77 A Model of the Limbic System and Basal Ganglia: Applications to Anxiety and Schizophrenia

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ABSTRACT The chapter presents a model of the behavioral functions and information processing discharged jointly by the limbic system (especially the hippocampal formation and amygdala) and the basal ganglia (both the dorsal and ventral striatal systems). In general terms, the limbic system plus basal ganglia act as a mechanism for the attainment of goals. The sensory aspects of this overall goal-direction function (recognition of goals and evaluation of the outcomes of action) are dealt with in the limbic system; the motor aspects (establishment and execution of motor programs) in the basal ganglia. The model is applied to an understanding of the neuropsychology of anxiety and schizophrenia, especially the positive symptoms of the latter.

The model of the limbic system plus basal ganglia (LSBG) presented here occupies three closely interrelated levels: behavioral, neural, and cognitive. Previous descriptions of portions of the model (e.g., Gray, 1982a, 1982b, in press; Gray, Feldon, et al., 1991; Gray, Hemsley, et al., 1991; Gray and Rawlins, 1986) have preserved the separation between these three levels of analysis; here, however, less attention is paid to these distinctions. The data on which the model is based are drawn from a wide variety of empirical results and have been summarized and reviewed elsewhere (Gray, 1977, 1982a, 1987; Gray and McNaughton, 1983; Gray, Feldon, et al., 1991). The anatomical regions and interconnections to which the model refers are set out schematically in figures 77.1 and 77.2. These diagrams include the structures familiarly clustered together under the terms *limbic system* and *basal ganglia*. The anatomical justification for these groupings, and for the separation of the limbic system and basal ganglia from other subsystems of the brain, is controversial. Resolution of this controversy, in my view, will require a clear understanding of the specific functions served by these systems (cf. the visual system, defined as it is at least as much by its function in the processing of visual information as by its anatomical interconnectivity). This chapter represents an attempt to contribute to such a functional understanding of the LSBG.

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The function of the limbic system and basal ganglia: A hypothesis

Let us start with a question of great generality: What function does the limbic system–basal ganglia (LSBG) serve? The answer proposed is that the LSBG is a mechanism for the attainment of goals. The sensory aspects of this overall function of goal direction (recognition of goals and evaluation of the outcomes of action) are dealt with in the limbic system; the motor aspects (establishment and execution of goal-directed motor programs) in the basal ganglia. To carry out the goal-direction function, a number of subsidiary functions must be executed and coordinated. A likely list of such subfunctions, and of the major regions of the LSBG most concerned with them, is as follows.

GOAL SETTING First, goals have to be recognized as goals. The final biological goals of action (positive reinforcers, or rewards) are, of course, innately determined (food, water, etc). An animal cannot, however, wait until one of these materializes and provides innately recognizable sensory stimulation. It must get to the place (in space and time) where such a goal is to be found; and, to do that, it needs to establish a series of linked subgoals that will permit it to achieve this approach behavior. Setting up such a series of linked

