Studies Toward the Subcortical Pathogenesis of Schizophrenia

by Terry Patterson

Abstract

In addition to introducing the six articles joined by our thematic outlook, this article addresses the importance of subcortical structures as they may be related to information processing and the life experience of schizophrenic patients. This is a heuristic exercise aimed at bridging the conceptual gaps between clinical and research approaches to schizophrenia. A brief overview is then provided of current conceptualizations of a number of subcortical structures, each of which may play a part in the subcortical pathogenesis of schizophrenia in specific patients. The central concepts are failures in the "automaticity" with which prior experience may be recreated in parallel with current stimulus input in schizophrenia (with concomitant failures in future orientation or contextually generated expectancy), and the view of subcortical structures as constituting a "system" in which no single type of defect may be common to all schizophrenic patients.

Because the material in this issue may be thought to be "some distance" from the clinical picture of schizophrenia, we depart from the usual "theme issue" format and use the editorial introduction for two purposes. The first part of the editorial attempts, in a very simplistic way, to show how subcortical structures may control brain processes and information processing, and how they might contribute to the pathogenesis of psychopathology. The second part of the editorial is a short, and highly selective, literature review focusing on the conceptualizations of experts in the various areas of subcortical exploration. This second aspect, we hope, will give the reader a more general perspective against which to appreciate the individual articles in the issue, and also serve as a starting point for further study.

In this issue the neurohistopathology of the hippocampus, a phylogenetically ancient brain structure, is presented by Conrad and Scheibel. Other authors have published similar data (e.g., Bogerts et al. 1985*a*, 1985*b*; Falkai and Bogerts 1986; Jakob and Beckmann 1986) so that the time is ripe to explore exactly how such pathologies might affect the multifaceted phenomena of schizophrenia. It should be emphasized that the hippocampus is perhaps *the* most heavily researched brain structure and, consequently, ideas about its function(s) will likely undergo considerable change. What is now fairly certain, however, is that the hippocampus is deeply involved in higher cognitive functions (see Grossberg 1984; Grossberg and Stone 1986). This is further evidenced by its involvement in the brain evoked potentials at the 200–300 ms time epoch (Okada et al. 1983).

The thalamus is a similarly phylogenetically ancient brain structure that has received remarkably little recent examination in schizophrenia research. This was not always so, and provocative findings by the Vogts nearly half a century ago (see Schlegel and Kretzschmar 1987*a*, 1987*b*) suggested neuroanatomical pathology in this complex "neurointegrating" area of schizophrenic brain. The torch of thalamic involvement in schizophrenia (in this issue) is carried by Oke and Adams, who examine the neurohistochemistry of dopamine/noradrenalin ratios of the thalamus. In their review of current

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concepts of thalamic functioning, the most spectacularly apparent picture is of massive reciprocal connectivity of thalamic nuclei with almost every brain structure ever believed to be of etiological or pathogenic significance in schizophrenia.

Another phenomenon, until recently somewhat neglected, is the speech of schizophrenic patients. In point of fact, this speech behavior is at the heart of the diagnosis of schizophrenia and crucial to the clinical assessment of "thought disorder." Recent articles in the *Schizophrenia Bulletin* and the very scholarly work of Schwartz (1984) have all helped to target this crucial behavior. For these reasons, the article by Crosson and Hughes, which specifically details the functioning of the thalamus within a complicated model of prespoken language formulation, is especially timely.

Our remaining three articles concentrate on relatively simple and essential aspects of nervous system functioning in the "whole" organism. The orienting response has been the subject of long inquiry by Bernstein, which he conceptualizes within a Sokolovian model of nervous system functioning. This Sokolovian perspective is outlined by Bernstein, and its links to modern concepts of information processing are also provided.

One of the most robust findings in schizophrenia research is of anomalies in the skin conductance orienting response based on the pioneering work of Venables, Bernstein, Zahn, and many others. It has been Bernstein's special contribution to the area to stress concepts of "significance" of stimulation.

The involvement of the limbic brain in control of the orienting response has a substantial history. For example, Bagshaw and colleagues (see Bernstein, this issue, references), in a series of studies beginning two decades ago, showed how lesions of the hippocampus and amygdala in the limbic brains of primates, could substantially alter both the skin conductance orienting response and its habituation. In an important theoretical article, Pribram and McGuinness (1975) put forward a model for control of the orienting response in which the amygdala was thought to be "decoupled" from direct interaction with the frontal lobes and the hippocampus "linked in" to the amygdala to forebrain circuit, in order to produce orienting and cognitively "effortful" behavior.

One of the special features of every higher level nervous system is that it can organize information to anticipate and protect its nervous system from destructive overload. That defects in this ability can be seen in schizophrenic patients is indicated by abnormalities in the control and attenuation of the startle reflex. Geyer and Braff review their own contributions to the area, and provide a current conceptualization at the neuroanatomical and neurochemical level of how the startle response system is thought to operate. The reader should note that the LSD model posited by Geyer and Braff is not a model for the whole of schizophrenia but might conceivably be thought of as an "animal preparation" to model those specific aspects of startle behavior that have been found to differentiate schizophrenic patients from controls. The startle response is of special interest because it is organized below the level of the cortex (see Leitner et al. 1980, 1981). It also shows an interesting phenomenon known as "prepulse inhibition" whereby a weak leading stimulus (about 100 ms before the startle stimulus itself) has the capacity to reduce the startle response substantially. The prepulse inhibition has been demonstrated to be defective in schizophrenic patients, and it will be of considerable interest in the future to ascertain whether this is due to failures within the brain stem prepulse mediating structures themselves (see Saitoh et al. [1987] for a more elaborate discussion of this point) or whether a more "cognitive" explanation is required. Certainly the time period of 100 ms forewarning is ample in human subjects for substantial information processing to take place.

The concept of "gating" in both electronic and mechanical terms is a sophisticated construct. Several decades of conceptualizing schizophrenia as an "input dysfunction" have provided a number of varieties of "gating failure" mechanisms thought to elucidate the phenomena of "sensory flooding" in schizophrenia. Freedman et al. invoke this concept using brain electrical potentials evoked to pairs of stimuli in schizophrenic and control brains. One of the implications of their observations is that "sensory flooding" may occur because initial sensory input is preempted by later input, resulting in incomplete processing of incoming information. The P_{50} component of the evoked potential used in these studies occurs after the brain stem evoked potentials (< 8 ms duration) and is part of a set of waves up to about 100 ms poststimulus that reflect complex interactions of the reticular activating system, thalamic (and possibly limbic) neurointegration structures, and various specialized cortical areas (depending to some extent upon the modality of stimulation). What is important about this 10–100 ms evoked potential epoch is its sensitivity to "attentional" factors and the response organizational de-

mands of the task (see Erwin and Buchwald [1986] for a more detailed discussion). What is also important about this time epoch is that it corresponds to the time frame within which the "early sensory store" (in information-processing theory) is being formed.

Clearly, in focusing on hippocampal and thalamic functions and their bearing on schizophrenia, we have addressed only restricted components of the totality of brain structures that are probably implicated in the disease. Within the past decade it has become apparent that many structures formerly thought to be exclusively "motor" (e.g., the cerebellum) can now be demonstrated to play a part in "cognition." Similarly, the dorsolateral prefrontal cortex would require a journal issue itself to elucidate its potential involvement in the problem. The amygdala may also play a pathogenic part in schizophrenia if the work of Reynolds (1983) is any indication. This list is far from exhaustive.

In the same vein, much of our exposition could be restated in specifically neurochemical as distinct from neuroanatomical and neurophysiological terms. Douglas (1972) showed convincingly that for every effect obtained with hippocampal lesion, a similar effect could be obtained by neurochemical manipulation of the cholinergic neurotransmitter system. When one is dealing with the subcortical brain, the outstanding feature is the complicated interconnectivity of the various structures. It is in the realm of interconnectivity that the concept of an alternative (neurochemical) neuroanatomy comes into play (Warburton 1975). (The recent volume by Nasrallah and Weinberger [1986] gives an introduction to this intertwining of the neuroanatomical and neurochemical domains.) It is, however, precisely because of the complicated interconnectivity of hippocampus and thalamus to a broad variety of brain structures, and their "neurointegrative" functions, as well as very recent evidence of their neurohistopathological and neurochemical "pathology" in schizophrenia, that we have placed these two structures at the center of a general conceptualization into which the neurobiological and biobehavioral articles in this issue may be fitted. Before that, however, some "diagnostic" issues must be mentioned.

Symptomatology and Schizophrenia Diagnoses

The fundamental bedrock of schizophrenia research is the decision about which patients to include as schizophrenic and which by implication are assigned to other groups. The fact that this can be done reliably in an internationally viable way is proof that at some "gut" level of intraspecies communication we broadly agree about the nature of the human psychopathology to which our inquiries are addressed. Indeed, the Research Diagnostic Criteria, *DSM-III-R* (American Psychiatric Association 1987) criteria, and the International Classification of Diseases have now provided an objective observational base for the diagnosis of schizophrenia that greatly facilitates scientific involvement in this area.

