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FROM MOTIVATION TO ACTION: FUNCTIONAL INTERFACE BETWEEN THE LIMBIC SYSTEM AND THE MOTOR SYSTEM

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1. Introduction

"Nervous systems are built for actions... Actions are directed towards goals". (Livingston, 1967.)

"Movements are parts of actions, and actions have to satisfy the needs of the organism and secure survival of the species. Therefore, they must be guided by messages from the internal milieu as well as from the environment". (Kornhuber, 1974.)

Animals initiate movements and actions to procure food, to escape from predators, to seek shelter, etc.—movements and actions that contribute to biological adaptation and survival. Such actions, which depend on complex integrative activities of the central nervous system (CNS), may be initiated by olfactory, visual and other sensory stimuli occurring in the external environment. They may be initiated also by perturbations of the internal environment; for example, low blood sugar may lead to feeding, body fluid deficits to drinking, and a lowering of body temperature to behavioral thermoregulatory responses. Indeed, as indicated by the above quotation from Kornhuber, some actions contribute along with visceral regulatory responses to the homeostasis of the internal environment as well as to adaptation to the external environment.

A major preoccupation of neurophysiologists for several decades has been with mechanisms for the control of posture and movement; as a consequence, the neural integrative activities that initiate biologically-significant movements or actions that contribute to adaptation and survival has been a relatively neglected subject. There is considerable evidence that limbic forebrain structures are important in "drives" and "motivational" processes (Mogenson and Huang, 1973; Mogenson, 1977) contributing to the initiation of actions, but little is known about the neural mechanisms by which limbic processes gain access to the motor system. In this paper we deal with this subject and in particular with tentative suggestions regarding the neural interface between limbic and motor systems.

2. Historical Background

The subject of the interface between motivation and action—between limbic and motor systems—can be traced back to the classical experiments of Hess (1957). This Swiss neurophysiologist is widely recognized for his fundamental contributions in mapping the central representation of the parasympathetic and sympathetic nervous systems, for which he was awarded the Nobel prize in 1949. He also demonstrated that attack, feeding and other complex, biologically-significant behaviors could be elicited by electrical stimulation of the hypothalamus in unanesthetized cats. These observations were confirmed and extended by other investigators and, as shown in the next section, there is considerable evidence from stimulation and lesion experiments implicating the hypothalamus and limbic forebrain structures in the initiation of attack, copulatory, drinking, feeding, thermoregulatory and other behavioral responses. The neural processes resulting from electrical stimulation of the hypothalamus or limbic forebrain must eventually influence the motor system to produce the attack, feeding or other behaviors observed. However, little progress has been made in elucidating the neural mechanisms by which the motor system is activated in such elicited behaviors. A major reason for the neglect of this important problem has been the absence of relevant anatomical evidence.

A consequence of neglecting this problem is that investigations of the limbic system and hypothalamus and investigations of the motor system have developed along rather separate lines. The major research tradition in neurophysiology has dealt with the neural mechanisms associated with sensory inputs, sensory information processing and the motor control of movements or actions. A second, and relatively separate field, has been concerned with neural integrative activities for visceral responses involved in the homeostatic regulation of the internal environment. These two research traditions correspond to the two basic kinds of functions performed by the CNS—the control of the movements or actions of the animal in its external environment and the vital homeostatic regulations of the internal environment (Mountcastle, 1974). Their relative separation is unfortunate, since the two kinds of functions of the nervous system have complementary roles in adaptation and survival and, as indicated by the quotations appearing at the beginning of this article, they involve closely related neural integrative activities.

Developments in recent years have drawn attention to the possible functional interface between limbic processes associated with the initiation of actions or goal-directed behaviors and the neural mechanisms for the motor control of such actions or behaviors. In one of the invited lectures at the Toronto meeting of the Society for Neuroscience, McGeer (1976) referred to mood (or motivation) and movement as "twin galaxies" of the brain and he emphasized the need to investigate the functional link between the neural processes concerned with motivation—or the "intention" to respond—and the motor control of movement or action. At the same meeting, Graybiel (1976) reviewed the evidence concerning neural connections of limbic structures and basal ganglia and suggested that recent anatomical evidence obtained with new techniques makes it possible to investigate the functional interface between motivational processes and movement. She suggested from anatomical connections that the nucleus accumbens is a key structure in linking limbic structures and the basal ganglia.

In a latter section evidence from anatomical, electrophysiological, neuropharmacological and behavioral experiments will be reviewed in relation to a tentative model for the limbic-motor interface. Before presenting the model, however, a brief account will be given of experimental findings which implicate limbic and related structures in motivational processes. It also seems necessary to provide a brief overview of the neural mechanisms for the motor control of movements or actions.

3. Evidence Implicating Limbic and Related Structures in the Initiation of Motor Responses

The limbic system is shown in Fig. 1. It refers to amygdala, hippocampus and other forebrain structures and their connections to the hypothalamus and to the midbrain—

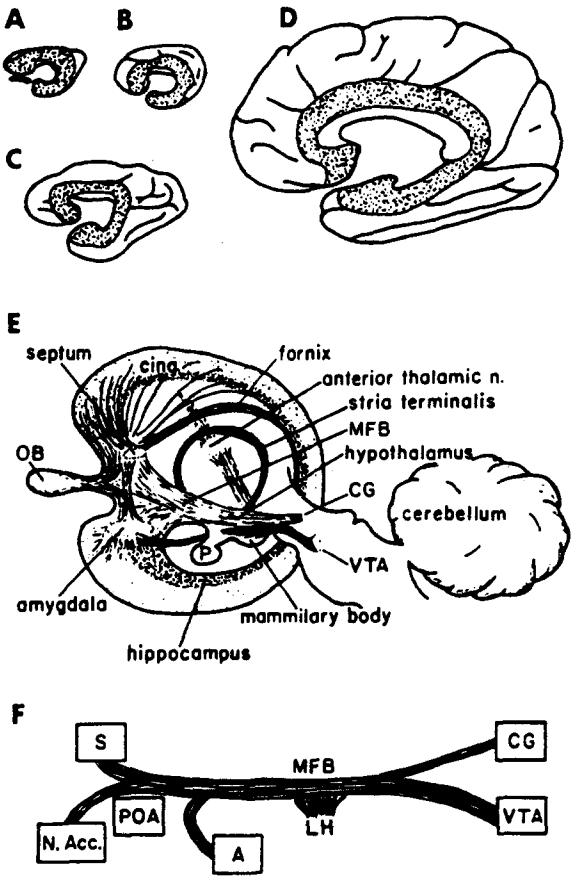

FIG. 1. The limbic system is a term introduced by MacLean (1952) to designate the forebrain structures associated with the higher neural integration of autonomic and endocrine responses for visceral regulations and with attack, feeding, sexual and other behaviors. The limbic system is shown for rabbit in (A), for cat in (B), for monkey in (C) and for the human brain in (D). (E) The amygdala, hippocampus, septal area and other limbic forebrain structures are connected with the hypothalamus and midbrain by neural pathways such as the stria terminalis, fornix and medial forebrain bundle. (F) The medial forebrain bundle is a major pathway through the lateral hypothalamus which interconnects limbic forebrain structures with the hypothalamus and midbrain. Attack, feeding and other behaviors are elicited by electrical stimulation of the medial forebrain bundle (see Fig. 2) and projections caudally to the ventral tegmental area have been implicated. Abbreviations: A, amygdala; CG, central gray; Cing, cingulate gyrus; LH, lateral hypothalamus; MFB, medial forebrain bundle; N.Acc., nucleus accumbens; OB, olfactory bulb; P, pituitary gland; POA, preoptic area; VTA, ventral tegmental area of Tsai.

and in particular to the ventral tegmental area of Tsai, via the medial forebrain bundle (Morgane, 1975; Nauta and Haymaker, 1969).

Only a brief account will be given here of experimental evidence that has accumulated over the last three or four decades which implicates limbic forebrain structures and hypothalamus in motivational processes that are prerequisite for various goal-directed behavioral responses. For further details, the reader is referred to reviews of this field (e.g. Stevenson, 1969; Mogenson and Calaresu, 1975; Mogenson, 1977; Livingston and Hornykiewicz, 1978).

As indicated above, some of the initial evidence came from the classic experiments of Hess (1957) in which he pioneered the technique of chronic electrical stimulation of the brain in freely moving animals. He observed that electrical stimulation of the lateral hypothalamus and related sites elicited attack, defense, feeding and other complex behavioral responses. These elicited responses were usually similar to the adaptive, goal-directed behaviors investigated in more natural settings by Charles Darwin and other biologists. Subsequently these observations were confirmed and extended by a number of other investigators (Fig. 2). It is now well established that electrical stimulation of the

lateral hypothalamus in the region of the medial forebrain bundle (LH-MFB) elicits attack, drinking, feeding, hoarding and sexual responses (Glickman and Schiff, 1967). Some of these responses are also elicited by electrical stimulation of the amygdala and other forebrain limbic structures and the ventral tegmental area of Tsai in the midbrain (Mogenson and Huang, 1973). Electrical stimulation of several limbic forebrain sites has also been shown to influence the behaviors elicited by electrical stimulation of the lateral hypothalamus (Siegel and Flynn, 1968; Siegel and Skog, 1970; Sibole *et al.*, 1971). These observations have been interpreted in terms of modulating effects of limbic forebrain structures on hypothalamic integrative mechanisms, a concept of hypothalamic–limbic interaction also supported by experiments in which cardiovascular and hormonal responses have been investigated (Eleftheriou, 1972; Gloor *et al.*, 1972; Mogenson, 1973, 1977).

Evidence from lesion and ablation experiments has implicated the hypothalamus and limbic structures in the initiation of goal-directed behaviors. The classic experiments with this experimental approach were concerned with dramatic changes in affective-aggressive reactions of animals following complete or partial decortication (Bard, 1928; Kluver and Bucy, 1937). In decorticate cats and dogs Bard observed "rage-like" reactions, designated "sham" rage, readily provoked by stimuli that were normally ineffective in influencing the behavior of intact animals. In later experiments involving discrete electrolytic lesions it was observed that aggressive rage reactions resulted from lesions of the ventromedial hypothalamus (Wheatley, 1944; Grossman, 1966). However, the attack responses were more directed following ventromedial hypothalamic lesions than following decortication, presumably because there was more sensory guidance of the behavior. In partially decorticate monkeys with bilateral temporal lobectomy, Kluver and Bucy (1937) observed reduced emotional reactivity and reduced fear-like behavior. Subsequent experiments showed that this attenuation of fear-like and aggressive behaviors could be produced by discrete electrolytic lesions of the amygdala (Schreiner and Kling, 1953) and that increased aggressive attack resulted from lesions of the septum (Brady and Nauta, 1953). Lesions of limbic forebrain structures have also been shown to influence feeding, drinking, thermoregulatory, sexual and other goal-directed behaviors (Mogenson, 1977).