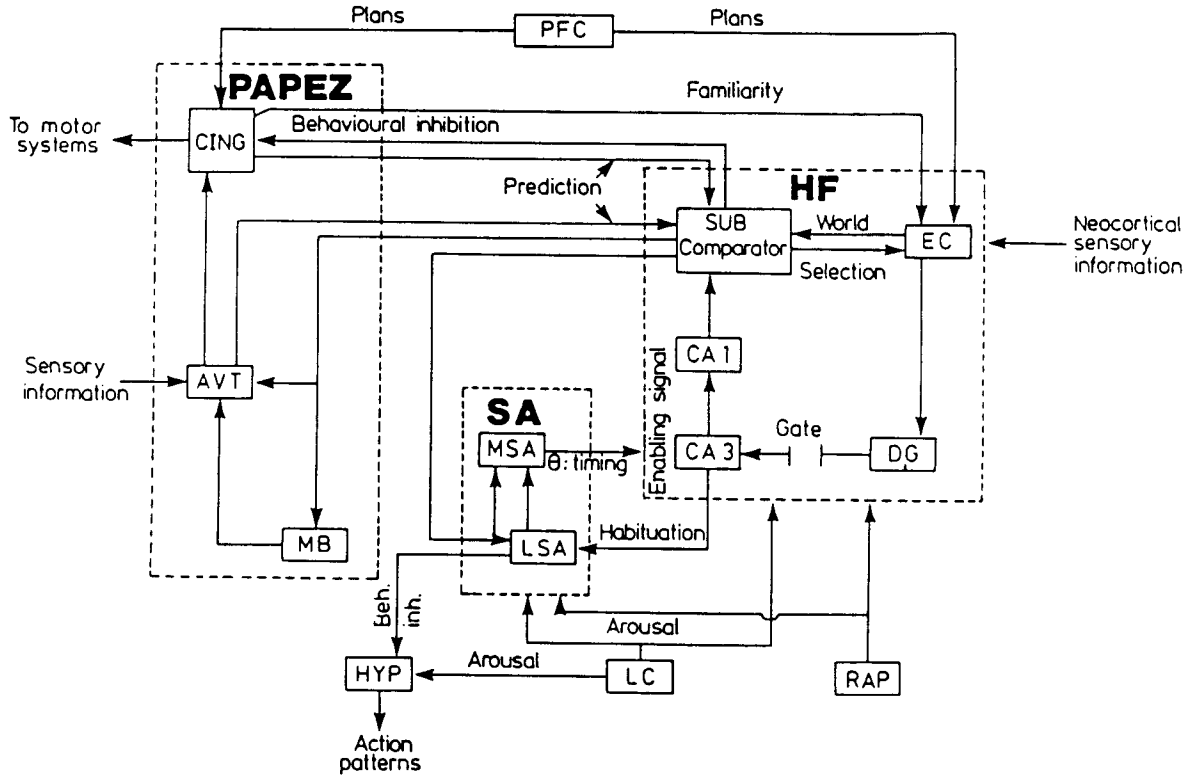


FIGURE 77.1 The septohippocampal system: The three major building blocks are shown in heavy print: HF, the hippocampal formation, made up of the entorhinal cortex, EC, the dentate gyrus, DG, CA3, CA1, and the subicular area, SUB; SA, the septal area, containing the medial and lateral septal areas, MSA and LSA; and the Papez circuit, which receives projections from and returns them to the subicular area via the mammillary bodies, MB, anteroventral thalamus, AVT, and cingulate cortex, CING. Other structures shown are the hypothalamus, HYP, the locus coeruleus, LC, the raphe nuclei, RAP, and the prefrontal cortex, PFC. Arrows show direction of projection; the projection from SUB to MSA lacks anatomical confirmation. Words in lower case show postulated functions; beh. inhib., behavioral inhibition. (From Gray, 1982b.)

subgoals depends upon the process described in animal learning theory as establishing a goal gradient. This process consists of the formation of Pavlovian associations between initially neutral stimuli, or cues, and innate positive reinforcers—the cues now becoming secondary positive reinforcers—followed by the formation of further associations between other cues and those already established as secondary reinforcers (Deutsch, 1964; Gray, 1975). In addition to learning about the spatiotemporal location of desired goals in this way, an animal must also learn about undesirable outcomes (negative reinforcers, or punishments), such as pain or proximity to a predator. This is achieved by a similar process of repeated primary and secondary Pavlovian conditioning, leading to the formation of linked series of secondary negative reinforcers. There is much evidence (LeDoux, 1987; Rolls, 1990) that a key role is played in this process of cue-reinforcer learning, for both positive and negative reinforcement, by neurons in the amygdala.

GOAL ATTAINMENT Once a cue-reinforcer association has been formed (and this can happen very quickly, often in only a single trial), the animal is in a position to do something about the cue: approach it (where the term *approach* includes any behavior that increases proximity in space and time to its occurrence) if it is a secondary positive reinforcer; or avoid it (performing any behavior that decreases proximity in space and time to its occurrence) if it is a secondary negative reinforcer. However, the complexities of the natural environment are such that, normally, a whole chain of linked secondary reinforcers will be required for effective action. The information concerning this chain,

