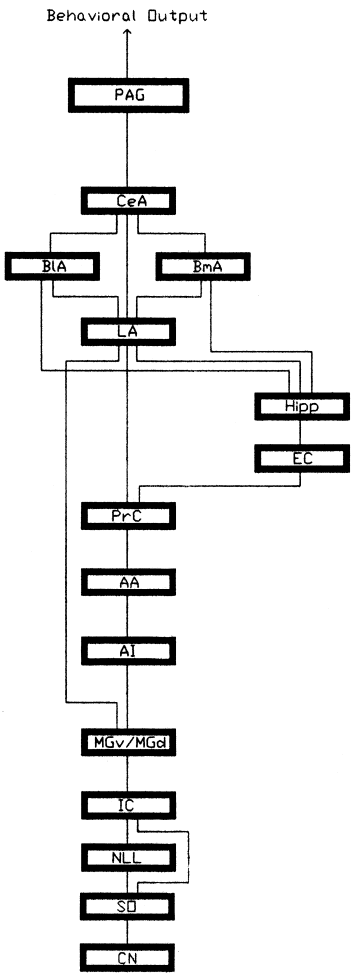

Fig. 7. System mediating conditioned fear responses to auditory stimuli developed by LeDoux and colleagues [249]. Function is discussed in the text. Abbreviations: AA, auditory association cortex; A, primary auditory cortex; BlA, basolateral amygdaloid nucleus; Ba, basomedial amygdaloid nucleus; CeA, central amygdaloid nucleus; CN, cochlear nucleus; EC, entorhinal cortex; Hipp, hippocampus; IC, inferior colliculus; LA, lateral nucleus of the amygdala; MGv/MGd, ventral and dorsal divisions of the medial geniculate nucleus; NLL, nucleus of the lateral lemniscus; ventral and dorsal divisions of the medial geniculate complex; PAG, periaqueductal gray; PrC, perirhinal cortex; SO, superior olivary complex.

the primary influence of sensory/mnemonic information processed in the hippocampal formation is mediated through direct and indirect projections to the medial hypothalamic nuclei (Figs. 4 and 5).

Papez [222] proposed a limbic 'circuit' that processes emotional information, which incorporates several of the components included in Figs. 4 and 5. In this system, information from external sensory receptors reaches primary sensory cortex, is processed in association cortical areas, and is relayed to the hippocampal formation. After processing in the latter structure, signals reach the mammillary nuclei via the fornix, and projections from this area reach both the hypothalamus, where emotion is expressed (i.e. which mediates behavioral output). The mammillary area also feeds information to the anterior

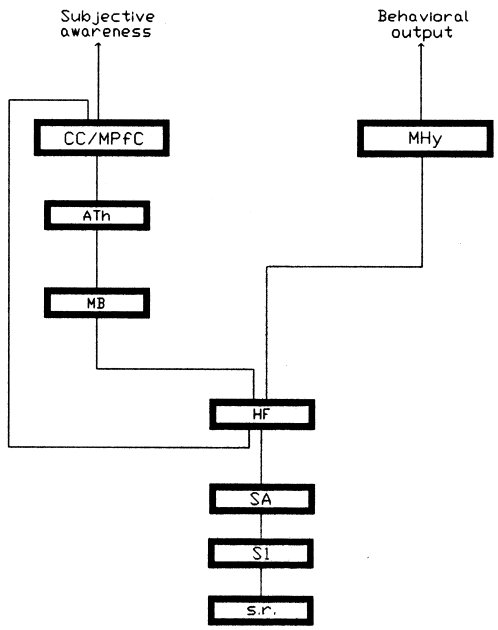

Fig. 8. Limbic 'circuit' of Papez [227]. Behavioral output is mediated by projections from the medial hypothalamus, and subjective awareness of emotion by activities in cingulate cortical areas. See text for description of function. Abbreviations: ATh, anterior thalamic nuclei; CC/MPfc, cingulate and medial prefrontal cortical areas, MB, mammillary nuclei; MHy, medial hypothalamus; SA, sensory association cortex; S1, primary sensory cortex; s.r., sensory receptors.

thalamic nuclei through the mammillothalamic tract, and this information is relayed to the anterior cingulate and medial prefrontal cortices, where conscious appreciation of emotions is generated. The 'circuit' is completed through a feedback route extending from the anterior cingulate gyrus through retrosplenial cortex to the hippocampus (Fig. 8). Papez' [222] inclusion of the anterior cingulate gyrus as a component of the system the subjective appreciation of emotion was based primarily on reports of decreased emotionality in human subjects with cingulate lesions. In accordance with Bard [22], Papez evidently did not believe that activities in subcortical structures could participate in generating subjective awareness, and thus regarded the hypothalamus as merely an output station for behavioral responses. As can be seen by comparison with Figs. 4 and 5, there is a definite resemblance between the Papez system and parts of the system proposed here.