Goal-directed behaviors, similar to adaptive behaviors observed in more natural circumstances, have also been elicited by injecting certain compounds (e.g., sodium chloride, neurotransmitters such as noradrenaline or acetylcholine, hormones such as testosterone or angiotensin) into the brain, either into the cerebral ventricles or into the hypothalamus or limbic structures. Behavioral experiments using this approach were undertaken by Andersson, a student of Hess, who adapted his mentor's research strategy of "electrical" stimulation to "chemical" stimulation. Andersson (1953) elicited copious drinking in the goat by injecting hypertonic NaCl into the cerebral ventricles or into the hypothalamus. Later, Fisher (1956) observed that copulatory behavior could be elicited by injecting testosterone into the hypothalamus and Grossman (1962) elicited feeding and drinking by injecting noradrenaline and acetylcholine respectively. More recently, drinking was also elicited by injections of angiotensin II into the preoptic region and other brain sites (Epstein *et al.*, 1970; Mogenson and Kucharczyk, 1978). Although the interpretation of some of these observations is not clear, it appears that the hypothalamus, preoptic region and perhaps the other basal forebrain regions are responsive to osmotic stimuli, neurotransmitters, and to hormones such as testosterone and angiotensin. These observations suggest that receptors for these compounds are in these regions of the brain but the nature and exact loci of the receptors are uncertain.

Two kinds of evidence indicate that the ventral midbrain and lower brainstem regions also contribute to attack, feeding and other goal-directed behaviors and suggest that neural pathways to these regions, which descend from limbic forebrain and hypothalamus (see Fig. 1F) have an important role in the initiation of these behaviors. First, behaviors such as attack and feeding have been elicited by electrical stimulation of the ventral tegmental area of Tsai and lower brain stem sites (Hess and Akert, 1955; Wyrwicka and Doty, 1966; Sheard and Flynn, 1967). Second, these behaviors have been

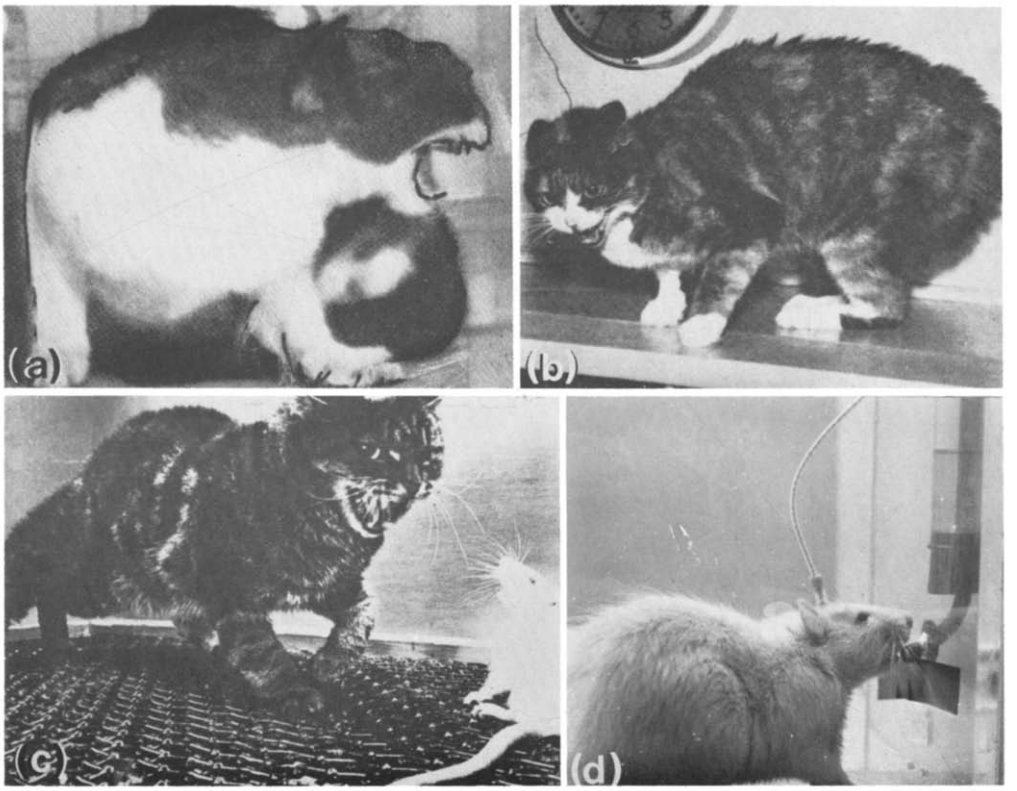

FIG. 2. Complex behavioral responses, similar to goal-oriented behaviors observed in natural circumstances, are elicited by electrical stimulation of limbic forebrain structures and of fiber projections from these structures in the medial forebrain bundle of the lateral hypothalamus. (A) Affective-defensive behavior observed by Hess (1957) during electrical stimulation of the lateral hypothalamus. (B) Defense reaction elicited by hypothalamic stimulation. This picture was taken a few seconds before a flight response occurred (jumping from table and attempting to escape) (after Brown *et al.*, 1969). (C) Attack behavior towards a rat elicited in the cat by electrical stimulation of the lateral hypothalamus (after Flynn, 1967). (D) Drinking of water elicited by electrical stimulation of the lateral hypothalamus of a rat (from Mogenson and Stevenson, 1966).

observed in decorticate and mesencephalic animals, thus indicating that neural integrative processes for their initiation are represented in the brainstem (Bard and Macht, 1958). It seems that there is a hierarchical organization of neural processes for goal-directed behaviors and that more rostral structures such as the limbic system and hypothalamus provide for additional initiators of these behaviors (Mogenson and Huang, 1973; Bernston and Micco, 1976).

4. The Motor Control of Behavior

"The motor system of the brain exists to translate thought, sensation, and emotion into movement". (Henneman, 1974.)

Before presenting a tentative model of the functional interface between limbic and motor systems, some consideration should be given to the motor system. This will be done briefly since motor physiology has been a vigorous field of research in recent years and the literature is extensive. For further details the reader is directed to the following articles: Eccles (1973), Ito (1974), Asanuma (1973), Sessle and Hannan (1976), Wetzel and Stuart (1976), Dubner *et al.* (1978), Evarts (1979), Nauta (1979) and Henneman (1974).

The function of the motor system is to organize and coordinate the activities of individual muscles to generate sequences of movements that are integrated into behavioral responses appropriate to the environment. The integrative activities of the motor system are complex, involving the cerebral cortex, cerebellum and basal ganglia as well as the brain stem and spinal cord, in a system of feedforward and feedback information processing. Considered from the functional point of view, the motor system is organized in a hierarchical manner, with increasing complexity of integration up the neuraxis (Bernstein, 1967; Allen and Tsukahara, 1974). A schematic of this organization is presented in Fig. 3. For simplicity, sensory feedback pathways are omitted from the figure. It must be emphasized, however, that sensory–motor integration at all levels of the hierarchy constitutes a very significant aspect of all motor responses (see Allen and Tsukahara, 1974; Brooks, 1979; Evarts, 1979). At the lowest end of the neuraxis, corresponding to the lowest level of the hierarchy of neural integration, are the motor neurons which synapse on and activate muscle fibers. Interneuronal pools within the spinal cord mediate spinal reflexes and intersegmentally coordinated limb movements. The brain stem in turn coordinates segmental motor activities representing a relatively limited integrative function.* Thus decerebrate animals with an intact brain stem are capable of performing crude but coordinated locomotor and oral motor activities (Sherrington, 1910; Shik and Orlovsky, 1976; Dubner *et al.*, 1978). Higher CNS structures including the basal ganglia, the cerebellum and the motor cortex represent a higher level of integration in the hierarchy (Fig. 3). These structures exert control over the brain stem and spinal cord and their contribution to sensory–motor integration make possible motor responses that are more complex and precise. This hierarchical organization of the motor system is also well illustrated by the differences in the variability of motor responses between lower and higher animals in the phylogenetic scale. Lower animals, in which these rostral structures have not been elaborated, or are absent, are restricted to relatively stereotyped motor responses. The range and complexity of motor responses seen in higher animals are notably absent (Romer, 1964).

The events underlying the motor control of behavior can be conceptualized as being divided into three phases: the initiation phase, the planning and program selection phase, and the execution phase (Fig. 3). Such a conceptualization is somewhat simplistic and arbitrary, but it is useful in discussing the motor system. In higher animals, a wide range of events initiate movements and actions, among which are cognitive processes involving

* For example, Henneman (1974) has stated that, "...brain stem centers...extend motor capacity far beyond the stereotyped regulatory behavior of the spinal animal. Animals with a brainstem (but without higher centers) are capable of integrative activities such as standing, walking and postural adjustments. These activities require the participation of various righting reflexes and antigravity mechanisms, they demand precise control of equilibrium and they involve the coordination of muscles throughout the body". (p. 606.)