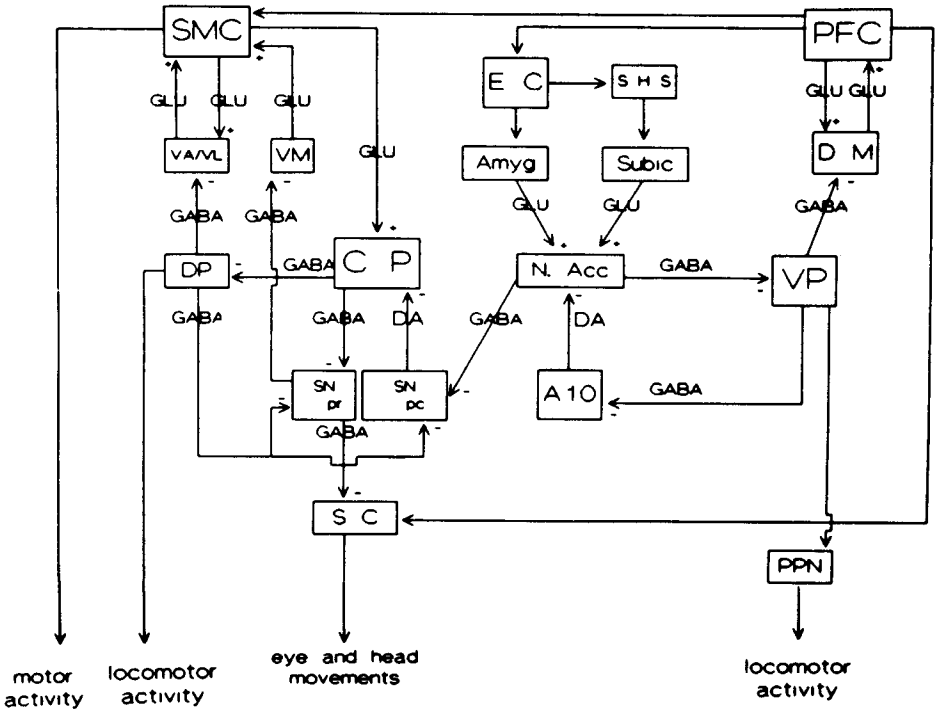


FIGURE 77.2 The basal ganglia and their connections with the limbic system. Structures: SMC, sensorimotor cortex; PFC, prefrontal cortex; EC, entorhinal cortex; SHS, septohippocampal system; Subic, subicular area; Amyg, amygdala; VA/VL, nucleus (n.) ventralis anterior and ventralis lateralis thalami; VM, n. ventralis medialis thalami; DM, dorsalis medialis thalami; DP, dorsal pallidum; VP, ventral pallidum; CP, caudate-putamen; N. Acc, n. accumbens; SNpr, substantia nigra, pars reticulata; SNpc, substantia nigra, pars compacta; A 10, n. A 10 in ventral tegmental area; SC, superior colliculus; PPN, penduculopontine nucleus. Transmitters: GLU, glutamate; DA, dopamine; GABA, gamma-aminobutyric acid. (From Gray, Feldon, et al., 1991.)

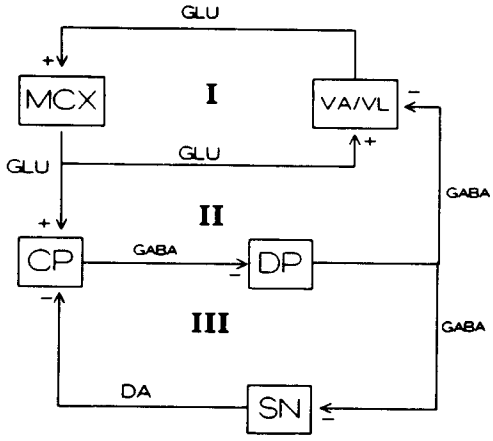
therefore, must be transmitted from the amygdala, where it is initially established, to motor systems in the basal ganglia. This step appears to be accomplished by the projection from the amygdala to the ventral striatum, or nucleus (n.) accumbens (Rolls and Williams, 1987; Gray, Feldon, et al., 1991). The latter structure has been recognized for some time as a key node in the interface between the limbic system and the basal ganglia (e.g., Mogenson and Nielsen, 1984). There is evidence from single-unit recording studies that accumbal neurons do indeed receive information about associations between cues and positive reinforcers (Rolls and Williams, 1987), as well as evidence for accumbal release of dopamine in close association with rewarded behavior (Fibiger and Phillips, 1988; Hernandez and Hoebel, 1988; Young, Joseph, and Gray, 1992). We have in addition recently demonstrated that cues associated with foot shock elicit conditioned dopamine release in n. accumbens (Young, Joseph, and Gray, 1993); thus n. accumbens receives information about secondary negative as well as secondary positive reinforcement.

That neurons receive a certain class of information does not indicate what they do with it. We have proposed that n. accumbens uses information about cue-reinforcer associations to establish and run the sequences of motor steps that are required to reach specific goals; but that the detailed sensorimotor content of each step is contained in the dorsal striatal system, which links the caudate putamen to sensory and motor cortices, to nuclei ventralis anterior and ventralis lateralis of the thalamus, and to the dorsal pallidum (Gray, Feldon, et al., 1991). To use a computer analogy, n. accumbens holds a list of steps making up a given motor program and is able to switch through the list in an appropriate order; but, in order to retrieve the specific content of each step, it must call up the appropriate subroutine by way of its connections to the dorsal striatal system. Drawing upon previous suggestions (Oades, 1985; Swerdlow and Koob, 1987), Gray,

Feldon, and colleagues (1991) further proposed that switching from one step to the next in a motor program is achieved by the intra-accumbal release of dopamine at terminals projecting from n. A10 in the ventral tegmental area. Swerdlow and Koob (1987) have presented a detailed analysis of the way in which the circuitry linking n. accumbens to the limbic cortex (prefrontal and cingulate areas), to the dorsomedial nucleus of the thalamus, and to the ventral pallidum, would allow activation of the A10 dopaminergic fibers by outputs from n. accumbens itself to achieve this effect (see figure 77.3).

What about the detailed sensorimotor content of the motor steps, as executed by the dorsal striatal system? Rolls and Williams (1987) have used the anatomical organization of this system, together with a general theory of random associative networks, to outline a mechanism by which assemblies of cells with the appropriate connections to motor outputs could be selected. In brief, these authors consider sets of Spiny I striatal cells (the major, GABAergic, output from the caudate putamen), which, because of the particular pattern of connections that they possess, would receive inputs from both (1) neurons that respond to environmental cues associated with positive reinforcers, and (2) other neurons that fire when the animal makes a movement that happens to affect the occurrence of this reinforcer. They show how such cells might initially respond only to the conjunction of cue and movement, but could come eventually to be activated by the cue alone, and so to participate in the production of the appropriate movement, given the cue. If we assume that neurons in set (1) receive information from n. accumbens (indirectly, e.g., by way of the dorsomedial nucleus of the thalamus and the prefrontal cortex), Rolls and Williams's proposal provides a mechanism by which the list of motor steps held in n. accumbens can be translated into a sequence of detailed sensorimotor steps in the caudate putamen and its associated thalamic, pallidal, and cortical connections.

