Role of the Thalamus in Language: Is it Related to Schizophrenic Thought Disorder?

by Bruce Crosson and Carroll W. Hughes

Abstract

Crosson (1985) proposed a model for language production which integrated cortical with subcortical functions. The implications of this model for schizophrenia are explored. One conclusion is that neural systems, as opposed to a single neural focus, account for schizophrenic symptoms. In this light, data regarding dysfunction in the limbic system, nucleus accumbens, globus pallidus, and prefrontal cortex, which are often seen as contradictory, can be viewed as complementary. Another conclusion is that Crosson's model may have implications specific to schizophrenic thought disorder. Random triggering of semantic segments and inability to maintain contextual referents are discussed in the context of the language production theory.

Schizophrenia is a multifaceted disorder that encompasses an array of signs and symptoms. A number of different neurobiological models have been postulated to account for the schizophrenic syndrome based on brain atrophy; aberrations of neurotransmitter and receptor systems (e.g., dopamine); or abnormalities of specific brain regions such as the dorsolateral prefrontal cortex, amygdala, hippocampus, basal ganglia, nigrostriatal and limbic pathways, and others (e.g., Hughes et al. 1985; Berger and Brodie 1986; Cooper et al. 1986). A few attempts have been made to deduce from such evidence the dysfunctions in specific brain systems accounting for schizophrenia (e.g., Weinberger 1986).

Similarly, Crosson (1985) has recently hypothesized a brain system linking traditional language areas of the cortex via thalamic and other subcortical pathways. In Crosson's model, subcortical mechanisms integrate various language functions, which explains why aphasia (language dysfunction) occurs after subcortical lesions (e.g., Cappa and Vignolo 1979; Alexander and Lo-Verme 1980; McFarling et al. 1982; Crosson 1984; Crosson et al. 1986). Crosson (1984) had previously contended that understanding the role of the thalamus and other subcortical structures in language would lead to a better understanding of how the brain produces language. If language production can be better described, it may enhance our understanding of related phenomena such as schizophrenic language and thought disorder.

Before proceeding further, it would be helpful to define a couple of terms, as well as the scope of our interest. Regarding terminology, our usage will be consistent with description of neurological systems (e.g., Boller 1982). *Speech* refers to the mechanisms involved in articulation; *language* refers to the verbal processes in communication, i.e., the comprehension of spoken or written statements and the formulation of spoken or written discourse. The primary interest of this article will revolve around the phenomenon of schizophrenic "thought disorder," by which we mean incoherent language output. Although we may touch upon hallucination and delusion, these problems are not our central focus.

The primary purpose of this article is to consider whether a particular model of language production, including the role of the thalamus

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(Crosson 1985), can shed any light on the nature of schizophrenia—in particular, thought disorder. The goals are heuristic. We do not contend that thalamic or other subcortical aphasias are the same as or the cause of schizophrenic thought disorders. Nonetheless, it does make sense to consider how thalamic functions might influence schizophrenic symptoms, especially when schizophrenia is viewed as a disturbance in some brain system or systems as opposed to a simple focal disturbance. Inputs to the thalamus come from most areas of the brain including the brainstem reticular formation, almost all sensory modalities, the cerebellum, the basal ganglia, the limbic system, and most areas of the cerebral cortex. Thus, it is highly likely that schizophrenic symptoms are determined by a brain system that includes at least some thalamic nuclei.

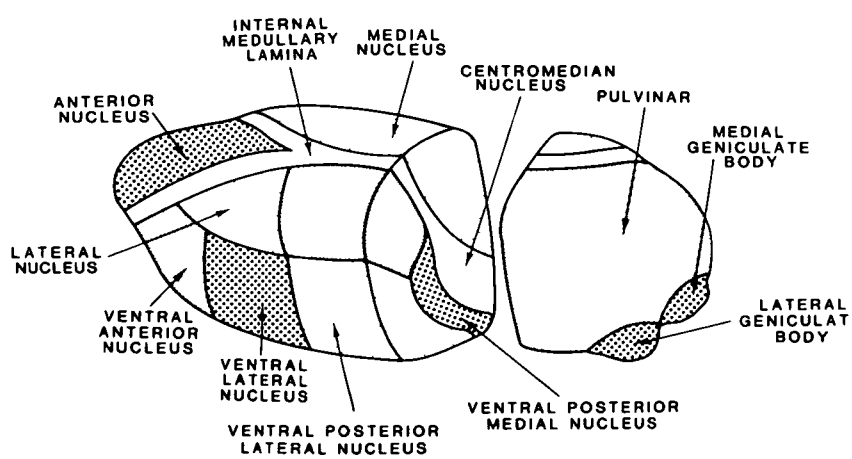
The Thalamus and Its Connections

The cerebral cortex is intricately involved in sensory processing, integration of information, and formulation of actions. Recent evidence suggests, however, that this cortical activity is facilitated by, controlled to some extent by, and perhaps integrated through a network of subcortical nuclei and connections with extensive thalamic involvement. It seems obvious that schizophrenic symptoms involve, somehow, the disruption of highly complex, integrated cortical functions, such as perception, language, and thought. If we hope to understand the contribution of the thalamus to these complicated functions, we must first understand how the thalamus is connected to other structures that are also involved. It is through these connections with various other structures that the thalamus plays a role in language, thought, and perception.

The thalamus (figure 1) is an oblong group of nuclei lying in the central most portion of each cerebral hemisphere. It is divided into three nuclear groups by a γ-shaped band of white matter, the internal medullary lamina. The three nuclear groups are the anterior nucleus, the medial (or dorsomedial) nucleus, and the lateral nuclear group. The lateral nuclear group is the most complex of these structures, and it is divided into several nuclei. There also are some small nuclei lying within the internal medullary lamina, collectively called the intralaminar nuclei. A good neuroanatomy text will give detailed information about the thalamus. Jones (1985) has written an entire, extended volume about the thalamus, though it contains considerably less detail about the connections of the thalamic nuclei than the neuroanatomy text of Carpenter and Sutin (1983). The latter text was the main reference used as a guide for this section.

Starting at the anterior pole of the thalamus is the anterior nucleus. Evidence suggests that the primary connections of the anterior nucleus are with the limbic system. For example, the anterior nucleus receives substantial input from the hippocampus via the fornix (which is the primary efferent pathway of the hippocampus). The hippocampus, interestingly, has been specifically implicated in some studies of schizophrenia (e.g., Kovelman and Scheibel 1984). One of the main outputs of the anterior nucleus of the thalamus is to the cingulate gyrus, which is also considered a portion of the limbic system. Although the anterior nucleus has connections with limbic structures implicated in schizophrenia, it has never seriously been considered to have a role in language.

