Information Processing and Attention Dysfunctions in Schizophrenia

by David L. Braff

Abstract

Abnormalities of information processing have played a central role in understanding schizophrenia since the time of Kraepelin and Bleuler. Clearly, schizophrenia spectrum patients have profound problems focusing attention on salient cues and overcoming the disrupting effects of distracting stimuli. Theoretically, such patients are rendered vulnerable to stimulus inundation, cognitive fragmentation, and thought disorder induced by this inability to adequately process self-generated cognitive cues and stimuli from the complex world that surrounds us. Adding to the strength of such theories, investigators have made considerable progress in clarifying the functional significance and neurobiological basis of information-processing/attentional dysfunctions. This article focuses on our understanding of information-processing/attentional dysfunctions in schizophrenia. The relevant material will be presented in four parts: (1) an overview; (2) a review of specific, conceptual issues in information-processing research of the group of schizophrenias, including the roles of antipsychotic medications and generalized versus specific deficits; (3) a review of 10 common techniques used to tap the information processing and attention dysfunctions of schizophrenia patients; recent advances and novel applications of these techniques in "boundary" populations such as high-risk children and schizotypal patients are discussed and psychopharmacological probes, animal models, and basic strategies are also reviewed; and (4) an integration and suggestions for future directions in information-processing/attention research in schizophrenia. Overall, information-processing research provides an important viewpoint from which we can understand the group of schizophrenias.

Overview

William Blake noted, "If the doors of perception were cleansed, everything would appear...as it is, infinite" (quoted in Huxley 1954). There is a rich tradition of looking at the critically important information-processing/attentional dysfunctions of schizophrenia spectrum patients that disrupt the "doors of perception." Careful descriptive clinicians, such as Kraepelin (1921), noticed "a certain unsteadiness of attention" in dementia praecox patients. Syntonic with these observations, Bleuler (1911/1950) recognized that "acute attention is lacking" in schizophrenia patients. Since McGhie and Chapman (1961) focused on "disorders of attention and perception in early schizophrenia" from a descriptive and phenomenological viewpoint, investigators have consistently tried to identify and understand the neurobiological substrate of these information-processing deficits that seem characteristic of schizophrenia patients (e.g., Braff 1985; Holzman 1987; Nuechterlein 1991).

Attempts to quantify information-processing/attentional deficits in schizophrenia patients have borne

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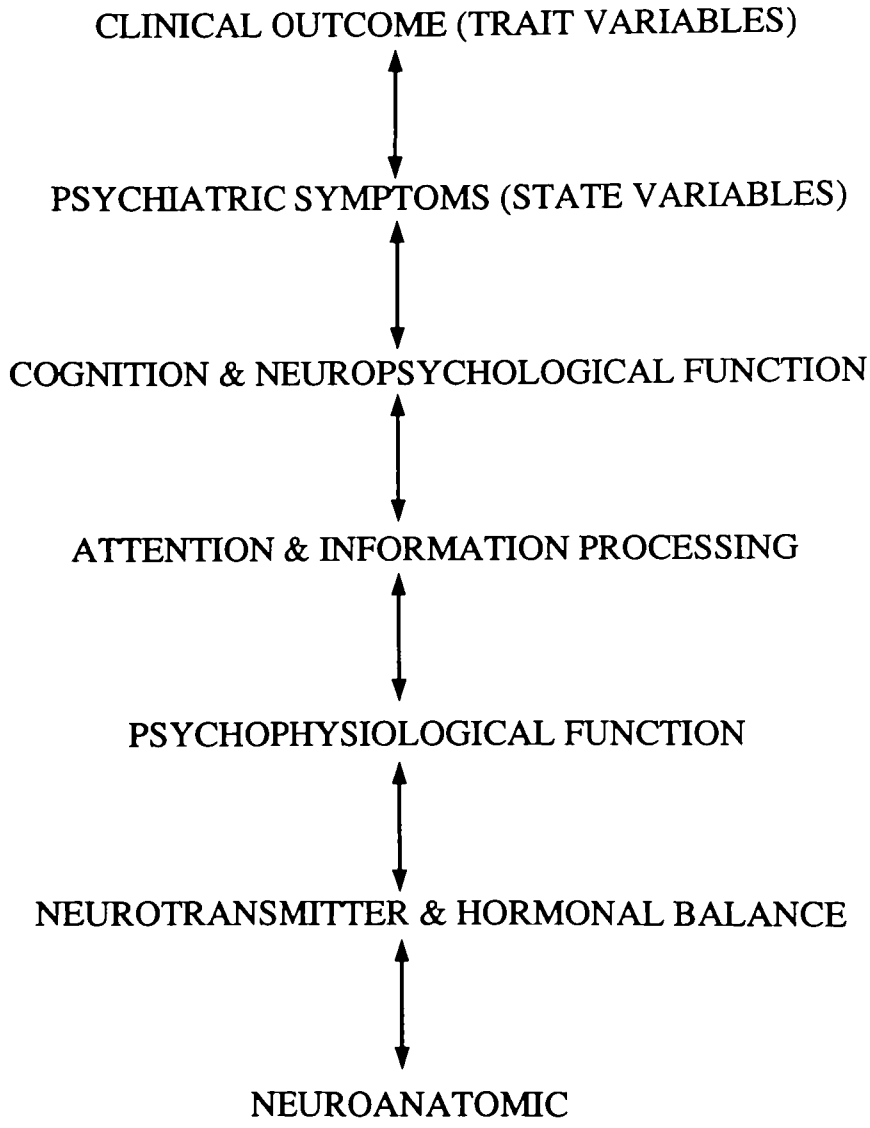
many positive results and have, in turn, stimulated considerable research and numerous reviews (Dawson and Nuechterlein 1984; Nuechterlein and Dawson 1984; Braff 1985; Kietzman et al. 1985; Dawson 1990). The fundamental focus of these studies and reviews is that schizophrenia patients have critical deficiencies in information-processing abilities that are revealed and enhanced when high processing loads, multiple tasks, distraction, or other stressors demand the rapid and efficient processing of information. These trait-linked deficits are seen not only in schizophrenia patients, but also in individuals at the "boundaries of schizophrenia" (i.e., schizotypal patients, high-risk children, "unaffected" family members [Siever 1991]). Along with the long-term, unremitting, trait-linked reduced capacity or inefficient processing of task-relevant cognitive operations in schizophrenia patients, other attentional deficits may be state-linked (e.g., Saccuzzo and Braff 1981). These state-linked collapses of information processing may be characteristic of psychosis in general (e.g., schizophrenia, mania, drug-induced psychosis).

A valuable model for examining both the trait- and state-linked information-processing disturbances in schizophrenia patients is graphically displayed in figure 1. In this context, information processing and attention form a fulcrum, and an upward analysis enables one to understand neuropsychological and cognitive dysfunctions that may flow from a fundamental information-processing abnormality. In this upward direction, both trait- and state-related symptoms and subtle cognitive deficits of schizophrenia spectrum patients can be understood. It is important to note that trait-linked deficits may extend to individuals at high risk for developing schizophrenia and to other individuals, such as the seemingly unaffected family members of schizophrenia patients. These unaffected family members, who should share deficits in information processing with a schizophrenia relative, are an interesting challenge to theories of psychosis because they apparently tolerate

Figure 1. A basic framework for understanding the significance of information-processing abnormalities in schizophrenia patients



some degree of aberrant sensory processing without psychotic decompensation. Thus, in an upward analysis, investigators strive to understand the neuropsychological, symptom, and outcome correlates of schizophrenia.

Information Processing. The terms "information processing" and "attention" are widely used but often inadequately defined. This is understandable; they are wide-ranging concepts and, at times, difficult to quantitate even in normal persons. The concept of information processing arose from attempts to define the sequence of operations that occur to stimuli in the central nervous system (CNS). Initially, theories stressed that stimuli were normally processed in a series of steps or "stages" that corresponded to operations performed on them at different levels and locations in the CNS. Stimuli were conceptualized as being processed and encoded in a way that facilitated perception, memory, and associations and gave this information meaning in terms of the outside world. Schizophrenia patients were viewed as having blocks or abnormalities in the early stages of information processing, which led to a cascade of "downstream" effects on cognition and social functioning (Saccuzzo et al. 1974).

In some rather surprising ways, these stage theories are quite syntonic with Freudian hypotheses of how energy is cathected and transferred within the psychic apparatus. From its roots in cognitive psychology, information-processing research originally concentrated on a "microgenetic" approach, which involved analyzing information processing in epochs or stages of several hundred milliseconds. Subsequently, communications theory led to an explosive growth of information-processing hypotheses and techniques (James 1950). Recently, information processing has been interpreted in terms of parallel and complex channels rather than in terms of serial and simpler stage models, which have been seriously challenged on multiple grounds (Edelman 1987). In the most advanced form of information-processing theory, computer-generated models are constructed that rely on neural circuit or network theory, which stresses how cascades of neurons in multiple loci fire in an integrated symphonic array of time-coordinated events that are impaired in schizophrenia patients (Hoffman and Dobscha 1989; Servan-Schreiber and Cohen 1992). This hypothesized neural network dysfunction in schizophrenia is given life (and the possibility of disconfirmation) only by specific data-based work on imbalances of neural circuitry underlying processes such as CNS inhibition in schizophrenia patients (Swerdlow and Koob 1987).