GOAL MONITORING In these ways, then, motor programs directed toward goals (primary and secondary positive reinforcers) can be established and executed. The next requirement is that the outcomes of each program be monitored, in order to ensure that the intended goals are indeed achieved. The model supposes that this monitoring or *comparator* process is mediated by the septohippocampal system and the associated Papez circuit, that is, the loop from the subiculum (the major output station for the septohippocampal system) via the mammillary bodies, anteroventral thalamus,



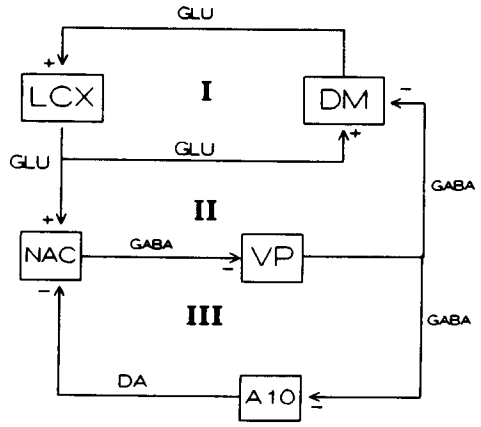


FIGURE 77.3 *Left* The caudate motor system: nonlimbic cortico-striato-pallido-thalamic-midbrain circuitry. MCX, motor and sensorimotor cortex; VA/VL, ventral anterior and ventrolateral thalamic nuclei; CP, caudate putamen (dorsal striatum); DP, dorsal pallidum; SN, substantia nigra.

Right The accumbens motor system: limbic cortico-striato-pallido-thalamic-midbrain circuitry. LCX, limbic cortex, including prefrontal and cingulate areas; DM, dorsomedial thalamic nucleus; NAC, nucleus accumbens (ventral striatum); VP, ventral pallidum; A 10, dopaminergic nucleus A 10 in the ventral tegmental area.

GLU, GABA and DA, the neurotransmitters glutamate, gamma-aminobutyric acid, and dopamine. +−, excitation and inhibition; I, II, III, feedback loops, the first two positive, the third negative. (Based on Swerdlow and Koob, 1987.)

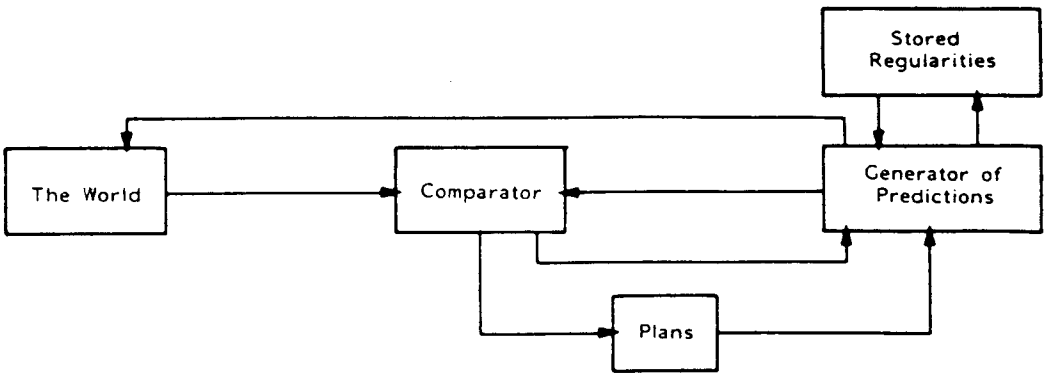


FIGURE 77.4 Information processing required for the comparator function of the septohippocampal system

and cingulate cortex back to the subiculum. The information-processing functions required for such a comparator to work are illustrated in figure 77.4.

Information about the current state of the animal's world is first analyzed in the sensory systems of the neocortex and then fed via the temporal lobe (more specifically, the entorhinal cortex) to the hippocampal formation. The information received by the hippocampal formation in this way has already been heavily processed, being certainly multimodal and probably highly abstract. O'Keefe and Nadel's (1978) influential hypothesis that this information consists of descriptions of spatial locations within a mapping system is supported by much evidence; but it is clear that the hippocampal formation also handles other, nonspatial kinds of information (Gray, 1982a; Rawlins, Lyford, and Seferiades, 1991). Whatever their exact form, these descriptions of the current state of the world must be compared to predicted states of the world. As shown in figure 77.4, the making of such predictions requires the following kinds of data: (1) the last verified current state of the world; (2) the next step in the current motor program; (3) access to stored regularities describing associations between states of the world resembling the last current one and other succeeding states of the world (i.e., stimulus-stimulus associations of the kind set up by Pavlovian conditioning); and (4) access to stored regularities describing associations between the current step in the motor program and succeeding states of the world (i.e., response-stimulus associations of the kind set up by instrumental conditioning).