Figure 1. Left thalamus, showing anterior nucleus, dorsomedial nucleus, lateral nuclei, and centromedian nucleus (1 of the intralaminar nuclei)[1]



[1]From *A Synopsis of Neuroanatomy* by H.A. Matzke and F.M Foltz. New York: Oxford University Press, 1983. Copyright © 1983 by Oxford University Press. Adapted by permission. (Ventral lateral nucleus is called "ventrolateral" in text for purposes of consistency in this issue.)

Moving medially and posteriorly to the anterior nucleus is the dorsomedial (or medial) nucleus of the thalamus. The dorsomedial nucleus has bidirectional connections with the nonmotor frontal lobe, including the dorsolateral and orbital frontal lobes. Indeed, it has been suggested that the "prefrontal" cortical regions should be defined as the cortical projection fields of the dorsomedial thalamus (e.g., Rose and Woolsey 1948; Leonard 1969; Fuster 1980). However, Reep (1984) opposed such a definition because it has tended to obscure the "structural and functional heterogeneity present in these cortical areas" (p. 12). The connections of the dorsomedial thalamus with the frontal lobes are of interest because the frontal lobes, particularly the dorsolateral prefrontal lobes, are implicated in schizophrenia (e.g., Ingvar and Franzen 1974; Levin 1984*a*, 1984*b*; Weinberger 1984; Andreasen et al. 1986; Weinberger et al. 1986). The dorsomedial nucleus also receives afferents from the amygdala, a portion of the limbic system. The dorsomedial nucleus has never received serious attention as a structure participating in language. Indeed, studies showing severe memory deficit with dorsomedial thalamic involvement (e.g., McEntee et al. 1976; Choi et al. 1983; Speedie and Heilman 1983) have not indicated serious disturbance in language.

The lateral nuclear group is the largest division of the thalamus and contains several nuclei. The ventral anterior nucleus is the most anterior of these. Traditionally, bidirectional connections with the frontal lobes, including the premotor cortex, have been emphasized for this nucleus (Carpenter and Sutin 1983); the possible importance of such frontal structures for schizophrenia was mentioned above. Jones (1985) has disputed the importance of frontal connections for the ventral anterior nucleus, instead of emphasizing the parietal lobe. But Jones (1985) provided scant evidence for his position compared to other sources, such as Carpenter and Sutin (1983). The ventral anterior thalamus also receives input from the intralaminar nuclei, the globus pallidus, and the substantia nigra (Carpenter and Sutin 1983). We shall discuss the importance of input from the globus pallidus for schizophrenia momentarily. The ventral anterior nucleus has occasionally been involved in cases of thalamic infarction with language dysfunction (Gorelick et al. 1984; Graff-Radford et al. 1984). Also, during stimulation of the ventral anterior thalamus and nearby structures, Schaltenbrand's (1965, 1975) subjects could not inhibit spoken language, even when asked to do so.

The ventrolateral nucleus is known to have bidirectional connections with the motor cortex. Because this nucleus also receives input from the cerebellum, the globus pallidus, and the substantia nigra, it is considered to be the motor nucleus of the thalamus. Studies of ventrolateral ablations for Parkinson's disease or other movement disorders found aphasia in varying frequencies (see Crosson [1984] for enumeration), but these language symptoms were usually short-lived. This latter fact suggests that these lesions temporarily disrupt activity in neighboring nuclei as opposed to the ventrolateral thalamus being directly involved in language.

A digression on the basal ganglia (caudate nucleus, putamen, and globus pallidus) is relevant at this point because of implications for both schizophrenia and language. Regarding their connections, the caudate nucleus and the putamen (collectively, the corpus striatum) receive input from most areas of the cortex but do not project fibers directly to the cortex. Yeterian and Van Hoesen (1978) have shown that cortical areas which are directly and reciprocally connected also project to overlapping zones in the striatum. The striatum has reciprocal connections with the substantia nigra; this link is one of the primary dopaminergic pathways in the brain (relevant to dopaminergic hypotheses of schizophrenia discussed below). The primary output of the striatum is to the globus pallidus. The globus pallidus also receives input from the nucleus accumbens, which receives input from the amygdala and is considered to link the limbic system with the basal ganglia (Carpenter and Sutin 1983). The nucleus accumbens receives dopaminergic input from the midbrain (ventral tegmental area).

The primary output of the basal ganglia is from the globus pallidus which, as noted above, has primary outputs to the ventral anterior and ventrolateral nuclei of the thalamus. On the basis of anatomical evidence, Crosson (1985) noted that any influence of the striatum on the cortex is probably mediated through the globus pallidus and the thalamic nuclei to which it projects. As just mentioned, the striatum has no direct output to the cortex. Early et al. (1987) recently found abnormally high regional cerebral blood flow in the left globus pallidus of never-medicated schizophrenic patients. (Other studies have not generally used never-medicated schizophrenic patients. Wolkin et al. [1985] showed greater metabolic asymmetry favoring the left lentiform nucleus in normals than schizophrenic patients, but they did not separate putamen from globus pallidus. The greater subcortical than cortical me-

tabolism in the schizophrenic patients of Gur et al., both off [1987*a*] and on medication [1987*b*], neither confirms nor detracts from the findings of Early et al. [1987]. It is of interest that Buchsbaum et al. [1987] showed large decreases in right globus pallidus metabolism relative to whole brain metabolism when schizophrenic subjects are medicated; yet, they reported the decrease in the left globus pallidus to be significant. Metabolism was higher in the left than right globus pallidus. There are very significant differences in methodology between studies.) Bogerts et al. (1985) found that the medial segment of the left globus pallidus was smaller than normal in a group of relatively chronic, never-medicated schizophrenic patients (Vogt collection).

In summary, the two main points of this digression are: (1) Thalamic nuclei are a link in the chain of connections leading from the cortex to the basal ganglia through the thalamus and back to the cortex. The relevance of these anatomical connections to language will be discussed shortly. (2) The globus pallidus is connected to limbic structures through input from the nucleus accumbens. Both limbic structures and the nucleus accumbens have been implicated in schizophrenia. Between the globus pallidus and the frontal cortex, which has also been implicated in schizophrenia, are thalamic nuclei.

Four sensory relay nuclei in the thalamus relay sensory information to the primary sensory cortex for tactile/proprioceptive, auditory, and visual information. The ventral posterior medial and ventral posterior lateral nuclei, located posterior to the ventrolateral nucleus, are primarily relay nuclei for touch and proprioception. The medial geniculate and lateral geniculate nuclei are located ventral to the pulvinar and are primarily relay nuclei for audition and vision, respectively. These nuclei are not related to any structures ordinarily thought to be involved in schizophrenia, though one might wonder if they play a part in auditory, visual, or tactile hallucinations, or even in catatonia.