Having said this, however, we must recognize that "schizophrenia" has not been *defined* by the process of diagnosis. The diagnosis has simply indicated another observation of its presence. Instead, we must accept that the definition of schizophrenia must "float," to be further refined into a definition by the data derived from each new level of mechanistic inquiry. As Cromwell (1984) has pointed out, to *define* schizophrenia we must know the mechanism(s) of its operation.

The current dilemma for scientific research in schizophrenia is the double horns of "mechanism" on one hand and "subclassification" on the other, and the essential indivisibility of the two. If a researcher claims a "mechanism" of schizophrenic causation, then it is essential to ask "to which schizophrenic patients is this applicable." If the experience of the last half century is anything to go by, then little if anything is common to all schizophrenic patients. Similarly, any predictive "subclassification" attempted in schizophrenia is based, explicitly or implicitly, on some notion of "mechanism."

At present, we cannot indicate whether a single dysfunctional mechanism gives rise to multiple experiential and symptomatic expressions; or if multiple mechanisms give rise to symptomatically similar expressions; or, in the same vein, if multiple mechanisms underlie a number of subtly different expressions.

One thing does seem to be clear: We need a more detailed and sophisticated analysis of the experience of the schizophrenic patient at the behavioral level to provide refinements that are not available to the observation of symptoms for diagnostic purposes. It is at this point that the tools of cognitive science and "information-processing" concepts, in particular, can be productively brought to bear to uncover behavioral "mechanisms" that may be covert in the diagnostic interview. Such concepts interface heuristically with new knowledge arising from the neuroanatomical and neurochemical explorations of brain.

Information Processing

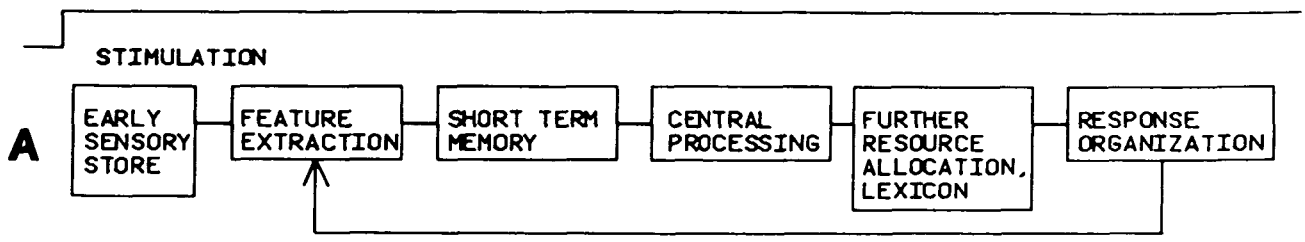
A formal theoretical framework for information processing (from the psychological or cognitive science perspective) dates back to Broadbent (1958). In simplistic terms (see figure 1A), this theoretical framework views information processing in the brain as taking place in a series of somewhat discrete stages. An initial sensory store (sometimes called the "icon" store or "iconic" image) is posited to last at most a second and, more likely, a few hundred milliseconds. This stage is believed to have a vast storage capacity but very limited duration. According to current theories, a subset of this information can be extracted from the sensory store, transformed into a short-term memory store (duration of around 10 sec), and relayed through a central processing stage at which point decisions are made about the degree of further processing needed for the new information. The central processing stage is the point at which resource allocation is made toward further information processing. One of the resources available through the hypothetical central processor is the lexicon or language faculty. Up to this point we are describing mostly the "input" stage of information processing. The "output" stage in information-processing theory is usually referred to as "response organization" and is conceptualized to follow decisions as to the category membership of the information and decisions as to the response requirements pertinent to it. It is implicitly assumed that the response requirement (which may reflect the current "state" of the organism) feeds forward in time to determine which features will be extracted from the next sensory store. Thus, a dynamic and ongoing information-processing system is in perpetual operation, sensitive to and interactive with the needs of the organism and changes in the environment.

This account of information-processing theory is oversimplified, and slights, for present purposes, controversies within this field. There is, however, one additional important point to be made: information may be processed in brains (in the cognitive sense) by a process of changing one form of representational code into another form of representational code. In all likelihood, the processes whereby the code is *represented* are different from the processes whereby the code is *changed* from one form to another (see Broadbent [1984] for further discussion of this point).

For many years the language and concepts of information-processing theory have been used to "dissect" the cognitive abilities of schizophrenic patients, and the process continues with some controversy. Thus, deficits have been posited at the level of the sensory store or the speed/efficiency of feature extraction from it (Saccuzzo et al. 1974; Braff et al. 1977; Saccuzzo and Schubert 1981; Braff and Saccuzzo 1985). Other theorists have attributed schizophrenic information-processing deficits to slowed central processing (Yates 1966; Yates and Korboot 1970) or to failures in response organization (Hemsley and Richardson 1980). It is, of course, perfectly possible that defects in schizophrenic information processing may be manifest at each of these stages, but from our point of view, the intactness or otherwise of the earliest stages must be fully ascertained, because defects at this point may well account for later (e.g., response organization) deficits. This tactic is justified because information-processing theory posits to some considerable extent a "serial" process. It is therefore a logical corollary of this theoretical framework that an inadequately constituted sensory code or feature extraction from it will result in a short-term memory—or working memory (Broadbent 1984)—that inadequately represents the stimulus events and their potential significance or response organizational demands.

The above conceptualizations are essentially a psychological or cognitive science view of information processing. Another conceptualization particularly directed at *stimulus*

Figure 1A. Information processing from a highly simplified cognitive science perspective

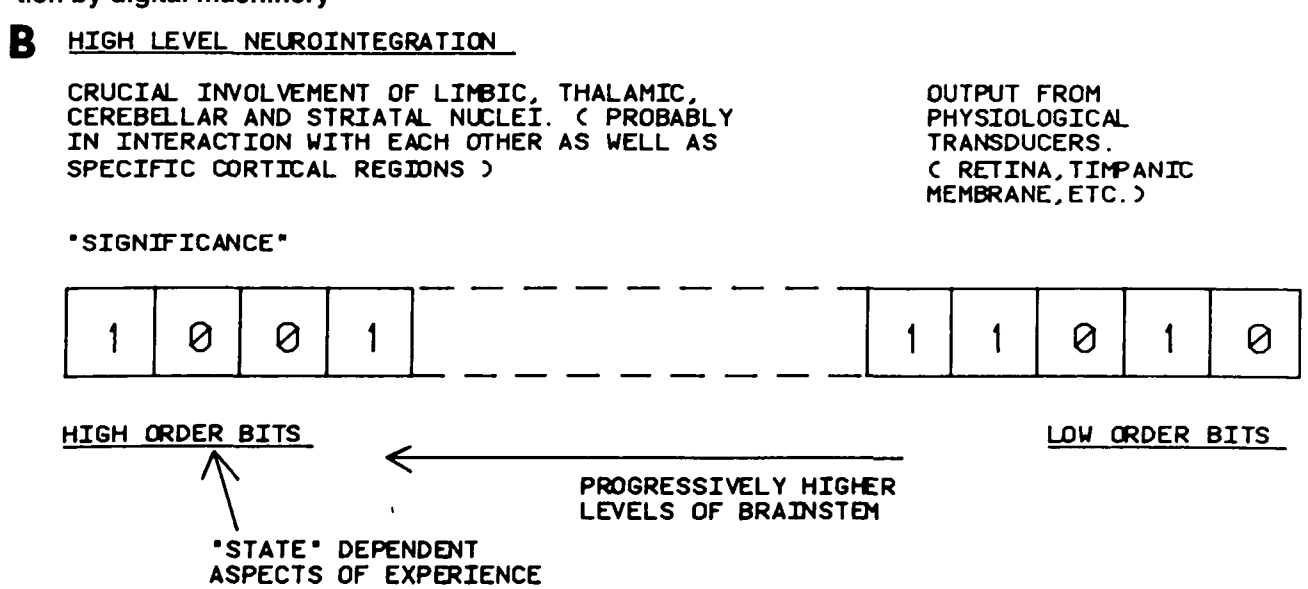


The elements may be rearranged in relation to each other (Broadbent 1984) and made more amenable to parallel processing (Posner and Presti 1987).

input derives from a neurological perspective (see figure 1B). We begin with the observation that light waves stop at the retina, sound waves stop at the timpanic membrane of the ear, and a similar argument might be advanced for other senses. Although there is nothing spectacular about that observation, the implications are profound because they indicate that information used in "cognitive processes" is actually created and assembled by brain structures. In a sense, after the functions of physiological transducers have been activated by stimulus energy, "information" is *created* by the organism. With reference to figure 1B, the activity of the physiological transducers can be thought of as constituting the "low order bits" of information assembly; then, as the afferent barrage ascends in the brain stem, through progressively "higher" brain structures, progressively higher order bits are added until the highest order bits are contributed by the "neurointegrating" structures such as the hippocampus, amygdala, and thalamic nuclei. (In reality in human subjects these high order bits are probably the complex interaction of cortex, frontal lobes, cerebellum, and the aforesaid "neurointegrating" structures.)