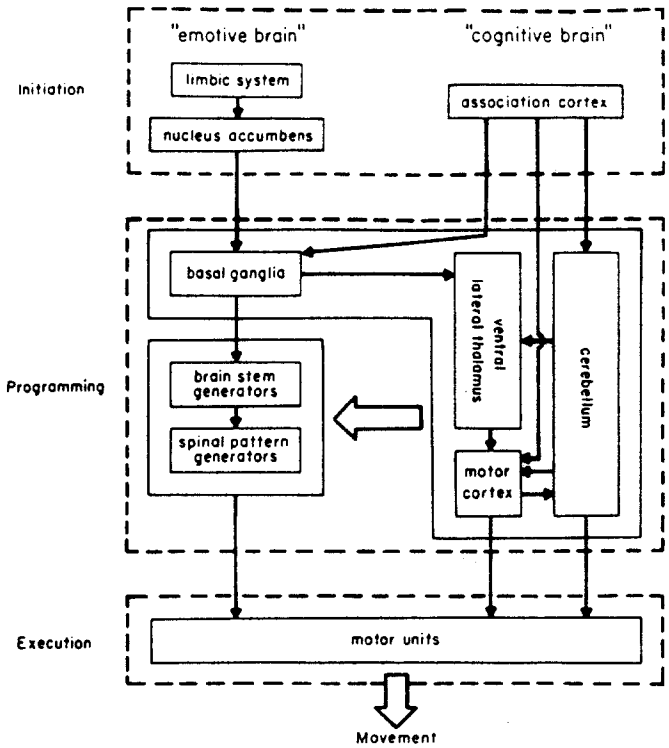

FIG. 3. A schematic representation of the organization of the neural mechanisms that translate emotive and cognitive processes into behavioral motor responses. Motor control of behavior is complex, involving feedforward and feedback information processing between the motor cortex, cerebellum, basal ganglia as well as the brain stem and spinal cord. The motor system can be viewed as being organized in a hierarchical manner generally corresponding to an increase in the complexity of sensory–motor integration up the neuraxis. For simplicity, sensory feedback pathways are omitted from this figure, but it must be emphasized that control of a motor response depends on the integration of extensive proprioceptive and exteroceptive information together with CNS feedforward commands (Evarts, 1979). It is also useful in the discussion of the motor system to conceptualize the processes involved in the generation of a motor response as being divided into three phases: initiation phase, programming phase, and execution phase (Allen and Tsukahara, 1974). The neural components involved primarily in each of the three phases are enclosed by the dotted rectangles. Motor units are the common terminus of all CNS motor commands. Integration of the activities of individual motor units form the basis of all movements. The temporal and differential activation of the motor units constitute a motor program that elicits a specific motor response. Both emotive processes including homeostatic (such as hunger, thirst) and non-homeostatic (such as sex, fear, rage) drives, as well as cognitive processes, which are more prominent in the higher mammals, initiate behavioral motor responses. At the top of the figure, the neural processes for the initiation of responses are depicted. The terms "emotive" brain and "cognitive" brain are from Konorski (1967).

the association cortex and emotive processes involving the limbic system. Although it is the objective of this article to consider response initiation by limbic integrative processes, and in particular to consider a tentative model of the functional interface between limbic and motor systems, a brief consideration will first be given to the programming and execution phases of movement.

In the programming phase of a motor act, particularly in volitional movements, the cerebral cortex, cerebellum and basal ganglia are involved in first selecting motor programs or strategies for the act, then preparing the brain stem and spinal cord for the appropriate responses and finally initiating muscular contractions. The concept, programming, is used by a number of motor physiologists to designate the integrative processes of motor control (see Young, 1978; Brooks, 1979). Motor programs are also considered to be organized in a hierarchical manner consisting of "high level" general programs that set task-related processes and which recruit lower level programs eventually activating "particular programs" which cause contraction of the muscles (Brooks, 1979). Investigators of locomotor and oral motor responses have suggested that fixed

neuronal circuits, referred to as pattern generators, exist within the spinal cord and brain stem which when activated, elicit stereotyped, coordinated movements (Dubner *et al.*, 1978; Stein, 1978). These pattern generators may be part of the particular programs accessed by higher brain centers to generate a complex behavior (Fig. 3). The pattern generators for locomotion appear to reside in the spinal cord and can be activated by discrete nuclei or regions of the brain stem. Two areas in the brain stem, one in the subthalamic area and another in close proximity to the nucleus cuneiformis, have been shown to elicit stereotyped stepping movements when stimulated (Grillner, 1969; Shik and Orlovsky, 1976). These areas have been termed subthalamic locomotor region (SLR) and mesencephalic locomotor region (MLR) respectively. It is proposed that these areas activate pattern generators in the spinal cord to elicit the coordinated stepping movements and in turn these areas may be accessed by higher level CNS structures. A similar organization has been found for oral motor responses with the pattern generators for chewing and swallowing located in the brainstem medullary–pontine reticular formation (Dubner *et al.*, 1978). Stimulation of the ventral tegmentum, diencephalon–medial forebrain bundle and anterolateral cortex elicits chewing and swallowing (Ferrier, 1876; Magoun *et al.*, 1933; Dubner *et al.*, 1978), possibly due to activation of the brainstem pattern generators by these "higher level" regions.

Locomotor and oral motor responses are of special interest in this article because they are fundamental components of food-seeking and ingestive responses, vocalization, escape from predators and other behaviors essential for adaptation and survival. Limbic structures appear to have access to these pattern generators suggesting that the limbic system may have a direct role in the initiation of motor responses. A more detailed discussion of this possibility will be the subject of the subsequent sections.

During the execution phase of a movement, peripheral proprioceptive feedbacks are utilized continuously to monitor the accuracy and precision of the movement.* Both the cerebellum and the motor areas of the cerebral cortex receive massive feedback sensory information for the smooth control of movement (see Eccles, 1973; Ito, 1974; Asanuma, 1973; Evarts, 1979). Projections from the visual cortex to the frontal and motor cortex provide visual guidance aiding spatial coordination of movements (see Mishkin, 1966; Haaxma and Kuypers, 1974).

As indicated by the quotation from Henneman at the beginning of this section, the motor system contributes to the translation of cognitive and emotive processes into movements. Unfortunately, although extensive research has been done to understand the mechanisms involved in the execution of a motor response, the initiating processes remain obscure. Some areas of the cerebral cortex have been suggested to contribute to the initiation of movements involving cognitive processes. For example, the recording of "readiness potentials" from association cortex prior to limb movements in response to a discrete signal has directed attention to the possible role of the cerebral cortex in response initiation (Kornhuber, 1974). Also, recent chronic microelectrode recording studies suggest that the parietal cortex may contain "command" neurons for the initiation of arm movements requiring visual guidance (Mountcastle *et al.*, 1975). The cerebral cortex sends strong, topographically-organized projections to the caudate nucleus which in turn projects to the globus pallidus and other motor structures (Kemp and Powell, 1971). As discussed more fully later, this could be a route for the initiation of movements.

Movements and "actions" are not only initiated in situations involving cognitive processes (e.g. verbal instructions to human subjects or pretraining of animals); they are also initiated by innate "drives" or "emotional states" related to biological adaptation and

* The distinction between the programming stage and the execution stage is somewhat arbitrary and oversimplified. However, it is a useful distinction as illustrated by the following: "In learning a movement, we first execute the movement very slowly because it cannot be adequately preprogrammed. Instead, it is performed largely by cerebral intervention as well as the constant updating of the pars intermedia (of the cerebellum). With practice, a greater amount of the movement can be preprogrammed and the movement can be executed more rapidly. For learned movements Eccles and Ito view the cerebellum as providing an internal substitute for the external world. This eliminates the need for peripheral sensory input and allows one to increase the speed of the learned movement by preprogramming". (Allen and Tsukahara, 1974, p. 993.)

survival. That is, in the terminology of Konorski (1967), the "emotive brain" as well as the "cognitive brain" contributes to the initiation of movements and "actions" (Fig. 3). The role of the "emotive brain" (e.g. limbic forebrain and related structures) in initiating "actions" is considered in some detail in the subsequent sections. The relevant evidence will be reviewed in relation to a tentative model of the limbic–motor interface presented in the next section. This will be followed in Section 6 by a discussion of the functional implications of the proposed model for locomotor, oral motor and other responses.

5. Limbic–Motor Interface: A Tentative Model

Examples were cited, in an earlier section, of attack, feeding and other behaviors elicited by electrical stimulation of hypothalamus and limbic forebrain and midbrain structures (see Fig. 2 and Section 3). These behavioral observations by Hess and other

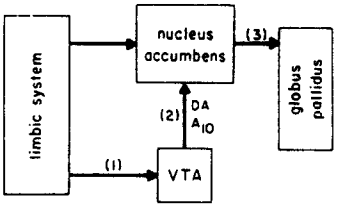

FIG. 4. Graybiel (1976) proposed that the nucleus accumbens is an important structure in the functional link between limbic forebrain structures and the motor system (for details see Barbeau *et al.*, 1977). The nucleus accumbens receives direct projections from amygdala, hippocampus and other limbic structures (Raisman *et al.*, 1966; De Olmos and Ingram, 1972; De France and Yoshihara, 1975), as well as indirect connections via the ventral tegmental area (VTA). The VTA is the source of mesolimbic dopaminergic afferents of the nucleus accumbens (Ungerstedt, 1971a). Recent anatomical evidence indicates that the nucleus accumbens in turn projects to the globus pallidus. Three components of the model are designated as follows: (1) neural projections from limbic forebrain structures, preoptic region and hypothalamus which converge in the medial forebrain bundle and descend to the VTA (see Fig. 1F); (2) projections of mesolimbic A10 dopaminergic neurons from VTA to nucleus accumbens; and (3) neural projections from nucleus accumbens to globus pallidus.

investigators implicated limbic and related structures in the initiation of movements and actions and also raised the question of how limbic mechanisms subserving "drives" and "emotions" gain access to the motor system. Recent neuroanatomical evidence makes it possible to suggest a tentative model for this limbic–motor interface, which may stimulate research on an important and neglected aspect of neuroscience (McGeer, 1976).

According to Graybiel (1976), the nucleus accumbens is a key structure in functionally linking motivation and action—at the interface of the limbic system with motor mechanisms (Fig. 4). It receives direct connections from amygdala, hippocampus and other limbic forebrain structures as well as indirect connections via mesolimbic dopaminergic projections from the ventral tegmental area of Tsai. In turn, the nucleus accumbens has direct connections to the globus pallidus as well as indirect connections via the substantia nigra and nigrostriatal dopaminergic system (details appear in Section 6). Therefore, the nucleus accumbens—whose status as to whether it is part of the limbic system or part of the basal ganglia was uncertain and controversial for a number of years (see Swanson and Cowan, 1975)—appears on anatomical grounds to be part of a functional link between limbic system and basal ganglia (Graybiel, 1976).

6. Experimental Evidence in Support of the Model

In this section the three major components of the model shown in Fig. 4 are considered separately in detail. We begin in each case with a presentation of anatomical and relevant electrophysiological evidence. This is followed by a consideration of behavioral

and physiological experiments that are relevant to the possible functional contributions of the three components that link the limbic and motor system. The experiments are concerned mainly with locomotor and oral motor responses. These responses were selected, as indicated earlier, because of their biological significance.

6.1. FIRST COMPONENT: LIMBIC PROJECTIONS TO VENTRAL TEGMENTAL AREA

6.1.1. *Anatomical and electrophysiological evidence*

Neural projections from limbic forebrain structures along the medial forebrain bundle to the VTA were demonstrated in the classical experiments of Nauta (1958). This major limbic pathway is shown in Fig. 1F.