The pulvinar is a large nuclear mass that contains most of the posterior portion of the thalamus. The pulvinar has reciprocal connections to the temporal, parietal, and occipital cortex. If a thalamic nucleus is involved in schizophrenic hallucinations, the pulvinar appears to be a more likely candidate than the sensory relay nuclei described above. The pulvinar has connections to the auditory, visual, and tactile association cortex where sensations are decoded into meaningful phenomena, e.g., a voice conveying meaningful language. Such meaningful phenomena bear a closer resemblance to schizophrenic hallucinations than the unprocessed sensation which is passed along by the sensory nuclei. With respect to language, electrical stimulation of the anterior superior lateral pulvinar has been shown to interfere with object naming (e.g., Ojemann 1977), and the pulvinar has been implicated in several cases of thalamic aphasia (e.g., Ciemans 1970; Mohr et al. 1975; Kameyama 1976/1977; Crosson et al. 1986).

The lateral posterior nucleus is anterior to but continuous with the pulvinar. It has bidirectional connections with the parietal cortex and possibly inputs from the thalamic somatosensory nuclei, i.e., ventral posterior lateral and ventral posterior medial (Carpenter and Sutin 1983). The dorsolateral (or lateral) nucleus is anterior to the lateral posterior nucleus. It projects primarily to the cingulate gyrus but also to the parietal lobe. Most parts of the limbic cortex, except for the most anterior, project to the dorsolateral thalamus. The reader will recall that limbic system structures, such as the hippocampus (e.g., Kovelman and Scheibel 1984), are implicated in schizophrenia.

The intralaminar nuclei are a group of small nuclei lying within the internal medullary lamina. These nuclei receive input from parts of the frontal lobe, including the motor and premotor cortex. These frontal inputs are not reciprocated as they are with other thalamic nuclei. This one-way flow of information means intralaminar nuclei can directly influence the frontal cortex, but the influence of the frontal cortex on the intralaminar nuclei must be mediated by other structures, perhaps the basal ganglia. There are some projections from the globus pallidus to the intralaminar nuclei. The intralaminar nuclei receive substantial afferents from the brainstem reticular formation. One major output from the intralaminar nuclei goes to the putamen and caudate nucleus. There are also projections to the ventral anterior thalamus. In fact, lesions of the ventral anterior thalamus in some animals block the cortical recruiting response elicited by electrical stimulation of the intralaminar and midline nuclei (Carpenter and Sutin 1983). The importance of this phenomenon to language is noted below. The recruiting response is also abolished by ablation of the orbital frontal cortex.

Summary. As we might surmise from the above discussion, neocortical areas are intricately involved in sensory processing, integration of information, and formulation of actions through what appears to be a network of subcortical nuclei with extensive thalamic involvement.

Several important points from this discussion should be reemphasized. Pertaining to language, both stimulation studies and lesion cases indicated some involvement of the pulvinar in language. Though the evidence is less abundant, stimulation and lesion evidence also indicates that the ventral anterior thalamus is involved in language. Given recent evidence of abnormalities in the dominant (left) globus pallidus of schizophrenics (Bogerts et al. 1985; Early et al. 1987), the ventral anterior nucleus may be one place at which the language system and the neurological system responsible for schizophrenia interface. It will be recalled that one of the main outputs of the globus pallidus is to the ventral anterior nucleus. Further, one input to the globus pallidus comes from the nucleus accumbens, which may link the limbic components in schizophrenic pathology to the basal ganglia.

The dorsolateral prefrontal lobes also have been implicated in schizophrenia (Weinberger et al. 1986). The ventral anterior and dorsomedial nuclei have reciprocal connections with frontal lobe structures, and the intralaminar nuclei have outputs directly to the frontal lobes.

Regarding the possible role of the limbic system in schizophrenia, it is worth noting that the limbic system interfaces with the anterior thalamus, the dorsomedial thalamus, and other thalamic nuclei. Emotions, in general, have been linked to a subcircuit of the limbic system and may well play a role in "flat" affect in schizophrenia. This circuit involves the anterior thalamus via the mamillothalamic tract, which in turn leads to the cingulate cortex and then projects back to the hippocampus. In addition to the hippocampus, which has been implicated in schizophrenia, the nucleus accumbens is thought to connect the limbic system to basal ganglia (globus pallidus). The nucleus accumbens receives dopamine-rich input from the midbrain tegmentum and has been thought to be involved in schizophrenia, which leads to our next topic.

Dopaminergic Systems and Schizophrenia

Thus, neurological pathways controlling emotion, memory, and arousal interface with speech and language mechanisms at multiple levels of the nervous system. Certainly, the thalamus is intricately linked in the process. The language system will be discussed in more detail later, but the common pathways and structures between it and other systems may be critical to our understanding of schizophrenia and thought disorder (e.g., Hoffman et al. 1986; Morice 1986).

Our knowledge of the neurochemistry of various pathways has advanced enormously in the past decade in terms of transmitters, receptors, and pharmacological response (Hughes et al. 1985; Berger and Brodie 1986; Cooper et al. 1986). For purposes of this discussion, we will focus on the dopaminergic pathways and mechanisms that continue to dominate contemporary neuroscience thinking about schizophrenia. (For recent reviews, see Matthysse 1973; Lewis 1980; Langer et al. 1981; Hornykiewicz 1982; Berger and Brodie 1986; Sedvall et al. 1986.)

Neurons containing dopamine (DA) are primarily mesencephalic in origin, although some groups found in the diencephalon and the telencephalon (Dahlstrom and Fuxe 1964; Ungerstedt 1971; Fuxe et al. 1974). Cooper et al. (1986; see chapter 10 for a more thorough discussion), refer to "long-length systems" of DA neurons that link the substantia nigra and ventral tegmental DA cells with three major targets: (1) the neostriatum consisting of the caudate and putamen (see discussion of involvement of the caudate nucleus and putamen in speech and language inhibition shortly); (2) the mesocortical projections of the medial prefrontal, cingulate, and entorhinal areas; and (3) the mesolimbic projections of the amygdaloid complex, nucleus accumbens, piriform cortex, olfactory tubercle, and the septum. In terms of prefrontal projections, recent research has revealed that the mesocortical neurons lack the autoreceptors that are a part of the rest of the DA projection systems. Consequently, DA receptor-blocking drugs such as haloperidol produce large increases in synthesis of DA in the nigrostriatal and mesolimbic neurons but only minimally so in the mesocortical system. Rather, neuronal responses in the mesocortical system to neuroleptics involve: (1) more rapid turnover of transmitter and (2) faster neuronal firing rate. These differences between the DA systems may prove critical to understanding the positive/negative symptom response to antipsychotics as well as the differential symptom profile often found in schizophrenia.

