Elevated Thalamic Dopamine: Possible Link to Sensory Dysfunctions in Schizophrenia

by Arvin F. Oke and Ralph N. Adams

Abstract

Sensory-processing dysfunctions, deficit states, and the combinations of seemingly disparate behavioral symptoms of schizophrenia are addressed with regard to a common thread—the possibility of dysfunctional processing in the thalamus. Recent views of the connectional neuroanatomy and electrical activity of thalamus are examined. A hypothesis is presented in which disturbances in the timing and phasic neuronal activity of the thalamus and, especially, its connections with other brain regions may result in many of the behavioral manifestations of schizophrenia. It is suggested that neurotransmitter or other chemical imbalances might produce such thalamic disturbances. Experimental findings of enhanced dopamine content in the thalami of schizophrenic patients are reported. Several varieties of distributional patterns of this elevated dopamine are shown and evaluated.

Beginning in 1982, the editors of this journal invited a group of experienced and respected psychiatrists to write short, essaylike articles on the topic "What Is Schizophrenia?" According to the editors, their expectation was not that this venture would produce a definitive answer, but that it might develop a useful overview, perhaps emphasizing areas of agreement or focusing divergent positions. The contributions served these purposes very well. Taken as a whole, the opinions emphasized a prevailing feeling that schizophrenia most likely develops from some form of genetic vulnerability, interacting with neurobiological, developmental, and environmental influences unique to each person. Honing diagnostic techniques to provide reliable subclassification was deemed essential to more refined understanding of the illness process. But the very heterogeneity of schizophrenia was also suggested to be an essential and unique element commanding continued attention. Most, though not all, of the writings were consistent with the generally accepted view that schizophrenia (or the schizophrenias) has a neurobiological substrate and represents some real form of brain dysfunction. These reports also may have provided an unforeseen benefit to numerous readers, the rank-and-file researchers who could take some comfort in the evidence that they were not alone: apparently no one is quite sure "what is schizophrenia." Although definitions may be scarce, there is no lack of words on anyone's part when it comes to describing the schizophrenic condition; the behavior and functioning of patients are enormously documented.

All schizophrenic patients, at some time during the course of their definable illness, talk and act as if they were receiving information that is markedly different from what others perceive. This is most apparent during the overt psychotic phases of the illness and may occur variously as delusions, hearing voices, or conversational manifestations of thought disorder. There is no evidence that their hearing, sight, or other peripheral sensory systems produce aberrant or incorrect signals. Instead, it appears that they process and interpret in some strange and different way the vast pool of sensory information from the outside world. Those patients who exhibit more of the so-called negative or deficit signs and symp-

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toms can be considered to ignore or fail to process most of the outside information. Their response—or lack of it—is evident in their anhedonia, poverty of speech, social withdrawal, etc.

Nor do schizophrenic patients seem only to distort outside messages. Information about the internal states of the body—the knowledge of body position and its relation to three-dimensional space, relationships of peripheral organs, and body boundaries are treated differently. The more elusive concepts of self versus nonself and body image are, in many cases, poorly used.

Interpersonal relationships involve fundamental information transfer between persons—direct verbal communication and the more subtle, yet extremely significant, nonverbal cues that provide us with the sense of context in a social interaction. A failure to engage in social interactions is one of the most common threads in descriptions of schizophrenic behavior. In an excellent book on treatment and rehabilitation, Dawson et al. (1983) suggest that this deficiency in adult social skills may be linked to the schizophrenic patient's poor performance in both verbal and nonverbal information transfer. Another respected clinician, Werner Mendel, puts this inability of schizophrenic patients to acquire information through interpersonal relationships in a slightly different way:

> In the schizophrenic existence there seems to be no remaining lived history at any one moment. When the experience stops, it is as though none of it stuck to the ribs of the schizophrenic existence. [Mendel 1974, p. 124]

The preceding paragraphs are not suggested to be authoritative in a diagnostic sense. No two schizophrenic patients display exactly the same behavior. Rarely is anyone schizophrenic at all times—periods of quite reasonable activity are present at some times in most patients. The very essence of individual behavior in schizophrenia is that it is totally variable and elusive. Nevertheless, the above descriptions are representative of one common phenomenological viewpoint. They are intended to introduce the theme of this article: that much of the behavior described may be the end result of dysfunctional processing of sensory information. This concept is hardly new. It has been reemphasized recently in descriptions of schizophrenic behavior (Torrey 1985). However, the present article proposes that these dysfunctions may result primarily from abnormal signal processing in the major sensory and neurointegrative organ of the brain, the thalamus.

Information-Processing Studies in Schizophrenia

Starting with pioneering work on attentional deficits, information-processing research has expanded to include a wide range of sophisticated psychophysiological testing techniques. These new avenues of research were significantly augmented by the Second Rochester Conference on Schizophrenia in 1976, which had as an integral part the Scottish Rite Conference on Attention and Information Processing. The important volume *The Nature of Schizophrenia* (Wynne et al. 1978) documents much of this endeavor. Other reviews of these areas are pertinent (e.g., Shagass 1976; Nuechterlein 1977; Spring et al. 1977; Chapman 1979; Spohn and Patterson 1979).

Today there is widespread agreement that schizophrenic patients have a basic disturbance in the handling and manipulation of sensory inputs. This impression is gathered from measurements of reaction times and crossover indices, continuous performance tests, acoustic startle responses, smooth pursuit eye movements, evoked (event-related) potentials (EP), and backward masking techniques. The disturbance frequently may be found also in schizophrenia "spectrum" disorders. Probably more significant, however, is that some forms of attentional disturbance tend to be trait-dependent and not just evidenced during overt psychotic state manifestations. They may also be observed in close relatives and high-risk groups, and may possibly be vulnerability markers (Nuechterlein and Dawson 1984; Kietzman 1985; Zubin 1986). It has been suggested that there is a significant processing disturbance in schizophrenia within about the first 1,000 ms following a stimulus input (Schwartz et al. 1983; Braff 1985; Braff and Saccuzzo 1985; Saccuzzo and Braff 1986).