Attention. Although attention seems a simple concept to understand, it is extremely difficult to define operationally. James (1950) noted that the process of attention is, on some level, known to everyone as the "taking possession of the mind ... of one out of what seems to be several objects or trains of thought." This simple intuitive observation has served as a gateway to an enticing but ambiguous topic in the only modestly successful attempt to define attention. Parallel to the simple, sequential stage models of information processing, attention at first seemed to be a clear, straightforward concept. Then various theoreticians began to discuss the involuntary, passive attentional processes that seemed effortless and are representative of the open doors of consciousness to the world around us. Involuntary attention has also been linked to the natural valence that a stimulus has for an individual (Braff 1985). These valences are both fixed and somewhat flexible. Thus, for a thirsty person in the desert, the sound of a bubbling brook is a stimulus with a powerful attention-grabbing property. The same person, fully hydrated, would have a different reaction to this stimulus. Thus, even at a simple appetitive level, attention seems to be plastic and changeable in nature. Writing or reading a difficult book chapter might be viewed as an attention-demanding task that forces the individual to direct a voluntary, effortful "beam" of attention on a specific topic or area. This voluntary attention and vigilance function must be consciously and continually focused on the task on hand, lest fatigue or other involuntary factors shift attention away from the task to some more naturally reinforcing or valenced activity. In the widest framework possible, one would conceptualize involuntary attention as linked to autonomous ego processes described by psychoanalysts for many years (e.g., Hartman 1939) and voluntary attention as linked to more demanding activities. As will be seen, these two attentional modes may form a continuum rather than a discontinuous form of cognitive processing (Braff 1992).

Callaway and Naghdi (1982) believed that schizophrenia patients have an attentional deficiency that can be characterized as specifically impairing conscious, serial, and

limited channel capacity operations. In contrast, automatic (unconscious) processes often appear to be spared in schizophrenia patients. This model stresses the distinction between controlled "serial" processing and automatic "parallel" processing in understanding information-processing and attentional deficits in schizophrenia patients. This framework is syntonic with the work of Posner, who emphasized the importance of the presence or absence of "cost" when systems are loaded with information (Posner 1978). Thus, there are limited channel capacity processes that are characteristic of controlled serial systems, which are disordered in schizophrenia. In contrast, parallel processes seem to be less impaired in schizophrenia patients. Although the details of the Callaway and Naghdi (1982) model are too complex to review here in detail, suffice it to say they make a critically important point: "to build a general model, we need to know how various phenomena relate to each other" (p. 346). For such comprehensive models to be built, multiple experimental measures must be obtained from the same patients to see how these converging as well as diverging measures relate to each other.

Integration of Information Processing and Attentional Theories. In building on the work of McGhie and Chapman (1961), Neale and Cromwell (1970), and other investigators, a slightly different approach has been taken to understand how information-processing and attentional deficits in schizophrenia patients can be translated into a common language. Granholm (1992) has reviewed this area and emphasizes that early stage theories of attentional deficits in schizophrenia were generated by Broadbent's (1958) idea that sensory input is mediated by a single, limited-capacity channel. Subsequently, Treisman (1969) expanded on this model and added the concept of filtering and "functional channels" that are actively selected for processing. Broadbent's model, which also flows from this sort of approach, stressed filtering, categorizing, and pigeonholing of information through limited information-processing channels. All the data about schizophrenia deficits do not fit limited channel capacity/passive attentional deficits in the model proposed by stage theorists. For example, Kahneman (1973) showed that the processing of a second stimulus does not always wait until analysis of and response to the first stimulus, indicating that multiple channels and active processes of selection may well be involved in tasks that, on the surface, seem quite simple. Thus, a series of alternative general theories and models of information processing/attention have been proposed. One type of theory that is currently being explored centers on the extent and manner of allocation of attentional resources. Such "allocation" theories generally stress schizophrenia-linked deficits in the active, functional allocation of attentional resources, rather than emphasizing a normal, passive, single channel with a "bottleneck" interpretation of deficits. Granholm (1992, p. 5) has pointed out that "the notion of a single pool of non-specific processing resources has been called into question and some theorists have proposed the existence of multiple independent resource pools" (Navon and Gopher 1979; Wickens 1984).

The concept of multiple resource pools and the numbers and types of pools that might exist is one of the more debated issues in resource theory (Granholm 1992). To some extent, the strengths of resource theory are its flexibility and its dynamical aspects. Unfortunately, when one discusses "resource allocation" it is often difficult to operationalize and quantify exactly what is being discussed. For example, when processing resources seem deficient in schizophrenia patients, this deficiency may result from excess stimulation due to sensory flooding, a smaller pool of resources, inability to mobilize and allocate resources, or excess resource allocation to task-irrelevant stimuli. In addition, automatic processes may be disrupted, requiring that resource demanding controlled processing be used to carry out processing normally accomplished through relatively resource-free automatic operations (Callaway and Naghdi 1982; Dawson and Nuechterlein 1984; Nuechterlein and Dawson 1984). In one study discussed below, Grillon et al. (1990) illustrate how these resource allocation concepts can be investigated.

Clearly, an extended discussion of information-processing/attentional theories is beyond the scope of this review, but the framework cited above is important in discussing and interpreting the results cited below. For heuristic purposes, this review will use mostly information-processing (vs. attentional) interpretations of schizophrenia-linked deficits.

Conceptual Issues

It is important to note that information-processing measures

and schizophrenia-linked deficits are not fixed or immutable. Moderate or even minor paradigmatic alterations may dramatically change the data of the dependent measure being examined. For example, in the event-related potential (ERP) P50 gating paradigm, it appears that altering the click that elicits the P50 wave on the order of 1 msec may dramatically change the observed pattern of schizophrenia-linked gating deficits (Judd et al. 1992). Some of these information-processing paradigms seem to be exquisitely sensitive to changes in stimulus intensity, interstimulus intervals, etc., in detecting the deficits of schizophrenia patients. Braff and Geyer (1990) noted that it is often assumed that information-processing functions (1) are significant for understanding the cognitive organization of organisms; (2) are plastic or alterable through changes of their neurobiologic substrates; (3) are normally operating at a threshold level so that even minor-appearing impairments can result in cognitive abnormalities; and that (4) a primary attentional or cognitive impairment may lead to dramatic symptoms of schizophrenia such as paranoia and delusional formation, which can be viewed as maladaptive attempts to integrate abnormal experience (Butler and Braff 1991).

Before the basic techniques and their novel applications are discussed, a number of key general issues must be addressed.

State and Trait Variables. The distinction between state- and trait-related variables is very important in schizophrenia research. Certainly, in the broad range of information-processing research, it appears that many deficits are characteristic of a psychotic state per se, whether it is caused by schizophrenia, mania, schizoaffective, or a drug-induced psychotic episode. This lack of diagnostic specificity is also mirrored by clinical and neurochemical changes since there appears to be a final common pathway of psychosis-linked abnormalities across a broad range of variables (e.g., Carlson and Goodwin 1973). After the acute psychosis abates, information-processing deficits seem to persist selectively in schizophrenia patients rather than in mania patients or those with drug-induced psychosis. They also persist in subjects at the boundaries of schizophrenia (e.g., Braff 1981). This pattern of findings supports the hypothesis that information-processing abnormalities are a trait-linked marker of vulnerability to schizophrenia disorders. This fact has important implications for identifying phenotypic markers in genetic studies of schizophrenia (see below).

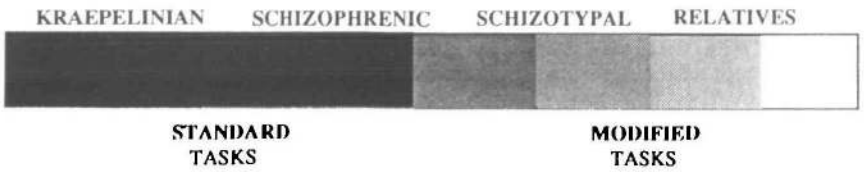
Many variables listed in table 1 under "Basic Techniques" appear to be fundamental trait-linked markers for schizophrenia. This conclusion is supported by two lines of research in schizophrenia patients. First, antipsychotic medications do not fully normalize these information-processing functions across a range of dependent measures (see below). Research also indicates that the observed deficits in schizophrenia patients are not medication-induced artifacts. Second, subjects at the boundaries of schizophrenia (e.g., unaffected family members, schizotypal patients [Siever 1991]) show a pattern of trait-linked information-processing deficits similar to those of schizophrenia patients. Thus, these deficits in "boundary" subjects seem to result not from "patienthood" (e.g., insti-

Table 1. Techniques used to assess information-processing/attention dysfunctions in schizophrenia patients

Basic techniques	Novel applications
Sensorimotor gating Prepulse inhibition P50 gating	Family members
Ocular motor function (smooth pursuit eye movement)	Schizotypal patients
Skin conductance orienting response	Psychosis-prone individuals
Span of apprehension	Sensory overload
Visual backward masking	Neuropsychology
Continuous performance task	Psychopharmacology
Event-related potentials (brain electrical activity)	Brain imaging
Reaction time	Positron emission tomography
Latent inhibition	Animal models/brain circuitry
	Neural tissue transplants
	Phenotypic markers (molecular biology studies)

tutionalization or treatment) but from a genetically linked dysfunction that is subclinical and unlikely to adversely affect motivation or performance. These studies indicate that information-processing deficits are somehow fundamental correlates of the schizophrenia diathesis. Still, it is true that at the boundaries of schizophrenia, task sensitivity may need to be enhanced by means of modified tasks to identify these deficits (see figure 2).

Figure 2. Psychophysiology and the schizophrenia spectrum



At the subtle boundaries of schizophrenia (in schizotypal patients or family members of schizophrenia patients), information-processing tasks may need to be modified to increase task difficulty. Figure courtesy of Dr. K Cadenhead.