D_1 and D_2 receptors are two of the neurotransmitter receptors sensitive to DA. Elevated levels of D_1 and D_2 receptors in several brain regions have been associated with schizophrenia, such as the nucleus accumbens, anterior perforated substance, caudate, putamen, ventral septum, and amygdala (Snyder et al. 1974; Lee and Seeman 1977; Owen et al. 1978; Bird et al 1979; Cross et al. 1981; Mackay et al. 1982; Seeman et al. 1982; Crawley et al.

1986). Although some of these studies have been criticized for medication artifacts, Wong et al. (1986), using positron emission tomography (PET), find that D_2 receptor densities in the caudate nucleus of schizophrenic brains (never exposed to neuroleptics) are elevated compared to controls.

Prefrontal cortex dopamine projection areas are believed to be involved in social withdrawal, emotional indifference, impaired attention, and flat affect often seen with schizophrenia (Teuber 1972). As mentioned above, the role played by the lack of DA autoreceptors in this region is unclear, but interesting to consider. The loss of neurons in the caudate nucleus, as well as the lower midbrain, has been suggested to lead to cortical atrophy (Fuxe et al. 1974; van Kammen et al. 1986). And recent work by Reynolds and Tourtellotte (1984) reports an abnormally high concentration of DA in the left amygdala of schizophrenic brains.

Recently, Adams and colleagues have neurochemically mapped the thalamus of a number of schizophrenic brains and report that the schizophrenic thalamus, in contrast to nonschizophrenic brains, shows high concentrations of DA in the ventral posterior lateral and medial nuclei as well as in the pulvinar (see Oke and Adams, this issue). There is no alteration in norepinephrine levels, which suggests that the high concentration of DA is not a metabolic byproduct of some change in the noradrenergic system. The DA pathways are intricately linked with thalamic, limbic, and prefrontal areas in an integrated communication network. Ultimately, there is every indication that the dopaminergic pathways are altered in the schizophrenic brain in comparison to controls.

The above data relating to schizophrenia remain controversial (Crow 1980; Hornykiewicz 1982; Iversen 1984) because each study often suggests a different brain region or receptor mechanism (Winblåd et al. 1979; Kleinman 1986). Yet, aberrations in DA pathways are a consistent theme. Hughes et al. (1985), as well as others (e.g., Weinberger 1986), have noted the heterogeneity of symptom clusters in schizophrenia. On this basis, they have suggested that schizophrenia is most likely a syndrome made up of many subtypes (e.g., Crow 1980), not a single disorder, with different schizophrenic patients reflecting slightly different aberrations in neuroanatomical pathways. For example, prefrontal aberrations may be responsible for the negative symptoms (Crow 1980) of flattening of affect, social withdrawal, and poverty of speech and thought. Other somatosensory, hippocampal, amygdaloid, and thalamic involvement may present as positive symptoms of hallucination or thought disorder. We would offer that the recent finding of different brain region impairment is to be expected given the complicated interplay of multiple neuronal networks, the complexity of the schizophrenic syndrome, and differences in methodology. Additionally, medication history is bound to be iatrogenic in assayed schizophrenic pathology. Finally, the differential clinical response of schizophrenic patients to pharmacological agents can be used to argue for multiple pathways, different receptor-binding affinities, and involvement in some cases of transmitter pathways other than the DA pathways in the schizophrenic syndrome (Hughes et al. 1985; Berger and Brodie 1986; Cooper et al. 1986).

Hypofrontality

Speculation about the role of the frontal cortex in schizophrenia has a long history (see Levin 1984*a*, 1984*b*; Stuss and Benson 1984; Weinberger 1986), and the suspected presence of frontal aberrations has been used to explain a number of the symptoms associated with schizophrenia. Recent techniques have allowed for mapping neuronal activity of various brain regions. These techniques include cerebral blood flow and metabolism using radiolabeled diffusible tracers such as iodoantipyrin and gases like xenon (^{133}Xe) or glucose utilization via autoradiography following 2-deoxyglucose (2-DG) administration (Hughes et al. 1985; Berger and Brodie 1986). The most sophisticated neuronal mapping technique to date, PET, uses short-lived isotopes like carbon (^{11}C), oxygen (^{15}O), or fluoride (^{18}F) to label 2-DG or other molecules important to brain function (e.g., Farde et al. 1986; Sedvall et al. 1986). Electroencephalographic (EEG) study of brain electrical activity has likewise evolved into sophisticated three-dimensional computer-generated mappings of ongoing brain activity (Abrams and Taylor 1980; Buchsbaum et al. 1982; Duffy 1982; Morihisa et al. 1983; Morstyn et al. 1983; Patterson et al. 1986). This latter technique accesses brain events within milliseconds, enabling investigators to study fast information-processing events in normal and pathological populations. The importance of all these techniques is that they allow for comparisons between normal and schizophrenic populations (as well as other psychiatric disorders).

Ingvar and Franzen's (1974) original cerebral blood flow observations of hypofrontality in older medicated

schizophrenic patients have been replicated by some (Ariel et al. 1983; Mubrin et al. 1982) but not other investigators (Mathew et al. 1982; Gur et al. 1983). PET studies have also had mixed findings (Buchsbaum et al. 1982, 1984; Shepphard et al. 1983; Farkas et al. 1984; Widen et al. 1984; Early et al. 1986; Gur et al. 1987). Some of the discrepancies of the earlier studies may be due to medication artifact or the fact that tasks requiring the activation of prefrontal areas from a "resting state" were not incorporated. Weinberger et al. (1986), in a well-designed study, addressed this latter issue by requiring nonmedicated schizophrenic patients to perform the Wisconsin Card Sort (a task activating dorsolateral prefrontal areas) and a number-matching test as a controlled comparison task (see Weinberger et al. [1986] for details). A resting period was contrasted with an activated period (the two different tasks requiring different regions of activation). This recent study appears to have confirmed hypofrontality in schizophrenic patients. Yet, the relationship of hypofrontality to factors such as chronicity of disease process or chronic administration of neuroleptics has not been determined. Early et al. (1987) failed to find hypofrontality in their cerebral blood flow study of never-medicated schizophrenic patients (using ^{15}O and PET), and noted that hypofrontality has not been demonstrated in schizophrenic patients who had never received antipsychotic medication.