Evoked potentials from stimulation of auditory (AEP), visual (VEP) and somatosensory (SEP) systems fall, of course, in the above time frame. The EP literature related to psychopathology is already extensive. A continuing series of studies by Freedman's group, using the P_{50} component of the AEP, has identified a sensory gating defect in schizophrenic patients, which has apparent trait-dependent characteristics and is also present in near relatives (Adler et al. 1982; Franks et al. 1983; Freedman et al. 1983; Siegel et al. 1984). The defect was not observed with the visual EP using similar paradigms (Adler et al. 1985). Using backward masking, Patterson et al. (1986) suggest EP deficits in schizophrenic subjects at intervals <100 ms. Reports of abnormalities

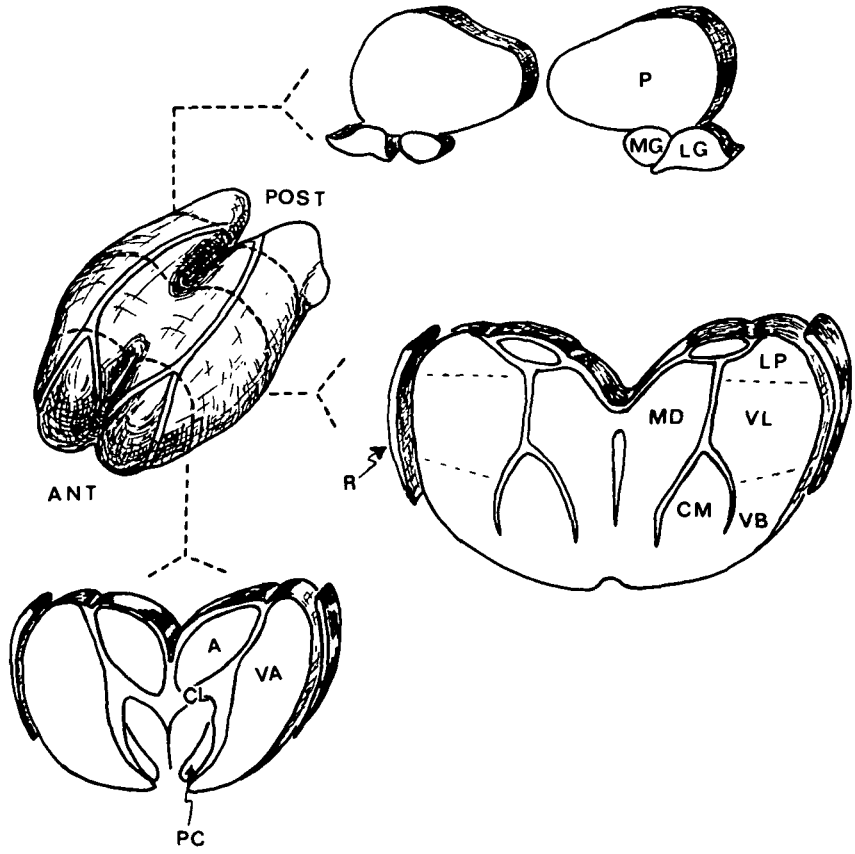
in EP responses of schizophrenics continue to appear regularly (e.g., Morstyn et al. 1983; Steinhauer 1985; Buchsbaum et al. 1986). The results are exciting because they offer the potential of matching sensory deficits to neurophysiological substrates through topographical mapping of the EPs. However, subcortical localization of EPs remains difficult (Vaughan 1982).

Thalamic Functioning

Every bit of sensory input from the outside world (as well as from internal body states) except smell comes to the thalamus before dissemination to more rostral aspects of the central nervous system (CNS). The recent authoritative text by E.G. Jones (1985) contains a thorough integration of all aspects of thalamic functioning, including historical perspectives of the present understandings. The thalamus is shown diagramatically in figure 1, along with coronal slices that illustrate a few of the individual nuclei to be considered later. This diagram is idealized, but the anatomical proportions are sufficiently correct for the present purposes. The nomenclature is one that is common (Angevine and Cotman 1981; Carpenter and Sutin 1983), although there are other designations in use. The literature has only seldom connected the thalamus with psychotic functioning (Hassler 1982), yet there are a number of thalamic nuclei whose disturbances might be closely related to signs and symptoms of schizophrenia. A few of these are briefly examined next.

The Mediodorsal Nucleus. A thin white band of myelinated fibers called the internal medullary lamina separates the ventral and lateral thalamic regions from the midline and medial nuclei. The most prominent of the latter is the mediodorsal (MD) nucleus (see middle coronal slice in figure 1). Especially pertinent is the fact that the cortical afferents of MD define what is known as prefrontal cortex (Nauta 1971; Markowitsch and Pritzel 1979). In human brain, cytoarchitectural arrangements in MD subdivide it into three distinct segments, each projecting to a specific prefrontal cortex region. A thin strip lying adjacent to the internal medullary lamina connects to the frontal eye field (Brodmann area 8). The significance of this relationship is dealt with later. The remaining lateral segment of MD projects to the superior frontal convexity (Brodmann areas 9 and 10), but not to the orbital surface, which receives projections from the medial segment of MD. Brodmann areas 9 and 10 are incorporated into what is called dorsolateral prefrontal cortex (DLPFC), a cortical region presently receiving much attention in schizophrenia research with re-

Figure 1. Schematic representation of human thalamus and selected subdivisions



Three coronal slices through the anterior, middle, and posterior portion are shown Abbreviations. A, anterior nucleus; CL, central lateral nucleus; CM, centrum medianum nucleus; LP, lateral posterior nucleus, LG, lateral geniculate nucleus; MG, medial geniculate nucleus; P, pulvinar; PC, paracentral nucleus; R, reticular nucleus; VA, ventral anterior nucleus; VB, ventrobasal complex; VL, ventrolateral nucleus.

gard to so-called hypofrontality (Andreasen et al. 1986; Weinberger et al. 1986).