Antipsychotic Medication Effects. It seems very unlikely that antipsychotic medications induce the observed information-processing deficits of schizophrenia patients. In fact, it seems probable that neuroleptics at least partially reverse attentional deficits. First, almost all studies since Spohn et al.'s. (1977) critical article in this area have indicated that antipsychotic medications do not induce deficits and that they probably cause at least a limited normalization of the basic information-processing and cognitive deficits of schizophrenia patients (Oltmanns et al. 1978; Braff and Saccuzzo 1982; Spohn and Strauss 1989). Second, studies have been conducted in nonmedicated groups or subgroups of schizophrenia patients, and these individuals show clear information-processing deficits (Braff and Saccuzzo 1982). Third, studies at the boundaries of schizophrenia indicate that nonmedicated schizotypal patients (Braff 1981; Siever et al. 1990) and unaffected, nonschizophrenia spectrum family members (Adler et al., in press) show information-processing deficits similar to those of schizophrenia patients. Fourth, animal model studies of information-processing functions such as prepulse inhibition indicate that although hyperdopaminergia induces schizophrenia-like information-processing deficits (Swerdlow et al. 1986), antipsychotic medications reverse these deficits, probably via their D_2 blocking properties (Swerdlow et al., in press) but possibly also via other mechanisms (e.g., serotonergic effects).

Cumulatively, the evidence is overwhelmingly supportive of the conclusion that most "core" information-processing deficits are characteristic of schizophrenia per se and are not an antipsychotic medication-induced artifact.

Fact/Artifact and Distractibility. For 40 years, investigators and critics have wondered whether the various cognitive and information-processing deficits seen in schizophrenia patients are central to the disorder or whether the observed deficits are merely an artifact or epiphenomenon of the general distractibility and psychopathology of schizophrenia (Sutton 1973). If schizophrenia patients simply do not pay attention to various tasks because of their generalized deficits, then information-processing deficits will not be very informative about the fundamental neurobiological substrate of schizophrenia because these deficits will be nonspecific. Some evidence argues forcefully that Sutton's original conclusion is valid—that is, schizophrenia carries with it a specific deficit in information processing that leads to distractibility.

First, neuropathological studies and imaging studies (e.g., Jernigan et al. 1991) have consistently identified abnormalities in various axes of the cortico-striato-pallido-thalamic (CSPT) circuitry that specifically controls the modulation of information processing in paradigms such as prepulse inhibition of the startle response (Braff et al. 1992). Specific frontal-temporal cortical and hippocampal deficits in the brains of schizophrenia patients are compatible with the schizophrenia-linked problems with "scratch-pad memory," attentional allocation, and memory read-in functions of these brain areas (e.g., Goldman-Rakic 1987, 1988; Jernigan et al. 1991). As we learn more about the neuropathology of schizophrenia, the correlated information-processing deficits subserved by the affected brain areas will be easier to identify and test. In the case of distractibility, many of the studies cited below offer an alternative possibility to viewing distractibility as a generalized, nonspecific phenomenon: It may be a highly specific neurobiological correlate of deficient gating and

information processing (Garmezy and Streitman 1974; Harvey and Pedley 1989).

Second, studies of high-risk children, family members, and schizotypal patients (cited above and below) support a basic, schizophrenia-linked information-processing deficit associated with the schizophrenic diathesis. This support is analogous to that provided by neuropsychological studies in which unaffected monozygotic twins of schizophrenia patients show subtle but clear deficits compared with normal subjects (Goldberg et al. 1991). Thus, individuals with no clear psychiatric symptoms that would disrupt information-processing functions perform abnormally on a variety of tasks. Although one could argue that these individuals have extremely subtle subclinical syndromes, such an argument would only underscore the implication that some neurobiological abnormality affects these information-processing functions independent of symptoms per se, even in putatively normal volunteers (Siever 1991; Butler et al., in press).

Third, recent studies (see gating studies below) indicate that, in paradigms that require minimal effort, the schizophrenia deficits are clear.

Fourth, the latent-inhibition deficits exhibited by schizophrenia patients (described below) and in studies of negative priming (e.g., Beech et al. 1989) result in superior rather than deficient performance but are attributable to an underlying inhibitory deficit. Overall, there seem to be highly specific deficits in information processing in schizophrenia patients.

Implications for Daily Functioning. Critical questions about information-processing dysfunctions in schizophrenia involve specifying how these abnormalities affect activities of daily living. If a person cannot process tachistoscopically presented rapid sequential stimuli or track a moving target, what does this mean for how the person navigates through the complex social and stimulus-laden world that surrounds us? The implication of figure 1 is that information-processing abnormalities are caused by a complex cascade of neuroanatomic, neurotransmitter, and physiological imbalances. In an upward direction, we see the implications of information processing for neuropsychological, cognitive, and symptomatic functioning. These assumptions are quite amenable to experimental confirmation. Indeed, various sensitive measures of information-processing dysfunction correlate with Wisconsin Card Sorting Test (WCST; Heaton 1981) perseverative responses (Butler et al. 1991), negative symptoms (Braff 1989), therapeutic prognosis and outcome (Zahn et al. 1978; Saccuzzo and Braff 1981), and trait-linked familial patterns of inheritance (Holzman et al. 1988; Clementz et al. 1992). All of these studies, discussed in detail below, reflect the fundamental importance and functional significance of information-processing measures in schizophrenia patients.

Basic Techniques and Recent Advances

Table 1 lists the basic techniques that will be described here as well as the novel applications and paradigmatic manipulations that allow investigators to tap into new issues at the frontiers of information-processing research in the schizophrenic spectrum. This section will first discuss the basic techniques listed in table 1 and those novel applications and new results (advances) that are relevant to these specific techniques.

A wide and imaginative armamentarium of research techniques has been used to quantify the information-processing abnormalities seen in schizophrenia patients. Although many of these techniques were pioneered in a simple form, there is an increment in the richness, variety, and alternative interpretations of the data and their meaning in psychopathological investigations. Ten techniques commonly used to assess information-processing/attentional abnormalities in schizophrenia patients are discussed below; certain other techniques are excluded because of space limitations. In fact, these 10 techniques could and have formed the basis for extensive reviews. An article of this length cannot do justice to the imagination and tenacity of the many investigators who have used one specific technique, sometimes for decades, to fully understand the implications of these information-processing functions in both normal control subjects and schizophrenia patients. It is to be hoped that the techniques chosen and the accompanying discussions will present a vivid picture of the importance of information processing in understanding schizophrenia.

After the discussion of each technique and its uses in schizophrenia, a section on advances will outline some important clinical and basic correlates of these deficits within the framework illustrated in figure 1. These advances will largely focus on information that has become available since Holzman's (1987) review of this

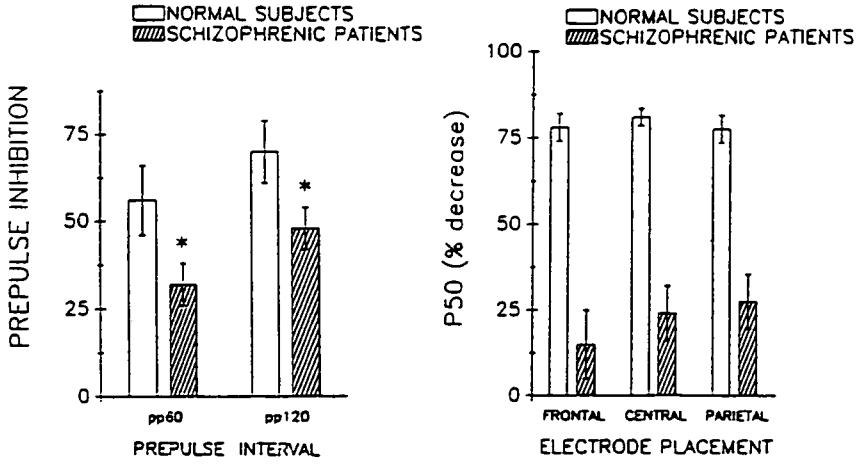
area in the 1987 "Special Report" issue of *Schizophrenia Bulletin*.

Gating as Measured by Prepulse Inhibition and P50 Gating. The concept of gating is derived from the clinical observation that schizophrenia patients are unable to "gate" or screen out irrelevant stimuli. McGhie and Chapman (1961) noted that patients with schizophrenic disorders are subject to inundation by sensory stimuli, which leads to sensory overload, cognitive fragmentation, and thought disorder (Venables 1960). There are two major methods by which gating deficits in schizophrenia-disordered patients are measured: (1) the gating of the human startle response by weak prestimuli at an interstimulus interval of 50 to 500 msec, known as prepulse inhibition; and (2) the gating of the P50 ERP component when two stimuli are presented in a close (i.e., 500 msec) temporal relationship (see figure 3). In each of these cases, the first stimulus acts to set up an inhibitory function or network that blunts and attenuates response to the second stimulus, a general process known as proactive interference (Merriam et al. 1989). Theoretically, schizophrenia patients have deficient gating and therefore the inhibitory effects of the first stimulus would be attenuated or blunted, which leads to disinhibited or ungated responses to the second stimulus. This loss of gating or reduction in preattentive buffer capacity removes an important safeguard that normally protects individuals against cognitive overload and fragmentation.

Prepulse inhibition of the startle response. Normally, a strong exteroceptive stimulus, such as a sudden, rapid-onset 100-dB tone or sudden bright light, elicits a series of flexion and extension responses —known as the startle response— in almost all mammals. The startle response is inhibited when the startling stimulus is preceded by 30 to 500 msec by a weak prestimulus in the same or a different modality. The effects of the prepulse on the reflex include amplitude inhibition (smaller blinks) as well as latency facilitation (faster blinks) on measures of latency to blink onset and latency to peak amplitude. This cross-modal, cross-species prestimulus inhibitory effect is often felt to be "preattentive" and to insulate the individual against being inundated by stimuli. Prepulse inhibition is diminished in many schizophrenia patients who display large startle responses (i.e., an absence of normal amplitude inhibition) and variably impaired latency facilitation in the prepulse paradigm (Braff et al. 1978, 1992). The efficacy of the weak prestimulus in inducing an inhibitory response in schizophrenia patients is dramatically attenuated when the prepulse precedes the startling stimulus by 60 to 120 msec. This loss of prepulse inhibition in schizophrenia patients occurs across a fairly broad range of prepulse intensities (Grillon et al. 1992).

