Startle Habituation and Sensorimotor Gating in Schizophrenia and Related Animal Models

by Mark A. Geyer and David L. Braff

Abstract

Studies of the habituation and sensorimotor gating of startle responses to strong exteroceptive stimuli provide some unique opportunities for cross-species explorations into information processing and attentional deficits in schizophrenia. The behavioral plasticity of startle paradigms greatly facilitates the development of animal models of specifiable behavioral abnormalities in schizophrenic patients. This article reviews the promising findings of studies in which measures of startle have been used to clarify the importance of habituation and central inhibition deficits in schizophrenia. In addition, the development of closely related animal models of habituation and sensory gating of startle is discussed. Such animal model studies allow us to make strong inferences about the neurobiological substrate of schizophrenia. Recent evidence from animal studies of prepulse inhibition provides strong support for a schizophrenia-like loss of sensory gating with nucleus accumbens dopamine overactivity. These data are consistent with hypotheses regarding the significance of mesolimbic dopamine overactivity in schizophrenia. New results are also presented from animal model studies of the effects of serotonergic drugs on startle habituation, extending earlier findings of LSD-induced habituation deficits which are similar to those exhibited by schizophrenic patients. These new data indicate that the serotonergic system, working through serotonin-2 receptors, may play a pivotal role in the modulation of startle habituation. The relationship of serotonergic and catecholaminergic mechanisms is also discussed. Collectively, these studies demonstrate the utility of operationally defined measures of preattentive processes in the study of the neurobiological basis of the group of schizophrenias.

There is a rich tradition of interest in attentional and information-processing dysfunctions in schizophrenia, as discussed in reviews of these complex and theoretically diverse areas (Braff 1985; Kietzman et al. 1985). Holzman et al. (1976) point out that Kraepelin originally believed that while "Auffassung" or sensory registration is normal, "Aufmerksamkeit" or active, sustained, or directed attention is almost always deficient in schizophrenic patients. Similarly, Bleuler (1911/1950) commented that "acute attention is lacking" in schizophrenic patients. These early observations engendered modern attempts to quantify and link schizophrenic psychopathology with its putative underlying disorders of attention and information processing. Since the 1950's, technical advances have led to a veritable explosion of information about cognitive and attentional dysfunction in schizophrenia. This specification of information processing and attentional functions has allowed researchers to demythologize and quantify the cognitive deficits of schizophrenic patients. It has become evident that schizophrenic patients have a unique problem in overcoming the disruptive or distracting effects that occur when stimuli that require information processing are presented in fairly rapid succession. It appears that
have applied the construct of impaired sensory gating to schizophrenia. For example, Gottschalk et al. (1972) found that sensory overload or LSD treatment could induce changes in normal subjects on social alienation-personal disorganization and cognitive-intellectual impairment scales that mimicked previously described schizophrenic performance deficits. Consistent with sensory gating deficit theories is the prediction that schizophrenic patients should have increased distractibility due to their impaired ability to screen out irrelevant cues. Indeed, a host of studies support the idea of a schizophrenic deficit in gating and an associated vulnerability to the performance-deteriorating effects of distraction (Creese et al. 1981; Schneider 1984; Nuechterlein and Dawson 1984). Admittedly, some of these studies are vulnerable to the criticism of Chapman and Chapman (1978) that poorer schizophrenic performance may be due to the increased difficulty and greater variance in the with-distractor vs. without-distractor conditions. However, Oltsmann and Neale (1975) controlled for these factors and found a complex but interpretable pattern of schizophrenic deficits in the with-distractor condition, supporting a distractibility hypothesis that is linked to the sensory overload/impaired sensory gating theory of schizophrenia.

One of the fundamental aspects of information processing consists of focusing attention on selected environmental stimuli. The simplest form of learning is considered to be the ability to habituate to initially novel stimuli, an ability that is essential to selective attention. Unconditioned responses to stimuli had historically been classified as orienting responses to mild, information-laden stimuli and defensive responses to powerful stimuli (Sokolov 1963). More recent categorizations have emphasized the distinctive pattern of physiological reflexes characteristic of startle responses and thereby separated them from defensive responses (Turpin 1986). Clinically based theories of schizophrenia cognitive deficits have used the concept of habituation deficiencies, largely on the basis of studies of the electrodermal skin conductance orienting response (SCOR) habituation to mild stimuli. For these purposes, habituation is generally defined as the exponential decrement in responding when the same initially novel stimulus is presented repeatedly at speeds too slow to produce sensory adaptation or receptor fatigue. According to Groves and Thompson's (1970) widely utilized dual process theory, the observed habituation of unconditioned responses to sensory stimuli is theoretically determined by two behaviorally opposite processes, called habituation and sensitization, which may have discrete neurophysiological and neuroanatomical substrates. In the present review, we typically limit our discussion to the observed phenomenon of habituation, not the inferred underlying process of habituation.