The model supposes that the circuit responsible for the making of predictions is the Papez loop (subicular area–mammillary bodies–anteroventral thalamus–cingulate cortex–subicular area), and that the actual comparison process is accomplished by subicular neurons. Thus, the last verified current state of the world is coded by subicular neurons at the outset of a cycle around the Papez circuit; a description of the next step in the current motor program is supplied by way of the projection from frontal to cingulate cortex, the frontal cortex itself receiving information about the list of steps in a motor program from n. accumbens via the dorsomedial nucleus of the thalamus; stimulus-stimulus and response-stimulus regularities are stored in the temporal lobe and accessed by way of the projections from the subicular area and the frontal cortex, respectively, to the entorhinal cortex. Finally, timing of cycles around this circuitry is accomplished by the hippocampal theta rhythm (approximately 6–12 Hz, resulting in a quantized timing unit of about 0.1 s).

At the end of each such predictive cycle, the subicular neurons responsible for the comparison process make a match-mismatch decision with regard to (1) the input representing the current state of the world derived from neocortical sensory analysis, and (2) the input representing the predicted state of the world derived from the Papez predictive circuit. A match decision is followed by initiation of the next predictive cycle coupled with the next analysis of the current state of the world. This analysis is biased toward features that will enter the next prediction, a biasing achieved by feedback from the subicular area to the entorhinal cortex. If, however, there is a mismatch decision, or if the predicted state of the world includes negative reinforcers, the current motor program is interrupted.

Match decisions must be communicated to the motor programming system in order to confirm that the

last intended step in the current program has been successfully completed. This is accomplished by way of the projection from the subiculum to n. accumbens. This projection terminates upon accumbal GABAergic Spiny I output neurons, which also receive dopaminergic inputs from A10 (Totterdell and Smith, 1989), in the same general caudomedial region where fibers from the amygdala reach n. accumbens (Phillipson and Griffith, 1985). The model therefore supposes that a match output from the subiculum terminates the current step in the motor program, permitting the amygdaloid projection, in conjunction with dopaminergic afferents, to switch in the accumbal output neurons corresponding to the next step. Weiner (1991) has proposed a detailed mechanism, utilizing the accumbens projection to the substantia nigra and the circuitry illustrated in figure 77.3 (taken from Swerdlow and Koob, 1987), by which such switching between steps within the accumbens can be transmitted to the caudate system coding for the detailed sensorimotor content of each step.

In this way, then, the model attempts to give a general account of how the LSBG is able to establish, run, and monitor goal-directed motor programs, although there are a number of features of the model not touched upon here (see Gray, 1982a, 1982b; Gray and Rawlins, 1986; Gray, Feldon, et al., 1991; Gray, Hemsley, et al., 1991).

Applications of the model

The model has developed gradually in a series of attempts to understand the brain functions that underlie particular psychological phenomena. In the second half of this chapter I shall briefly review its application to two of these phenomena.

THE NEUROPSYCHOLOGY OF ANXIETY The hypothesis that the septohippocampal system and its associated Papez circuit discharge a general comparator function, comparing actual and predicted states of the world, was first developed in the context of an account of anxiety. This account was based in the first instance on an analysis of the behavioral effects in experimental animals of antianxiety, or anxiolytic, drugs, including principally benzodiazepines, barbiturates, and ethanol. A review of some 400 studies of this kind in species ranging from goldfish to chimpanzees led to the conclusions summarized in figure 77.5 (Gray, 1977). This figure proposes that anxiety reflects activity in a behavioral inhibition system (BIS) that responds to the threat of punishment, the omission of anticipated reward ("frustrative nonreward"; Amsel, 1992), or extreme novelty by the inhibition of ongoing behavior, increased readiness for vigorous action, and increased attention to environmental cues; and that anxiolytic drugs exert their effects by reducing activity in the BIS. This proposal—or other similar formulations—has been widely accepted. Much more controversial has been the answer to the question, What brain system(s) mediate anxiety?

To a large extent the answer given to this question depends upon the starting point chosen for an experimental analysis of aversively motivated behavior in animals. If one starts from the anxiolytic drugs, one is led to the septohippocampal system by the considerable degree of similarity that exists between, on the one hand, the profile of behavioral change produced

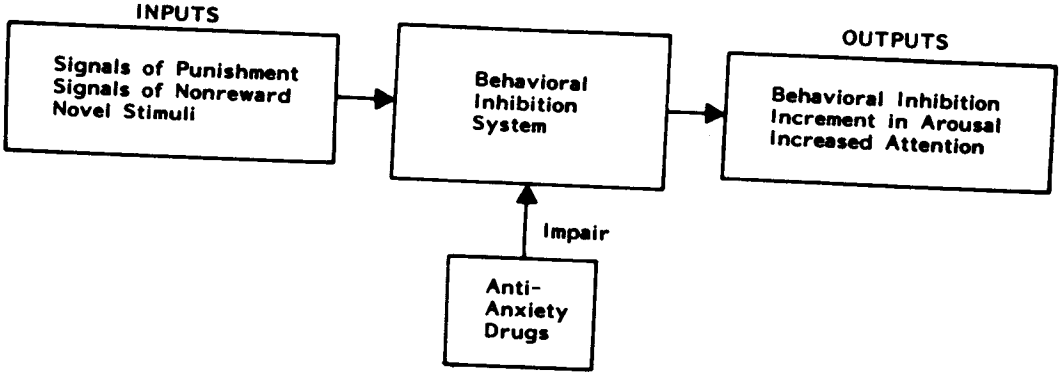


FIGURE 77.5 The behavioral inhibition system (BIS) as defined by its inputs and outputs.