The VTA has recently been investigated with electrophysiological recording techniques. Single unit recordings obtained from the VTA were found to fall into two separate groups with different electrophysiological characteristics (Yim and Mogenson, 1980). One group had unusually long spike durations (>2.8 ms), slow firing rates and non-rhythmical firing patterns. The majority of this group of neurons were inhibited by iontophoretically applied dopamine. Since the electrophysiological properties of these neurons were similar to those of nigral dopamine neurons, they were assumed to be A10 dopaminergic neurons. Another group had shorter spike durations, fast firing rates and rhythmical firing patterns. Because the properties of this group of neurons were quite different from those of dopamine neurons, they were considered non-dopaminergic.

In a related study, the effects of electrical stimulation of the preoptic area on the spontaneous activity of neurons in the VTA were studied (Yim *et al.*, 1979). Most VTA neurons were inhibited, although occasionally some units were excited. These data provide evidence of direct synaptic input from the preoptic area, a limbic structure, to the VTA, complementing Nauta's anatomical studies.

6.1.2. *Behavioral evidence*

Neural projections from limbic structures along the medial forebrain bundle to the VTA (see Fig. 4) contribute to the initiation of goal-directed behaviors. Some experiments supporting this suggestion will now be reviewed.

As indicated earlier, attack responses are elicited by electrical stimulation of the amygdala and lateral hypothalamus (Hess, 1957; Flynn, 1967). When small lesions were made at the tips of electrodes in the lateral hypothalamus from which attack responses were elicited by electrical stimulation, degenerating fibers were traced to the VTA (Chi and Flynn, 1971a, b). Attack responses are also elicited with electrical stimulation of the VTA (Bandler *et al.*, 1972). When lesions were placed at the VTA site from which attack responses were elicited, attack responses previously elicited by electrical stimulation of the lateral hypothalamus were no longer observed (Proshansky *et al.*, 1974). These observations indicate that neural projections from limbic forebrain structures and hypothalamus along the medial forebrain bundle to the VTA make an important, and perhaps essential, contribution to the initiation of attack responses.

Similar results have been observed for ingestive behaviors. When discrete lesions were placed at the tips of the electrodes in the MFB-LH, from which electrical stimulation elicited drinking and feeding, degenerated fibers were traced to the VTA (Huang and Mogenson, 1972). Also, lesions placed caudal to stimulation electrodes in the MFB-LH were observed to attenuate elicited feeding, presumably by disrupting the neural connections to the VTA (Bergquist, 1970).

More recent experiments have shown that discrete lesions of the neural connections between limbic forebrain structures and the VTA disrupt signals for the initiation of goal-directed behaviors and not merely the motor components of these behavioral responses. Lesions of the medial aspect of the lateral hypothalamus were shown to attenuate drinking responses elicited by injections of angiotensin II into the preoptic

region but did not alter drinking responses elicited by injections of hypertonic saline into the preoptic region (Kucharczyk and Mogenson, 1976). Drinking responses elicited by injections of angiotensin II into the cerebral ventricles or the subfornical organ were not influenced by these lesions (Kucharczyk *et al.*, 1976). On the other hand, discrete lesions of the lateral aspect of the lateral hypothalamus attenuated drinking elicited by injections of hypertonic saline into the preoptic region but not drinking elicited by angiotensin II. These findings suggest that separate neural pathways projecting through the lateral hypothalamus subserve extracellular and intracellular thirst, initiated by angiotensin II and hypertonic saline respectively. The possibility that these projections extend to the

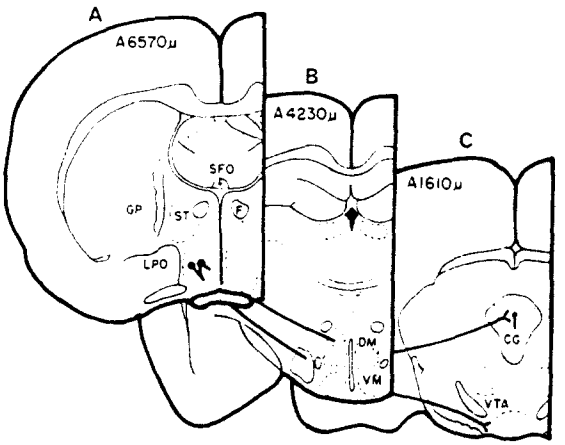

FIG. 5. Drinking is elicited by injections of angiotensin II into the caudal part of the medial preoptic area and rostral tip of the anterior hypothalamic area. (A) Microinfusions of ^{3}H-amino acids were made into this region and autoradiographically labeled pathways to the midbrain were demonstrated (see sections B and C). Note the pathway passing through the medial aspect of the lateral hypothalamus and terminating in the ventral tegmental area (VTA). Projections to the central gray (MCG) were also observed (after Swanson *et al.*, 1978).

VTA is suggested by experiments in which midbrain lesions attenuated drinking elicited by injections of angiotensin II into the preoptic region (Kucharczyk and Mogenson, 1977). Autoradiography and the axonal transport of amino acids have been used recently to demonstrate neural projections to the VTA from sites in the preoptic region from which injections of angiotensin II elicited drinking in rats. Labelled leucine and proline were injected into the preoptic region either in combination with angiotensin II or after pretests of elicited drinking in response to injections of angiotensin II. The projections were observed to extend caudally through the MFB-LH to the VTA (Fig. 5). These observations are consistent with the results of lesion experiments presented in the previous paragraphs.

It is of interest that electrical stimulation of the MFB has been reported to elicit locomotor responses in rats (Bland *et al.*, 1972) and lesions result in hypoactivity and in some cases akinesia (Gladfelter and Brobeck, 1962). Locomotor activity was also elicited by electrical stimulation of the VTA and reduced by lesions of this region (Wyrwicka and Doty, 1966; Bernston, 1972).

6.2. SECOND COMPONENT: PROJECTIONS FROM VENTRAL TEGMENTAL AREA TO NUCLEUS ACCUMBENS

6.2.1. *Anatomical and electrophysiological evidence*

Dopaminergic and other monoaminergic neurons were first visualized by Swedish investigators using the technique of fluorescence histochemistry and their fiber projections determined (Dahlstrom and Fuxe, 1964). The VTA is the locus of mesolimbic dopaminergic neurons which project to nucleus accumbens as well as to amygdala,

lateral septum and medial prefrontal cortex (Ungerstedt, 1971a; Moore and Bloom, 1978). Non-dopaminergic neurons are also present in the VTA (Butcher and Talbot, 1978), and some of them project to the nucleus accumbens.

The neural projection from the VTA to nucleus accumbens has been the subject of electrophysiological studies (Fig. 6). It was indicated in Section 6.1.1. that recordings obtained from the VTA fell into two groups with different electrophysiological properties and one of the two groups appeared to be mesolimbic dopaminergic neurons. Both groups of neurons could be antidromically activated by electrical stimulation of the nucleus accumbens (Fig. 6). The group of presumed dopaminergic neurons had relatively long latency of activation (15–25 ms), corresponding to an estimated conduction velocity of 0.45–0.6 m/sec, which is consistent with anatomical evidence indicating that fibers of dopaminergic neurons are non-myelinated and have small diameters (Fig. 6A). The latency of antidromic activation of the second group of VTA neurons—considered to be non-dopaminergic—is considerably shorter with an estimated mean conduction velocity of about 1.2 m/sec (Fig. 6B). These observations suggest that the pathway from the VTA

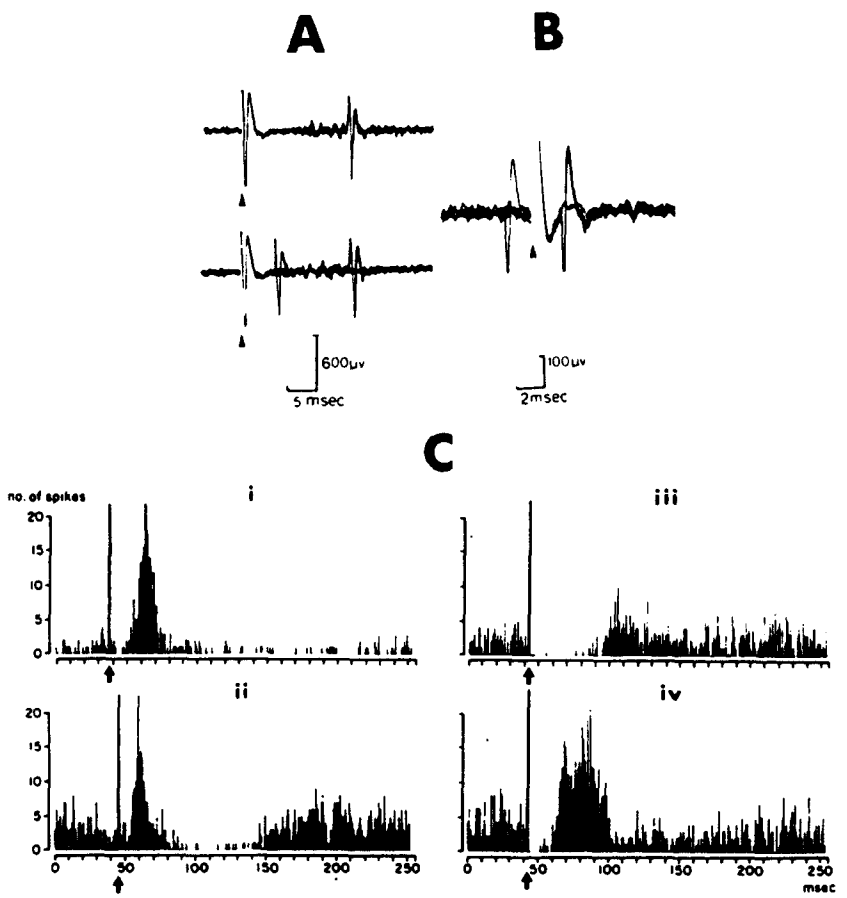

FIG. 6. The pathway from the ventral tegmental area (VTA) to the nucleus accumbens appears to consist of dual projections of dopaminergic and non-dopaminergic fibers. Single unit recordings from the VTA revealed two distinct populations of neurons with different spike characteristics and firing patterns (see text for criteria of classification). Both groups of neurons could be antidromically activated from the nucleus accumbens. (A) Antidromic activation of a dopaminergic neuron in the VTA by electrical stimulation of the nucleus accumbens. Note the relatively long spike duration. (B) Antidromic activation of a non-dopaminergic neuron in the VTA by electrical stimulation of the nucleus accumbens. Note the shorter spike duration and short latency of activation. Recordings from the nucleus accumbens showed that firing rates of neurons in this area can be modified by electrical stimulation of the VTA. Responses include excitation, inhibition and sequential combinations of both. (C) Peristimulus time histograms to show the various response patterns: (i) an excitatory response; (ii) an excitatory response followed by inhibitory response; (iii) an inhibitory response; and (iv) an inhibitory response followed by excitatory response. Experiments using various putative neurotransmitter blockers are underway to relate these response patterns to the dual projections observed (Yim and Mogenson, 1979a).