Since schizophrenia has been linked to the abnormal processing of sensory information and the dysregulation of selective attention, studies of SCOR habituation to repetitive stimuli provided an appealing experimental approach to schizophrenia researchers. The work of Bernstein et al. (1982) and many others (Gruzelier and Venables 1978; Spohn and Patterson 1979; Levinson et al. 1984) has been important in defining the possible psychophysiological and psychopharmacological bases of alterations in SCOR responsiveness and habituation in schizo-
It first appeared that some groups of schizophrenic subjects exhibit a reduced rate of SCOR habituation (Depue and Fowles 1973; Spohn and Patterson 1979). However, more recent work has shown that the differences in electrodermal orienting responses in schizophrenia are not limited to deficits in habituation, since many schizophrenic patients exhibit abnormal baseline or few or no responses (Bernstein et al. 1982) and others aspichizophrenic patients exhibit latency with which slow-habituating or rapid-habituating schizophrenic patients are identified depends greatly on the criteria used to score the electrodermal responses (Bernstein et al. 1982).

Startle Reflex in Schizophrenia Research

Graham (1975), Davis (1980), Ison and Hoffman (1983), and others have pointed out that the startle reflex is an ideal means of assessing sensorimotor reactivity and habituation in humans and animals. The startle reflex is a ubiquitous, cross-species response to strong expeactive stimuli. Researchers have measured whole body startle to acoustic or tactile (air-puff) stimuli in rats. In humans, the eyelink component of startle has typically been measured using either eyelid displacement or electromyogram (EMG) of facial muscles. As cited by Davis (1980, 1984), the work of Kandel, Sokolov, Thompson, and their associates has highlighted the importance of studies of "reflex excitability and stimulus reactivity in their own right." Davis (1980, 1984) eloquently discusses the neurochemical modulation of sensorimotor reactivity, and interested readers are referred to these reviews for further details.

The startle reflex specifically has a number of special advantages for human schizophrenia research and studies of animal models of schizophrenia: (1) Stimulus control: The startle reflex has a nonzero baseline, which is sensitive to interstimulus interval, tone intensity, and background noise. This baseline enables researchers to measure both excitatory and inhibitory effects. (2) Simple neural circuit: In the rat, this circuit is reflected by a time-locked relationship between eliciting stimulus and response (Davis et al. 1982a). The primary acoustic startle circuit probably involves three to five central synapses in the auditory nerve/cochlear nucleus/lateral lemniscus/nucleus reticularis pontis caudalis/reticulo-spinal tract pathway. Recent work has begun to delineate the tactile startle circuit as well (Cassella and Davis 1986). (3) Automated measure: This simple, time-linked neural circuit allows for automated measurement in humans and inhuman, facilitating the elimination of voluntary blinks from reflexive, startle-mediated blinks. (4) Plasticity: Most important for schizophrenia research is the fact that the startle reflex, despite its relative simplicity, is flexible or plastic and reflects important processes such as habituation and prepulse inhibition or sensorimotor gating. Specifically, startle shows habituation in normal humans and animals in response to the repeated presentation of an initially novel, strong expeactive stimulus. This habituation occurs during a single session of multiple stimuli (within-session habituation) and across several sessions (between-session habituation). Lastly, weak prestimuli induce the phenomenon known as prepulse inhibition of startle, an important reflection of an independent, powerful, active process of inhibition that develops in young animals at a different rate than does startle itself (Parisi and Ison 1979). Since habitation and central inhibition are both so critically important to understanding schizophrenia, startle offers a unique window from which to assess these processes. (5) Pharmacological effects: Another advantage of startle is its well-known modulation by psychoactive drugs and various manipulations of monoaminergic neurotransmitter systems (Davis 1980), which allows us to form tentative bridges between startle abnormalities in schizophrenia and underlying neurotransmitter abnormalities.

Startle Habituation in LSD-Treated Rats and Schizophrenic Patients

Due to the central theoretical role of information-processing deficits in schizophrenia, we became interested in examining habituation deficits in animal model and clinical schizophrenia studies. Since, as discussed above, SCOR responsiveness and habituation had been found to be variably altered in schizophrenic patients, it was important to determine if such alterations in sensorimotor responding would extend to other sensory and response systems.