by these agents and, on the other, the profile seen after lesions to either the septal area or the hippocampal formation (Gray, 1982a, 1982b; Gray and McNaughton, 1983). Alternative starting points lead to different destinations. A favorite has been the fight-or-flight behavior elicited by unconditioned punishment and frustrative nonreward; since this type of behavior can also be elicited by electrical stimulation of a range of sites in the amygdala, medial hypothalamus, and central gray of the midbrain, it is naturally a system comprising these regions that is seen as the neural substrate of anxiety (Panksepp, 1982). A second alternative lies in the formation of Pavlovian conditioned fear responses; LeDoux (1987) has marshaled a considerable body of evidence, much of it from his own laboratory, implicating the amygdala in conditioning of this kind.

There are strong reasons why these different flowers cannot be allowed to bloom together—at least, not all under the same name, whether it be *anxiety* or something else. Chief among these reasons is that there is a double dissociation between responses to unconditioned punishment and nonreward, on the one hand, and responses to conditioned stimuli signaling these events, on the other. This dissociation is observed behaviorally (unconditioned stimuli typically provoke vigorous locomotor activity, whereas conditioned stimuli typically provoke behavioral inhibition or "freezing"), pharmacologically (anxiolytics do not generally reduce responses to painful stimuli, except at high doses, and analgesics do not generally reduce responses to conditioned stimuli associated with pain), and neurally (e.g., fight-or-flight behavior is reduced by amygdaloid lesions, and responses to conditioned frustrative stimuli are reduced by septal and hippocampal lesions); for review, see Gray (1982a). A second, though less firmly established, relevant distinction is between fear conditioning (that is, the establishment of a Pavlovian conditioned response using a painful unconditioned stimulus) and the responses elicited by a conditioned fear stimulus after conditioning. Anxiolytic drugs appear to have little if any effect upon the process of formation of the conditioned response, but they weaken the responses elicited by the conditioned stimulus (Gray, 1977, 1982a). Thus, a choice has to be made: One can identify anxiety with the processes antagonized by the anxiolytic drugs, in which case it is the septohippocampal system that is nodal; one can identify anxiety with the process of fear conditioning, in which case it is the amygdala; or one can identify it with fight-or-flight behavior, in which case it is a system involving the amygdala, medial hypothalamus, and central gray—Graeff's (1987) "behavioral aversive system," or Gray's (1987) "fight/flight system" (FFS).

This, of course, is a choice of names only (Gray, 1991). Substantively, there is no reason why all these systems should not coexist, each performing its own function, as supposed, for example, by Graeff (1987) and Gray (1987). In the long run, relatively neutral names, or indeed abbreviations such as BIS or FFS, are to be preferred to terms like *anxiety*, with their burden of surplus meaning. However, if a choice has to be made, there is good reason to equate the term *anxiety* to *activity in the BIS*. Anxiolytics, such as diazepam or chlordiazepoxide, when administered to relevant patient groups, reliably elicit lower ratings and self-ratings of "anxiety" (Rickels, 1978); thus, in the construction of an animal model of anxiety, these compounds benefit from greater face validity than other possible starting points. On this assumption, therefore, the neural substrate of anxiety becomes the one that mediates activity in the BIS. (A complementary suggestion is that activity in the FFS underlies the human emotions of panic and/or rage. This proposal is consistent with evidence that anxiety and panic are susceptible to different drug treatments; Klein, 1981; Graeff, 1987; Gray, 1987.)

As already indicated, lesion evidence implicates the septohippocampal system as a nodal point in the substrate of the behavioral inhibition system. Given the behavioral model of the input-output relations that define the BIS (figure 77.5), the neural systems that instantiate it must be capable of detecting threat (i.e., stimuli associated with punishment or with nonreward) or novelty (i.e., the occurrence of an unexpected stimulus or the nonoccurrence of one that is expected). This role is consistent with the predictive and comparator functions allocated to the septohippocampal system and its associated Papez circuit, and indeed motivated this allocation in the first place (Gray, 1982a,b). Information about threat can be seen as reaching the septohippocampal system in two mutually compatible ways. First, in agreement with LeDoux's (1987) analysis, the formation of the cue-reinforcement associations that underlie fear conditioning takes place in the amygdala; this information can be relayed to the hippocampal formation via the entorhinal cortex (Braak and Braak, 1992). Second, information about predicted

outcomes of current motor programs, including the possibility that these will include aversive events, can be relayed to the hippocampal formation via the prefrontal-entorhinal connection (the prefrontal cortex itself receiving information about motor programs via the dorsomedial thalamus). (Important roles are also played by the ascending noradrenergic and serotonergic systems, but there is no space to consider them here; see Gray, 1982a,b.)