Thus, we see the total assembly of input information as a barrage of pulses that contains codes generated at many levels of brain nuclei which have participated in and contributed to the afferent input. Most importantly, however, the "significance" of the information or its "connotative" aspects are specifically hypothesized to be contributed by the limbic, thalamic, and perhaps cerebellar and striatal nuclei in conjunction with the cortex. Our view of the organism is obviously one in which "active" information processing constitutes the environment within which behavior occurs. It is perhaps noteworthy that "affective" information, in this formulation, is seen as being derived from (and consisting of) the functioning of the "neurointegrative" structures whose activity is reflected in the high-order bit assembly. In other words, each instant of experience or perception contains not only the "objectivity" (or sensory content) or stimulus input but an array of subtle affective or connotative tags, which collectively will add a dimension of "meaning" to the experience or perception. A corollary to this idea is that subsequent experience of a similar "objectivity" (or sensory content) that induces a similar "neurointegration" from the limbic, thalamic, and other structures as part of its information assembly will, in some "automatic" manner, "re-create" aspects of the previous experience in parallel with the current stimulus input. In all likelihood, this process of re-creation will be very rapid and allow a speedy understanding (in the light of previous experience) of the cur-

Figure 1B. An analogy between the "creation" of information by brains and the assembly of information by digital machinery



The total assembly is conceptualized to constitute both the addresses of subcortical to cortical relay and the contents transferred in such relay.

rent experiential "context."

By the term "neurointegration," we mean the process whereby multisensory aspects of the current information input are relayed to common neuronal structures. These common neuronal structures (e.g., limbic, thalamic, and striatal) receive input from all sensory modalities and, in addition, are believed to be the brain structures most involved in emotion. Thus, the "integration" of multisensory input and affective state is the "output" from these neurointegrative structures. We have conceptualized this neurointegrative state as the last stage of the assembly of information that must be relayed to the appropriate cortical columns. At this point the entire afferent barrage probably possesses what is termed "content addressability" (see Pay 1980*a*, 1980*b*, 1981, 1982). In other words, the actual content of the upward barrage not only determines *where* it will be directed in cortex but is also the *content* of the upward relay. We have used the terms "significance" and "connotative" interchangeably to refer to the specific aspects of the assembled information that will carry the code derived from the neurointegrative structures that designates the *affective state.* As these are the last stages of information assembly before cortical relay, their influence upon precisely which cortical columns will be activated is greater than that of those structures whose contributions were added earlier. The neurointegrative structures are specified as adding "high-order bits," and the lower brain structures are specified as adding "low-order bits" to the upward assembly of information; the term "bit" is a shorthand annotation for the summated activity of the neuronal structures at any given level in brain.

As the limbic, thalamic, striatal, cingulate, and cerebellar structures form a very complicated set of systems (see Gray 1972; MacLean 1985; Doane and Livingston 1986) that control much of the subcortical interaction with the cortex, and as specific *developmental* aspects of cortical column differentiation may depend upon the nature of subcortical relay (see Pay 1980*a*, 1980*b*, 1981, 1982), it is probable that defects such as those ontogenetically depicted by Conrad and Scheibel (and also those suggested by Oke and Adams) may be responsible for an experientially mediated differentiation within cortical column structures (and mapping between them) that is abnormal in afflicted individuals. The behavioral ramifications of such a process may be both profound and variable. One possibly ubiquitous defect might be the incapacity to have the "neurointegration" of current stimulus input give rise to the simultaneous re-creation and parallel processing of aspects of experience that gave rise to the same "neurointegration." This is the process of "automaticity," which we hypothesize may be defective in schizophrenic patients and lead to slowness, inconsistency, and inaccuracy in rapidly understanding a current behavioral context. Further and more behaviorally damaging consequences may follow if expectancies based on current contextual understanding cannot be generated. (That subcortical to cortical relay may be variably defective in schizophrenia might be further suggested by the recent positron emission tomography [PET] findings of Gur et al. [1987*a*, 1987*b*].)

If we believe that there is an information-processing malaise in schizophrenia (although its nature may be variable), and if we also anticipate that the brain examination of schizophrenic patients will reveal pathogenic mechanisms (anatomically or neurochemically), then it would seem logical that the examination of brain processes during information processing in schizophrenic patients might tell us both about the brains of these patients *and* about the (covert) nature of their information processing. The mapping of neurological activity upon the "psychological stages" of information processing is currently taking place, and in a later section we will describe how brain imaging is used as a "second window" into brain process when specific information-processing tasks are undertaken by schizophrenic and control subjects.

Schizophrenia and Brain Models

As virtually all research in schizophrenia is conducted with an implicit or explicit model of brain in mind, we believe that it may be useful to make explicit some simple underlying considerations about the brain so that these assumptions (which play a large part in how investigators "think" about schizophrenia) may also become targets for debate and inquiry.

Repeated failures to develop an adequate animal model of schizophrenia might be held to indicate that schizophrenia is a specifically human pathology involving specific human capabilities and therefore specific human brain structures. From a simple-minded viewpoint, those brain structures that most indicate the human might be an increased total mass of the cortex and, especially, an increase in the relative volume of the frontal lobes. We find it difficult to believe, however, that these "top" structures in brain have evolved without some corresponding changes in the lower brain.

As a general consideration of brain evolution, it does not appear that structural development takes place without being "driven" in

some fashion by increased capability in other structures. From this perspective it seems probable that the increased cortical development in humans has been "driven" by increased capability in the phylogenetically older "neurointegrating" structures of the lower brain—more specifically, the limbic brain, thalamus, and perhaps also the cerebellum. (We are assuming for the moment that striatal development has taken place in parallel with cortical development, although certain of its structures may be phylogenetically as old as the limbic brain and thalamus.)

Many hundreds of species of organisms have survived and adapted over billions of years without much or any cortex, and in many species the limbic, thalamic, and cerebellar nuclei constitutes the totality of the organism's "neurointegrative" capability. In short, if we have evolved from such (or similar but more generalized) species, and if our cortical structural development has taken place as a function of increased capability in phylogenetically older structures, then in some sense the older "neurointegrative" structures of the limbic and thalamic regions must still exercise a considerable total executive function in the control of human brain. Such a conceptualization does not seem so far-fetched in light of the many reports by Meyer (e.g., Meyer 1984; Meyer et al. 1985) wherein total removal of rat cortex still leaves relatively intact a number of experimentally demonstrable conditioned associations and relevant behaviors. One possible conclusion from such observations is that the older (specifically limbic and thalamic) structures function as the "memory mapping" devices that provide access to ever more specialized regions of cortex and thus allow the additional computational power of the cortical layers and columns to be fully used. In short, cortical development may be the structural manifestation of greatly expanded lower brain differentiation resulting in the increased capacity for "information assembly" conceptualized in the previous section on information processing.

Such increased processing power can logically be held to underlie those specifically human functions of abstract thinking (the capacity to re-create, synthesize, and extrapolate from previous experience and to bring the fruits of such computation to bear upon the "perception" of current context) and the capacity to use current experience to plan into the future so as to anticipate and change the course of behavior, in accordance with expectations.

We suggest that those specific aspects of human function just mentioned constitute a significant part of the schizophrenic experiential and symptomatic malaise and that it is heuristic to hypothesize that they could be caused by defective structures and functioning in the lower brain.

The functional attributes of the frontal lobes in all likelihood play a crucial role in the teleological functions sketched out above, and we will integrate a brief understanding of their role into our section on neuropsychodevelopment in a following section. Before that, however, it may be profitable to consider further the additional attributes of large structural cortical mass and speculate upon the significance of "visualization" as the organic manifestation of massive parallel information processing.

Machine Considerations and Brain

The design of any complex machine that is composed of a number of different structures must first address the crucial problem of how the "timing" of the different parts can be successfully integrated. Although there is great danger inherent in extrapolating from how silicone-based (and mechanical) intelligence operates, and then applying these principles to carbon-based intelligence, the tradition of such error is a long and noble one, as humans have always thought of brain in terms of the machinery they could create (e.g., Leonardo da Vinci and hydrostatic models of brain). The machine analogy, in this instance, allows us to ask the question of how the multiplicity of brain regions have their timing integrated so that information "assembled" in one region reaches another region at an appropriate time for reception in the second region.