Startle Habituation in Schizophrenia. Initially, the degree to which human startle responses would exhibit appreciable habituation was uncertain. Blink reflex measures of startle had been extensively studied in the context of prepulse inhibition induced by weak prestimuli (see below), but little information was then available about
the habituation of the response. The prevailing view was that startle was a prototypical defensive response, as described by Sokolov (1963), and defensive responses were frequently characterized as exhibiting little or no habituation. Animal studies of whole body startle had been used frequently in behavioral, pharmacological, toxicological, and neurochemical studies of habituation, but little work had been done with humans. However, Gogan's (1970) work had indicated that human startle responses habituated, albeit more slowly than did orienting responses, and that this habituation described an exponential decay curve. We used a potentiometric method to measure the blink reflex component of the acoustic startle response in humans. Normal volunteers and both schizophrenic and patient controls were tested in a 121-trial paradigm with acoustic stimuli (Geyer and Braff 1982). The stimuli were 40-ms bursts of 116 dB(A) tones presented at variable intervals averaging 15 sec. As in the work of Graham (1975), we used a potentiometer attached by a thread to the eyelid to detect displacement of the eyelid and topographical criteria to distinguish voluntary from reflex blinks. A small microcomputer was used to control stimulus presentations and record blink responses (Geyer and Braff 1982). The results from normal volunteer subjects are graphically presented in figure 1, in which it is clear that human blink reflex measures of startle habituated at a rate comparable to what was expected from the many studies of startle habituation in animals. This result is consistent with the revised thinking about the important distinctions to be made between Sokolov's (1963) nonhabituating defensive responses and startle responses, as recently reviewed by Turpin (1986).

More important, however, were our findings about the differences between schizophrenic patients and either normals or patient controls in their respective rates of behavioral habituation. The first response and means of blocks of 5 trials each are shown. Procedural details are described in Geyer and Braff (1982), in which these data are more fully presented.
habituation. To assess these differences, we analyzed first responses and then subsequent blocks of trials separately in a mixed-design analysis of variance (ANOVA) with the three groups being the between-subjects factor and trial blocks being the within-subjects factor. Habituation decrements were calculated as the difference between the first and last trial blocks, and slopes of the habituation curves were analyzed by a multiple linear regression analysis. The data comparing schizophrenic and control patient groups are graphically presented in figure 2. Schizophrenic patients showed decreased amplitude habituation, as reflected by the group trials interaction and by the first-to-last trial block measure of habituation. Normal and patient controls were equivalent, but schizophrenic patients differed from both groups. A regression analysis revealed significant linear and quadratic components, as expected for habituation curves in the absence of appreciable sensitization. The linear slope comparison further confirmed the group differences in rates of habituation (Geyer and Braff 1982).

This study's major finding was that schizophrenic patients had impaired startle habituation compared with normal or patient controls. While conclusions about alterations in habituation of electrodermal responses in schizophrenia depend on the baseline response variability, the initial level of reactivity, and perhaps other factors related to scoring criteria, the scoring of startle responses is much less problematic. Although voluntary blinks are typically identified and deleted from the analyses by the application of somewhat arbitrary criteria, our inspections of the data indicate that our fundamental findings are not influenced by changes in these criteria. The data thus support the presence of an important habituation deficit in schizophrenia in the absence of any detectable alterations in startle reactivity. While this finding seems to conflict with recent evidence of hyporesponsiveness of SCOR in schizophrenia, this seems...

Figure 2. Habituation of blink reflex component of acoustic startle in schizophrenic and control patients

Data are presented as in figure 1. Procedural details are described in Geyer and Braff (1982), in which these data are more fully presented.
ing contradiction may be more apparent than real. If, as suggested by Bernstein and Patterson elsewhere in this issue, the SCOR response reflects the subject’s attachment of significance to the stimulus, SCOR hyporesponsiveness may result from the schizophrenic patient’s slowness in information processing and difficulty in rapidly identifying the significance of even mild environmental stimuli. In this context, the schizophrenic patient’s inability to decrease responding to the more intense and stressful stimuli used to elicit startle may be attributable to a parallel fundamental slowness of information processing.

**An Animal Model of Habituation Deficits in Schizophrenia.** It has often been suggested that the effects of LSD or related psychotomimetics might provide an appropriate model for symptoms related to one or more of the group of schizophrenias (i.e., acute, intermittent vs. chronic schizophrenia). Animal models of schizophrenia based on hallucinogens have been challenged in part because, while schizophrenia is a chronic condition, many animal and human effects of these drugs exhibit rapid tolerance following chronic administration (Braff and Geyer 1980). However, it is unclear whether tolerance develops for all relevant dependent variables and whether tolerance is full and equal for all hallucinogens (Davis et al. 1984b).