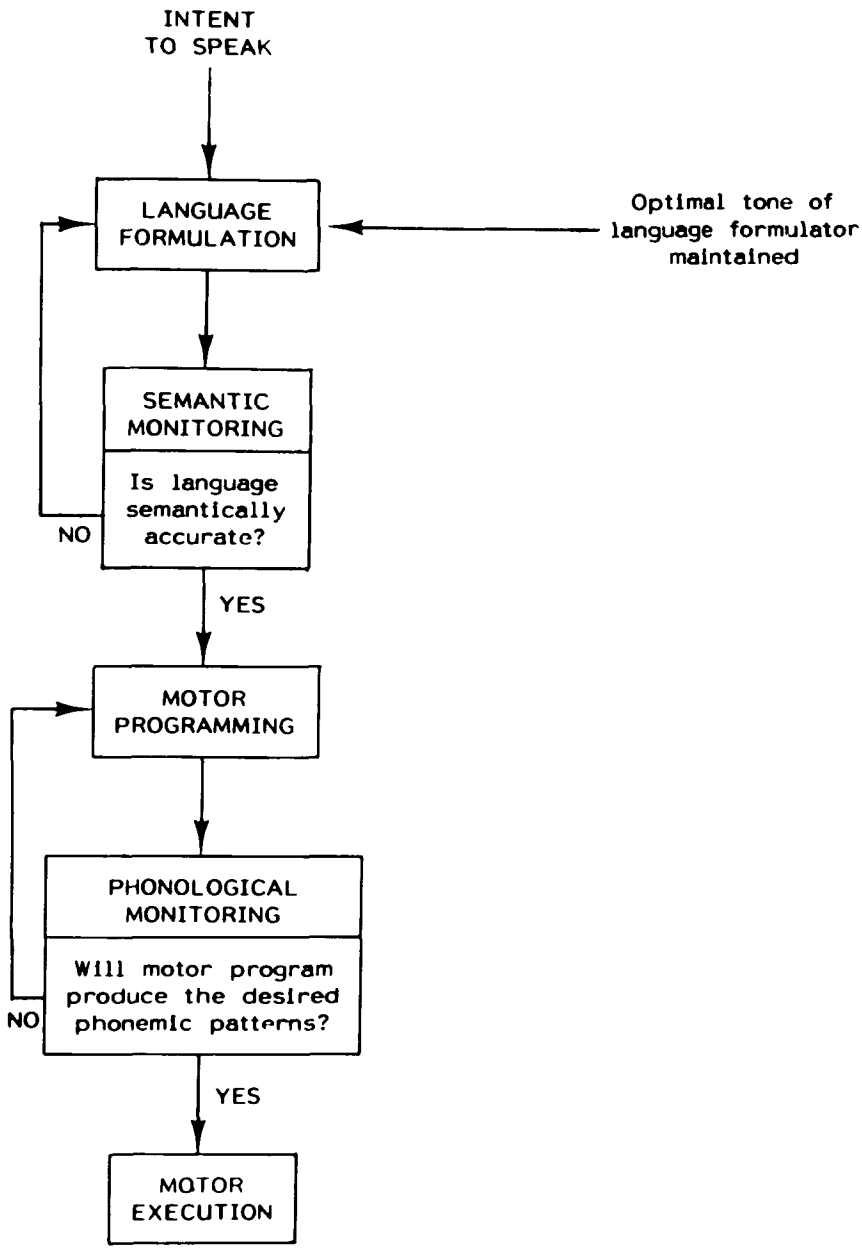
As noted above, the frontal cortex has reciprocal connections with the dorsomedial and ventral anterior nuclei of the thalamus as well as outputs to the thalamic intralaminar nuclei. It is possible, then, that activity in thalamic nuclei could mediate hypofrontality. For example, Crosson (1985; see discussion below) hypothesized the ventral anterior thalamus to relay activation from the midbrain reticular formation to the frontal cortex. According to his theory, inhibitory mechanisms within the globus pallidus regulate the amount of activation conveyed to the frontal cortex via the ventral anterior thalamus. Although they did not find hypofrontality, the increased activity in the left globus pallidus found by Early et al. (1987) would be consistent with increased inhibition of the ventral anterior nucleus and, therefore, decreased left frontal activation in accordance with Crosson's theory. One might also speculate that the increased activity in the globus pallidus could be related to increased dopamine activity in the nucleus accumbens, linking the limbic system and the globus pallidus.

A Thalamic Language Model

This section briefly describes a model of language production that posits a system consisting of cortical and subcortical components, including thalamic nuclei (Crosson 1985; Crosson et al., in press). The model focuses on two stages of production controlled by the anterior (frontal) language cortex, but monitored by the posterior (temporoparietal) language cortex (figure 2*a*). The first stage involves formulation of language, including semantic and syntactic processes. Adequate language formulation depends on maintaining optimal tone of the centers for language formulation in the anterior language cortex. Once language has been formulated, it is monitored for semantic accuracy by centers for language decoding in the posterior language cortex. The second stage is motor programming, which is performed in the anterior motor language centers. Because the sounds produced in spoken language depend on the correct movement of articulatory structures, motor programming must be monitored to ensure that it will produce the desired phonological patterns (i.e., speech sounds). This monitoring is performed by posterior language structures that initially decode speech sounds during auditory-verbal comprehension. The thalamus is involved in three facets of these processes.

Maintaining Cortical Tone. First, on the basis of electrical stimulation data (Schaltenbrand 1965, 1975) and lesion data (Gorelick et al. 1984; Damasio et al. 1985), it can be hypothesized that the ventral anterior thalamus plays a role in maintaining optimal tone of the anterior cortical language formulation centers. The ventral anterior nucleus transmits excitatory impulses from the midbrain reticular formation to the language cortex via its connections with the intralaminar nuclei, which receive direct input from the reticular formation. (See connections illustrated in figure 2*b*.) In other words, the activity of the ventral anterior thalamus is thought to regulate the tone of anterior language formulation centers of the left hemisphere. This role is supported by evidence suggesting that ventral anterior lesions will block cortical recruiting responses elicited through stimulation of the intralaminar nuclei (Carpenter and Sutin 1983), as mentioned above. The amount of excitation conveyed to anterior language centers via the ventral anterior thalamus is governed by the inhibitory influence of the globus pallidus. Lesion data (Svennilson et al. 1960) and stimulation data (Hermann et al. 1966) support this role for the globus pallidus. The globus pallidus

Figure 2a. Flow of the 2 stages of language production (language formulation and motor programming)