Advances. Deficient prepulse inhibition appears to extend to hypothetically psychosis prone (Simons and Giardina 1992) and schizotypal patients (Cadenhead and Braff 1992; Cadenhead et al., in press) who are at the boundary of schizophrenia and are not medicated or inundated with psychotic symptoms, indicating that there is a fundamental deficit in the

Figure 3. Measurement of gating deficits in schizophrenia patients



Left panel: In the 60- and 120-msec prepulse (pp) conditions, 26 schizophrenia patients (compared with 26 normal controls) show loss of prepulse inhibition or gating of startle response. Prepulse inhibition is displayed as group means (±SEM) for difference in response magnitudes between pulse-alone and prepulse+pulse trials. $^*p < 0.05$, analysis of variance. Right panel: Separate groups of 20 schizophrenia patients and 20 normal control subjects show loss of gating in the event-related potential P50 conditioning test (gating) paradigm.

schizophrenic prepulse inhibition response. Also, in an upward analytical direction, deficient prepulse inhibition correlates significantly with the inability to screen out enteroceptive stimuli elicited in schizophrenia patients by Rorschach cards and quantified by Perry et al.'s Ego Impairment Index (1992). Preliminary results indicate that prepulse inhibition deficits correlate with increased perseverative responses on the WCST (Butler et al. 1991), which may point to a common neural substrate for these two deficits.

An important area of prepulse studies is the effect of volitional allocation of attention to the prepulse, which results in an increase in prepulse inhibition (Filion et al., in press *a*). The work of Dawson, Nuechterlein, Schell, and Filion (e.g., Filion et al., in press *b*) has been especially important in beginning to delineate this area. It appears that the prepulse inhibition phenomenon has involuntary and voluntary components and that it may offer one way to parse out deficits in these two systems in schizophrenia patients (Braff 1992) and to enhance task sensitivity in detecting prepulse inhibition deficits in boundary populations (figure 2).

In addition, startle response measures are particularly amenable to animal modeling because the startle reflex occurs in all species of mammals. In a series of investigations conducted on rats, the primary startle circuit has been delineated and has been found to consist of five neurons between the auditory nerve and the spinal outflow, as specified by Davis (1984). The work of Swerdlow, Geyer, Koob, Braff, and their associates has indicated that there is an integrated CSPT circuitry that serves a powerful inhibitory function on the startle response (Swerdlow and Koob 1987). Lesion and biochemical (Swerdlow et al. 1986) manipulations at multiple levels of the CSPT circuitry cause a loss of normal inhibitory function of the prepulse and a loss of gating that seems analogous to that seen in schizophrenia patients. This work is compatible with hypotheses of neural cascades or networks that serve inhibitory functions. Systemic pharmacological manipulations, such as the administration of the dopamine agonist apomorphine, can also induce loss of gating (Swerdlow et al., in press). Cumulatively, this work indicates that such manipulations as increasing nucleus accumbens dopamine tone (Swerdlow et al. 1986) cause a loss of normal gating and that this loss can be reversed by the D_2 receptor blocking properties of efficacious antipsychotic medications (Swerdlow et al., in press). The ability of antipsychotic medications to block the apomorphine-induced loss of prepulse inhibition is significantly correlated with their clinical potency and their affinity for the D_2 receptor; thus, prepulse inhibition may serve as a useful screening tool for new antipsychotic drugs (Swerdlow et al. 1992).

P50 gating. The history of the P50 gating paradigm is parallel to that of the prepulse inhibition of startle. Basically, Freedman and his colleagues have repeatedly shown that when two rapid-click stimuli are separated by 500 msec, the P50 ERP response to the first click is always fairly large but the P50 response to the second click is blunted or attenuated in normal subjects by the inhibitory effect of the first stimulus. In schizophrenia patients, whether they are medicated or not (Adler et al. 1982; Freedman et al. 1983), this normal inhibitory process is lost. Although Kathmann and Engel (1990) failed to replicate these results, it appears that this nonreplication is due to the much longer duration of the click stimuli that were used (Judd et al. 1992). The pattern of results found by Freedman et al. (1983) has now been confirmed at least twice in the published literature (Boutros et al. 1991; Judd et al. 1992).

Advances. Freedman, Adler, Waldo, and their colleagues (e.g., Waldo et al. 1991) have done critical studies that show that family members of schizophrenia patients and other boundary groups who are not symptomatic and who are not receiving antipsychotic medications also show increased rates of inhibitory and gating failures. These findings are critically important because they show that the gating failure is not due to the effects of illness, medication, or institutionalization but seems to be related to the schizophrenic diathesis per se. Freedman and associates have found that the P50 gating deficit is familially associated with schizophrenia and is suitable for the study of potential phenotypes in families to be studied by means of linkage analysis with polymorphic genetic markers (e.g., Waldo et al. 1991).

In a series of very innovative studies now under way, Freedman and associates are examining hippocampal tissue from the aborted fetuses of women that have schizophrenia. The hippocampal tissue is dissected out of these fetuses and implanted into the anterior chambers of the eyes of rats, where it can grow and the gating properties of the neural tissue can be measured. It should be noted

that the hippocampus seems to be critically important in the gating phenomenon, according to Freedman et al. (1983), and the hippocampal efferents to the ventral striatum are part of the CSPT neural circuit. Freedman et al. (1983) have also shown that the gating phenomenon, at the level of the hippocampus and temporal lobes, may rely on cholinergic mechanisms and that gating dysfunction in unaffected relatives of schizophrenia patients is normalized by the administration of nicotine, indicating that gating deficits may be a nicotinic receptor-based phenomenon (Adler et al., in press). These findings are consistent with the induction of gating deficits in rats by the administration of nicotinic (but not muscarinic) antagonists (Luntz-Leybman et al. 1992). Dipole localization and magnetoencephalography (Reite et al. 1988) have initially indicated that the generator of the P50 wave, like the generator of the P300 wave (McCarley et al. 1989, 1991), is based in the temporal lobe. Undoubtedly, the neurobiological basis of P50 gating will also be delineated in animal model studies (Schwarzkopf et al. 1992*b*) analogous to the work done on startle prepulse. Recently, Schwarzkopf et al. (1992*a*) reported that P50 gating and prepulse inhibition in normal subjects covary and may thus be related to each other. This correlation speaks to the possibility that there is a common underlying neural substrate and mechanism that leads to generalized gating deficits in schizophrenia patients and other subjects at the boundaries of schizophrenia.

Ocular Motor Function/Smooth-Pursuit Eye Movement. Ocular motor functioning is an area of psychophysiological research that appears to be simple but has multiple layers of complexity. There are a variety of measurement issues to consider (see Holzman et al. 1976; Friedman et al. 1991; Iacono and Clementz 1993), including stimulus parameter characteristics, eye movement recording techniques, and methods for quantifying data. Careful consideration of these issues is required before ocular motor methodology can be maximally helpful in the study of brain pathology (Clementz and Sweeney 1990).

A substantial body of evidence indicates that schizophrenia patients and their first-degree relatives have ocular motor abnormalities (Iacono and Clementz 1993) and that these abnormalities correlate with other markers of schizophrenia and their symptoms (Siever et al. 1982). The ocular motor system comprises several subsystems, not all of which are affected in schizophrenia patients (e.g., Yee et al. 1987). Dysfunction of the smooth-pursuit system, however, is consistently reported in schizophrenia patients (Holzman 1987; Abel et al. 1991). Smooth-pursuit eye movement abnormalities are also related to other deficits on tasks such as the WCST (Litman et al. 1991).

Problems with smooth pursuit are not the only ocular motor abnormalities found among schizophrenia patients. Such patients have mild to moderate abnormalities of saccadic latency and peak velocity (Moser et al. 1990). They also have great difficulty in inhibiting reflexive glances during an antisaccade task (Thaker et al. 1989). Patients with specific lesions of dorsolateral prefrontal cortex (Pierrot-Deseilligny et al. 1991) or loss of striatal and cortical cholinergic and GABAergic neurons (Tian et al. 1991) also have difficulty in inhibiting reflexive glances during this task. This finding perhaps implicates dorsolateral prefrontal cortex and/or basal ganglia abnormalities among such patients. Further research with neuro-ophthalmologically informed measurement techniques will be able to more clearly address this hypothesis.

Advances. It is well known that a large proportion of first-degree relatives of schizophrenia patients (Holzman et al. 1973; Blackwood et al. 1991; Clementz et al. 1992) and a large proportion of patients with schizotypal personality disorder (Siever et al. 1990) have abnormal ocular motor performance.

The overall pattern of findings is consistent with the hypothesis that ocular motor dysfunction is a marker of genetic liability for schizophrenia (Iacono et al. 1988; Iacono and Clementz 1993). In fact, two separate research groups have further demonstrated that ocular motor abnormalities follow a Mendelian inheritance pattern in families ascertained via a schizophrenia proband (Holzman et al. 1988; Grove et al. 1992). These results are promising and suggest that the use of ocular motor abnormalities in linkage analyses may facilitate the identification of a major gene conveying substantial risk for this disorder.

Skin Conductance Orienting Response (Habituation and Nonresponsivity). The use of the skin conductance orienting response (SCOR) in psychophysiological research in schizophrenia has a long and varied history. Stimuli have been divided into two categories: strong exteroceptive

stimuli that induce defensive and startle responses and milder information-laden stimuli that induce orienting responses (e.g., skin conductance changes, heart rate deceleration). Within this context, many investigators have concerned themselves with the electrodermal SCOR to milder stimuli, and these studies have examined three variables: responsiveness versus nonresponsiveness, nonspecific fluctuations in electrodermal skin responsivity, and habituation of the SCOR.