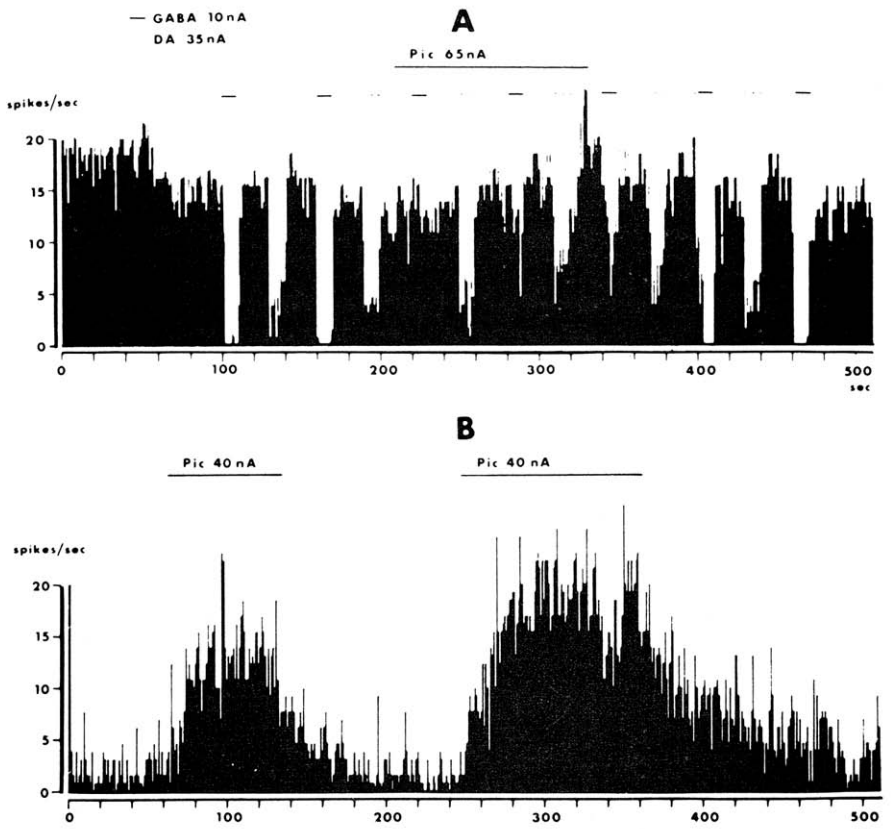

FIG. 7. Electrophysiological experiments using microiontophoretic techniques provided evidence that dopaminergic neurons in the VTA receive a tonic GABA input. (A) Frequency histogram of a dopaminergic neuron in the VTA to show inhibition by GABA and dopamine. GABA and dopamine (DA) were applied in alternate pulses of 10 sec duration. Picrotoxin (PIC) was applied continuously for 2 min after the second pulse. Responses to two subsequent GABA pulses were seen to be attenuated but the inhibitory effect of DA remained relatively unaffected. Inhibitory responses to GABA returned after picrotoxin was shut off. Neuron had a spontaneous firing rate of 2.2 spikes/sec and was accelerated to about 20 spikes/sec by continuous application of glutamate at 8 μA. (B) Frequency histogram of a dopaminergic neuron in the VTA to show activation by picrotoxin. Horizontal bars represent application of drugs.

to nucleus accumbens consists of projections of dopaminergic and non-dopaminergic fibers.

Electrical stimulation of the VTA was shown to alter the spontaneous firing rate of neurons recorded from the nucleus accumbens (Yim and Mogenson, 1979). Responses included excitation, inhibition and sequential combinations of both (Fig. 6C). Inhibitory responses usually had short latencies of less than 10 ms, whereas excitatory responses usually had longer latencies, often greater than 15 ms. It is not yet known how the dual dopaminergic and non-dopaminergic projections may account for these responses. However, the latencies of the inhibitory responses were too short to be due to the slow conducting dopaminergic neurons.

VTA neurons receive inhibitory GABA synaptic inputs (Wolf *et al.*, 1978; Yim and Mogenson, 1980). Electrophysiological evidence is presented in Fig. 7. Both dopaminergic and non-dopaminergic neurons were inhibited by the iontophoretic application of GABA and the GABA inhibition was reversed by iontophoretically applied picrotoxin. When picrotoxin was iontophoretically applied, approximately 70% of the neurons were activated. Some VTA neurons were inhibited by electrical stimulation of the nucleus accumbens. This inhibition was blocked by the iontophoretic application of picrotoxin and bicuculline, suggesting that the nucleus accumbens is one source of the GABA inhibitory neurons that synapse on VTA neurons (Wolf *et al.*, 1978; Yim *et al.*, 1979).

6.2.2. *Behavioral evidence*

Injections of dopamine into the nucleus accumbens, the region of axon terminals of the mesolimbic dopaminergic pathway, has been reported to initiate locomotor responses in rats recorded in an open field (Costall and Naylor, 1976; Pijnenburg *et al.*, 1976; Jones *et al.*, 1978). Injections into the nucleus accumbens of the dopamine agonist, apomorphine, of the dopamine precursor, L-DOPA, or of amphetamine, which causes the release and blocks the reuptake of dopamine, also increase locomotor responses (Kelly *et al.*, 1975; Costall and Naylor, 1976; Pijnenburg *et al.*, 1976). The well-known hyperactivity effect of systemically-administered amphetamine is no longer observed when the dopaminergic projections to the nucleus accumbens from the ventral tegmental area are damaged by injections of 6-hydroxydopamine (Kelly *et al.*, 1975). These experiments clearly implicate mesolimbic dopamine projections to the nucleus accumbens in locomotor responses.

Locomotor activity was also increased by injections of picrotoxin, a GABA receptor antagonist, into the VTA, the site of the dopaminergic mesolimbic neurons (Fig. 8C).

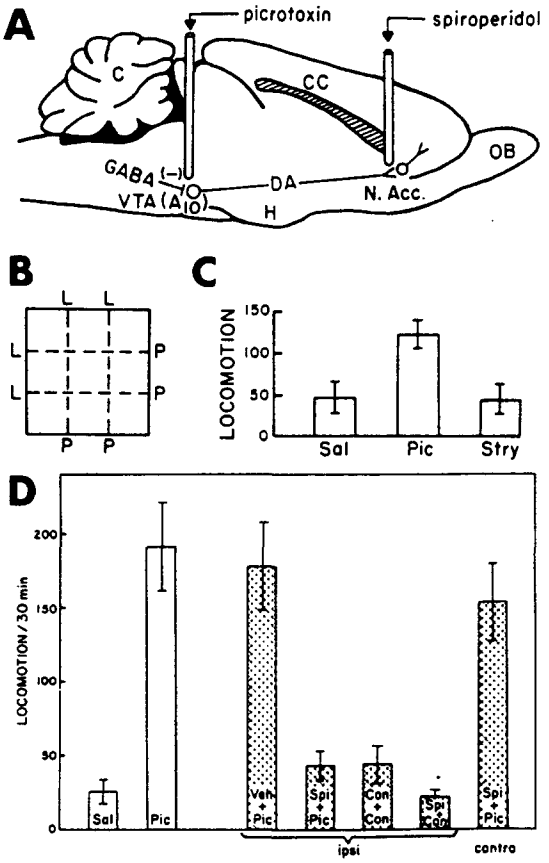

FIG. 8. Evidence that mesolimbic dopaminergic neurons projecting from ventral tegmental area (VTA) to nucleus accumbens (N.Acc.) have GABA synaptic inputs. (A) Parasaggital view of the rat brain showing cannulae positioned into the VTA for injections of picrotoxin, the GABA antagonist, and into the nucleus accumbens for injections of spiroperidol, a dopamine antagonist. (B) Schematic diagram of open-field chamber (75 × 75 cm) with light sources (L) and photocells (P) for measurement of ambulatory activity. (C) Locomotor activity recorded in 30-min tests following bilateral injections of isotonic saline (Sal), picrotoxin (Pic, 0.10 μg in 0.5 μl) and strychnine sulphate (Stry, 0.10 μg in 0.5 μl) into the VTA ($n = 9$). (D) Increased locomotor activity resulting from unilateral microinjection of picrotoxin (Pic) into the ventral tegmental area (VTA) is significantly attenuated by the ipsilateral (ipsi), but not by contralateral (contra) microinjection of spiroperidol (Spi) into the nucleus accumbens (N.Acc.). Bars from left to right: Sal, saline into the VTA; Pic, picrotoxin (0.15 μg in 0.2 μl) into the VTA; Veh + Pic, vehicle (Lactic acid) into N.Acc. followed by Pic into ipsilateral VTA; Spi + Pic, spiroperidol (1.0 μg in 1.0 μl) into N.Acc. followed by Pic into ipsilateral VTA; Con + Con, sham microinjections into N.Acc. and VTA; Spi + Con, spiroperidol into N.Acc. and sham microinjection ipsilateral VTA; Spi + Pic, picrotoxin microinjected into VTA and spiroperidol (1.0 μg in 1.0 μl) microinjected into contralateral nucleus accumbens ($n = 9$) (modified from Mogenson *et al.*, 1979).

Injections of strychnine sulphate, a glycine receptor antagonist, did not increase locomotor activity. There is electrophysiological evidence that the mesolimbic dopaminergic neurons receive GABA synaptic inputs (Fig. 7) and it appears that they are disinhibited by picrotoxin, resulting in increased release of dopamine from axon terminals in the nucleus accumbens. In support of this interpretation, it was observed that pretreating the nucleus accumbens with spiroperidol, a dopamine receptor antagonist, attenuated the increase in locomotor activity elicited by injections of picrotoxin into the VTA (Fig. 8D).