In computer and mechanical design, some central "clock" provides this function, usually at very high speed (for example, 50 MHz). Each of the individual structures then has "timing lines" derived from the central clock at a speed ("divided" down from the central clock frequency) appropriate to its timing needs. Therefore, it is not unusual to find (in a complex machine) many timing lines graded in frequency from a few cycles/sec to millions of cycles/sec, all exact multiples of each other and perfectly integrated to synchronize the various subassemblies. It is reasonable to ask this question about brains, even though the very act of asking it may demonstrate inadequacies in our approach to understanding brain.

If one were to single out a brain structure that displayed the possibility for central "timing" functions in brain, it would most likely be the thalamus. Much of the rhythmical activity seen in the electroencephalogram (EEG) (whose power spectra can be seen to range from about .5 to 40 Hz, although some

may argue for extension at both ends of the frequency range) may be derived from the oscillatory activity of the thalamus. (See also a provocative article by Liberson and Liberson [1986].)

Human language is perhaps one area of behavior that requires the most minute perception and synchrony of fine temporal duration. Accordingly, it is consistent with the argument advanced above that Crosson and Hughes put forward the thalamus as a candidate for much of the synchrony orchestration controlling the production of spoken language formulation. It is further of considerable importance that the entirety of the thalamus with its manifold separate nuclei specifically dedicated to different functions may be (at least neurochemically) dysfunctional in schizophrenia, according to Oke and Adams in their article.

The structure and functioning of the striatum has been the subject of intense inquiry by Groves and colleagues (e.g., Groves 1983, 1986), and it is Groves' contention that the striatum may be conceptualized as a massive "resistive bed" between the cortex and the lower brain structures. As such, the question of timing again becomes crucial to the striatal function, and the thalamus is again the most likely candidate to provide this function. We offer a "psychological" notion (purely illustrative and probably erroneous) of how and why this striatal function takes place, based on our understanding of aspects of current brain research.

In a previous section we mentioned the phylogenetically increased capability of the lower brain, the increase of total cortical mass, and the corresponding increase of teleological capability possessed by humans over other species. We would like to extend that argument by conceptualizing much human information processing as using the enlarged cortical mass (often under frontal lobe control) to produce a "holographic" representation of planned future and past events. From the design of graphic computers, we know that pictorial generation requires a very large total dedication of computer memory locations—hence the requirement for an enlarged cortical mass. We also know how easily humans can "take in" large quantities of information presented visually, which might indicate that this type of information processing is readily available to humans. We would contend that this capacity to generate highly pictorial images is, in fact, a form of massive parallel information processing available to the human brain. However, the vast majority of human intraspecies signaling is auditory (language, for example), which is why the deaf are more debilitated (in human terms) than the blind. It would therefore follow that the massively parallel information (pictorial) processing must be "timed" in some sense to integrate with the slower acoustic faculties, especially those associated with language and speech predicated upon "pictorial" information generated by brain. The functions of integration between the fast (pictorial) capability and slower acoustic/linguistic capability may be handled by the striatum with timing derived from thalamic connections. In the article by Crosson and Hughes, the globus pallidus (and the caudate and putamen in the striatum), as well as the thalamus, are considered crucial to spoken language formulation.

There is a sense in which correctly communicative language/speech must have the motoric aspects of speech directly "connected" with pictorial images, and there is also a sense in which pure motoric function may also (in humans) depend on the capacity to attain (and maintain) visual images of the planned behavior (this view is elegantly expounded in a recent article reviewing the cerebellum and its contributions to "cognition" by Leiner et al. [1986]).

Thus, to summarize our argument to this point, we may posit aspects of a mechanistic view of schizophrenia as follows:

- The "neurointegrating" structures of the hippocampus and thalamus fail to provide the "high-order bit assembly" of ongoing information processing.
- Such failures result in inappropriate "affective" and "significance" assessments of the ongoing stimulation.
- The thalamic and limbic dysfunctions mentioned may be seen to participate directly in failures of "timing" in relation to speech processes, and failures in temporal mapping of pictorial (holographic) information generation, in motoric and linguistic/speech mechanisms.

The question now arises as to what the ramifications of critical dysfunction of the hippocampus and thalamus in schizophrenia might be. For answers to these questions, we now turn to psychodevelopmental considerations.

Neuropsychodevelopment

One of the most consistently puzzling aspects of schizophrenia is why its age of onset peaks in the second and early third decades of life. Not only is the onset of the disease without adequate explanation, but the course of the illness, whether it shows progressive deterioration or not, is also a source of confusion. In this issue, Conrad and

Scheibel hypothesize that the pathogenesis of the illness may involve ontogenetic failures in cell migration to form the hippocampus. (Jakob and Beckmann [1986] suggest a similar mechanism relative to limbic cortex.) In an attempt to understand the pathogenesis of the disorder from a biobehavioral perspective, we will try to "think through" some of the implications of subcortical ontogenetic pathology and its consequences for psychodevelopment.

It is our fundamental assumption that information processing is a constant state of brain function, from gestation to death, and that learning (and its "state-dependent" nature) interacts with neural development to form many aspects of the functioning brain. It is a corollary of such a premise that no "off-line" storage (memory) is required since the brain is never shut down (not even in deep coma). Therefore, everything that constitutes "memory" is implicit within brain structure and function. Let us develop our conceptualization by positing that the course of existence consists of experience at every instant in time and that information processing at each instant takes place in the manner depicted in figure 1, both in the cognitive and neurological senses. If we now consider the data and ideas presented by Conrad and Scheibel, we may advance the argument that the ontogenetically maldeveloped limbic brain gives rise to an information "assembly" that is subtly defective, in that the "high-order bits" derived from the functioning of these "neurointegrative" structures are not correctly assembled.

With continued experience throughout childhood, we conceptualize a situation in which, although the "lower-order bits" of information assembly may take place normally (as directed by the physiological energy transducers and other structures), the higher order neurointegration is variably defective—as dictated by the degree of ontogenetic failure. The psychological ramifications of this are that the "significance" or "affective tagging" of each instant of experience may be continually abnormal, relative to the normal developing brain. The neurological significance of such a situation may be that there are considerable inconsistencies in the "mapping" with which a given (and repeated) information assembly may be directed to cortical columns. This inconsistency is conceptualized to be due to alterations in the control of the limbic and thalamic nuclei over the most significant "bits" which determine this addressing or "mapping" of the upward barrage. Perhaps even more importantly, the differentiation within the cortical columns and therefore communication between them may be affected. It must be emphasized that we are discussing very subtle effects, about defects that may have little to do with the production of a behaviorally acceptable response to any given situation in childhood. We are also more concerned with the subtleties of *affect* in each situation than with the manifestations of intelligence or rational problem solving. We contend that the long-term viability of the organism is as much a function of appropriate affect as of intellectual differentiation, and that the limbic and thalamic nuclei are the neurological foundation of affective application.

An important extension of this argument is that "memory" processes (and their characteristic distortions over time) may rely heavily upon affective elements both for memory organization and the appropriateness of recall in a given situation. These considerations may apply equally to cognitively "effortful" recall, and to the rapid re-creation of instances of similar experience in parallel with current stimulus input. It is the affective tags used to gain access to previous experience of a currently pertinent nature that we have dubbed "affective vectors."

It is important at this point to understand that all learning may display "state-dependent" aspects and that the regeneration of experience (memory) has implicit within it all of the "state factors" applicable to its original experience. What may be more important, however, is that the "state" of the organism may be reflected in the "high-order bit" assembly and that these high-order bits over long-term experience may constitute the "affective vectors" that allow accurate re-creation of experience to play a role in current "perception" and allow the abstract generation of "principles," rules, expectancies, confidences in perception, and ideas about the world. In short, it is possible that defective assembly of the "neurointegrative" aspects of instantaneous experience eventually comes back to haunt the preschizophrenic adolescent in the form of failures to find the appropriate vectors through previous experience that will allow those most human qualities of abstraction and teleological understanding to become manifest.

In a very important sense "perception" may be largely learned (witness the plight of the congenitally blind who, through restorative surgery, may have the capacity for sight enabled). This may indicate that aspects of previous experience must be "re-created" in parallel with current stimulus input. If this is so, then it is highly likely that the "neurointegrative" structures play a very important part in this "re-creation" or "automatic" categorization (in the sense of Schneider and Shiffrin 1977, 1985). Any failures in the "automaticity" with which this process

takes place will almost certainly lead to instabilities of perception, within a temporal context.

Let us summarize this section by stating that defective cell migrations in the limbic brain ontogenetically are hypothesized to give rise to deficiencies in the significance, connotative, and affective "high-order bit" information assembly of all aspects of instantaneous experience. As a corollary of this phenomenon, the re-creation of previous experience, needed for abstract and principle learning and to form ideas about the world of a species constant nature, is compromised. The "perception" of the world may also be compromised to the extent that prior experience cannot be re-created in parallel with current stimulus input. These various afflictions may be visited upon the preschizophrenic adolescent in varying degrees, as a function of the degree of limbic ontogenetic developmental failure. It is possible that ultimate schizophrenic behavior depends upon the function of late-maturing brain structures, and to these we now turn.