Much of the original work on SCOR involved quantifying habituation. Habituation, often viewed as the simplest form of learning (Geyer and Braff 1982), is the observed decrement in response magnitude when the same initially novel stimulus is presented repetitively at rates that do not induce receptor sensitivity changes or end organ fatigue. In this context, observed habituation is the sum of two underlying opposite processes: habituation and sensitization. Viewed in this way, habituation is related to gating and is a way for the organism to "damp down" or decrease its responsivity to repeated stimuli. This type of adaptive mechanism has functional significance. If background noises can be excluded from consciousness, trivial stimuli will not inundate the individual and cause cognitive disruption and sensory overload, parallel to the sort of problems that might occur with sensory gating failures. The most common way of measuring the habituation failure hypotheses in schizophrenia patients has been the use of the SCOR. There is an assumption that if an individual shows habituation failures on the SCOR, this sort of habituation deficit would extend to other stimulus and response systems and would be a characteristic marker of the preschizophrenia or schizophrenia individual.

There is variable evidence that at least some schizophrenia patients (Bernstein 1987) show deficits in SCOR habituation, a finding that is consistent with the impaired filter or defective habituation theories of schizophrenia and may have validity in predicting outcome (Dawson et al. 1992). However, it turns out that the measurement, observation, and modulation of skin conductance orienting responsivity is extremely complex. In contrast, a parallel complex pattern of habituation impairments has also been observed with the startle response (Geyer and Braff 1987; Braff et al. 1992). This complexity is not surprising, because almost all information processing/attention functions, even those that appear at first to be simple, are under very complex CNS control and can be fragmented or interrupted at multiple levels in multiple directions.

Advances. Bernstein's review (1987) does an excellent job of summarizing the literature. Basically, although some support was found for the hypothesis that schizophrenia patients are poor habituators, a major surprising finding of a multinational study of a variety of patients indicated that 40 to 50 percent of schizophrenia patients were nonresponders to stimuli of mild to moderate intensity. These nonresponders were more clearly a group than were the poor habituators, a fact that may result from excess nonspecific electrodermal fluctuations in schizophrenia patients (Frith et al. 1982). Per Buchsbaum and Haier's (1987) recommendation to examine subgroups on the basis of dependent measures and biological criteria such as nonresponsivity, it was found that nonresponders were characterized by high levels of emotional withdrawal and cognitive disorganization (Bernstein 1987). These clinical characteristics did not seem to be the result of hospitalization, medication (Spohn et al. 1989), or social consequences of being labeled "schizophrenic," and these nonresponders seemed also to respond poorly to neuroleptics.

More recently, Dawson et al. (1992) reported that tonic electrodermal arousal is associated with the onset of psychosis, whereas nonresponding is a vulnerability marker. Sensory nonresponsivity is consistent with the profile of negative-symptom patients who are putatively antipsychotic nonresponsive, having inflated critical stimulus durations on the visual backward masking task (Braff 1989). Additionally, slow SCOR habituation seems to be a marker of subsequent schizophrenia among high-risk children, indicating that the measure of habituation can be discriminated from the measure of nonresponsivity. Hollister et al. (submitted for publication) have recently unearthed 30-year-old data that support the prognostic significance of SCOR abnormalities in high-risk children. Nonspecific fluctuations associated with impaired adaptation/habituation in SCOR in 15-year-olds were related to the genetic loading for schizophrenia within their families (Hollister et al., submitted for publication).

In a downward direction, there is in the literature an animal model of the SCOR response. Specific noradrenergic lesions induced by 6-hydroxydopamine injected into the ascending noradrenergic bundle but not the ventral tegmen-

tal area induced the type of nonresponsivity seen in some schizophrenia patients (Yamamoto et al. 1990). This result suggests that there is a potentially important noradrenergic component to the observed nonresponsivity that seems to be even more important in schizophrenia patients than SCOR habituation failures. Nonresponsivity has also been linked to various hippocampal abnormalities (Bernstein 1987). Thus, in the SCOR system, we may be seeing the effects of multiple neurotransmitters at multiple sites, perhaps within a unified neural circuit.

Span of Apprehension (SOA). The SOA in schizophrenia has been extensively reviewed by Asarnow et al. (1991). SOA is a measure of the number of stimuli that can be attended to, apprehended, and reported in a single brief exposure. There are numerous forms of the SOA task. A large array of letters may be presented, followed by a cuing stimulus at 100 msec that indicates to the subject which line to report. More commonly, subjects are required to report predesignated target letters presented in arrays of surrounding nontarget stimuli. When SOA is used as a measure, it becomes clear that the amount of information in labile storage is very large. The ability of subjects to recall one stimulus from a large display also erodes over time, so that when the cue is used, the cue that identifies the reported stimulus must appear soon after (e.g., within 100 msec) the display. The history of SOA was initially linked to stage models of attention, as the fundamental technique in the SOA paradigm takes advantage of the surprisingly large store of information available in an initial labile form. The SOA technique originally was linked to a simple early iconic storage hypothesis that subjects store large amounts of information in labile, easily erasable storage then transfer it to a more permanent stage of memory. Given that one can control the number of stimuli, type of stimuli, amount of exposure, etc., the most important aspect of the SOA task is that schizophrenia patients show a dramatic and robust deficit in SOA across numerous tasks that tap this function, especially with a large number of stimuli and a wide visual angle (Asarnow et al. 1991).

Advances. The SOA task has been used to look at high-risk children of schizophrenia mothers. Studies have consistently shown that children at high risk for schizophrenia show SOA deficits compared with control children. In an iterative procedure, the dependent measure (in this case the SOA task) is used to select subjects. Apparently normal subjects who performed poorly on the SOA task scored significantly higher on the schizophrenia-related Minnesota Multiphasic Personality Inventory (MMPI; Golden and Meehl 1979) and the Magical Ideation Scale (Eckblad and Chapman 1983). As Asarnow et al. (1991) have pointed out, these studies "provided three different tests of the sensitivity of these span tasks to the trait of vulnerability to schizophrenic disorder" (p. 354). That is, first-degree relatives of schizophrenia patients show deficits, and SOA performance is stable over time and across variations in clinical state and seems to tap a trait-related function. Individuals with no past psychiatric history who performed poorly on this task show personality characteristics on rating scales associated with some sort of proneness to psychosis. Unfortunately, the last point is somewhat ambiguous because it is not clear exactly what "abnormal" scores on the MMPI or the Magical Ideation Scale actually mean clinically. Still, the SOA task is a robust and well-validated measure of vulnerability to schizophrenic psychopathology at the boundaries of schizophrenia.

Asarnow et al. (1988) also examined psychopharmacological influences on the SOA task. They showed that schizophrenia patients most refractory to antipsychotic-induced diminution of thought disorder also show the least change on the SOA test, indicating that antipsychotic actions may be correlated with the improvement of this information-processing task. As is the case with many information-processing tasks, it appears that neuroleptics generally normalize or enhance the performance of schizophrenia patients on this task. It is important to note that for the SOA and many other information-processing tasks, a pure stage or iconic interpretation of these results is no longer tenable. Thus, recent models of information-processing deficits have evolved beyond structural limitations on cognitive processing, such as bottlenecks and filters. Instead, emphasis is now placed on the allocation of varying pools of attentional resources. These results are affected by time pressure, complexity of task demands, and allocation of attentional resources. We are currently learning more about these processes and the neural substrates that subserve them.

Visual Backward Masking. Visual backward masking also has historical roots in stage theories of

information processing, but it has evolved beyond stage models. The visual backward masking task uses a tachistoscope or computer-generated stimuli. The tachistoscope enables the experimenter to rapidly present stimuli to a subject who is sitting at a viewing port attached to a set of rectangular boxes with stimulus presentation fields controlled by a millisecond-calibrated timer. The advantage of tachistoscopic presentation is that the exact luminance, size, and timing of the stimuli may be precisely controlled. The visual masking phenomenon refers to the fact that normally a test stimulus, for example the letter T or the letter A, can be identified by subjects when it is under midrange conditions of illumination and is exposed for about 20 msec. The suprathreshold exposure duration can be selected for most subjects or duration can be individually determined (the critical stimulus duration). When this identifiable test stimulus is followed at a variable interval by a powerful noninformational masking stimulus (e.g., an overlapping series of Xs), the masking stimulus seems to interrupt or interfere with the processing of the target so that it may no longer be identifiable. As in many information-processing tasks, this phenomenon is exquisitely time-dependent in a range of values (e.g., 60 to 240 msec), which fits the functional pattern of monoaminergic neurons (Bloom 1985). For normal control subjects, under many of the stimulus conditions typically used, the target stimulus "escapes" from the disruptive effects of the mask when the interstimulus interval is in the 60 to 240 msec range. Thus, a mask that effectively erases or interrupts target stimulus identification at a 5- or 10-msec interstimulus interval is no longer effective at 100 msec. Schizophrenia patients, however, show an excessive vulnerability to the effects of the mask at 100 msec, as reflected by the fact that the masking stimulus interferes with or interrupts target identification at interstimulus intervals that normally are long enough to allow for the target to escape from the effects of the mask.

Initially, this pattern of abnormal masking functions in schizophrenia patients was interpreted to mean that the stage of iconic memory in schizophrenia patients was abnormally vulnerable to the effects of the mask, resulting in slow processing (Saccuzzo et al. 1974). It was interpreted to mean that schizophrenia patients kept information in an erasable or vulnerable form for excessive lengths of time and that this was true of both medicated and unmedicated schizophrenia patients (Braff and Saccuzzo 1982) as well as patients in remission (Miller et al. 1979).