Since locomotion is a basic component of attack, food procurement and other goal-directed behaviors it is of interest whether mesolimbic dopaminergic neurons contribute to the initiation of these behaviors. This possibility has not been investigated. However, injections of 6-hydroxydopamine into the cerebral ventricles or midbrain of rats, presumably damaging mesolimbic as well as nigrostriatal dopaminergic neurons, results in akinesia as well as hypophagia, hypodipsia and somnolence (Ungerstedt, 1971; Marshall *et al.*, 1974; Stricker and Zigmond, 1976). These deficits have usually been attributed to damage to the nigrostriatal dopaminergic pathway but the possibility that damage to the mesolimbic dopaminergic pathway also contributes to the observed deficits has not been ruled out. Experiments are proposed in a later section to investigate the possible contribution of the mesolimbic dopaminergic projections, the second component of the model shown in Fig. 4, to the initiation of behaviors.

Central dopaminergic neurons have also been implicated in oral motor responses. Chewing and swallowing occur after the peripheral and central administration of apomorphine, a dopamine agonist (Ernst, 1967; Costall *et al.*, 1975). Oral dyskinesias are a problem for some Parkinson's patients receiving L-DOPA therapy. Involuntary oral motor responses ("Tardive dyskinesias") are annoying and often disruptive side effects in certain psychiatric patients being treated with neuroleptic drugs (Sigwald *et al.*, 1959; Costall and Naylor, 1976; Pohto, 1977). Neuroleptics are potent dopamine receptor antagonists and the oral dyskinesias have been attributed to dopamine receptor supersensitivity (Klawans and Weiner, 1976).

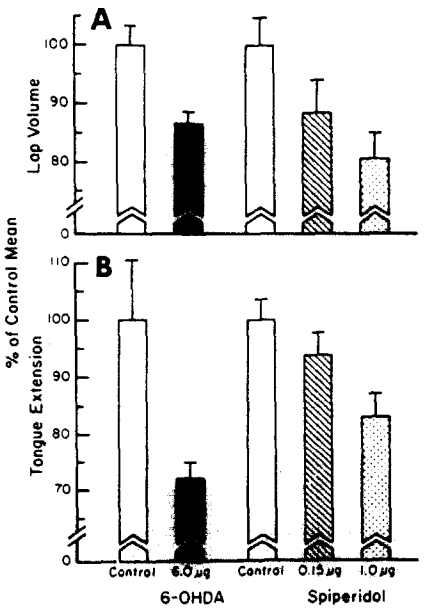

FIG. 9. Deficits in oral motor performance following damage to mesolimbic dopaminergic projections by injecting 6-hydroxydopamine into the nucleus accumbens or following blockade of the dopamine projections by injecting spiroperidol into the nucleus accumbens. (A) Lap volume expressed as percentage of the control mean lap volume. (B) Tongue extension expressed as percentage of the control mean tongue extension (modified from Brimley and Mogenson, 1979; Jones and Mogenson, 1979).

Whether the effects referred to in the previous paragraph are associated with actions of apomorphine, L-DOPA and the neuroleptic drugs on dopaminergic synapses in the nucleus accumbens or in the caudate nucleus is not known. However, the contribution of mesolimbic dopaminergic projections and of the nucleus accumbens to oral motor responses is suggested by several animal studies. Electrical stimulation of the nucleus accumbens elicits chewing and swallowing (Lund and Dellow, 1971; Hockman *et al.*, 1979) and stimulation of the VTA, as well as the adjacent substantia nigra and reticular formation, has been reported to enhance reflex swallowing (Lund and Dellow, 1971; Bieger, 1974; Bieger *et al.*, 1976). Damaging mesolimbic dopaminergic fibers by injections of 6-hydroxydopamine into the nucleus accumbens resulted in deficits in tongue extension and lap volume (Fig. 9). Similar deficits were observed when spiroperidol, a dopamine receptor antagonist, was injected into the nucleus accumbens (Fig. 9).

6.3. THIRD COMPONENT: PROJECTIONS FROM NUCLEUS ACCUMBENS TO GLOBUS PALLIDUS

6.3.1. *Anatomical and electrophysiological evidence*

Neural connections from the nucleus accumbens to the globus pallidus were demonstrated by Swanson and Cowan (1975) using axonal transport of tritiated amino acids and autoradiography. The major projections were observed to go to the ventral region of the globus pallidus. Subsequently this nucleus accumbens–globus pallidus projection was confirmed in the rat by other investigators (Conrad and Pfaff, 1976; Williams *et al.*, 1977; Nauta *et al.*, 1978) and demonstrated in the monkey (Powell and Leman, 1976) and cat (Troiano and Siegel, 1978). Based on neuropharmacological experiments, the suggestion was made that, as with the caudate nucleus to globus pallidus projection, some of the nucleus accumbens–globus pallidus fibers are GABAergic (Pycock and Horton, 1976). This suggestion is supported by electrophysiological recording experiments (Dray and Oakley, 1978; Jones and Mogenson, 1980b).

Antidromic action potentials were recorded from neurons in the nucleus accumbens in response to electrical stimulation of the globus pallidus (Jones and Mogenson, 1980b). These observations are consistent with the anatomical findings of direct projections from nucleus accumbens to globus pallidus. When the nucleus accumbens was stimulated and recordings made from the globus pallidus, a number of neurons were inhibited (Fig. 10A). The latency of the inhibitory effects was 8–20 msec and the conduction velocities were estimated to be 0.4–1.5 m/sec. The inhibitory effects of nucleus accumbens stimulation on GP neurons were attenuated or blocked by the iontophoretic application of picrotoxin (Fig. 10B). Approximately 60% of the GP neurons increased their firing rates after the iontophoretic application of picrotoxin, consistent with the removal of a tonic inhibitory GABA input (Jones and Mogenson, 1980b). These findings support the Pycock and Horton (1976) hypothesis that a GABAergic pathway projects from the nucleus accumbens to the globus pallidus.

6.3.2. *Behavioral evidence*

Neural connections from nucleus accumbens to globus pallidus were recognized by the pioneer neurobiologist, Herrick (1926) over 50 yr ago. He speculated about their functions by suggesting that the nucleus accumbens "... and its efferent fibers... to the globus pallidus... may be concerned chiefly with locomotor and facial reflexes involved in feeding" (pp. 113–114). These suggestions were forgotten over the years, however, and only recently, following reports of nucleus accumbens–globus pallidus connections (see Section 6.3.1), has their functional significance been considered again (Graybiel, 1976). From the limited evidence now available, it appears that there may be something to Herrick's early speculations.

Injections of the GABA antagonist, picrotoxin, into the globus pallidus were shown to increase locomotor responding in rats. Injections of GABA into the globus pallidus

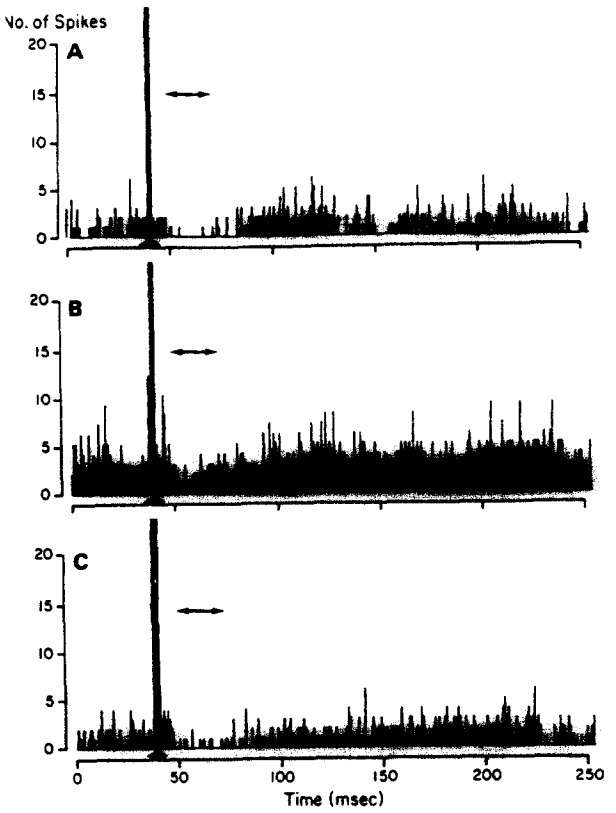

FIG. 10. Peristimulus time histograms of probability of firing of a globus pallidus neuron with stimulation of the nucleus accumbens shown by large vertical arrow (200–256 msec sweeps, 0.2 mA, 0.15 msec pulses). (A) Initial inhibitory effect of stimulation (inhibitory period given by the horizontal double headed bar). (B) The same stimuli as in A but after picrotoxin administration at 50 nA for 15 min (the time of the inhibitory period from A is again represented by the horizontal double headed bar). (C) The same stimuli as in A and B but 25 min after the cessation of picrotoxin administration (again the inhibitory period from A is represented by the double headed bar for comparison).

attenuated the locomotor responses initiated by injections of dopamine into the nucleus accumbens (Fig. 11). Furthermore, injections of GABA into the globus pallidus were observed to attenuate locomotor responses elicited by injections of picrotoxin into the VTA (Mogenson *et al.*, 1980). These observations are consistent with the suggestion of Pycock and Horton (1976) that the projections from the nucleus accumbens to the globus pallidus are GABAergic and furthermore, they suggest that this neural pathway may contribute to the initiation of locomotor responses. A recent paper by Price and coworkers (1978) suggests that this inhibitory GABAergic connection from the nucleus accumbens may also be involved in Parkinson's disease. They reported low levels of dopamine in the nucleus accumbens of Parkinson patients and suggested, in view of the neuropharmacological studies in rats implicating the nucleus accumbens–mesolimbic dopamine projections in the initiation of locomotor responses, that the akinesia of Parkinson's disease may be related to a deficiency of the dopamine projections to the nucleus accumbens. This suggestion is consistent with our working hypothesis; a deficiency in the mesolimbic dopaminergic system and the resulting overactivity of the GABAergic inhibitory pathway to the globus pallidus would exert an unduly strong inhibitory effect on motor circuits over which the globus pallidus exerts an influence.