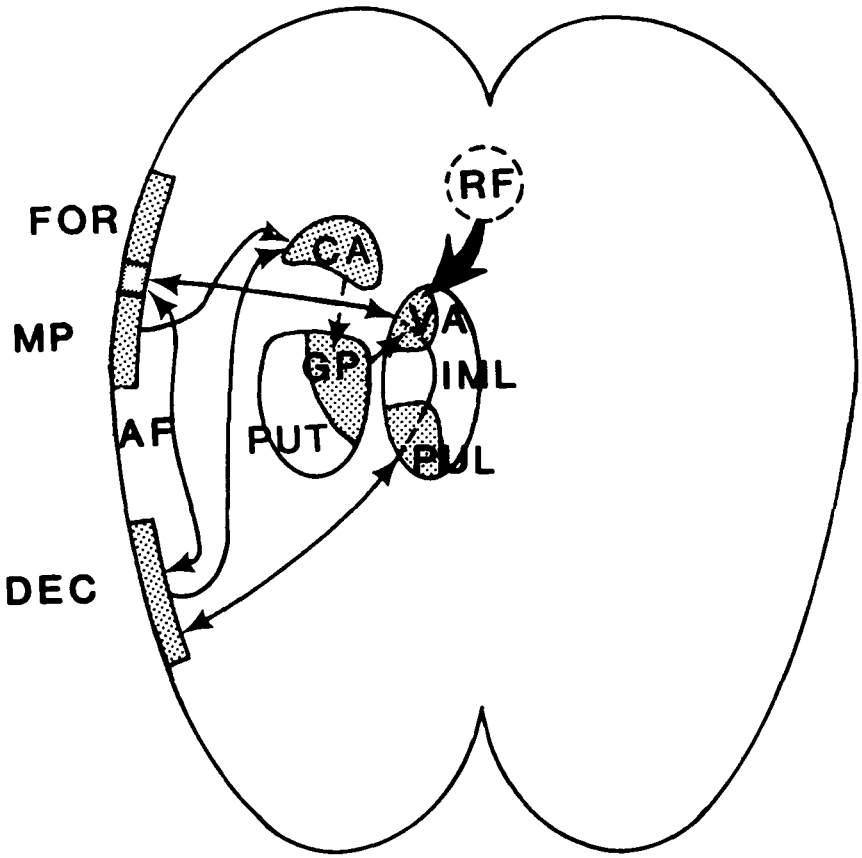
Note that errors in semantic content or motor programs which are revealed during semantic monitoring or phonological monitoring, respectively, lead to a correction process.

is, in turn, under the inhibitory influence of the caudate head, and the anterior language cortex can modify its own activation level through its connections with the caudate head.

Malfunctions in this system for activating the anterior language cortex could lead to either overactivation or underactivation of the language formulator. Overactivation would result in programming of extraneous words or phrases in language. Underactivation could result in either a paucity of spontaneous language (i.e., a lack of initiation) or inefficient (e.g., slow) formulation.

Semantic Monitoring. The second aspect of language in which the thalamus is involved is semantic feedback. Upon reviewing the literature on thalamic aphasia, Crosson (1984) concluded that a syndrome of thalamic aphasia could be described. This syndrome involved speech normally articulated, with normal rhythm, intonation, and a variety of grammatical forms, but speech in which one word is substituted for another, sometimes so frequently that language degenerates into a jargon devoid of meaning. The ability to understand the language of others is better preserved in thalamic aphasia than would normally be seen with this type of language output (i.e., Wernicke's aphasia). The ability to repeat spoken sentences or phrases remains relatively intact in the thalamic aphasia syndrome. This is exactly the pattern one would expect if a monitoring mechanism for the semantic aspects of language (i.e., those conveying meaning) had been affected by thalamic lesion, but more basic mechanisms for the initial phonological and semantic decoding of language were left intact (Crosson 1981). Indeed, the relatively intact repetition could be accomplished by a separate system for

Figure 2*b*. Schematic drawing representing cortical, thalamic, and basal ganglia mechanisms, and the pathways between them



FOR = language formulator (anterior cortex); MP = motor programmer (anterior cortex); DEC = language decoder (temporoparietal cortex); AF = arcuate fasciculus, VA = ventral anterior thalamus; PUL = pulvinar; IML = internal medullary lamina of thalamus; CA = head of caudate nucleus, PUT = putamen; GP = globus pallidus; RF = reticular formation. Note that the connections between the pulvinar and the anterior cortex were difficult to display. Connections between the reticular formation and the ventral anterior thalamus actually are mediated by the intralaminar nuclei. Pathways used in the motor execution of language (motor cortex to putamen, temporal cortex to putamen, putamen to *globus pallidus, globus pallidus to ventral lateral thalamus, and ventral lateral thalamus to motor cortex*) were not represented due to the complexity of the drawing The figure is reprinted, by permission, from Crosson, B., Subcortical functions in language: A working model, *Brain and Language*, 25.257–292, 1985. Copyright © by Academic Press, Inc., New York, 1985.

processing the phonological aspects of language, i.e., those aspects relating to sound but not meaning (McCarthy and Warrington 1984).

It is hypothesized that semantic feedback takes place between the anterior language cortex, where language formulation occurs, and the posterior language cortex, where language decoding occurs. In other words, language formulation is monitored for accuracy by those mechanisms responsible for understanding language. The pulvinar may mediate this semantic monitoring since it has reciprocal connections to the temporoparietal cortex and probably connections to the posterior frontal cortex as well (Carpenter and Sutin 1983). Studies with post-mortem verification of lesion location have implicated the pulvinar in aphasia (Crosson 1984); indeed, a small segment of the pulvinar (anterior superior lateral pulvinar of the dominant hemisphere) may be involved in language functions (Van Buren and Borke 1969; Ojemann 1977; Crosson et al. 1986).

Response Release Mechanisms. Crosson (1985) emphasized that the semantic monitoring and tonic excitatory mechanisms could not be understood without referring to the third aspect of language formulation involving the thalamus, i.e., response release mechanisms. Other investigators have hypothesized that the basal ganglia are responsible for releasing or running motor programs already formulated in the cortex (Marsden 1984; Wing and Miller 1984) or for integrating sensory input with motor output (Stern 1983; Iversen 1984). The basal ganglia may play this role in language, in which case the release of motor programs would be further mediated through the ventral anterior thalamus. Such functions are called "response release mechanisms."

If a segment of formulated language were subjected to semantic monitoring, the segment would have to be stored in some kind of buffer and kept from execution while the semantic monitoring was accomplished. (We shall relate this aspect of language formulation to schizophrenia momentarily.) According to the theory, the temporoparietal language cortex maintains an inhibitory control over the head of the caudate nucleus. The head of the caudate nucleus, as

hypothesized above, normally maintains an inhibitory influence over the globus pallidus, and the globus pallidus, in turn, usually maintains an inhibitory influence over the ventral anterior thalamus. When temporoparietal language decoding mechanisms determine that a language segment is semantically accurate, the temporoparietal language cortex will release mechanisms in the caudate head from inhibition, and this will result in increased inhibition of pallidal mechanisms by caudate mechanisms. Increased inhibition of pallidal mechanisms will, in turn, release the ventral anterior thalamus from inhibition, causing a temporary increase in the excitatory impulses conveyed to the language formulation centers in the anterior language cortex. This increase in excitation acts as a trigger to the language formulation centers to release the monitored language segment for motor programming. Inhibition of the caudate mechanisms by the temporoparietal cortex is reestablished by a signal from the language formulation centers to the caudate nucleus once motor programming has been completed. (It will be recalled that cortical centers which are reciprocally connected project to overlapping zones in the striatum [Yeterian and Van Hoesen 1978].) Stimulation data (Van Buren 1963, 1966) support such a role for the dominant caudate head, and our own recent review of the literature indicates that 79 percent of the lesions in the caudate head that cause language dysfunction produce nonfluent aphasia, a fact also supporting the above-mentioned role for the caudate head.