The Emergence of Schizophrenia

If our construction in previous sections is anywhere close to true, then it should come as no surprise to find that schizophrenia as a debilitating state first manifests itself at a point when "independence" of the young adult is demanded. In other words, deficits in experience from the earliest years culminate in producing a defective internalized conceptualization of the living process—an inadequate model of the world. The independence of the young adult (from direct parental control) occurs at a point in experience where the internalized "world" should be capable of directing the intraspecies communication and behavior of the organism. The outstanding necessity for this condition to occur is the development of the complex frontal cortices, which we contend to be essential in the human for the capacity to execute future planning predicated upon the re-creation of vectors through experience. Both a neuroanatomical and a psychodevelopmental aspect are pertinent here.

From a neuroanatomical perspective there are direct connections from the mediodorsal thalamus to the frontal lobes (especially the dorsolateral prefrontal cortex) and, in older literature, aspects of the neuroanatomy of the frontal lobes were actually defined by these thalamic afferents. An even more complex relationship exists between the limbic brain and the frontal lobes, which Reep (1984) has suggested should be conceptualized as a complex three-ring structure. In this journal issue, specific researchers implicate both the thalamus and the limbic brain as dysfunctional in schizophrenia. The inevitable corollary is that the frontal lobes should be dysfunctional also. Recent neural imaging from Weinberger et al. (1986) indicates that this may be so in schizophrenic patients.

A long series of studies by Goldman-Rakic et al. (1983) indicated strongly that areas of the frontal lobes mature very slowly in all primates, that they begin to show increased activity at adolescence, and that the frontal lobes become more important in information-processing situations that involve delays. Our extrapolations on the basis of the work of Goldman-Rakic and others are that the frontal lobes become progressively more important as adolescence progresses to adulthood. We conceptualize a normal process of neurological and psychological development as involving *consistent* patterns of "neurointegration" from the limbic and thalamic nuclei and that the firing patterns of these subcortical structures constitute the "mapping" of experience to cortical columns. The structural interconnectivity and development of the latter column structures is probably strongly dependent upon the consistency with which they receive a closely similar input. With the onset of adolescence and early adulthood there is an increased demand for the planning of future behavioral ramifications. We suggest that these future-oriented functions are achieved by a capacity of the frontal lobes to set in motion a firing pattern in the limbic and thalamic nuclei which will activate specific patterns of cortical columns and thus re-create aspects of previous experience. This self-regeneration of experience is probably important in itself for the planning of future action and prediction of outcome. However, it may also play a more critical function in allowing such previous experience to be re-created in parallel with current stimulus input. This formulation would suppose that any experience that generates a particular neurointegration from the limbic and thalamic nuclei will also "automatically" activate cortical columns activated by similar "neurointegrations" in the past. This would provide the neurological base for the capacity of any given stimulus input to be able to generate rapid contextual understanding and expectation.

In schizophrenia there may be a double-sided malaise. First, ontogenetic defects in the limbic and thalamic nuclei may lead directly to defects in frontal lobe anatomical development, as well as the limbic and thalamic nuclei providing an abnormal "neurointegration" of experience. A second and further debilitating factor may be that abnormally developed frontal lobes

may not be able to successfully access the "neurointegrating" limbic and thalamic nuclei in order to effectively "re-create" previous experience, producing a fundamental incapacity to plan the ramifications of behavior. Perhaps the behaviorally most disturbed aspects of schizophrenia occur when prior experience must be re-created in parallel with current stimulus input in order to achieve an accurate understanding of the current behavioral "context." In short, the actual "experience" may be subtly flawed neurologically; consequently the capacity to "re-create" it becomes inconsistent and inaccurate, and as a function of both, the teleological capacity of future orientation becomes seriously debilitated. All of this becomes evident as behavioral "independence" is reached.

We must stress at this point that our outlook is consistent with a wide range of severity of schizophrenia and with a myriad of symptomatologies. Considerable variability of pathogenesis is possible depending upon the location of subcortical defect(s). At present, a taxonomy of specific experiential/symptomatic clusters predicated upon extent and variety of defect in any specific subcortical region cannot be achieved. What is important for future work, however, is the recognition that no specific type or extent of defect in any specific subcortical structure may be common to all schizophrenic patients. Instead, the type and extent of defect in any particular structure (e.g., the hippocampus, the amygdala, the various thalamic nuclei, the striatum, the brainstem nuclei, and the various cerebellar nuclei), may be of great importance to a particular patient. The high degree of interconnectivity of subcortical structures (in addition to their individual cortical connections) argues for a "systems" approach to subcortical pathogenesis.

Much of our theorizing has concerned the hippocampus or thalamus directly. However, apparent malfunction in these structures may be occasioned by alterations in the structures to which they are connected. When hypotheses about schizophrenia are derived from the standpoint of lesioned or defective neuroanatomy, there is often an erroneous assumption that only the chronic, process, deteriorating type of schizophrenia can be "explained" in this manner, whereas the clinical "facts" are such that the majority of schizophrenic patients may have an episodic course of illness with substantial symptomatic remission in later life. Even in episodic cases, "residual" schizophrenic symptomatology is often evident (in remission) and the capacity to withstand stressors of any kind may be drastically reduced. The life experience of the schizophrenic patient does not cease with the onset of the first acute episode, and if there is symptomatic remission both in the short-term course and over a lifetime, then the application of intelligence, learning, maturation, "therapies," and medication may all assist the patient (through more cognitively "effortful" processes) to compensate for defects in fast and "automatic" categorization capability, which includes a finely modulated affective articulation. The latter is presumably the underpinnings (in a psychological sense) of the normal subject's ability to produce a world view of adequate species-specific consensus, which will be used to direct the organism (in a "future"-oriented manner) throughout life.

It is sometimes useful when contemplating a "theory" of schizophrenia to ask which aspects of schizophrenia are being "accounted" for by this theory and what aspects are not. The central focus here is that there may be abnormalities in affectively tagging stimulation over a long period leading to failures in "automaticity" in schizophrenia which do not allow the subject's past experience to be rapidly and appropriately brought to bear upon present stimulation, thus failing to provide an experientially rooted understanding of the present "context." This failure has its greatest behavioral manifestation in failures of "contextually generated expectation," a behavioral function which appears crucial in speech behavior and perhaps in many other ways. The end result is that the schizophrenic is seen as being "stimulus bound," with neither past nor future providing guidance within short temporal duration.

Brain Events Concurrent With Information Processing

Over the past decade new technologies of brain imaging such as magnetic resonance imaging, PET, and topographical evoked potentials (among others) have become available for *in vivo* observation of brain events. In addition to the examination of aspects of brain structure using these techniques, observation of brain functioning within controlled experimental conditions has been possible. Although in their infancy, such investigative strategies have already given us valuable information.

With respect to the frontal lobes, early investigation by Ingvar and associates (Franzen and Ingvar 1975; Ingvar et al. 1979; Ingvar 1982) demonstrated a lack of frontal regional blood flow in the brains of schizophrenics (relative to controls) when cognitive exercises such as mental arithmetic were conducted. More recent studies (Weinberger et al. 1986)

have confirmed this is so. The most convincing demonstration so far has shown that the dorsolateral prefrontal cortex fails to increase its activation (in schizophrenic patients) in the Wisconsin Card Sorting Task.

Without conducting a more extensive review of this area, we wish to point to this set of findings as indicative of the frontal lobe *dysfunction* that would be predicted from failures in frontal lobe *activation* by both the limbic and thalamic nuclei. We would also like to posit the view that such empirical evidence is in keeping with our more "psychological" construction of failures in the ability of the frontal lobes to gain access to the limbic and thalamic nuclei whose assistance is required to re-create appropriate vectors through previous experience and to bring the results of such a re-creative process to bear upon the current behavioral context.

The recording of regional cortical blood flow requires several minutes for the tracer element to become variably perfused throughout the brain. The end result is that the brain scan shows only the "integrated activity" of brain regions over several minutes. Information processing as posited in figure 1A and 1B is conceptualized to have early components operating in the thousandths and tenths of a second. To gain access to this time domain, brain evoked potentials may be useful. Patterson et al. (1986*a*, 1986*b*), in preliminary reports from a study of backward masking (a paradigm thought to manipulate the formation of early sensory store and feature extraction from it), demonstrate that brain events during the presentation of the target (in the 70–100 ms range) show marked attenuation or absence, in schizophrenic patients, of an early negative-going waveform (possibly the N_{100} wave). (There is a discussion of other investigations and paradigms which also indicate marked attenuation or absence of electrical waveforms within the 100-ms range in Patterson et al. [1986*b*].) Abnormalities in the N_{100} and similar waves have been observed in both schizophrenic adults and children.