A limited number of subcortical efferents project onto MD. Areas recognized include the hypothalamus, ventral gray, and the sites of origin of the catecholamine and serotonin pathways (Sapawi and Divac 1978). Most generous contributions are received from cortical areas. These include reciprocal connections from the prefrontal regions mentioned above as well as the entorhinal cortex which, not so incidentally, is the major cortical input to the hippocampus. The hippocampus itself does not project to MD, but rather has major contact with the anterior thalamic complex through projections within the fornix (Aggleton et al. 1986). Recently, the hippocampus has emerged into prominence with the findings of Scheibel and Kovelman (1981) and later Kovelman and Scheibel (1984) that hippocampi from brains of schizophrenic patients show dramatic disorientation of pyramidal cells. No less interesting is the projection that MD receives from the amygdala and inferior temporal gyrus via the inferior thalamic peduncle. This direct route onto the medial segment of MD recognizes that "...orbitofrontal cortex is not more than a few synapses removed..." (Nauta 1971, p. 177) from temporal lobe neurons by way of this thalamic bridge. Chapman (1966) and Stevens (1973) noted the commonality of cognitive symptoms in temporal lobe epilepsy and schizophrenia. There is a large literature which shows that electrical stimulation of amygdala and periamygdalar tissue provokes schizophrenic-like experiential phenomena. These include complex hallucinations, delusions, intruded thoughts, feelings of depersonalization, visceral sensations, and fearful reactions (for review, see Halgren 1981). These effects would appear to be consequences of an experimentally induced overactive or overinhibited amygdala. In this sense, it is of interest and congruent with the dopamine hypothesis of schizophrenia that Reynolds (1983) discovered an unusually high dopamine content in the left amygdala of brains from schizophrenic patients. In summary, the MD can be regarded as an anatomical crossroad. The frontal lobe, with dysfunctional qualities resembling the negative or deficit symptomology of schizophrenia (Levin 1984), converges onto the same thalamic substrate (MD) as does the amygdala in the temporal lobe, whose stimulation behavior mirrors the so-called positive signs and symptoms.

The Ventrobasal Complex. The ventral posterolateral (VPL) and ventral posteromedial (VPM) regions are often called the ventrobasal complex (VB). VB is the terminus of afferents of the ascending somatic sensory systems. In general, medial lemniscal inputs from the contralateral dorsal column nuclei (cuneate and gracile) terminate in VPL along with spinothalamic fiber tracts. VPM (also known as the arcuate or semilunar nucleus), lying medial to VPL, primarily receives somatic sensory inputs from head, face, and intraoral structures via trigeminal tracts, etc. It also contains a small portion representing taste sensations, and certain visceral afferents are believed to be received by it.

VB contains among its sensory repertoire the neurons that respond to light touch, joint position, and muscle stretch, and is thus related to proprioceptive and kinesthetic integration. Schizophrenic patients have long been known to have deficits in tests of proprioception and estimation of small weight differences (Ebner et al. 1971; Rosenbaum 1971; Ritzler and Rosenbaum 1974).

The monitoring by the thalamus of all the interoceptive and total body surface somatosensory information is presumably a major contribution to one's concept of body boundaries and body image. It has been suggested that an elementary construct of body image may be represented in VB (Scheibel and Scheibel 1971). Distortions of body image and boundary have occupied a significant place in the schizophrenic literature (Schilder 1935; Fisher and Cleveland 1968; Torrey 1985), but interest has waned, probably because of the difficulty of quantitative measurements.

Possible dysfunctions of VB may also be involved in a subset of the so-called soft neurological signs often associated with schizophrenic patients (Rochford et al. 1970; Tucker et al. 1975; Quitkin et al. 1976; Cox and Ludwig 1979; Torrey 1980; Nasrallah et al. 1982). Although the tests may vary from study to study, three somatosensory-related examinations are consistently included—stereognosis, graphesthesia, and double simultaneous tactile stimulation. These tests require the subject to identify a familiar object using only tactile cues, recognize numbers written on the palm of the hand, and perceive the locations of simultaneous touching of two body locations, respectively. Sensory information from each of these tasks channels through VB during processing.

Ventrolateral (VL) Region. It can be suggested that the VL area of thalamus is in part the organizer of a variety of segmental functions in speech production. Such apparently diverse operations as the expiratory phase of breathing (Ojemann 1977),

orofacial movements (Ojemann 1983), language expression, and retrieval of verbal memories (Ojemann 1977) have all been affected by electrical stimulation (below sensory threshold intensity) of common or closely related sites within VL of the left thalamus. Deficits produced during the period of electrical stimulation or from tissue damaged by VL thalamotomies range from total arrest of speech or dysnomia for specific objects, to the perseveration of words/word phrases or the injection of sensible words but without context (Mohr et al. 1975; Luria 1977; Ojemann 1977). The indication is that VL itself is not the origin of these segments, but that its precise timing and sequential ordering are essential for formal speech production (Ojemann 1984). The particular form of speech disruption is dependent upon the neuroanatomical locus within the VL complex and may be as far posterior as the pulvinar.