Because the phonological mechanisms of language (i.e., those having to do with sound) have limited implications for schizophrenia, our comments will be brief. Once semantic accuracy has been ascertained, or a language segment has been corrected for semantic inaccuracies, the language segment is released for motor programming. Since the sounds produced in speech depend directly on the motor programming of the articulatory apparatus, the motor programming is monitored for phonological accuracy. Such monitoring occurs between the motor programming mechanisms for language in the anterior cortex and the phonological decoding mechanisms for language in the posterior cortex via the arcuate fasciculus. Such a role for the arcuate fasciculus is consistent with concepts of conduction aphasia in which difficulty with repetition occurs (e.g., Goodglass and Kaplan 1983), as well as with empirical evidence regarding conduction aphasia (e.g., McCarthy and Warrington 1984). Response release mechanisms related to phonological monitoring are controlled by the premotor cortex, the putamen, the globus pallidus, the ventrolateral thalamus, and the motor cortex.

This proposed system for language may seem quite cumbersome to the reader, and indeed it would be if not for some inherent capabilities of the adult language system. The smooth flow of conversation in the mature language system depends on two such facets. First, as indicated above, language is not formulated in the adult system on a word-by-word basis. Most frequently, formulation takes place at the phrase, or possibly even the short-clause level. Thus, semantic monitoring is also accomplished on units larger than the individual word. The second principle, and one that may bear some importance for schizophrenia, is the simultaneous processing of different segments of a communication that are in the various stages of production. In other words, while one segment of language is being executed, the ensuing segment is being programmed for motor output and is being monitored for phonological accuracy. At the same time, a subsequent segment in the communication chain has been formulated and is being monitored for semantic accuracy. Thus, the formulation of one segment of language takes place while the immediately preceding segment is being monitored for semantic accuracy, and the segments preceding these are in the stages of motor programming, phonological monitoring, and motor execution, respectively. This simultaneous processing would require intricate coordination between anterior and posterior language mechanisms; Morice (1986) has discussed the implications of an inability to coordinate these mechanisms in schizophrenia. Further, one very important property of the language formulation system is that it must be able to maintain a contextual reference to the previous segments of language as well as to the intent of the communication and the environmental constraints. Ingvar (1985) has discussed similar concepts and related them to schizophrenia.

Summary. Since understanding of this language model is critical to the next section of the article, the reader is again referred to figure 2b. Anterior (frontal) cortical mechanisms are responsible both for the formulation of language and the motor programming of language for speech. Before motor programming, temporoparietal mechanisms monitor semantic aspects of language encoded by anterior mechanisms. Before spoken execution, phonological aspects of language are monitored in conjunction with motor programming via

the arcuate fasciculus. Semantic monitoring is performed through reciprocal connections between the anterior cortical and temporoparietal areas passing through the pulvinar of the thalamus. If semantic errors are discovered during the monitoring process, information is carried back to the anterior language zones via the thalamic pathway, and semantic refinement is initiated. When necessary, refinement of the phonological aspects of language is accomplished via the arcuate fasciculus.

Activation of anterior cortical language mechanisms responsible for formulation of meaningful language is performed by the ventral anterior nucleus of the thalamus by regulating the flow of excitation from the reticular formation to the anterior language mechanisms. Inhibitory influences of the globus pallidus over the ventral anterior thalamus determine how much excitation is allowed to pass to the anterior cortical mechanisms. It is necessary to limit the level of anterior cortical excitation on a tonic basis to prevent the entrance of extraneous material into the encoding process, yet allow enough excitation for the encoding process to occur at appropriate times.

Regarding response release mechanisms, excitation conveyed to anterior language mechanisms by the ventral anterior nucleus is also controlled by cortical mechanisms through the caudate nucleus which, in turn, inhibits pallidal inhibitory mechanisms. Normally, this caudate mechanism is under inhibition from temporoparietal mechanisms; however, once encoded language has been verified for semantic content, the temporoparietal mechanisms will release the caudate head from inhibition. This action causes the caudate head to inhibit the mechanism in the globus pallidus which is responsible for limiting the amount of excitation from the ventral anterior thalamus to frontal language mechanisms. The result is a temporary increase in excitation of anterior mechanisms that initiates motor programming of the semantically verified language, leading to spoken expression of the language segment. Once the motor programming process has been completed, impulses from the frontal mechanisms to the caudate head reestablish the inhibitory control over the caudate head by temporoparietal mechanisms until the next language segment has been semantically verified and is ready to be programmed. Frontocaudate connections also influence tonic activation of anterior language mechanisms to prevent overactivation or underactivation of these mechanisms by influences not directly associated with language, e.g., the limbic system.

Implications of the Language Theory for Thought Disorder in Schizophrenia

Two related concepts recently set forth in the literature on thought disorder and schizophrenia have some relevance to the language production theory just discussed. The first, examined by Lanin-Kettering and Harrow (1985) among others, is that schizophrenic patients are unable to maintain the proper internal and external contextual referents across the course of extended verbal communications. The second, described by Chaika and Lambe (1985), is that abnormalities in expressed schizophrenic language can be explained by "random triggering of 'interlocking semantic networks'" (p. 10). Considering these two phenomena together may raise some "chicken or egg" type of questions. Is the random triggering of interlocking semantic networks, or at least the appearance of this phenomenon, a result of an inability to maintain the proper contextual referents during the course of extended communication? Or is the inability to maintain the proper contextual referents across extended communications the result of random triggering of interlocking semantic networks? Both ideas can be considered separately as they relate to the language theory just discussed.

As mentioned above, the ability of language formulation mechanisms to maintain the proper contextual referents is critical to the process of extended communication because the language system is engaged in several processes at the same time. Different segments of language are being simultaneously formulated, monitored for semantic accuracy, programmed for motor execution, monitored for phonological accuracy, and executed by the articulatory apparatus. If something affects the language system in such a way as to make it difficult or impossible to maintain contextual referents, something very much like schizophrenic language might emerge. This concept is consistent with the idea of diminished discourse planning abilities set forth by Hoffman et al. (1986).