The time epoch of the evoked potential is consistent with the time period in which complex interaction of hippocampus, thalamus, and cortex are thought to take place. It is also the time interval during which the actual formation of the early sensory store is taking place as depicted in figure 1A. We suggest that the concurrent evoked potentials indicate a failure in higher-order bit assembly as depicted in figure 1B. The psychological ramification of these failures is that an "automaticity" of re-creation of vectors (or templates) through (or derived from) previous experience is not achieved by schizophrenic patients in the same time frame as by normal subjects. In short, we suggest that the "perception" of the current "context" is faulty within a short temporal duration in many schizophrenic patients, and that such subjects will be forced to use slower and cognitively more effortful "controlled" (in the sense of Schneider and Shiffrin [1977, 1985]) processes to achieve adequate "perception."

The rapid assembly of information within short time frames might have additional importance in that the autonomic and visceral concomitants of experience are an integral part of the experience and of some importance in the "affect" labels that will be generated by the experience. Both limbic and thalamic nuclei have important contributions to hypothalamic and pituitary function, and several decades of autonomic measurements from psychophysiological research in schizophrenia have indicated a plethora of subtle autonomic defects (see Zahn [1986] for a particularly comprehensive review). These data are consonant with failures in short time frame neurointegration as posited above.

The time frame of 100 ms has been fruitfully explored and, in addition to the evoked potential anomalies in schizophrenia mentioned above, failures in prepulse startle inhibition, failures in self-initiated evoked potential amplitude reduction, and alterations in evoked potential "recovery" functions (see Shagass 1975, 1976, 1977) have also been demonstrated.

Expectancies based upon current contextual understanding appear crucial for human speech/language behavior and perhaps for many other aspects of behavior also. In the use and understanding of sentences, the material early in the sentence may be substantially modified in the light of later sentential material, and vice versa. It has become apparent that humans handle the situation by generating expectancies about the completion of a sentence based on its early elements. That schizophrenic patients may be defective in this "expectation" can be argued from the data and conceptualizations put forward by Schwartz (1984). He has argued convincingly that schizophrenic patients have little (if anything) wrong with their understanding of individual words, nor is there any convincing evidence that schizophrenics do not understand their native language. (Here the term "language" denotes a body of lexical knowledge—for example, the English, German, or French language.) However, it is readily apparent (from Schwartz [1984] and commentaries on the target article by a large number of investigators) that their difficulties with sentences may stem from an inability to use the context of the early sentential material to generate appropriate expectancies for later sentential ele-

ments. This is further demonstrated by lowered cloze probabilities in schizophrenic patients (Schwartz 1984).

Brain electrical activity concomitant with linguistic information processing has recently been explored (Kutas and Hillyard 1980, 1982, 1983, 1984). It has become apparent that specific time epochs of the evoked potential can indicate such linguistic factors as the detection of semantic congruity and incongruity both in visual and auditory presentation (for a more thorough description, see Herning et al. [1987]). A study by McCallum et al. (1984) has shown convincingly that the N_{400} wave (evoked by the detection of semantic incongruity) begins to develop as early as 270 ms, although for many of the semantically incongruous words used by the investigators, the auditory duration of the word is in excess of 360 ms. In other words, human brains had begun to detect a deviation from the expected phonemic structure some time before the total phonemic construction had taken place to form the completed words. On the basis of our prior hypotheses and following the demonstration of reduced cloze probability in schizophrenia, we suspect that if the McCallum et al. study were to be replicated with schizophrenic patients, many would fail to show the N_{400} wave, or that its latency would be increased and its amplitude reduced—thus demonstrating at the neurological level failures to generate appropriate linguistic expectancies.

An Overview of Additional Sources, Theories, and Concepts

> In a very general sense the models of Broadbent, Shiffrin and Schneider, and Posner and his colleagues may be seen as illustrating the way in which the spatial and temporal regularities of past experience influence the processing, and more speculatively, awareness of current sensory input. *It is a weakening of the influences of stored memories of regularities of previous input on current perception which is postulated as basic to the schizophrenic condition.* [Hemsley, in press, author's italics]

From the above quotation it is obvious that the line of reasoning which we have developed is congruent with the outlook of other investigators.

In a recent article on the pathogenesis of schizophrenia from a neurodevelopmental perspective, Weinberger (1986) has suggested that theories about the pathogenesis of schizophrenia must address two crucial questions: (1) Why does schizophrenia become clinically apparent in the late second and early third decades of life? (2) Why do the neuroleptic (antidopaminergic drugs) have therapeutic efficacy? Not only is Weinberger's chapter worthy of contemplation, but the entire volume (Nasrallah and Weinberger 1986) is perhaps the most up to date and comprehensive extant view of the neurology of schizophrenia.

We have chosen (in this synthetic intellectual exercise) to present material that is complementary to, rather than a duplication of, currently published material—hence, our concentration upon the more psychological perspectives and, especially, information processing. An excellent, more comprehensive view of information-processing difficulties in schizophrenia is given by Knight (1984). It is particularly interesting that the "perceptual disorganization" theory offered by Knight (1984) can be well integrated with the outlook posited here, and perhaps also with the views of Hemsley quoted above.

A necessity for schizophrenia research in the year of the National Institute of Mental Health's "schizophrenia research initiative" is the stimulation generated by new ideas as distinct from the continued acquisition of data within existing paradigms (not that that is not also necessary).

> . . .frontal/prefrontal cortex handles the temporal organization of behaviour and cognition, and . . . the same structures house the action programs or plans for future behaviour and cognition. As these programs can be retained and recalled, they might be termed "memories of the future." It is suggested that they form the basis for anticipation and expectation as well as for the short- and long-term planning of a goal-directed behavioral and cognitive repertoire. This repertoire for future use is based upon experiences of past events and the awareness of a Now-situation, and it is continuously rehearsed and optimized. Lesions or dysfunctions of the frontal/prefrontal cortex give rise to states characterized by a "loss of future," with consequent indifference, inactivity, lack of ambition, and inability to foresee the consequences of one's future behaviour. It is concluded that the prefrontal cortex is responsible for the temporal organization of behaviour and cognition due to its seemingly specific capacity to handle serial information and to extract causal relations from such information. Possibly the serial action programs which are stored in the prefrontal cortex are also used by the brain as templates for extracting meaningful (serial) information from the enormous, mainly non-serial, random, sensory noise to which the brain is constantly exposed. Without a "memory of the future" such an extraction cannot take place. [Ingvar 1985, p. 127]

The quotation from Ingvar is especially pertinent to our discussion.

It is probably no coincidence that the increased awareness and emphasis on the frontal lobes in recent years has been paralleled by the view of an organism that is "active" in the "construction" of its environment. Ingvar has drawn attention in a most stimulating way, in his essay on "memory for the future" (quoted above), to the necessity for considering humans as especially "future oriented" and that "perception" may in fact be some powerful function of the imposition of templates derived from future planned outcome computations:

> *... it is the temporal structure, the serial nature, of the sensory input which is a prerequisite for the experience of causality and, hence, the production of serial neuronal action plans underlying the anticipatory concepts of the future.*

This argument may be taken one step further. Could it be that the serial concepts, or "memories," of the future, which are handled by the pictorial cortex, are of fundamental importance for the perception of—as well as for the selection of—meaningful serial afferent messages? Our serial programs and concepts of the future may be used as templates with which the input is compared. If there is a correspondence between the two, the input is understood, its "meaning" is perceived. Such a notion forms, into fact, the basis for the above cited "motor theory of speech perception" (Liberman et al. 1967). Without access to serial action plans for word articulation and sentence production, we cannot perceive the meaning of serial word messages and speech. Possibly such a notion has general validity: *it is only by access to serial plans for future behaviour and cognition, i.e., access to our "memory of the future," that we can select and perceive the meaningful messages in the massive sensory barrage to which our brains are constantly exposed.* [Ingvar 1985, p. 134, author's italics]

What we have tried to do in this issue is to show that subcortical structures, their function and development, strongly underlie the experiential base that has made the future orientation possible. Failures in hippocampal development or defects in the thalamic nuclei may in a very real sense lead to defects both in the structure (and almost certainly in the functioning) of the frontal lobes (see review by Reep [1984]). This, however, is only one part of the problem as the converse may also be true, i.e., that the "future planned outcome computations" or "memories for the future," which are so elegantly argued by Ingvar to be a function of the frontal cortex, may not be able to gain access to and recruit the assistance of the limbic and thalamic brains to "reiterate" the vectors through previous experience that may be the underpinnings of the "future planned outcome computations." The hippocampus is in all likelihood a crucial structure in the process, and its importance has led to a voluminous literature, only a tiny fraction of which is mentioned here.