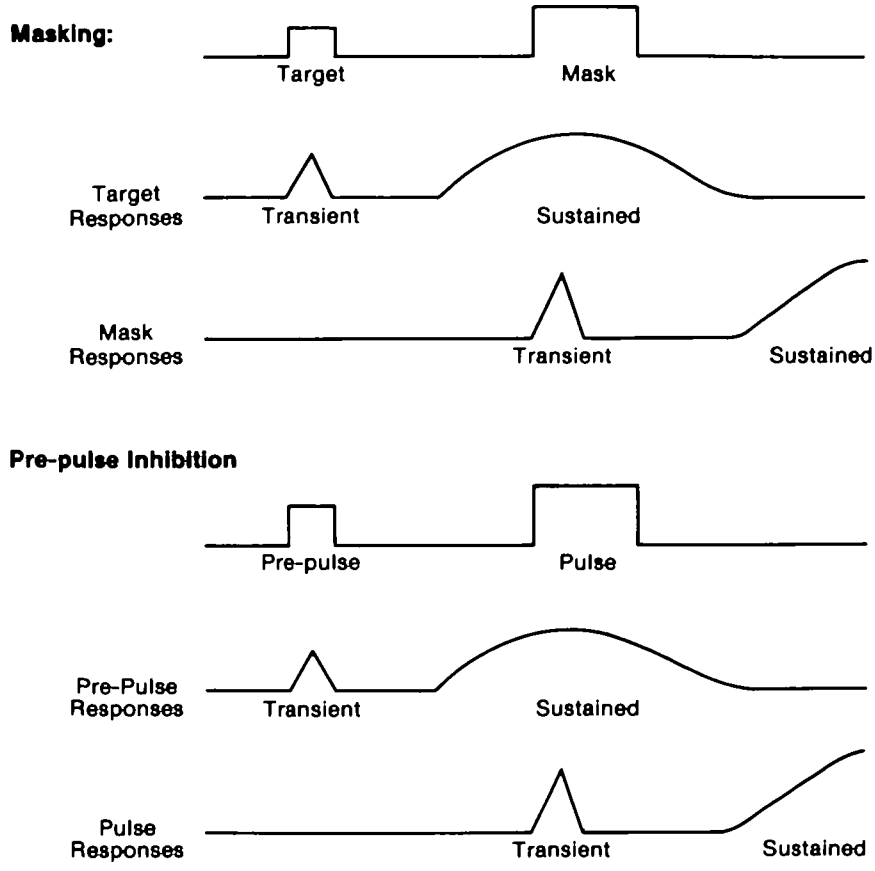
Advances. In probes at the boundaries of schizophrenia, investigators have detected visual backward masking deficits in schizotypal patients (Braff 1981). In related work with putatively psychosis-prone or schizotypal subjects with a 2–7–8 MMPI profile (Merritt and Balogh 1990), deficits were also detected. Unfortunately, although these 2–7–8 individuals tended to have visual backward masking deficits, they were drawn from "normal" volunteer groups, and the lack of detailed and structured clinical interviews with them makes it impossible to know whether these individuals were actually schizophrenia-spectrum subjects. In terms of symptom correlates, negative-symptom schizophrenia patients show inflated critical stimulus durations and poorer masking performance (Green and Walker 1984; Braff 1989).

> In sum, there is a longitudinal, probably trait-linked vulnerability to a meaningless, high energy, visual backward noise mask in poor prognosis, chronic schizophrenic patients and in genetically linked schizotypals. This deficit cannot be parsimoniously attributed to generalized deterioration, hospitalization, or medications. The masking deficit can also be found in acute, good prognosis schizophrenic, schizoaffective, and psychotic but not non-psychotic bipolar patients (Saccuzzo and Braff 1981). For the non-schizophrenic groups, the deficit appears to be a state- (rather than a trait-) related phenomenon that is associated with their psychosis and perhaps with thought disorder (see Braff and Saccuzzo 1985; Braff and Saccuzzo 1986). The mechanism(s) underlying this masking deficit in schizophrenic spectrum patients remains far from clear. [Braff et al. 1991, p. 323]

In a downward analytic direction, there is a vast literature trying to dissect the underlying neural substrate of visual backward masking deficits. When pharmacological probes are used, methylphenidate, a catecholaminergic agonist, induces schizophrenic-like visual backward masking deficits (Braff and Huey 1988). However, the debate about underlying visual backward masking mechanisms and related deficits (Schwartz and Winstead 1988) is quite broad. A pure slow-processing hypothesis seems unsupportable (Braff et al. 1991). Rather, it appears that transient and sustained neural channel interactions may well underlie masking mechanisms (Breitmeyer and Ganz 1976). In this context, rapidly triggered Y cells of the transient channel are sensitive to

low spatial/high temporal frequencies and emit a rapid-onset/rapid-offset stimulus. The sustained-channel X cells respond to high-spatial/low-temporal frequency signals with a larger, information-laden signal. These systems seem to correspond to Gersuni's (1965) "fast" and "slow" neural systems, which underlie the prepulse inhibition of the acoustic startle response. In this context of converging measures and underlying mechanisms, both visual backward masking and prepulse inhibition can be parsimoniously understood in the framework of this common neural substrate rather than in a simple stage model of processing (figure 4).

Figure 4. Transient and sustained responses to sequential stimuli (possible common neural substrate of backward masking and prepulse inhibition, based on transient and sustained neural responses to various stimuli)



Continuous Performance Task (CPT). A frequently used technique that assesses information processing is the CPT (Rosvold et al. 1956). In the basic form of this task, subjects are asked to attend to a series of letters or numbers and to detect an intermittently presented target stimulus presented along with other letters or numbers. The stimuli may be presented in a tachistoscope or by a computer-generated program via a computer screen. At a fairly brief interstimulus interval (i.e., 1 sec), these repetitive stimuli are presented and the subjects are asked to identify the target. In one early version of the CPT, the task continues with 1 target per 5 stimuli until 50 targets are presented (Kornetsky and Orzack 1978). Across many paradigmatic alterations, investigators have found that schizophrenia patients, even those who are "remitted," show abnormally poor detection of the target or critical stimulus. This pattern of results has been interpreted to mean that the subjects are somehow inefficient in directing their active, voluntary attention to identifying these target stimuli. After initial studies of the CPT in schizophrenia patients were accomplished, numerous questions were raised. For example, are schizophrenia patients deficient on some basic vigilance operations or are they merely affected by the general symptomatology and gross (i.e., nonspecific) inattention?

Advances. To answer the question of specific versus nonspecific effects, a variety of different CPT paradigms have been used. For example, there can be a distraction condition in which subjects detect the critical stimulus in the presence of distracting light or tones, and this adds an ipsimodal (visual/visual) or cross-modal (auditory/visual) type of distracting stimulus condition to the fundamental CPT (Asarnow and MacCrimmon 1978). Across many studies, it has become clear that schizophrenia patients in both

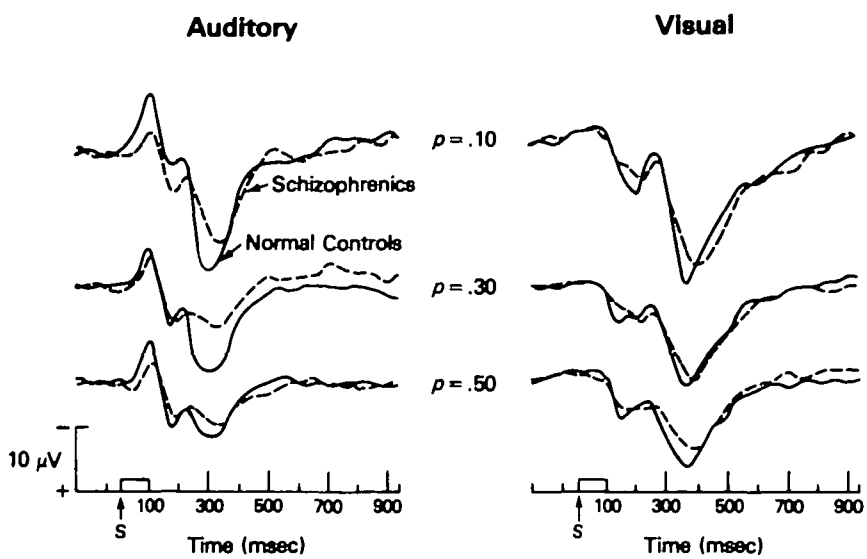
acute and remitted stages have pervasively abnormal CPT performance that seems to reflect fragmented and inefficient attentional mechanisms. Two major advances in the use of the CPT in schizophrenia research are (1) Nuechterlein's (1991) degraded stimulus CPT in which target letters are blurry, which increases task difficulty and correspondingly increases task sensitivity in detecting deficits, and (2) Cornblatt's CPT, identical pairs version (Cornblatt et al. 1989), an attention-demanding version of the CPT that is thought to tap controlled, effortful processing.

One of the major applications of the CPT has been at the boundaries of schizophrenia in an upward analytical direction (see figure 1). Asarnow and MacCrimmon (1978) tested patients who were in remission and found that these patients showed more errors of omission and commission than did normal control subjects. They suggested that the cross-sectional study of three stages of schizophrenia (premorbid, acute, and remitted) is a reliable strategy for identifying core schizophrenic processes and markers of vulnerability to schizophrenia. This research raises the question of whether decreased vigilance in the CPT may be an artifact of general psychopathology.

Arguing against this generalized deficit interpretation, Asarnow and colleagues have tested children who are at risk for but do not yet have schizophrenia and found a pattern of CPT deficits. It is interesting that Asarnow and MacCrimmon reported in their original study (1978) that there were deficits in schizophrenia patients on both the CPT and SOA tests but that these deficits did not significantly correlate with each other. The lack of correlation raised questions about interpreting data as reflecting a global attentional impairment in these sorts of tasks. Most recently, important data from the New York High-Risk Study indicate that children of schizophrenia parents show attentional (CPT) deficits that help to predict the later onset of schizophrenia (Cornblatt et al. 1989). The interested researcher is referred to Nuechterlein's (1991) definitive discussion of "vigilance in schizophrenia and related disorders" to gain indepth knowledge of the pattern of CPT paradigms and the associated neural deficits in schizophrenia and high-risk populations. Finally, a number of studies have shown that unaffected relatives of schizophrenia patients show CPT deficits, a finding that strengthens the interpretation of a diathesis-linked attentional dysfunction (Grove et al. 1991; Lenzenweger et al. 1991; Keefe et al. 1992). These studies also raise questions about other factors that may be necessary to produce schizophrenia in schizophrenia-prone, information-processing-impaired individuals.