Corresponding VL areas in the right thalamus have been studied less extensively. Impairments associated with electrical stimulation or thalamotomy have few speech consequences, but are more related to performances requiring visuospatial capabilities—tasks such as face matching and inkblot recognition (Vilkki and Laitinen 1976; Vilkki 1978). Despite the difference in function, it is supposed that the underlying principle of thalamic processing is being used. That principle is the precise timing and integration of diverse response segments.

Thalamic Involvement With Smooth Pursuit Eye Movements. Deviant eye pursuit movements, originally noted by Diefendorf and Dodge (1908) and later characterized by Holzman and coworkers (for review, see Holzman and Levy 1977), have now been substantiated by numerous investigators (Shagass et al. 1974; Cegalis and Sweeney 1979; Pivik 1979; Iacono et al. 1981; Mialet and Pichot 1981) and with a variety of techniques (Crouch and Fox 1934; Lindsey et al. 1978). Qualitative attributes of oculomotor pursuit movements, quantitatively different from normal, have been separated into various types (Holzman and Levy 1977; Iacono and Koenig 1983). Despite this subtlety of categorization, the underlying feature is an impairment in the compensatory eye adjustments that center object placement within the fovea.

In schizophrenic patients and many of their first degree relatives (Holzman et al. 1974; Hurt 1974), these rapid eye movements (called saccades) show increased intrusions on the slower smooth eye movements when following a target in motion. Intrusive saccades disappear when the eye movements are driven by vestibular servomechanisms (Levy et al. 1978; Latham et al. 1981). This normalcy of eye movement in schizophrenic patients, when engaged by vestibular signals (Lipton et al. 1980; Levin et al. 1982), implies minimal, if any, contributions from the suggested locus of generated saccades—the paramedial zone of the pontine reticular formation (Raphan and Cohen 1978). Higher regions in the CNS apparently influence this pontine area and the saccadic eye movements it generates. Support of this notion comes from the induced saccadic eye movements that result from electrical stimulation of such CNS regions as frontal eye field cortex (Robin and Fuchs 1969), superior colliculus (Robinson 1972), and vermis of the cerebellum (Ron and Robinson 1973).

The thalamus likewise contributes toward initiating and controlling eye saccades. Varying regions within the thalamus have been shown to become activated just before saccadic movements. These areas include the central lateral nucleus (Schlag and Schlag-Rey 1981; Schlag-Rey and Schlag 1981), the posterior portion of the MD (Albano and Wurtz 1981), and the pulvinar region in man (Straschill and Takahashi 1981; Ogren et al. 1984). It is not now known whether these different areas belong to the same system and represent duplication of function or whether each is a specific component of eye movement working in parallel for the final saccadic expression.

Modern Views of the Thalamus and Its Functioning

For years, thalamic functioning has been considered to consist primarily of faithfully relaying sensory information to the neocortex. The evidence for this view was, and still is, very clear, e.g., the point-to-point representation of discrete sensory stimulation at the periphery to the corresponding thalamic relay nucleus and on to its counterpart in cortex. We were always reminded that the thalamus actually was more than this simple relay and that it had integrative properties, too. But this latter function usually was considered signal-shaping before sending the informaton on to cortex where the "real" processing presumably took place. Given this view, it is perhaps not surprising that neurobiological theories of schizophrenia have never seriously involved the thalamus as a potential site of dysfunction. During recent years research has been preoccupied (with good reason) with the dopamine hypothesis. This directed most investigations toward well-established dopamine-rich areas of the

brain, and the thalamus is not one of these.

The present picture of precisely organized sensory information transfer remains relatively unchanged. However, the earlier emphasis on classifying which thalamic nucleus is principal or associational, etc., is no longer relevant. Every (dorsal) thalamic nucleus receives subcortical inputs and, furthermore, sends and receives information to and from neocortex. The cortical projections of some nuclei go to very localized cortical regions (specific projections); others send to several cortical areas, and some have both specific and diffuse projections. Thalamus also clearly connects with major subcortical regions.

There is apparently no direct connection between the two halves of the thalamus, nor any evidence for communication pathways between the nuclei of the same side. One morphological feature is clear—given regions of thalamic nuclei send axons to the columns of neocortex and receive corticothalamic returns from a quite restricted set of the same vertical columns. This almost reciprocal innervation is unusual; few other brain regions seem to have such architecturally precise and extensive reciprocal arrangements. Some thalamic regions have other reciprocal cortical interactions impinging on the same area and, of course, all the dynamic information passed is continuously being updated by cortex and sensory afferents.

While the thalamic nuclei do not talk to each other, the reticular nucleus (actually part of the ventral thalamus) is aware of all the reciprocal transactions passing between thalamus and neocortex. The reticular nucleus is pictured in the coronal slices in figure 1. In man it is a thin layer, sometimes irregular in thickness and shape, which surrounds most of the sides and front of the thalamus. In the most anterior portions, it curves up and covers the superior surface. It has no cortical connections of its own, but all thalamocortical and corticothalamic fibers pass through it. It is somewhat like a patchwork quilt with individual sections related to the particular thalamic nucleus whose fibers traverse its region. Fibers in both directions have collateral terminals in the reticular nucleus, and its own cell bodies send axons into the thalamic nucleus with which it is associated.

Two or more thalamic nuclei may (independently) subserve the same sensory modality, i.e., parallel processing. Thus, visual processing is well known to be handled by lateral geniculate, but additional channels related to vision proceed through the lateral posterior-pulvinar complex to cortex. This same thalamic region also appears to have additive involvement, including speech processing, as discussed earlier.