> ... the role of the hippocampus is to form and retain an index of neocortical areas activated by experiential events. The hippocampal index, thus, represents those unique cortical regions activated by specific events. The neuronal mechanism underlying the memory index is hypothesized to be long-term potentiation. It is asserted that the reactivation of the stored hippocampal memory index will serve to also reactivate the associated unique array of neocortical areas and thus will result in a memorial experience. This hippocampal reactivation of a neocortical array may also be involved in establishing a cortically based memory trace. [Teyler and DiScenna 1986, p. 147]

This quotation from the work of Teyler and DiScenna (1986, 1987) not only points toward the neural mechanism of long-term potentiation (the "facilitation" of firing in neuronal structures for long periods after strong stimulation), but also underscores the "cortical mapping" capacity of the hippocampus as we previously mentioned in a more fanciful manner. We have known since the famous case of H.M., whose bilateral temporal lobe removal led to the first strong indications (in humans) that the temporal lobes were involved in memory, that some form of mnemonic function must be ascribed to the hippocampus. Precisely how the phenomenon should be conceptualized has been the subject of heated debate. O'Keefe and Nadel (1978, 1979) strongly posited the view that the hippocampus was involved in "spatial mapping" of the environment. Although many of O'Keefe and Nadel's observations are still an integral part of the debate, Olton et al. (1986, 1987) and Rawlins (1985) have also contended that temporal factors strongly implicate the hippocampus in associations across time and the term "memory" has justifiably cracked under the conceptual strain, to yield fractionated concepts of "working memory" and "reference memory," among others.

> The cognitive processes involved in the perception of space, time, and memory may all be interrelated, psychologically and neurophysiologically. If the hippocampus is involved in all three of these processes, any description of hippocampal function must be able to incorporate all of them. In the same way that a cognitive map establishes the topological interrelations among different places, a temporal map may establish the chronological interrelation among different events. Both types of maps require the interrelation of components within the map, a process that must involve memory in

order to establish the correct contextual framework. The hippocampus may be the brain structure that allows each of the various components of a place and an event to be linked together and compared with other places and events (Marr 1971; Teyler & DiScenna 1986).[Olton et al. 1986, p. 854]

The study of commissurotomy patients under appropriate conditions might further elucidate the nature of output from the subcortex. Such a study has recently been conducted by Cronin-Golomb (1986) using three patients with total commissurotomy. She concludes:

> The information relayed subcortically is neither verbal nor imagic in nature, but appears to correspond to contextual or connotative associates of the stimulus. [Cronin-Golomb 1986, p. 517]

These conclusions appear to be in accord with our speculations above. As much "neurointegration" must also involve the precise integration of motoric elements along with sensory and affective components, it would be surprising if the hippocampus were not involved in motoric control. Strong evidence from Arezzo et al. (1987), using motor-related potentials recorded from within and around the hippocampus, shows that this structure is involved both in initiation and control of even simple voluntary movements in primates. However, even in the absence of movement, the recent report by Port et al. (1987) shows that the hippocampus may be vital to the association of sensory events.

Just as the hippocampus and its functioning have come under increasing attention, the role of the thalamus is being further elucidated. The recent book by Jones (1985) provides much of the current conceptualization about this bewilderingly complex structure. What is most immediately apparent is that the thalamus (perhaps like every other subcortical structure) cannot be considered in isolation. Its massive connectivity to other brain structures has almost mandated that in behavioral/neurophysiological investigation its functioning be investigated in parallel with other regions of brain. This is well exemplified in a recent investigation of Winocur (1985) in which both the dorsal hippocampus and the dorsomedial thalamus were investigated to establish their roles in short- and long-term memory.

> It was concluded that memory loss following thalamic damage is related to a deficit in the early stages of new learning, whereas hippocampal amnesia results from impairment at a later, integrative stage in which long-term memories are formed and durably stored. [Winocur 1985, p. 136]

The story concerning the thalamus is, however, much more complicated. The subtle interaction (and integration) of aspects of motor control, auditory processing, visual processing, and speech/lexical components is exemplified by the reports of Yirmiya and Hocherman (1987) and Raeva (1986). An even more ambitious attempt to show how the thalamus interconnects between associative and limbic cortices is made by Maugière and Baleydier (1986).

Clearly, we still have much to learn about this ancient and crucial "neurointegrating" brain structure, which is why the articles in this issue by Oke and Adams and Crosson and Hughes are so timely.

We do not have space in this introductory article to deal with Weinberger's (1986) admonition to account for the therapeutic efficacy of neuroleptic drugs as part of our description of the pathogenesis of schizophrenia. The volume by Nasrallah and Weinberger (1986) substantially addresses this issue, which amounts to a highly detailed description of the functions of the different types of dopamine receptor and their alteration in schizophrenia. (See also Wong et al. [1984, 1986].) It is, however, the findings of altered dopamine patterning in the thalamus that have led to the report of Oke and Adams, and in the same view it is possible that the amygdala should be entered into the "schizophrenia equation" by virtue of a number of reports, most notably that of Reynolds (1983). Reynolds has demonstrated both altered dopamine concentrations and lateralized asymmetries in the distribution of dopamine in the postmortem schizophrenic amygdala. The amygdala (in the limbic brain) is also a phylogenetically ancient "neurointegrating" structure, and some estimate of its importance in the totality of brain functioning can be obtained from the brain-modeling conceptualizations of Pay (1980*a*, 1980*b*, 1981, 1982). The article by Bernstein contains some discussion and references to data by Bagshaw and colleagues concerning alterations to the skin conductance orienting response resulting from lesions to the primate amygdala. Clearly, further elucidation of this structure's contribution to schizophrenia is needed.

In our somewhat fanciful exposition in previous sections, we have referred to the striatum and basal ganglia. This region of brain is called upon heavily in the report by Crosson and Hughes, and further gains our attention by known involvement in Huntington's disease and the concomitant psychological symptoms which, a few decades ago, frequently led to the diagnosis of some form of schizophrenia (the

case of Woody Guthrie being perhaps the most widely known). Crosson and Hughes draw a most intriguing parallel between choreic movement and the possibility of a speech equivalent, pertinent to schizophrenia. Groves (1983, 1986) has been a persistent explorer of the structure of this region. Recent reports have also implicated the striatum in state dependent learning:

> There is evidence that the striatum is involved in comparing sensory input with already established behavioral programs and serves an adaptive function in allowing the organism to shift sets in association with competing sensory input (Schneider 1984). [Reus 1986, p. 32]

The report by Schneider (1984), which details the potential involvement of the striatum in "sensory gating," is of direct relevance to the article by Freedman and colleagues in the issue, especially in light of the dopaminergic and adrenergic manipulations which these authors perform in the elucidation of mechanisms underlying their evoked potential P_{50} findings. Recently, Hikosada and Sakamoto (1986) have investigated this area (especially the caudate nucleus) in relation to selective attention, short-term memory, and anticipation in primates. Their results directly implicate pathways from the caudate to substantia nigra (pars reticulata) and superior colliculus in these functions. The most intriguing data which they present (from the present perspective) is that control of eye movement (and specifically saccades) is derived from these regions. (The dysfunctions of various aspects of eye movements in schizophrenia have recently achieved the status of a putative biological marker for schizophrenia and have inspired a model of genetic transmission [Matthysse et al. 1986].) The fact that such saccadic control appears to have "state-dependent" aspects ties the work strongly to that of Reus (1986), mentioned above.

A direct investigation of never-medicated schizophrenic patients by Early et al. (1987) using regional cerebral blood flow techniques (PET-O^{15}) strongly indicates hyperactivity in the schizophrenic left globus pallidus. This is an important finding in light of the crucial function of this structure in interaction with striatal structures, thalamic nuclei, and other brain regions. Further, its involvement in speech processes (see Crosson and Hughes' article), and its neurohistopathology in the schizophrenic brains of the Vogt collection (Bogerts et al. 1985*a*, 1985*b*), suggest its importance for further investigation. Bogerts et al. (1985*a*, 1985*b*) indicate that it is the medial area of the globus pallidus which shows histopathology. The techniques of Early et al. (1987) are not sensitive enough (at present) to allow discrimination between the internal and external capsules. Nonetheless, this is an important cross-validation of *in vivo* and *in vitro* findings in schizophrenic humans.