Cerebral ERPs. The area of cerebral ERPs has traditionally been central in attempts to understand brain function in schizophrenia. This discussion presents an extremely selective sample of data from the vast ERP literature. ERP techniques rely on repeated stimulation wherein each stimulus is associated with a tiny electrical event in the cerebral cortex or subcortical structures of the brain. Surface electrodes can pick up these tiny shifts, and by repeating stimuli many times and time-linking these responses to stimuli, the investigator can measure the summed brain electrical activity to stimuli (figure 5). The early components, such as events that occur

Figure 5. Event-related potential waveforms elicited by auditory and visual stimuli in schizophrenia and control subjects



in the first 10 to 40 msec, are generally considered to be more sensory in nature, whereas the later components, such as the positive wave that occurs at about 300 msec after stimulus delivery (P300 wave), are usually interpreted as reflecting higher level cognitive or information-processing functions (Morstyn et al. 1983). In general, early sensory and middle latency responses (e.g., 40 msec) are normal in schizophrenia (Grillon et al. 1991). The use of the two-click P50 sensory gating paradigm was discussed above; therefore, several studies of later components will be examined here. The most used later component is the ERP P300 wave, which normally is larger when the eliciting stimulus is relatively novel and unexpected and when it conveys new information. Schizophrenia patients have traditionally shown blunted or decreased P300 responses to salient, information-laden stimuli, and this phenomenon is thought to reflect impaired cognitive processing of information (see figure 5) (Roth and Cannon 1972; Callaway and Jones 1975; Duncan et al. 1987) in schizophrenia.

Advances. Duncan (1988) pointed out that improvement in clinical state correlates with more normal visual but not auditory P300 responses. This visual event-related P300 may be a state marker of schizophrenic psychopathology. In contrast, the core deficit in schizophrenia seems to involve the auditory information-processing system (perhaps reflecting the greater dopaminergic innervation of the auditory cortex than of the visual cortex). The vast ERP literature reaches out to myriad other relevant issues, such as correlating ERPs and skin conductance abnormalities (Roth et al. 1991). From studies of high-risk and schizophrenia children to correlations with clinical state, ERPs have proven to be of great importance, and this area could fill a textbook. To illustrate the utility of ERPs in research in the group of schizophrenias, two areas will be very briefly reviewed here: (1) correlating ERPs with other techniques and (2) identifying the possible generator of the P300.

1. The use of converging measures has been of great utility in studying schizophrenia. Grillon et al. (1990) simultaneously assessed the behavioral (i.e., reaction time [RT]) and ERP effects of distracting stimuli. After measuring and correlating P300 ERPs and RT performance, the authors concluded that fewer processing resources are allocated to external stimuli and that these resources are abnormally apportioned to task-irrelevant stimuli. This pattern of results is important because it supports theories of impaired allocation of attentional resources in schizophrenia. Strandburg et al. (1990) compared schizophrenia and normal children in a task that measured ERPs to CPT stimuli and found that the schizophrenia children were impaired on the CPT with associated deficits in the P300 amplitude.

2. In another line of investigation, researchers have explored the possible generator of the deficient P300 response in schizophrenia. McCarley et al. (1989) reported that reduced P300 amplitude correlated with decreased temporal lobe volume, implicating temporal lobe abnormalities in the deficient P300 amplitudes of schizophrenia patients. Their results have been informally replicated by several groups whose work is in various stages of preparation or publication. This pattern of findings is consistent with the results of "dipole" localization studies that identify the temporal lobes as major generators of the P300 ERP wave.

RT. If "reaction time studies are the closest thing to a north star in schizophrenia research" (Cancro et al. 1971, p. 352), then this north star has not been used much recently to navigate the way through the complexities of this research area. Yet the sheer volume of the literature in this area is supported by a 53-page review by Nuechterlein (1977)! A much briefer review will have to suffice here.

In its simplest form, investigators use the regular and irregular forms of the RT task, which Shakow and his colleagues used so widely (see Nuechterlein 1977). The regular and irregular forms of the RT task use uniform and varied preparatory intervals between a warning signal (i.e., a warning that the next stimulus will arrive soon) and the imperative stimulus (i.e., press the key) (Zahn and Rosenthal 1965). Originally, even relatively cooperative schizophrenia patients (Huston et al. 1937) showed slower RTs and an inability to benefit from the regular and predictable preparatory intervals when these intervals exceeded 2 sec, reflecting an inconsistancy of attention. Later, Rodnick and Shakow (1940) demonstrated that the "set index" was sensitive in discriminating schizophrenia-linked deficits in RT. The set index was designed to minimize superficial attentional artifacts and to identify a more core deficit in schizophrenia patients' attentional performance. The set index takes into account the slower RTs of schizo-

phrenia patients in the regular versus the irregular larger preparatory intervals, the generalized slower RTs of schizophrenia patients, and the distinct, maximal performance (i.e., fastest RTs) by normal subjects for regular 2-sec preparatory interval stimuli. Rodnick and Shakow (1940) believed that the set index minimized the contamination of schizophrenic performance by potential artifacts such as poor levels of cooperation or motivation or both. It turns out, however, that "high scores on the set index are not universal among nor unique to schizophrenics" (Nuechterlein 1977, p. 377).

Advances. Zahn et al. (1978) reported that those schizophrenia patients who had better hospital-admission, off-medication RTs tended to be those patients who showed more clinical improvement. Another relevant theme in the RT literature is exemplified in the studies by Zubin (1975) on deficits that are related to segmental set, deficits linked to inflexible attentional mechanisms. These investigators assessed segmental set by using cross-modal RT in tasks in which the warning and imperative stimuli were presented in the same modality (auditory-auditory) and in opposite modalities (visual-auditory). It turns out that the RT of schizophrenia patients is selectively impaired in the cross-modal condition, reflecting attentional inflexibility or difficulties in smoothly shifting attention from one modality to another. It appears that the schizophrenia patients are "stuck" and cannot shift their attention. This sounds strikingly similar to research conducted by Weinberger and associates at the National Institute of Mental Health, in which the researchers identified increased perseverative errors on the WCST in schizophrenia patients and found these errors to be associated with low frontal lobe activity (Weinberger et al. 1986, 1992). It is no great leap to translate "segmental set" into "perseverations" and thus form a bridge between newer studies linking hypofrontality and perseverative responses in schizophrenia patients. Koob and associates have now created an animal (rat) model of the RT paradigm, which may stimulate interest in the use of this technique (e.g., Amalric and Koob 1987).

Unfortunately, RT studies have lately fallen out of fashion. Still, recent RT studies have detected "cross-over" abnormalities in relatives of schizophrenia (Maier et al. 1991) and schizotypal (Chapin et al. 1987) patients. It is quite possible that these tried and true RT techniques, in combination with other measures of information processing and cerebral activity (e.g., positron emission tomography [PET]), may yield important new information. It is also possible that RT segmental set may serve as a phenotypic marker for downward analyses using molecular biology strategies. Only time (and the zeal of investigators) will tell.

Latent Inhibition. Another technique that is used in both humans and animals is latent inhibition (Baruch et al. 1988). In one variation of the fundamental task, a subject is asked to listen to and count meaningless syllables while the stimulus of interest (e.g., a 30-msec burst of white noise) is presented concurrently (Gray et al. 1991). The subjects are then asked to identify the 30-msec noise burst. It has been found that normal subjects preexposed to the noise burst stimuli subsequently take significantly more trials to identify these stimuli, reflecting the induction of inhibition. Acute schizophrenia patients identify the target stimuli more rapidly than do control subjects, indicating a failure of inhibitory functions.

Advances. Amphetamine challenges induce failure to develop normal latent inhibition in humans (Gray et al. 1991) and animals (Weiner et al. 1987), strengthening the validity and applicability of this cross-species paradigm. Although amphetamine challenges in humans are useful in modeling schizophrenia, more work is being done with latent inhibition in both humans and animals to understand the implications of these results. One critical point is clear about latent inhibition and some related techniques, such as Kamin blocking (Jones et al. 1990) and the negative priming effect (Beech et al. 1989): When latent inhibition is impaired in schizophrenia patients, the subject takes a decreased number of trials to reach a predetermined performance criterion. That is, normal performance consists of increased levels of inhibition and a correlated deterioration in performance; schizophrenic performance reflects decreased levels of inhibition with a more rapid identification of target stimuli. The latent inhibition paradigm thus addresses the issue discussed by Sutton (1973)—that it is critically important to rule out artifact and nonspecific effects in studies of schizophrenia patients. The latent inhibition paradigm cleverly induces a situation in which failure of inhibition causes "better" performance, a major advantage in this area of research. Latent inhibition studies, alone and in conjunction with other measures, will undoubtedly be of future importance.

Integration and Future Directions: What We Know and What We Need to Find Out

An integrated information-processing framework provides us with a critical viewpoint that enhances our understanding of the complex and far-reaching neurobiological and psychosocial facets of the group of schizophrenias. As illustrated in figure 1, the information-processing dysfunctions we have discussed offer a unique window through which to observe and understand the psychopathology of schizophrenic disorders in both an upward and a downward analytic direction.