Electrical Activity of the Thalamus. The electrical activity of the thalamus has fascinated electrophysiologists for many years. The elegant studies of modality and place-specific electrical responses (e.g., Poggio and Mountcastle 1963; Mountcastle 1980*a*) are not of so much concern here. Of more interest is the extraordinary ability of the thalamus also to serve as a neuronal oscillator—to have intrinsic properties that generate a wide range of electrical activity representing timing and gating operations (Purpura 1970; Rougeul-Buser et al. 1978; Angel 1983; Gottschaldt et al. 1983; Steriade and Deschenes 1984). These properties have been known for a long time and are implicated in thalamic generation of rhythmic activity of the cortex. The differences between the relay and oscillatory behavior of thalamic neurons *in vivo* have been explained, especially by Steriade and coworkers (Deschenes et al. 1984; Steriade 1984). Llinas and Jahnsen recently used guinea pig brain slices to show that thalamic neurons have voltage-sensitive ionic conductances capable of generating two distinct functional states—repetitive and burst firing modes. They are thus capable of producing oscillatory behavior. The authors also concluded that neurons from various thalamic regions had similar properties (Llinás and Jahnsen 1982; Jahnsen and Llinás 1984*a*, 1984*b*).

The reciprocal interchange between thalamus and cortex cannot be emphasized too strongly. Thalamic relay neurons pass on sensory input as a powerful excitatory impulse to cells in the cortical columns. Corticothalamic fibers in the very same vicinity project back to the corresponding thalamic area. The termination of the corticothalamic fibers seems to be on dendrites of the relay neurons, but some distance removed from the point of the afferent sensory inputs. Whatever the details of fine organization, the important view is the almost point-to-point reciprocity and the electrical activity passed between the sites. These connections are one part of the major reentry and distributive systems for information flow in the brain. A reentry system is one in which internally generated signals are reentered (usually at lower brain levels) to interact continuously with incoming external signals and provide ongoing spatiotemporal correlations (see Edelman 1978, pp. 74–83; Edelman and Finkel 1984, pp. 656–657). Phasic reentry systems represent one of the fundamental operations

in new theories of higher brain function (Edelman 1978; Edelman and Finkel 1984; see also Mountcastle 1978). To quote Mountcastle (1978):

> Finally, distributed systems are by definition and observation both reentrant systems and linkages to inflow and outflow channels of the nervous system. This suggests that the large numbers of processing modules in the neocortex are accessible to both internally generated activity and externally induced neural activity. Phasic cycling of internally generated activity, accessing first primary sensory but then successively more general and abstract processing units of the homotypical cortex, should allow a continual updating of the perceptual image of self and self-in-the-world as well as a matching function between that perceptual image and impinging external events. This internal readout of internally stored information, and its match with the neural replication of the external continuum, is thought to provide an objective mechanism for conscious awareness. [p. 41]

Possible Relations Between Transfer/Oscillatory Modes of the Thalamus and Phasic Reentry. Steriade (1984) and Steriade and Deschenes (1984) have characterized the state-dependent styles of thalamic functioning as the transfer mode, corresponding to the high-fidelity passage of sensory information to cortex, and the oscillatory mode, which generates the slow rhythmic behavior produced during drowsiness, slow wave sleep, and various anesthetized states. The shifting between these modes is intimately tied to vigilance, alertness, and attention (Mountcastle 1980*b*).

There is considerable evidence that the shift between modes may not be completely abrupt, i.e., it is not necessary to be behaviorally drowsy to afford the first evidences of oscillatory behavior, nor in the complete state of vigilance to get transfer mode response. Both response modes are inherently "available" in the thalamic neurons, as reported by Jahnsen and Llinás (1984*a*, 1984*b*). There is also evidence to suggest that vestiges of both modes may always be present *in vivo*. Transitions between them may be a sort of continuum, albeit with distinct jumps at either end. Steriade and Deschenes have shown that enhancement of evoked discharges in thalamic neurons can precede, by a few seconds, the overt signs of electroencephalographic (EEG) desynchronization (i.e., cortical alert state). Similarly, monosynaptically evoked waves in thalamus diminish in intensity before behavioral indications of sleep. Antidromic responsiveness of thalamocortical cells also shows that they can respond seconds before corresponding cortical state changes (Steriade 1984; Steriade and Deschenes 1984).

We propose that even minor alterations or interruptions of the timing and phasic activity of the thalamus and, especially, its corticothalamic reentry system might be responsible for the sensory-processing dysfunctions seen in schizophrenia. Such a disturbance need only proceed, during normal alertness, partially along some continuum between highly efficient sensory processing in the transfer mode toward the less capable, somewhat "disengaged" oscillatory mode. The disturbance could be variable, not always present, depending on the nature of the timing disturbance. The thalamic reticular nucleus is at all times informed of reentry processing in the entire thalamus. The disturbance itself might be associated with it, but it might reside anywhere in thalamic circuitry where mistimed or dysphasic signaling were generated. Purpura (1970, see p. 468) much earlier suggested the deleterious effects of abnormal perturbations in thalamic timing operations.

If such a disturbance can be shown to exist, its origins might well reside in genetic factors and, especially, the developmental neurobiology of thalamus and cortex. Both the thalamus and cortex have high proportions of local circuit neurons. It is local circuit neurons, appearing late in gestation and maturing for long periods postnatally in humans, which may be particularly vulnerable to early developmental insults or influences (see Rakic 1975). In general, a thalamic/connectional disturbance of the sort proposed has inherent in it both a basic genetically vulnerable neurobiological dysfunction and the environmental and social influences that might augment or exacerbate its emergence as behavioral consequences—a theme consistent with contemporary thinking in the possible etiology of schizophrenia(s).

We suggest that one possible source of this proposed thalamic/connectional disturbance in schizophrenia could be an unbalanced neurochemical milieu in the thalamus, affecting the timing and phasic properties of the neuronal circuitry. The brain cell microenvironment and how its chemical composition affects neuronal activity is a major issue in modern neurobiology (Nicholson 1980; Schmitt 1984; Cserr 1986). Some preliminary experimental evidence for a chemical imbalance—namely, excess dopamine in the thalamus of schizophrenic brains—is given at the end of this article.