Once threat or novelty is detected, the outputs of the BIS (figure 77.5) must be operated. The behavioral inhibition output proper requires inhibition of any ongoing motor programs. The evidence from lesion studies that the hippocampal formation plays a major role in such inhibition of motor programs is very strong (Gray and McNaughton, 1983; Jarrard et al., 1986), although the neural substrate of the "freezing" posture that often accompanies such behavioral inhibition appears to be principally mediated by lower structures in the central gray of the midbrain (Fanselow, 1991), perhaps under amygdaloid control (LeDoux, 1987). It is still unclear, however, which pathway mediates this hippocampal control over motor programs. The projection from the subicular area to n. accumbens appears not to be involved, since section of this pathway (Rawlins et al., 1989) fails to reproduce the increase in resistance to extinction of rewarded running that is characteristic of large hippocampal lesions (Gray and McNaughton, 1983; Jarrard et al., 1986). The most likely alternative is the projection from the subicular region to the cingulate cortex (Gray, 1982a; Gabriel, Sparenborg, and Stolar, 1987). If this hypothesis is correct, the hippocampal formation would be able to facilitate the continuation of motor programs by way of its output to n. accumbens or, alternatively, to interrupt them by way of its output to the cingulate cortex.

The attentional output of the BIS requires increased attention to environmental cues, and especially those that are novel or associated with the threat that has brought the ongoing motor program to a halt. This can be achieved via two complementary routes. First, neocortical sensory analysis can be influenced by way of the subicular projection to the entorhinal cortex and from there to the sensory cortices. Second, the output to n. accumbens can be utilized to influence accumbal projections to two regions controlling exploratory behavior: the pedunculopontine nucleus, part of the mesencephalic motor region concerned with exploratory locomotion (Yang and Mogenson, 1987); and the superior colliculus (Williams and Faull, 1988), a structure known to be of importance in the control of head and eye movements and visual attention (Dean and Redgrave, 1984; Wurtz and Albano, 1980).

Finally, the arousal output of the BIS provides a general facilitation of motor behavior, so that whatever motor program is engaged following the interruption (including the original, interrupted one) occurs with greater-than-normal vigor. This output appears to be discharged by the ascending noradrenergic and serotonergic pathways. In general, activation of these pathways appears to increase the capacity of the organs they innervate to process other neural messages arriving at the same time via more specific, point-to-point afferents (e.g., Segal, 1977). Thus, the monoaminergic inputs to the hippocampal formation increase threat-related cognitive processing while simultaneously increasing the readiness for prompt and vigorous motor behavior by way of parallel projections to, for example, n. accumbens and the caudate-putamen. In this way, these pathways act as a general alarm system, as proposed by Redmond (1979) for the noradrenergic pathway originating in the locus coeruleus.

This model of the neuropsychology of anxiety was based entirely on experiments with animals. How does it fare as an account of the symptoms observed in the major anxiety disorders, such as agoraphobia, social phobia, and anxiety state (Gray, 1982a)? Such symptoms fall into three classes: autonomic (e.g., respiratory and cardiac changes, sweating), which will not be considered here (see Redmond, 1979; Graeff, 1987); behavioral (chiefly, phobic avoidance); and cognitive (e.g., worry, obsessional rumination). The behavioral symptoms of anxiety may be analyzed simply as reflecting the behavioral inhibition output of the BIS, giving rise to phobic avoidance in response to threat-related stimuli. The cognitive symptoms may be analyzed as a search for such stimuli (experienced as worry or, in the extreme, obsessional rumination). This would be mediated by way of the hippocampal outputs (via the subicular area) to the entorhinal cortex, and so to neocortical sensory systems; and to n. accumbens, and so to exploratory systems (mesencephalic locomotor region, superior colliculus), as outlined above. In addition, however, it is necessary to postulate further mechanisms to permit, at the human level, the control of such search processes by symbolic threats formulated linguistically (e.g., the threat that one may fail an

examination). This mechanism can plausibly (Gray, 1982a) be found in the pathways linking cortical language areas to the prefrontal cortex and thence both to motor programming circuits in the basal ganglia and to the hippocampal formation via the entorhinal cortex.

THE NEUROPSYCHOLOGY OF SCHIZOPHRENIA The analysis of pathological anxiety in the preceding section treats this condition as overactivity in a normally organized brain. In contrast, it is now generally agreed that schizophrenia reflects a structural *dis*organization in the brain, though one of as-yet-uncertain etiology. The neuropathology of the schizophrenic brain has been widely described; it involves both loss and abnormalities of packaging of neurons, especially in the temporal and frontal neocortex and in the hippocampal formation and amygdala (for references, see Gray, Feldon, et al., 1991). This neuropathology is difficult to reconcile with the leading neurochemical hypothesis of schizophrenia, namely, that it reflects overactivity in one or another (probably the mesolimbic) ascending dopaminergic pathway. This hypothesis is based upon the drugs (indirect dopamine agonists) that give rise to or exacerbate psychotic symptoms, and those (dopamine receptor blockers) that are able to reduce these symptoms; but schizophrenic neuropathology does not usually extend to either the cell-body region (A10, in the ventral tegmental area) or the principal terminal region (n. accumbens) of the mesolimbic dopaminergic pathway. Some pathology is found in terminal regions (in parts of the frontal and temporal neocortex) of the mesocortical dopaminergic pathway, which also originates in A10—but not as a prominent feature of the schizophrenic brain.