Upward Analysis. In an upward analysis (see figure 1), information-processing dysfunctions correlate with cognitive, neuropsychological, and symptomatic impairments in a number of important ways. First, it appears that nonresponsivity and failures of sensory registration carry with them a loading for deficit state-related factors such as withdrawal and blunted affect. Thus, inflated (i.e., impaired) recognition thresholds (critical stimulus durations) on the visual backward masking task are associated with negative symptoms (Braff 1989). Nonresponsivity on SCOR is associated with an affective blunting or withdrawal from normal interactions (Bernstein 1987). Indeed, this lack of responsivity may tap into a dimension related to negative symptoms, poor outcome, and brain atrophy characteristic of a Type II syndrome (Crow et al. 1981).

The fact that deficient prepulse inhibition is associated with increased perseverative responses on the WCST (Butler et al. 1991) is also of interest. Perhaps the hypofrontality associated with increased perseverative responses may correlate with the frontal disinhibition of mesolimbic dopamine tone (e.g., Pycock et al. 1982; Weinberger et al. 1986) that is associated with impaired prepulse inhibition. Merriam et al. (1989) have suggested that visual backward masking and other deficits in two-stimulus tasks involve the general process of "proactive interference," which they view as frontally mediated. As we better understand the neural circuits that subserve brain function, more studies must concentrate on how information-processing measures relate to cognitive and neuropsychological probes of frontal, temporal, and the subcortical parts of the CSPT circuit that seem so critical to the neuropathology and neurophysiology of schizophrenia.

The symptom and state-related correlates of information-processing deficits in schizophrenia patients constitute a fascinating area of research. Ever since the early RT studies, it has been useful to see that information-processing impairment does not simply correlate with gross (i.e., nonspecific) symptomatology (Nuechterlein 1977). In some paradigms, information-processing deficits are accentuated in negative-symptom, compared with positive-symptom, schizophrenia patients (Green and Walker 1984; Braff 1989). This finding tends to invalidate any explanation that information-processing deficits accrue from the distracting effects of positive symptoms, such as hallucinations and delusions. It also appears that there are relatively nonspecific information-processing deficits that covary with a psychotic state per se but selectively persist in some poor-prognosis schizophrenia patients (Saccuzzo and Braff 1981). It is interesting that many studies point to the utility of information-processing measures in predicting outcome, an important validating and practical issue for future research. This finding leads to an important area in the bottom-up analysis: the occurrence of trait-related deficits in information-processing functions in schizophrenia and boundary patients.

In an upward analysis, studies of trait-related variables have had and will continue to have a critical role. If subjects at the boundaries of schizophrenia (e.g., schizotypal patients, high-risk children, unaffected family members) have information-processing deficits similar to those of schizophrenia patients, then the observed deficits are unlikely to be due to the gross disruption caused by generalized symptoms or treatment variables (e.g., antipsychotic medications, institutionalization). The results of numerous studies dramatically illustrate the centrality of these trait-related studies (e.g., Steinhauer et al. 1991). Boundary subjects have information-processing dysfunctions in a clear schizophrenia-like direction. These deficits are demonstrable across a wide spectrum of information-processing measures, including virtually all of the measures discussed in this review (CPT, smooth-pursuit eye movement, gating, ERP, SOA, visual backward masking, SCOR, and RT). In sum, almost every information-processing technique that taps into a schizophrenia deficit also taps into a deficit in some boundary population. The ubiquity of trait-linked deficits in these nonpatient boundary subjects is perhaps the most compelling and dramatic in-

terlocking series of findings in this area of schizophrenia research. There appears to be something very basic and central about information-processing deficits in the group of schizophrenias, especially when these tasks are time-linked and tap into high processing loads. In future work, these information-processing measures should be correlated with each other and with the other psychological and biological measures listed in table 1. We must also begin to understand which other factors (e.g., neonatal hippocampus damage) may interact with these deficits to produce schizophrenia in some but not all subjects with a diathesis-linked vulnerability to developing schizophrenia (Weinberger 1987). Researchers must also probe for sensitive phenotypic markers to characterize the mode of inheritance of these schizophrenia-linked information-processing deficits. These markers will be used in family molecular genetic studies (Holzman et al. 1988; Clementz et al. 1991). Clearly, the known association of neurotransmitter dysregulation and information-processing dysfunctions makes these information-processing measures ideal as differentially sensitive markers for molecular biology studies (Waldo et al. 1991; Keefe et al. 1992).

Downward Analysis. In a top-down analysis (see figure 1), the known neurobiological substrate of stimulus processing in the group of schizophrenias can be examined. The established anatomic substrate of information-processing functions interacts dramatically with the known neurobiological substrate of the group of schizophrenias; the frontal lobes, temporal lobes, hippocampus, striatum, pallidum, and thalamus are all implicated (e.g., Swerdlow and Koob 1987; Gray et al. 1991; Jernigan et al. 1991; Braff et al. 1992).

The most prominent theme in this research area is the shift in thinking from concepts of single locus/single neurotransmitters to more elaborate schemas of integrated networks or cascades of neurotransmitters located in widely distributed but related or connected areas of the CNS (Goldman-Rakic 1988; Braff and Geyer 1990). The most recent advances in this area stress the widely distributed brain substrate of even simple-appearing tasks. Thus, an information-processing task may involve the integrated, time-linked, and distributed activity of millions of neurons in networks located in related but widely distributed cortical and subcortical areas (e.g., Servan-Schreiber and Cohen 1992). For example, at an even more basic non-cognitive level, the optimal modeling of a monkey arm movement may involve neuronal population encoding of millions of neurons in a functionally integrated cell population that can best be described by very intricate topographic mapping (Georgopoulos et al. 1986). It is not surprising, therefore, that the complex information-processing functions discussed above are not related to single sites, single transmitters, or (unfortunately for model creators) single paradigms or functions. The navigation of these often muddy waters can be only outlined in this review, but some clear directions must be explored in the future.

One way of tapping into the neural substrate of information-processing functions is by means of systemic drug challenges in humans and systemic and local drug challenges in animal models. Many of the combined psychopharmacologic/information-processing strategies employed by investigators are nonetheless somewhat ambiguous. For example, an amphetamine or methylphenidate challenge in humans might be used to test the dopamine hypothesis of schizophrenia, but both drugs are also noradrenergic agonists, leaving alternative hypotheses to be tested. Still, "coarse" psychopharmacological studies have given us important information. First, stimulant challenges have induced schizophrenia-like information-processing dysregulation. For example, Braff and Huey (1988) showed that methylphenidate induced visual backward masking deficits in nonschizophrenia patients, tentatively supporting a role for dopamine (or at least catecholamine) overactivity in the group of schizophrenias.

Studies of schizophrenia and normal subjects have begun to correlate brain images of structure (e.g., magnetic resonance imaging) and function (e.g., PET) with information-processing and neuropsychological measures. The most prominent group of studies in this area has correlated structural brain deficits with cerebral ERPs. The P300 and P50 generators have tentatively been localized to the superior temporal lobes, an interesting location for a gateway to the processing of information. For example, McCarley et al. (1989) found that temporal lobe cortical volume loss correlates with abnormal P300 results in schizophrenia patients. Pfefferbaum et al. (1989) obtained related correlations of clinical and other factors and impaired P300.

Combining PET with cognitive tasks is an exciting new area that must be fully explored. Functional

brain probes of neural circuits are also being combined with information-processing measures. PET studies of coherence measures of the CSPT circuitry have supported the hypothesis that these integrated circuits are indeed part of a coherent but plastic and alterable whole (Buchsbaum and Haier 1987). Combining information-processing measures, such as the CPT or SCOR, in schizophrenia patients with PET imaging is a very promising area for future schizophrenia research (Hazlett et al., in press). This combination flows from other attempts to stress a hypothetically vulnerable system such as the prefrontal cortex to evoke otherwise dormant deficits (e.g., Weinberger et al. 1986).

Animal model studies of techniques that can be tested in humans (e.g., prepulse inhibition of the acoustic startle reflex, P50 gating, latent inhibition, ERPs) have been very important in augmenting our understanding of information processing in normal and biologically altered states. These exciting and imaginative studies will undoubtedly be a central and critical area of inquiry in future years. Overall, several themes run prominently through this work. First, stimulant challenges (i.e., latent inhibition, P50 gating, prepulse inhibition) create schizophrenia-like deficits. Still, chronic as well as acute challenges will need to be used increasingly in the future to mimic a chronic disorder. Second, detailed information can be obtained in studies using specific anatomic lesions or regional infusions (Swerdlow et al. 1986, in press). Future strategies may use neonatal lesions combined with adult behavioral observations or innovative psychopharmacological challenges (e.g., Lipska et al. 1992). In the case of prepulse inhibition, these studies lead us to believe that in this animal model of schizophrenia there is a complex imbalance or dysregulation of the CSPT circuitry. Third, new paradigms being investigated offer noninvasive methods of inducing neurobiological abnormalities that mimic schizophrenia. For example, isolation rearing of rat pups (Geyer et al. 1992) induces subcortical hyperdopaminergia and impaired prepulse inhibition, and this finding of gating deficits extends to isolation effects on primates (Lewis et al. 1992). This paradigm allows investigators to clearly induce mesolimbic hyperdopaminergia without the contamination that frequently accompanies neurotoxin-induced or pharmacologically induced lesions. Social manipulations leading to biological changes will assume increased importance during the next decade. The animal model studies cited above offer investigators a unique way to delineate the neural basis of information-processing deficits in schizophenia.

Conclusion

Information-processing measures will continue to provide a critically important window through which we can observe and probe the clinical characteristics and neural substrate of the group of schizophrenias. Because these disorders appear to be heterogeneous, much care and patience must temper our enthusiasm about the emerging complex but rational picture of schizophrenia that is being painted by investigators working at such an intricate level of detail. As more studies use converging measures (e.g., prepulse inhibition and P50 gating) and combine old and new technologies (e.g., CPT and PET), the picture of the group of schizophrenias will undoubtedly grow clearer and more stimulating to our intellect and imagination.

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