Chemical Neuroanatomy of the Thalamus

Thus far, practically no mention has been made of chemical neurotransmitters involved in thalamic circuitry. In fact, there is a paucity of information. Qualitatively, the thalamus contains considerable amounts of acetylcholine (ACh) and glutamate (Glu), ordinarily considered to be excitatory transmitters, and γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter. Synapses of the sensory afferent and corticothalamic return fibers are believed to be excitatory. ACh has been suggested as the transmitter for the former and Glu for the latter. However, there is little hard proof for these assignments. GABA is thought to be used at inhibitory synapses of the reticular nucleus and other local circuit neurons in thalamus.

A major norepinephrine (NE) pathway ascends from the pontine locus ceruleus to innervate the thalamus. Thorough descriptions of the locus ceruleus-norepinephrine (LC-NE) system and its functions are available (Lindvall and Björklund 1978; Moore and Bloom 1979; Foote et al. 1983; Jacobs 1986). The serotonin or 5-hydroxytryptamine (5HT) projections ascending from the midbrain raphe nuclei also supply most areas of thalamus (for reviews of anatomical and functional characteristics, see Azmitia 1978; Jacobs et al. 1984). Interestingly, the dopamine (DA) systems, while reaching many brain regions, innervate thalamus very sparsely (Lindvall et al. 1974; Lindvall and Björklund 1978; Moore and Bloom 1978). Pertinent to all discussions of biogenic amines in thalamus is their distribution in neocortex because of their possible modulation of the corticothalamic reentry system (Descaries et al. 1984) and their general biochemistry and pharmacology in the brain (Cooper et al. 1982). Few workers suggest that catecholamines or 5HT are functioning in the direct neurotransmitter sense in the thalamus; most feel that they belong to the less understood class of "modulators." A variety of peptides are reported in thalamus, but are not reviewed here. Most of the neurotransmitter postulations are fairly well studied in mammalian brain, including some primates, but far less is known for humans (Phillis 1971; Fonnum et al. 1981; Jones 1983).

Quantitative Mapping of Catecholamines in Human Brains

Our laboratory is engaged in quantitative mapping of catecholamines in the thalami of small animal and human brains. The results of some of these studies are summarized below.

Whole human brains were obtained at routine autopsy and were frozen at −70°C as soon as possible after removal. The brain was sliced into 3 mm thick coronal sections on a mechanical slicer. A 3 × 3 mm grid was marked on the surface of each slice over the thalamic structure and each cube of tissue dissected out. Color photography documented all neuroanatomical details. The individual samples were analyzed for catecholamines, serotonin, and their metabolites by high performance liquid chromatography with electrochemical detection. This technique was developed in our laboratory (Kissinger et al. 1973; Keller et al. 1976). In one form or another, it is now used in most laboratories for catecholamine brain assays.

By assembling the results of the individual analyses for each coronal slice, an effective three-dimensional map of the transmitters, metabolites, their ratios, etc., can be constructed for a selected brain region. We believe this kind of detailed mapping is very important because it can discern significant gradients and patterns of concentrations. Chemical assays which homogenize some chosen brain region (e.g., "lateral portion of thalamus") give values averaged over too large a space. In the case of the catecholamines in thalamus, while absolute values may vary among normal (control) brains, the overall distribution pattern of concentrations does not—it represents a "chemical signature" of the brain region that is reproducible. Comparisons of such maps between brain tissue from normal versus psychopathological sources may reveal significant differences. Hornykiewicz (1981) has cogently reviewed brain sampling problems.

Earlier studies, using in some cases circular punches rather than total grid dissection, established important catecholamine distribution profiles in rat thalamus (Oke et al. 1980, 1983) and illustrated chemical laterality of NE distribution in human thalamus (Oke et al. 1978). Kanazawa's (1983) laboratory also does quantitative grid mapping of human brains. Indeed, a recent publication from this group illustrates the Glu, GABA, and aspartate maps in human thalamus (Muramoto et al. 1984).