LeDoux [174] made an extensive criticism of the concept of the limbic system as a mediator of emotional responses. He argued that although some of the areas included by Papez [222] in his limbic 'circuit' have been implicated in emotional processes, most of them are not necessary for emotional response that have been studied in the laboratory, including conditioned fear. In addition, he noted that several of the components of the limbic system are involved in cognitive, rather than emotional processes. In particular, the hippocampal formation is not necessary for fear conditioning to an explicit auditory stimulus, and the cortical areas of the cingulate gyrus exert, at best, a modulatory action on the

primary structures involved in fear conditioning (i.e. the amygdala and PAG), but are not necessary for this type of learning. The latter observation is undoubtedly true insofar as involuntary responses such as freezing to conditioned auditory and visual stimuli, since lesions to the medial prefrontal cortex produce, in general, only minor effects on these responses. However, the arguments presented above suggest that the cortical fear and power-dominance representations' major contribution to behavior is in the motivation of learned (instrumental) and voluntary behaviors. The primary differences between the system proposed by Papez [222] and Rogan and LeDoux [249] lie in the output structures for behavioral output (medial hypothalamus vs. periaqueductal gray), the inclusion of the amygdala as the principal sensory-mnemonic structure by Rogan and Ledoux [249], and of the hippocampal formation by Papez [222], and the additional inclusion of the cortex of the cingulate gyrus by Papez as the locus of subjective emotional experience. The problem of the output station for behavior is clarified by the results of Hunsperger's [144] experiments. The remaining differences may reflect in part the fact that Papez based his system on observations of the effects of lesions and electrical stimulation in human subjects, while LeDoux and colleagues based theirs on experiments with rodents.

5.4. Drive, reward value, and reward

It is generally agreed that reward is linked to behaviors motivated by the power-dominance drive and other drives such as hunger and sexual need. However, reward occurs as a result of the behaviors motivated by any of the motivational drives. The drive itself simply provides the impetus for the behaviors necessary to achieve the reward, but does not specify which behaviors should be employed, nor which objects should be sought after. The hunger drive motivates any behavior that will result in the acquisition and consumption of food. Which food is actually acquired depends on the reward value of each of the available foods in the nearby environment. Reward itself—the pleasure experienced—(rather than reward value which merely predicts reward) is achieved by consuming the food item, and the subjective experience of the reward is presumably mediated by neuronal activities in hedonic representations in the gustatory pathways. For animals, the reward value of individual food items is determined for the most part innately (sweet foods are 'good', grains less so), while for humans the reward value may be largely learned. Reward value for visual, olfactory, somatosensory and taste stimuli is represented in the lateral hypothalamic area and caudolateral orbitofrontal cortex [218,251]. The choice of which behaviors will be used in order to acquire the chosen (highest value) object may be determined by neuronal activities in the ventral striatum, including the nucleus accumbens, but this is by no means certain. The reward prediction (value) system may operate in tandem with the drive system during behaviors motivated by the various drives, but in essence drive and reward value are represented separately.

Overt power-driven behaviors such as the acquisition of wealth and athletic competition are predominant in western societies. The rewards that occur as a result of these behaviors are given high value in these societies. However, since almost all human values are learned, it is to be expected that different societies will have different values. In many societies, behaviors such as the acquisition of wealth and power are not socially acceptable (i.e. their reward value is very low) so they are not pursued. In these societies, behaviors designed to acquire 'merit' in the eyes of one's fellow human beings are given high value. These behaviors often involve self-abasement and self-denial, and stand in stark contrast to the acquisition of material objects and power seen in western culture. However, the result (reward) that occurs as a consequence of these behaviors is the same: an increase in self-esteem, which is the ultimate goal of the power-dominance drive. The fact that many behaviors motivated by the power-dominance drive are not overtly 'powerful', particularly insofar as human behaviors are concerned, suggests that the term 'power-dominance' might not be all that appropriate, and the term 'ego drive' might better describe this form of motivation, given its goal.

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