In an effort to combine these neuropathological and neuropharmacological data, we have proposed (Gray, Feldon, et al., 1991) that the structural basis of schizophrenia is to be found in an abnormality in the connections between the limbic forebrain (especially the hippocampal formation, via the subicular area) and the basal ganglia (especially n. accumbens). Neurochemically, it is suggested that this structural abnormality is equivalent to an increase in dopaminergic transmission in n. accumbens (as we have seen, the subiculo-accumbens projection terminates in the same region, and, probably on the same neurons, as the projection from n. A10; Totterdell and Smith, 1989). Psychologically, given the general model of limbic–basal ganglia interactions outlined above, an interruption in the subiculo-accumbens projection would have the effect that steps in a motor program should fail to receive the confirmatory messages signaling the occurrence of the expected outcome of each step. By the same token, outcomes that would have been expected to occur, given normal information processing, should appear to be novel and so provoke continuing exploratory behavior. Hemsley (1987) has shown how such a failure to utilize past regularities of experience in the control of current behavior and perception could account for the bizarre positive symptoms (Crow, 1980) of schizophrenia, such as delusional beliefs or the capturing of attention by apparently trivial stimuli. Experimental investigations of this account, using tests of selective attention based upon animal learning theory—latent inhibition (Lubow, 1989) and Kamin's (1968) blocking effect—with rats, normal human subjects, and acute and chronic schizophrenics, have provided generally supportive results (for references, see Gray, Feldon, et al., 1991; and, more recently, Gray, Hemsley, and Gray, 1992; Gray et al., 1992; Jones, Gray, and Hemsley, 1992; Young, Joseph, and Gray, 1993). (It may be possible to develop a similar, and complementary, account based upon disruption in the projection to n. accumbens from the amygdala, but this remains to be done; Gray, Feldon, et al., 1991.)

An alternative hypothesis (Frith, 1987) to account for the symptoms of schizophrenia calls upon the same general machinery but proposes that the abnormal connection lies between the prefrontal cortex and the septohippocampal comparator system, that is, in the prefrontal connections to the cingulate and/or entorhinal cortices (figure 77.1). According to the general model developed above, these projections provide information about intended motor programs to the comparator system. Thus an interruption in their functioning would have the consequence that outcomes of such programs would appear to be unexpected and unintended. Frith (1987, 1992) shows in detail how such an abnormality in information processing could give rise to such positive psychotic symptoms as hallucinations, thought insertion, and delusions of alien control. This hypothesis is consistent with the proposal that a disruption in the subiculo-accumbens projection forms the neural substrate of schizophrenia. The pathology observed in the schizophrenic hippocampal formation and parahippocampal gyrus may indicate impaired output from prefrontal to entorhinal cortex (as may

the pathology in the frontal cortex itself), impaired output from subiculum to n. accumbens, or both. Another relevant model is that of Weinberger (1987). In line with evidence for lowered functional activity, detected in neuroimaging studies, in the schizophrenic prefrontal cortex, Weinberger sees the primary neural basis of schizophrenia as lying in an *underactive* mesocortical dopaminergic innervation of the dorsolateral prefrontal cortex, thought to lead (as shown in experiments in the rat; Pycock, Kerwin, and Carter, 1980) to increased mesolimbic dopaminergic activity. The pathways responsible for such compensatory changes in dopamine release in different terminal regions of the mesocortical and mesolimbic projections are at present unknown. One possibility is that they include frontotemporal connections, followed by the same subiculoaccumbens projection emphasized in the model of Gray, Feldon, et al. (1991); in that case, Weinberger's (1987) hypothesis is consistent with both this model and the circuitry proposed by Frith (1987).

Conclusion

The model of the functions of the limbic system and basal ganglia presented above is one of wide generality that is undoubtedly capable of application in contexts other than those of anxiety and schizophrenia (see, e.g., Gray, 1993b; Gray and Rawlins, 1986). One particularly interesting possibility is that the model may throw light on the nature of the contents of consciousness, although profound theoretical and possibly philosophical problems have first to be resolved (Gray, 1993a, submitted); both anxiety and acute schizophrenic disturbance, of course, have profound effects upon conscious experience. At present, the model is hampered by being couched in verbal terms, which rob it of precision and leave open the possibility that it contains internal contradictions. However, we have recently made a start upon the construction of a neural-network computer simulation of part of the model (Schmajuk, Lam, and Gray, in preparation). This simulation appears to be able to account for many of the detailed features of a behavioral phenomenon—latent inhibition—that is critical for the application of the model to acute schizophrenia (Gray, Feldon, et al., 1991). Thus, if it achieves nothing else, the model illustrates the possibility in principle of constructing an integrated theory of brain function that straddles structural, physiological, computational, behavioral, and experiential levels.

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