Herrick's other speculative suggestion that efferent fibers from nucleus accumbens to globus pallidus contribute to "facial reflexes involved in feeding" has not been investigated. However, several previous studies have shown that food and water intakes are disrupted by lesions of the globus pallidus (Levine *et al.*, 1971; Levine and Schwartzbaum, 1973), the hypophagia and hypodipsia being attributed to motivational deficits

(Morgane, 1961). Food and water intake deficits have been linked to damage to descending projections from the globus pallidus (Morgane, 1975) and to ascending projections of the trigeminal system (Zeigler and Karten, 1974). In electrophysiological recording experiments the discharge rates of neurons in the globus pallidus change during feeding behavior, apparently related to the taste and palatability of the food or fluid (Lidsky *et al.*, 1975; Soltysik *et al.*, 1975; Schwartzbaum and Moore, 1978). The possibility that the feeding deficits referred to above are due in part to damage to projections to the globus pallidus from the limbic system via the nucleus accumbens has not been considered. Experiments are needed to investigate the effects of damage or blocking of the globus pallidus on elicited feeding and drinking responses.

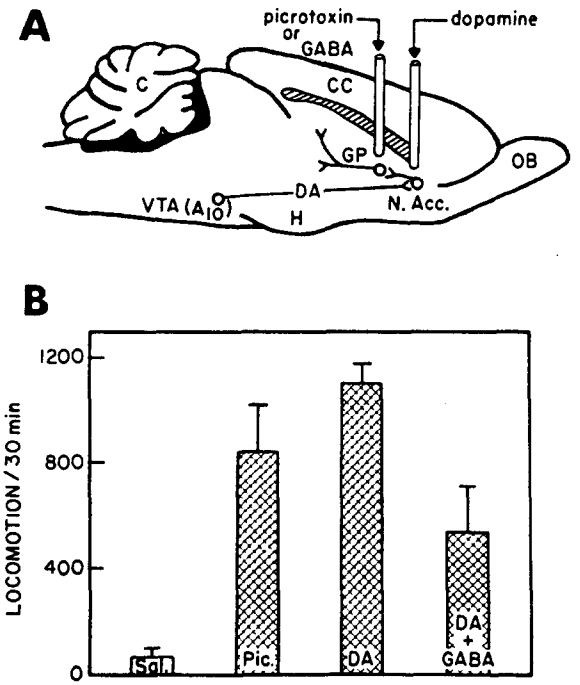

FIG. 11. Evidence that a GABAergic pathway from the nucleus accumbens to globus pallidus contributes to locomotor activity. Injection of picrotoxin, a GABA antagonist, into the nucleus accumbens increased locomotor activity. Locomotor activity was increased by injections of dopamine into the nucleus accumbens and this increase was significantly attenuated when GABA was injected into the globus pallidus ($n = 6$) (modified from Jones and Mogenson, 1980a).

7. The Limbic–Motor Interface in Relation to Current Views concerning Response Initiation

The evidence reviewed in the previous section indicates that the nucleus accumbens, together with its mesolimbic–dopaminergic afferents and its efferent projections to the globus pallidus, may be an important functional link between limbic and motor systems. The three components of this neural link, shown in Fig. 4, apparently contribute to the translation of "motivation" to "action" by transmitting signals from limbic structures to the basal ganglia. The model, in this section, will be considered in relation to other CNS mechanisms for response initiation.

In lower vertebrates, such as reptiles and fish, in which the cerebral cortex has not been elaborated, the phylogenetically older basal ganglia probably represent the highest level of motor integration (Romer, 1964). Behavioral responses of these animals are largely reactive and stereotyped, being primarily initiated by limbic structures and hypothalamus (MacLean, 1970). In rodents and lower mammals, in which behaviors tend to be species-specific and basic drives dominate, the limbic system retains a major role in response initiation. The limbic system—or in the terminology of Konorski (1967) the "emotive brain"—continues to contribute to response initiation in higher mammals,

including monkeys and man, but other initiators of actions and behaviors become prominent. In the course of biological evolution, encephalization of the brain has resulted in the remarkable elaboration of the basal ganglia, cerebral cortex and cerebellum. With the the appearance of association cortex in higher mammals, there is a greater contribution of cognitive processes, accompanied not only by increased complexity and skill of motor performance but also an increase in the range of initiators of actions. As indicated earlier, "readiness potentials" recorded from posterior association cortex of human subjects about 200 msec before they pressed a button in response to a warning light is evidence that the "cognitive brain" (also Konorski's term) is an initiator of movements involving instructions, response set, or other cognitive processes (Kornhuber, 1974). Neural projections from association cortex to the neostriatum and from there to the globus pallidus and eventually to thalamus and motor cortex (Kemp and Powell, 1971) may be a route by which "cognitive command signals" initiate actions (see Fig. 3).

There are converging inputs to the globus pallidus from the nucleus accumbens (ventral striatum) and the caudate nucleus (neostriatum), as shown in Fig. 12, and they in turn receive neural projections from limbic structures and cerebral cortex respectively. Costa (1977) has suggested that the nucleus accumbens and caudate nucleus filter signals from the limbic structures and cerebral cortex (from the "emotive brain" and "cognitive brain"). These filtering or "gating" mechanisms are influenced by dopaminergic projections—the mesolimbic dopaminergic pathway to the nucleus accumbens, and the nigrostriatal dopaminergic pathway to the caudate nucleus. If these dopaminergic projections are diseased, as in Parkinson's disease, or damaged in experimental animals, severe motor deficits are observed. Thus, the gating mechanisms no longer permit appropriate signals to reach the globus pallidus from the "emotive brain" and "cognitive brain", and severe behavioral deficits result.

It has been reported, as indicated earlier, that dopamine levels are depleted in the nucleus accumbens of Parkinson patients as well as in the caudate nucleus (Price *et al.*, 1978). Hornykiewicz and coworkers suggest that akinesia in Parkinson's disease might be the result of a combined dopamine deficiency in nucleus accumbens and caudate nucleus.

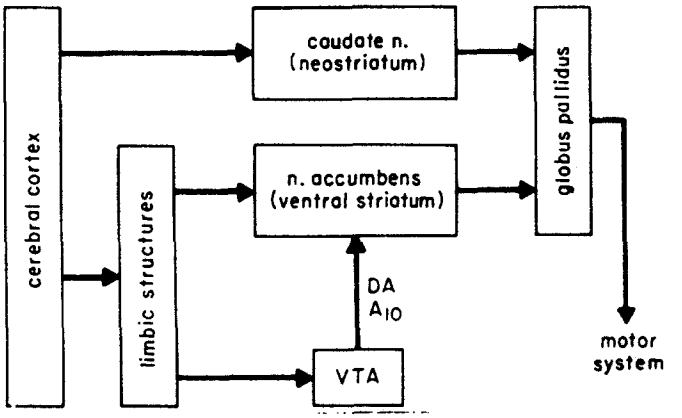

FIG. 12. Two systems which contribute to the initiation of movements or "actions" are shown. The first system subserves "actions" initiated by the "cognitive brain" (see Fig. 3) and involves projections from association cortex to the caudate nucleus or neostriatum (Kemp and Powell, 1971). There are projections from the caudate nucleus to the globus pallidus, which in turn sends signals to the motor cortex and the thalamus and to lower brain stem structures concerned with motor function. This system has been implicated in the initiation of movements of "actions" that depend on instructions to the subject ("response-set") and cognitive processes (Kornhuber, 1974). The second system subserves "actions" initiated by hunger, fear and other drives or motivational–emotional states—by the "emotive brain" (see Fig. 3). It is this system that was activated by Hess (1957) and later investigators who elicited attack, feeding and other biologically-significant behaviors by electrical stimulation of the MFB-LH, preoptic region and limbic forebrain structures. The nucleus accumbens or ventral striatum is a key structure in this system. It receives inputs from limbic forebrain structures both directly and indirectly via the mesolimbic dopaminergic projections from the ventral tegmental area. Recently it has been shown that nucleus accumbens also projects to the globus pallidus and the suggestion made that the nucleus accumbens is an important link between the limbic system and motor system (Graybiel, 1976).

According to their proposal, the Parkinson patient suffers a dysfunction in the initiation of basic locomotor responses because of depleted accumbens dopamine and a dysfunction in the initiation of more sophisticated movements involving cognitive processes because of depleted caudate dopamine.

Although with encephalization of CNS function the "cognitive brain" assumes an increasing role in response initiation, the "emotive brain" and "cognitive brain" frequently operate together. The "emotive brain" initiates actions related to hunger, fear and other basic biological drives. In addition, it may also provide a tonic or sustaining influence on the motor system when "actions" are initiated by the "cognitive brain" which involve verbal instructions, response set and other cognitive processes which depend on past experience and learning. The "cognitive brain", initiates motor responses and thereby contributes to the initiation of specific and adaptive movements as the behavioral sequence progresses towards the target or goal. Thus, for example, when a hungry cat hunts for a bird or a hungry dog searches for a bone that it buried previously in the park, the "emotive brain" and "cognitive brain" apparently function concurrently. The "cognitive brain" contributes to the initiation of various specific movements appropriate to moment-to-moment changes in the environment as the behavioral sequence progresses in locating the bird or bone. The "emotive brain" contributes a tonic influence on the motor system.

The prefrontal cortex makes unique contributions to behavior and may have a distinctive role in initiating and maintaining motor responses. This region of association cortex, which becomes highly elaborated in primates and man, has strong neural projections to limbic forebrain structures and is considered the cortical representation of the limbic system (Nauta, 1971). It, like other areas of cerebral cortex, also projects to the caudate nucleus (Kemp and Powell, 1971).

Frontal lobe dysfunction in patients and frontal lobe lesions in primates result in striking, well-documented behavioral deficits. They are characterized by a disruption in the temporal organization and sequencing of behavioral responses. Frontal lobe damage and dysfunction, according to the preceding discussion, could reflect the disruption of higher order integrative activities which coordinate response-initiating signals from the "emotive brain" and the "cognitive brain". Reports of hyperactivity and "aimless pacing" in frontal animals are consistent with this speculative suggestion (Jacobsen, 1935; Fulton, 1951; Brutkowski, 1965; Divac, 1972). It appears that the "gating mechanisms", referred to above, permit the transmission of signals from the "emotive brain" that initiate these locomotor responses but do not permit the transmission of signals from the "cognitive brain". Thus complex response components which normally accompany locomotion, and which ensure that the behavioral sequence is appropriate to the changing environment and influenced by learning and previous experience, do not occur. As a consequence, the animal lacks the appropriate cognitive input and continues a non-appropriate response. This behavior of the frontal animal is described as "aimless pacing" or "response perseveration" (Nauta, 1971).