What could cause an inability to maintain contextual referents? Morice (1986) has suggested that schizophrenic language might result from "impairment of some executive function coordinating the two main language areas of the brain" (p. 8). Such a lack of "coordination" could cause the language formulating mechanisms to lose their contextual referents because they cannot control all the simultaneous processes necessary to produce spoken language (cf. Ingvar 1985). Another

candidate would be aberrant attentional processes that make it impossible for the schizophrenic speaker to focus on context while all the other language processes are engaged (see Grove and Andreasen 1985).

Finally, Patterson et al. (1986) have discussed the importance of time buffers necessary for sentence formulation. These authors have also suggested that an early information-processing deficit in schizophrenia makes it difficult to store information in these buffers. The dysfunction in the buffers, in turn, can destroy the context within a sentence or extended communication because of an inability to refer back to a previous segment of the sentence or communication. Also, recall the theory presented above. Semantic segments must be held in a buffer before motor programming until semantic monitoring has taken place. An inability to *store* information in the buffer might result in random language segments replacing the correct semantic segment in the buffer. Thus, when semantic verification is completed, the random replacement is released for motor programming (via excitation from the ventral anterior thalamus) instead of the correct semantic segment, which could not be stored.

The second concept we will discuss is the idea of random activation of interlocking semantic networks (Chaika and Lambe 1985). Crosson (1985) made a similar proposal to account for the choreiform movements in Huntington's disease. Choreiform movements resemble voluntary movements or fractions of voluntary movements, but they are activated in the absence of volition. In other words, these aberrations might be the result of "random release of movements" for motor programming and execution. Since Huntington's disease is known to involve degeneration of the basal ganglia, particularly the caudate nucleus (Hayden 1981), it is reasonable to assume that response release mechanisms involving the basal ganglia may be involved. A similar process would make an equally plausible explanation for random triggering of semantic networks in schizophrenic thought disorder.

Although the basal ganglia have not received much attention in the search for etiological mechanisms of schizophrenia, it is worth a little time to consider some of the parallels between Huntington's disease and schizophrenia. First, Hayden (1981) has noted not only that schizophrenic-like psychoses can occur in Huntington's disease, but also that these symptoms may precede the onset of motoric symptoms in some cases; in such instances, patients may even be misdiagnosed as schizophrenic. A second interesting parallel is that some of the same medications used to control psychotic symptoms in schizophrenia (dopamine antagonists) have also been found effective in reducing the motor symptoms in Huntington's disease. This fact raises the issue of whether the motor symptoms in Huntington's disease may have some parallel to symptoms of schizophrenia but in partially distinct neuroanatomic substrates. Finally, it should not escape the reader's notice that Huntington's disease is known to be an autosomal dominant inherited disease. Although schizophrenia has escaped such precise genetic definition, substantial data indicate a genetic component (Elston and Campbell 1971; Farmer et al. 1983; Rice and McGuffin 1986).

It is not our intention to equate schizophrenia and Huntington's disease. Yet, there may be some parallels in neurological substrates between thought disorder in schizophrenia and chorea in Huntington's disease. Schizophrenic thought disorder may be caused by the random release of language segments for motor programming, thereby interfering with the normal maintenance of internal and external contextual referents by the schizophrenic patients. Such random release of language segments would be due to dysfunction in the inhibitory circuits (temporoparietal cortex to caudate nucleus to globus pallidus to ventral anterior thalamus to frontal language formulation mechanisms) described above. Just as patients early in the process of Huntington's disease attempt to compensate for choreiform movements by incorporating them into some seemingly purposeful act, some schizophrenic patients attempt to compensate for random release of language segments by using a very basic set of internal contextual referents which are inappropriately repeated in numerous circumstances, giving the appearance of idiosyncratic and personalized thinking. It might be that the caudate nucleus or the nucleus accumbens is involved in such a mechanism for schizophrenia. In this case, random triggering of semantic segments would be the result of excitation of frontal language formulation mechanisms at inappropriate times during a language formulation sequence, and this mistimed excitation would be mediated through the globus pallidus and the ventral anterior thalamus.

Conclusions

This article has explored the possible involvement of thalamic and other subcortical mechanisms in schizophrenic thought disorder and schizophrenia in general. If one asks

whether the thalamus is involved in schizophrenia, the answer is most likely "yes" when one looks at schizophrenia as a probable disorder of complex brain systems as opposed to a disorder of some specific nucleus or cortical area. This has certainly proved to be the case for the language theory presented above. The cognitive and other functions with which schizophrenia interferes are too complex to be localized to a single brain structure. Therefore, one must think of schizophrenic syndromes in terms of brain systems as opposed to specific locations.

Previous studies discussed above have implicated limbic structures, the basal ganglia, and the prefrontal cortex in schizophrenia. Crosson (1986) has pointed out that one must look at connections between the various structures involved in memory if one hopes to understand memory. This principle was also demonstrated in the language theory just discussed. For schizophrenia, it is important to note that the limbic system has direct connections with the nucleus accumbens, which also receives dopaminergic input from the midbrain tegmentum. The nucleus accumbens, in turn, has outputs to the globus pallidus, which has outputs to the ventral anterior thalamus. Finally, the ventral anterior thalamus has outputs to the dorsolateral prefrontal cortex. Past findings regarding involvement of these structures in schizophrenia may seem contradictory if the structures are viewed in isolation. Yet if the connections between these structures are explored, the various research findings may be seen as complementary.

In this vein, Weinberger (1986) has discussed a brain-systems theory of schizophrenia. He also highlighted how developmental factors operate in schizophrenia, though he did not include thalamic structures in his theory. He relates "negative" symptoms to depletion of prefrontal dopamine from the mesocortical system, while "positive" symptoms are related to relative overactivity in the mesolimbic dopaminergic system.

In addition to these implications for a neural systems approach to schizophrenia, Crosson's (1985) language theory can also be used to generate two specific, and possibly related, hypotheses about schizophrenic thought disorder. The first hypothesis states that the schizophrenic patient is unable to maintain control of all the simultaneous processes necessary to formulate and express ideas in language successfully. This lack of control results in a loss of contextual referents used to produce meaningful, connected language (cf. Ingvar 1985; Morice 1986). One critical factor here may be an inability to store semantic segments of a communication in time buffers (Patterson et al. 1986). The second hypothesis states that dysfunction in the inhibitory mechanisms involved in language results in the random release of language segments. This random release of language segments further interferes with maintenance of the appropriate contextual referents.

It is hoped that studies exploring possible sites of dysfunction in schizophrenia will attempt to integrate new information with existing information involving other sites. The anatomical connections and neurochemical pathways between structures must be explored and integrated with knowledge about the various behaviors influenced by parts of emerging systems. If we fail to make this integration by favoring localization to specific structures, we will "not see the forest for *a tree*" (Crosson 1986).

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