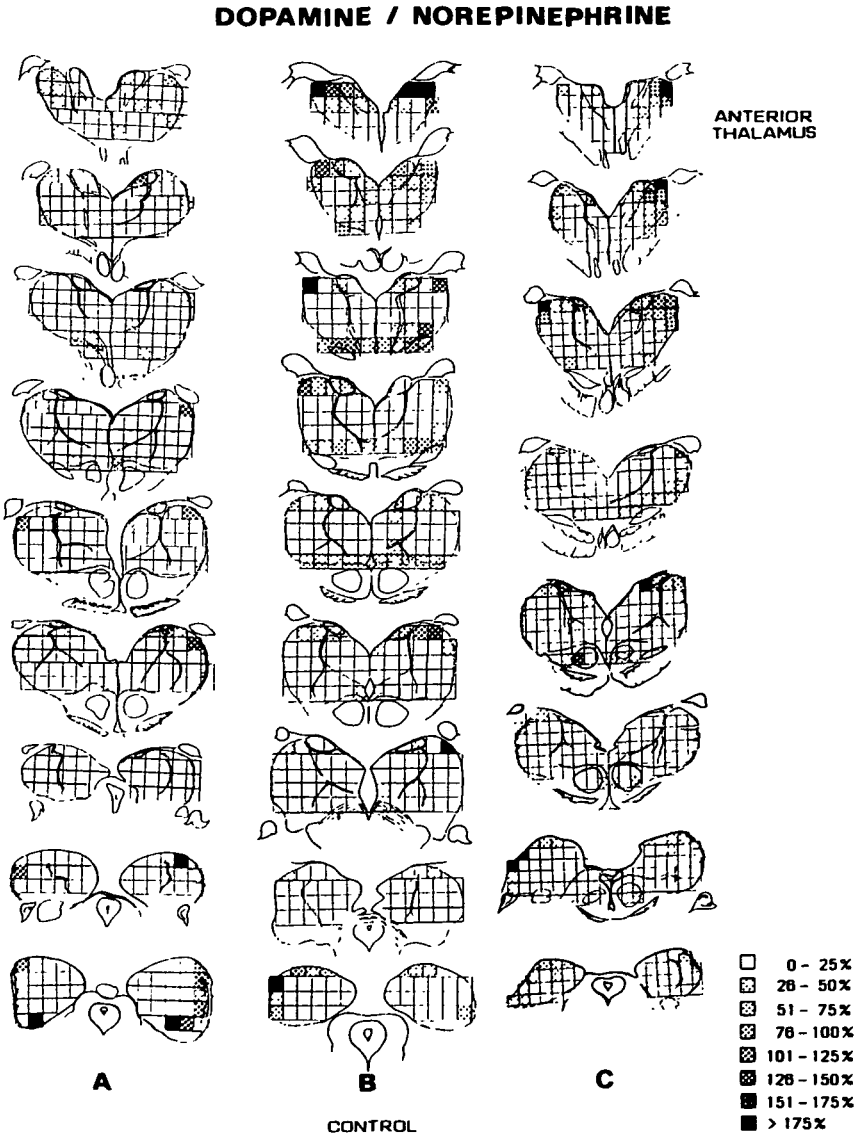
The analysis of the chemical composition of post-mortem brain tissue has its set of difficulties as does any other experimental approach. Most of these variables and their effects are documented (Riederer and Usdin 1981; Perry and Perry 1983; Riederer and Reynolds 1985), and post-mortem studies are now widely

used. With the detailed mapping procedure and a large enough data base of control brains, one can be reasonably sure of the validity of the results. Instead of using absolute values (i.e., ng/g tissue weight) in the case of NE and DA, one expresses the data as the ratio, e.g., DA/NE × 100. Examples of such comparisons for thalami from control versus schizophrenic brains are shown next.

DA/NE Ratios in Normal vs. Schizophrenic Thalami. In figure 2 the detailed maps for the thalami of three control brains are drawn with etched overlays from tissue photographs. The shading density for each grid, indicated at the lower right, is in terms of DA/NE ×100. It is immediately evident that most thalamic areas have very little DA compared to NE, i.e., DA is <25 percent of the corresponding NE concentration. These three patterns are representative of 14 control thalami examined to date. (Of all the individual samples in these 14 control thalami, only 2 percent show DA≥NE.) The general picture of figure 2 can be considered a reliable representation (i.e., a DA/NE "signature") of control human brains—the thalami simply have very little endogenous DA content. The term "control" in this instance indicates brains from persons with no history of major psychoses.

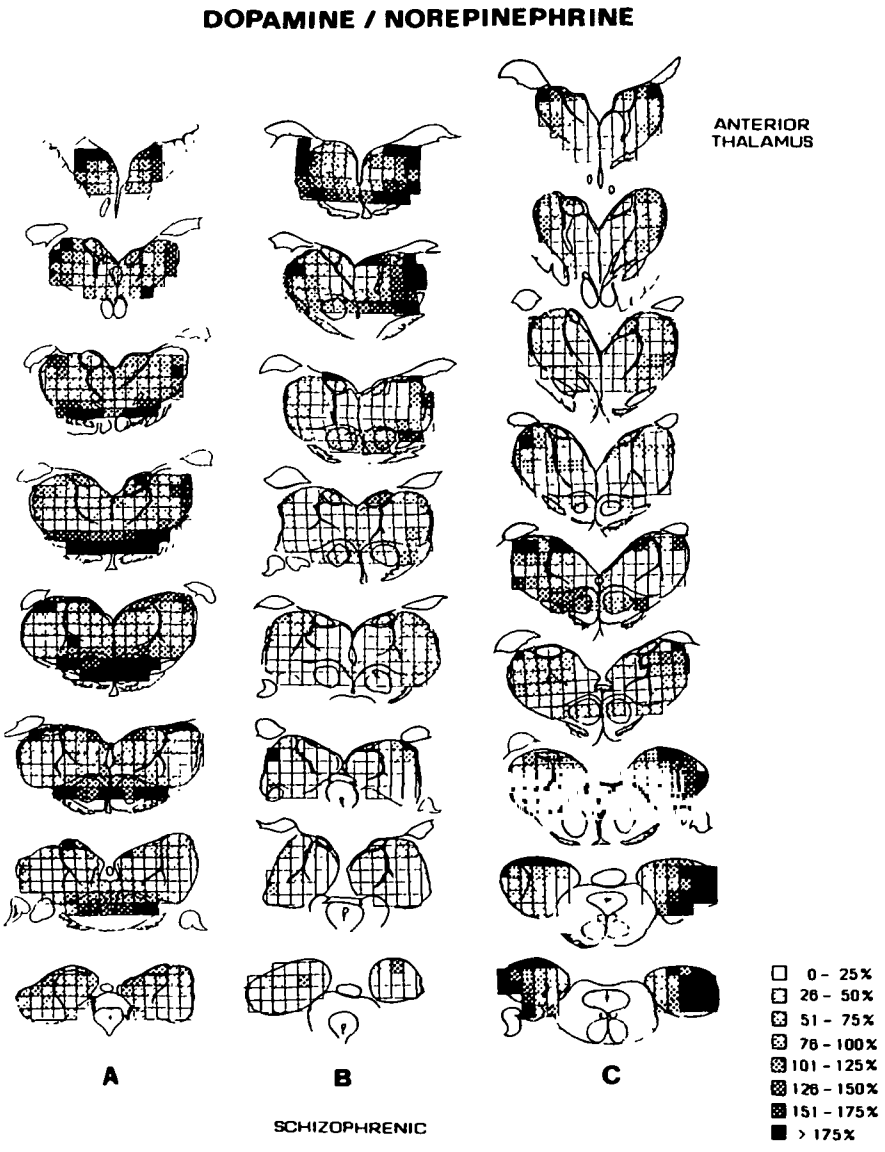
Figure 3 illustrates similar maps for the thalami of three selected brains from schizophrenic patients. First, it is evident that there is an overall enhancement in the DA/NE ratios in most regions. More significant are the patterns of high DA/NE ratios (e.g., DA/NE in the ≥125–175 percent range). These "hot spots" of elevated DA/NE are distinctly different in each schizophrenic thalamus. In figure 3A, the high ratio DA/NE zones incorporate the ventral surface of the dorsal thalamus and spread into aspects of the ventral thalamus (zona incerta and subthalamic nucleus). Much of the dorsal thalamus, including the somatosensory VB region, has relatively high DA/NE ratios.