8. Suggested Experiments to Investigate the Model

The model shown in Fig. 4 for the translation of "motivation" into "action" is a rather tentative one. It was suggested by recent anatomical evidence demonstrating afferent connections to the nucleus accumbens from the VTA and efferent projections from the nucleus accumbens to the globus pallidus. Since limbic structures project to both VTA and nucleus accumbens, it was recognized that this could provide the anatomical basis of a mechanism by which "motivational" signals are transmitted from the limbic system to the motor system. The model provided a conceptual framework for the experiments described in Section 6 in which the three components were implicated in locomotor and other responses. Since locomotion is a prerequisite for attack, procurement of food etc., it seems likely that the proposed model will be relevant to the investigation of a number of complex behaviors. However, further experiments are needed to obtain direct evidence

that the three components serve as a functional unit in the initiation of attack, feeding and other similar behaviors. The components of the model were also investigated with electrophysiological techniques, but these experiments only provide a beginning in elucidating the neuronal organization of the components of the model—further investigations are needed.

Before considering some examples of questions and experiments suggested by the model, it should be noted that the nucleus accumbens is probably not the only link between the limbic and motor systems for initiating behavior. Because of the anatomical complexity of the two systems it is highly likely that future research will demonstrate other functional links for the translation of "motivation" into "action". Furthermore, as indicated in the previous section, the "cognitive brain" also has an important role in response initiation, frequently operating in conjunction with the "emotive brain".

The possibility of other functional links between the limbic and motor systems is suggested by the observation, shown in Fig. 9, that injecting GABA into the globus pallidus attenuated, but did not completely abolish, locomotor responses initiated by injecting dopamine into the nucleus accumbens. In addition to projections to the globus pallidus, the nucleus accumbens has efferent connections to the thalamus, midbrain reticular formation, substantia nigra and habenular nucleus (Swanson and Cowan, 1975; Conrad and Pfaff, 1976; Powell and Leman, 1977; Williams *et al.*, 1977; Carter and Fibiger, 1978; Nauta *et al.*, 1978). Experiments are needed to investigate whether or not these structures which receive neural projections from the nucleus accumbens contribute to the initiation of locomotor responses.

Investigation of the possible contribution of the nucleus accumbens and the components of the model to the initiation of complex behaviors could utilize a research strategy similar to that for the locomotor experiments described in Section 6—attempting to attenuate or enhance elicited attack, feeding, nest building and other behaviors by injecting appropriate compounds into the nucleus accumbens, globus pallidus or VTA. For example, attack could be elicited by electrical stimulation of the amygdala or the lateral hypothalamus (Flynn, 1967), drinking by injecting angiotensin II into the preoptic region (Kucharczyk and Mogenson, 1975) or by electrical stimulation of the lateral hypothalamus (Mogenson and Stevenson, 1966) and copulatory behavior in male rats by injecting testosterone into the anterior hypothalamus (Fisher, 1956). Investigations could then be made of the attenuating or disruptive effects on elicited behavior of (1) injections of a local anesthetic such as procaine into the VTA or nucleus accumbens; (2) injections of 6-hydroxydopamine into the VTA or nucleus accumbens to selectively destroy the mesolimbic dopamine projections between these structures: (3) injections of a dopamine antagonist such as spiroperidol into the nucleus accumbens; and (4) injections of GABA into the globus pallidus.

Further investigation is needed of the neuronal organization of the nucleus accumbens and the integration of signals that converge from limbic structures and VTA (see Fig. 5). Experiments could be done with electrophysiological recording techniques, for example, to investigate the interaction of the dopaminergic and non-dopaminergic fiber projections, referred to in Fig. 6, on nucleus accumbens neurons. In addition, the nucleus accumbens receives serotoninergic projections from the raphe nuclei and has intrinsic GABAergic and cholinergic interneurons. Yet little is known regarding the synaptic organization within the nucleus accumbens or the interaction of these synaptic inputs with dopaminergic and non-dopaminergic fiber inputs from the VTA. The results obtained from such electrophysiological recording experiments might suggest possible neural mechanisms that could be investigated in behavioral experiments involving elicited locomotor or other more complex behavioral responses.

The model, and the results considered in Section 6.3, point to the need for investigating the functions of the globus pallidus, a structure not usually considered by motor physiologists to be concerned with response initiation (although two recent studies consider this possibility and reach rather different conclusions, Amato *et al.*, 1978; Hore and Vilis, 1979). The converging inputs to the globus pallidus from nucleus accumbens and caudate

nucleus (see Figs 3 and 12) further highlight the need to elucidate the mechanisms for the conjoint contributions of the "emotive brain" and the "cognitive brain" to response initiation. These converging inputs to the globus pallidus could be investigated with electrophysiological recording techniques. On the "output side" of the globus pallidus, efferent connections are shown in Fig. 3 to the ventral lateral thalamus and from there to the motor cortex. This could be the route for the initiation of certain motor responses, as suggested by Kemp and Powell (1971). Of particular interest is a recent report of electrophysiological evidence for neural projections from the entopeduncular nucleus of the cat, a homologue of the primate internal segment of the globus pallidus, to the mesencephalic locomotor region (Skinner *et al.*, 1979). However, since spontaneous locomotion occurs in "decorticate" and "thalamic" animals (Bard and Macht, 1958), these may not be important or essential routes for the initiation of the locomotor responses considered in detail in Section 6. The nature of the neural integrative events "beyond the globus pallidus" in the initiation of locomotor responses awaits future investigation.

The close functional relationship of the "emotive brain" and the "cognitive brain" raises questions concerning the nature of neural integration of the sophisticated response components utilized in the moment-to-moment adaptations to the continuously changing external environment with the locomotor responses utilized for progression by the animal in the environment. It is probably a gross oversimplification to consider complex responses initiated by the "cognitive brain" as being merely superimposed on locomotor responses initiated by the "emotive brain". The nucleus accumbens and "emotive brain" have functions in addition to initiating locomotion. Decorticate higher mammals have a reduced response repertoire but they can still perform rather complex behaviors (Bard and Macht, 1958). Animals lower on the phylogenetic scale also perform relatively complex behaviors, although they are more species-specific and stereotyped. What is added by the elaboration of the "cognitive brain" through evolution is a remarkable increase in the range of response initiators and greater sophistication and complexity in motor performance. For this to occur, there has to be coordination of the "cognitive brain" and the "emotive brain" which, as indicated at the end of Section 7, appears to involve the prefrontal cortex. The role of the prefrontal cortex in the higher order integration of response-initiating signals from the "emotive brain" and the "cognitive brain" is an important and fascinating subject for future investigation.

9. Summary

Limbic forebrain structures and the hypothalamus are essential in the initiation of food-seeking, escape from predators and other behaviors essential for adaptation and survival. Neural integrative activities subserving these behaviors initiate motor responses but the neural interface between limbic and motor systems has received relatively little attention. This neglect has been in part because of the emphasis on the motor control of the movements and on the contributions of the cerebral cortex, cerebellum, spinal cord and other components of the motor system, but more importantly, because of a lack of relevant anatomical evidence of connections. Anatomical findings obtained in recent years now make it possible to investigate the neural interface between limbic and motor systems—neural mechanisms by which "motivation" gets translated into "action". It has been proposed that the nucleus accumbens is a key component of this neural interface since it receives inputs from limbic forebrain structures, either directly or indirectly via the ventral tegmental area of Tsai, and sends signals to the motor system via the globus pallidus.

The nucleus accumbens has been implicated in locomotion, a fundamental component of attack, feeding and other behaviors utilized in adaptation and survival. It has also been implicated in oral motor responses, utilized in feeding, drinking, vocalization and other adaptive responses. The role of the nucleus accumbens and its functional relationship with the ventral tegmental area and globus pallidus has been investigated using neuropharmacological–behavioral techniques to initiate and disrupt locomotor and

ingestive responses and using electrophysiological recording techniques. The results of these investigations are interpreted in relation to a proposed model of the limbic–motor interface and further experiments are suggested. This model for the initiation of actions by limbic forebrain structures (e.g. the "emotive brain") is considered in relation to what is known about the initiation of actions by cognitive processes involving previous experience and learning, which include response set or instructions (e.g. the "cognitive brain"). A major challenge for future research is how the "emotive brain" and the "cognitive brain" operate together in response initiation.

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Note Added in Proof

(1) This article deals with recent evidence concerning a suggestion that the nucleus accumbens is an important functional link between the limbic and motor systems. Although the projection from the nucleus accumbens to globus pallidus was emphasized, it is not intended to suggest that other projections from the nucleus accumbens, demonstrated in recent years (e.g. Nauta *et al.*, 1978) are not involved. Also, the projections from the globus pallidus have not been considered, and the reader is referred to the following articles: Filion and Harnois, 1979; Poirier *et al.*, 1979). As pointed out in Section 8, we do not intend to suggest that the neural circuits shown in Fig. 4 are the only ones by which limbic processes subserving motivation can influence the motor system to initiate actions.

(2) Some of the experiments described in this article have been extended as follows: (1) Inputs to dopaminergic neurons of the VTA from the amygdala and septum have been investigated with electrophysiological recording techniques (Maeda and Mogenson, 1980). More than 70% of neurons in the VTA responded to electrical stimulation of the amygdala and the septum. Of the dopamine neurons that responded, approximately 80% received convergent inputs from both areas, the effects being mostly asynergistic. It was also found that the inhibitory input from the nucleus accumbens to the VTA appeared to be a feedback projection, since DA neurons inhibited by electrical stimulation of the nucleus accumbens could be antidromically activated from the same area (Yim and Mogenson, 1980). (2) In some preliminary experiments, Jones and Mogenson (1980) observed that drinking, elicited by injections of angiotensin II into cerebral ventricles, was attenuated by pretreating the nucleus accumbens with spiroperidol, the dopamine antagonist. With increasing doses of spiroperidol, there was an increase in the latency to drink as well as a reduction in the volume of water consumed. These results provide some evidence for a functional role of the VTA to NAc dopaminergic projections in the goal-directed behavior, drinking. These experiments are being extended to include administrations into the VTA and GP.

(3) In a recent study it has been reported that attack behavior elicited by electrical stimulation of the lateral hypothalamus was suppressed by electrical stimulation of the VTA or nucleus accumbens, while other brain sites were ineffective (Goldstein and Siegel, 1980). Attack behavior was suppressed, the visceral and endocrine responses continued.

Although electrical stimulation does not selectively activate neurotransmitter specific projections, these results suggest that VTA and nucleus accumbens contribute to the goal directed attack response.

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