The function of the cerebellum in "cognitive" processes has recently been reviewed by Leiner et al. (1986) in a most authoritative manner. These authors muster evidence indicating evolutionary changes toward greater sophistication in the cerebellum:

> The phylogenetically newest structures of the cerebellum may contribute to mental skills in much the same way that the phylogenetically older structures contribute to motor skills. In both cases the cerebellum can send signals from the dentate nucleus to the cerebral frontal cortex via the thalamus. Signals from the older part of the dentate nucleus certainly help the frontal motor cortex to effect the skilled manipulation of muscles, and signals from the newest part of the dentate nucleus may help the frontal association cortex to effect the skilled manipulation of information or ideas. [Leiner et al. 1986, p. 443]

This quotation serves to underline the massive interconnectedness of subcortical structures and the evolutionary increases in capacity of many (or all) of them, which we hypothesize to have "driven" the development of the cortex. In a more directly applicable vein, however, there is a confused and perhaps seemingly contradictory picture of cerebellar defects in schizophrenia. A recent review of this area, along with examination of Purkinje cell density in schizophrenic and control brains, by Lohr and Jeste (1986) is especially relevant here. The body of data that indicate pathology of the cerebellum in schizophrenic patients is not overly impressive. However, the importance of such pathology to the affected individual patients may be considerable and, as such, further investigation to establish distinguishing function characteristics of a subgroup of schizophrenics (established by PET and blood flow studies during specific forms of information-processing activation), may be a profitable undertaking in the future.

In earlier sections of the introduction we have speculated upon the importance of "visualization" or pictorial imagery, which must be directly mapped upon motoric and speech/linguistic-controlling mechanisms. In relation to the cerebellum, a striking example of this phenomenon in a Japanese case history is cited by Leiner et al. (1986).

> Subjective evidence of a mental deficit caused by a cerebellar le-

sion is provided by a reliable patient in Japan. In this interesting case, described by Sasaki (1985, p. 82), the patient was a doctor of medicine who suffered an infarction in the posterior lobe of the cerebellum. He exhibited a motor deficit on the side of the lesion. In addition, however, he experienced a peculiar deficit when trying to execute an intended movement of the hand on the damaged side. He reported that he could not keep in mind the target of his intended action: When he started to point his finger at his nose or eye or ear or navel, he felt the nose or eye or ear or navel disappear from his mental image of his body. Instead, he imagined the target as if it were in a "sea of clouds," and he had to point his finger in the middle of this vague space. [Leiner et al. 1986, p. 450]

We have had little to say about the cortex as a whole, although we have drawn implications for functioning of the frontal/prefrontal cortex in a neurodevelopmental sense. This is not to be taken as an indication that we consider concepts of cortical development and functioning to be irrelevant to schizophrenia. Instead, it should be taken to indicate that such concepts may be worthy of an entire issue of their own to do justice to the sophistication of their data and its implications. The contributions of "cortex" theorists have led to the observation that cortical areas may be sharply defined, functionally heterogeneous, and variable in number between species. In addition, some cortical fields may be common to all mammals, but species-specific capabilities may be marked by increases in the number of unimodal sensory areas that are multiply interconnected, dynamically maintained, and to some extent self-organizing (Kaas 1987).

In primitive to at least moderately advanced mammals, most of cortex is occupied by orderly sensory representations. Thus, sensory processing is the dominant cortical function, and most processing is concerned with a single modality.

In advanced mammals, perception is based on the coactivation of a number (5–20 for a single modality) of cortical fields. Even simple attributes of stimuli (such as color, motion, form) are unlikely to be based on processing within a single field. However, each activated area undoubtedly makes a field-specific contribution to the resulting perception. [Kaas 1987, p. 148]

Such conceptualizations have a direct empirical bearing upon investigations such as those of Posner and Presti (1987) and Posner et al. (1987). These investigators have addressed the issues of how covert attention may be directed specifically within regions of the visual field. Their work has strongly implicated the parietal lobes in this function, most particularly in the ability to disengage attention from a current focus to redirect it elsewhere. This may have direct implications for schizophrenic patients in whom "perseveration" of response may be predicated upon such factors as failure in ability to disengage attention in a more general way, thus leading to a "stimulus bound" mode of current contextual experience. That the functioning of the posterior parietal lobe may be dependent upon information from the lateral pulvinar (posterior portion of the thalamus) again targets the importance of the Oke and Adams findings reported in this issue. The fact that parietal to frontal lobe communication exists has led Posner et al. (1987) to suggest that this connectivity may be crucial to the avoidance of control by sensory stimuli in order to enable more "cognitive" functions to be undertaken. Posner and Presti (1987) theorize that sensory input may activate in an "automatic" way internal visual, phonetic, and semantic representations, and that "attention" may select any of these representations for further processing. This conceptualization thus reinforces our contention earlier (based upon Broadbent 1984) that information may be represented in different forms or representational codes and that information processing may involve changes from one form to another by processes as yet not fully understood.

In the work of Posner and colleagues, the concept of "automaticity" frequently arises. Such a concept involves the rapid imposition of some form of "significance" assessment which, in our view, can only come from the coherent organization of previous experience and its "forward projection" in time. Hence, our concentration upon neuropsychodevelopment as the source of such "organizational" indisposition in schizophrenic patients.

We may be criticized by our psychiatric colleagues for failing to address the actual "symptomatology" of schizophrenia and then attempting some direct neurological correlation. This approach has been (and will be) attempted by others. We have chosen to conceptualize the entire schizophrenic life experience in an information-processing framework which, we believe, has greater scope for neurological/neurochemical interface. Studies and theories that regard schizophrenic symptomatology as central or peripheral may profitably be conducted in parallel with reasonable hope for success. That such a central symptom of schizophrenia as hallucinations may be peripheral to the condition is well illustrated in a recent report by Bick and Kinsbourne (1987) in which subvocalization blocking led to ces-

sation of auditory hallucinations in schizophrenics.

> The patients complied readily but seemed indifferent to the fact that they could abolish the voices by a simple movement. Patients who had characterized the voices they heard as burdensome or terrifying expressed no relief that they could control them. One patient who reported hearing continuously harassing voices was reinterviewed 1 week later. Asked if she had used the mouth-opening maneuver when the voices became intolerable, she said that she had not and expressed no interest in doing so. [Bick and Kinsbourne 1987, p. 223]

Conclusion

Ideas are at their most fragile in the embryonic stages of their development. Many of the ideas which we have touched upon are in precisely that stage of growth. It is extremely important (and a responsibility to the field as a whole) that such ideas are not being "oversold" and claimed as "the answer" by an overly enthusiastic band of neurobiological devotees on the basis of politics or simply zeal. We have all lived through many "pink spots" and the lessons taught are plain to see. Rather, such ideas as we have alluded to should be regarded more as setting us upon the road to *ask the right questions* rather than providing us with "the answer."

There are weaknesses, very substantial weaknesses, in the neurobiological positions, and we feel that they should be forthrightly and honestly stated, if for no other reason than to do justice to the generations of behavioral and clinical investigators who have learned by bitter experience the enormity of the schizophrenia enigma. The most glaring weakness is the minute number of schizophrenic brains subjected to neurohistopathological and neurohistochemical analysis. The individual investigators have usually been extremely conservative in their claims for the "generality" of their data. Their "supporters" have often been less circumspect. In most cases the pre-mortem behavioral data base (of even demographic variables) has been sketchy to say the least and diagnoses often doubtful. In almost no case has a post-mortem brain been histopathologically regressed against pre-mortem behavioral measures of a sophisticated (cognitive science) information-processing variety. Yet the whole neuroscience/cognitive science convergence cries out for such data. In no neurobiological investigation, to our knowledge, has a large sample of schizophrenic patients (>100) with carefully (age/sex/premorbid status) matched controls been subjected to longitudinal symptomatic study with finely detailed neuropharmacological workups and tightly specified behavioral ratings; then also subjected to a fine-grained (repeat testing) information-processing examination in conjunction with many "second window" variables such as PET, regional blood flow, and topographic evoked potential analysis. The logical conclusion would be to follow and ultimately obtain the brains for *total* neurohistology and neurochemical analysis. The regressions through such data would then constitute a definitive test of many of the clinical and neurobiological hypotheses.

The emphasis upon total brain examination bears restatement in that most neuropathological investigations have had available only a small part of each brain and usually in one hemisphere only. It is an especially sobering thought to realize that no current studies of magnetic resonance imaging have adequately imaged the temporal horn. Furthermore, not a single schizophrenic brain has been comprehensively analyzed with the scanning electron microscope.

Our message is clear; in this issue there are the seeds of new data, new ideas, and, above all, new questions for schizophrenia research. However, nothing which was clinically and epidemiologically true in the past has changed. Large-scale (perhaps multicenter) new investigations are called for with the most sophisticated behavioral and neural imaging tools available. However, all the previous (hard-learned) lessons of clinical investigation must be borne in mind.

In building the edifice of science, data constitutes the building blocks; yet in a very real sense the "science" is the "story" that is finally told. What we see (and therefore what we tell) will change as the years go by and the data (carefully filtered) accumulate. We have tried in a future-oriented and heuristic manner to tell the story as we currently see it. We now pass the floor to our colleagues who have provided the building blocks from which we have seen and told our story.

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Acknowledgment

The research reported was supported, in part, by MH–35367 from the National Institute of Mental Health.

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