Figure 2. Graphical representation with anatomical delineations drawn from photographed coronal slices of human thalamus in 3 selected normal brains



Grid markings overlay each slice. Density shading indicates the ratio % of dopamine/norepinephrine (DA/NE × 100).

Figure 3. Graphic representation with anatomical delineations drawn from photographed coronal slices of thalamus from 3 selected schizophrenic patients



Grid markings overlay each slice. Density shading indicates the ratio % of dopamine/norepinephrine (DA/NE × 100)

In a second brain (figure 3B), the high ratio field encapsulates the anterior aspects. A DA-rich shell surrounds the ventral anterior and ventral lateral nuclear groups and partially overlays the thin reticular nucleus. Notice that more caudally, throughout the ventral posterior and pulvinar regions, the DA/NE ratio is seemingly indistinguishable from controls. A third brain (figure 3C) illustrates a high DA/NE field in the posterior thalamic complex, mostly in the laterial pulvinar. More anteriorly, the DA/NE ratio decreases in intensity through the region of the posterior intralaminar nuclei (see CM, figure 1), but remains higher in the lateral mass of the more anterior aspects of the thalamus.

The DA/NE maps for thalami from seven schizophrenic brains have now been examined. In six of the seven cases, the maps show high DA/NE ratios comparable to those of figure 3, with varying pattern distributions. The thalamic map for one of the schizophrenic brains cannot be distinguished from that of controls. It should be emphasized that any elevated DA/NE ratios are not caused by low NE levels in the schizophrenic thalami. The mean endogenous NE concentrations are 140 ± 9 ng/g and 129 ± 6 ng/g (SEM) for control and schizophrenic thalami, respectively; these values are not significantly different.

These preliminary results are quite striking; the patterns of DA/NE ratios in the thalami of schizophrenic brains appear to be markedly different and increased over those of controls (Oke et al. 1987). Most of these brains came from patients with lengthy hospital records of schizophrenia—reevaluation of the hospital charts to verify the diagnoses by modern criteria is in progress. These patients had received long-term neuroleptic medication, which could influence the results. However, two recent studies concluded that neuroleptic medication has no obvious effect on DA levels in nucleus accumbens and caudate (Crow et al. 1980; Mackay et al. 1982). If neuroleptics are ineffective in such DA-rich areas, it seems un-

likely that they would alter endogenous levels in the thalamus, where DA ordinarily is so low in concentration. Preliminary treatment of rats with chronic doses of haloperidol has failed to produce any change in the DA/NE ratio in rat thalami (unpublished results). Hence, it appears that the elevated DA/NE ratios are not induced by neuroleptic treatment. Nor do they appear to be due to variables such as age or time from death to autopsy, etc.

The above findings are very preliminary; so far they are only chemical analysis data representing endogenous tissue content. For example, it is not known if the elevated DA exists in nerve terminals and, if so, whether corresponding receptor sites are present. One point is clear—the NE content of the schizophrenic thalami is not different from that of controls. Hence, the "extra" DA is not due to a faulty metabolic pathway of DA to NE. (Such an error in the normal dopamine-β-hydroxylase conversion might lead to a buildup of DA and a lowering of NE.) We suspect instead that the effect comes from excess innervation of DA terminals in the schizophrenic thalami, although there is no anatomical evidence to support this. Such innervation might come via aberrant projections of a dopaminergic cell group such as that designated A-11. Such an A-11 DA system has, as far as is known, not yet been characterized in humans, but has been established as the source of minor innervation of DA in the rat thalamus (Lindvall and Björklund 1978).

In our studies we have not yet ascertained whether other areas in the brains of schizophrenics show elevated DA. We are beginning detailed catecholamine mapping of the thalamus together with prefrontal and somatosensory cortex as well as amygdala, i.e., regions having intimate connections with thalamus and being of primary significance to the arguments presented here.

Actually, many of the above questions are premature. What is needed is a much larger data base of quantitative chemical brain mapping from patients with schizophrenia, bipolar illness, neurological disorders, etc., together with carefully documented modern diagnoses. Such studies are continuing, and we hope that independent verifications of the present results will be forthcoming soon.

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Announcement

The **6th World Congress of the World Association for Dynamic Psychiatry WADP Bern** will be held in **Munich, Germany, March 4–8, 1988.** The theme of the Congress will be "The Science of Treatment and Research Conceptions in Dynamic Psychiatry." The postclinical day will take place on March 9 at the Dynamic-Psychiatric Hospital Menterschwaige in Munich.

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