Furthermore, in the present context, our focus is on the modeling of the specific deficit in startle habituation exhibited by schizophrenic patients. We are not attempting to create models for the entire syndrome of schizophrenia. As discussed elsewhere (Segal and Geyer 1985), the development of animal models relevant to psychopathology is greatly facilitated by focusing on specific symptoms rather than longitudinally defined, global diagnostic entities. In the mid-1970’s, we and others reported that LSD and phenylethylamine hallucinogens increased the magnitude of either tactile or acoustic startle responses in rats (Davis and Sheard 1974; Geyer et al. 1975, 1978). While hallucinogens related to mescaline appeared to increase startle reactivity on all trials, independently of habituation or sensitization, we found that rats treated with 100 μg/kg LSD showed a selectively increased first response and decreased habituation in a 240-trial tactile startle paradigm (Geyer et al. 1978).

The LSD-induced impairment of habituation seemed to support LSD as a viable drug treatment that mimicked the schizophrenic deficit in startle habituation. We then extended that work by comparing the effects of acute and chronic LSD on measures of rat startle as a bridge to looking at acute and chronic psychosis. Using air-puffs as tactile stimuli, we studied 20 animals in a 240-trial tactile startle paradigm response and decreased habituation reflecting impaired habituation and sensitization, we found that rats treated with 100 μg/kg LSD induced acutely by LSD was absent by the chronic treatment. In contrast, the impairment of habituation induced acutely by LSD was absent following chronic administration, perhaps reflecting an induction of behavioral tolerance on the habituation measure.

This study produced three major findings: (1) Acute administration of LSD induces an impairment of startle habituation that provides an interesting bridge to theories of habituation deficits in some schizophrenic subgroups; (2) chronic LSD effects on reactivity measures do not show complete tolerance; (3) startle reactions in infrahuman paradigms offer hope for creating a useful cross-species model of some specific cognitive deficits of schizophrenia. Collectively, these results challenge the assumption of complete behavioral tolerance with chronic LSD administration and also call into question the theoretical position that the indoleamine hallucinogens are necessarily inappropriate as models for the symptomatology of one or more of the group of schizophrenias.

**Possible Neurobiological Substrates of Startle Habituation Deficits.** Since habituation deficits are theoretically important in understanding schizophrenia, identifying the neurobiological substrates of startle habituation has become more important. Clearly, one of the values of any animal model of a clinical phenomenon observed in humans lies in the possibility that it will enable us to elucidate the underlying anatomy and the functional mechanisms relevant to the clinical disorder. As noted above, one of the major ad-
vantages of animal studies using startle response measures is that the neuronal circuitry responsible for the behavior is largely known (Davis et al. 1982a; Cassella and Davis 1986). Accordingly, given the resemblance between the impairment of startle habituation induced by LSD in rats and the deficit in startle habituation in schizophrenic patients, there is considerable interest in determining the mechanism(s) responsible for this habituation-imparing effect of LSD. In contrast to the startle response itself, the neuronal systems of importance in the mediation or modulation of habituation are not well understood. Although it has frequently been assumed that short-term or "within-session" habituation is mediated by changes intrinsic to the startle reflex pathway itself (Thompson and Spencer 1966; Groves and Thompson 1970), this assumption does not preclude the importance of extrinsic modulatory influences on the habituation of the response. These extrinsic influences are important since no habituation appears to be produced when startle-like responses are repeatedly elicited by direct electrical stimulation of parts of the startle circuit itself (Davis et al. 1982b).

There have been few reports in which experimental manipulations were found to affect startle habituation. Lesions of the inferior colliculus (Jordan and Leaton 1983) and cortical spreading depression have been found to impair the habituation of acoustic startle (Van der Staak 1976). While lesions of the mesencephalic reticular formation tend to decrease between-session habituation, they have no effect on the within-session habituation of startle (Jordan and Leaton 1983). More recent studies indicate that the between-session habituation of acoustic startle requires an intact cerebellar vermis (Leaton and Supple 1986), corroborating other evidence that short- and long-term habituation of both startle and other behavioral responses are subserved by different mechanisms (Williams et al. 1974; Van der Staak 1976).

While we have no information as yet about possible alterations of long-term startle habituation in schizophrenia, it is of some interest to note that Heath (1977) has suggested that stimulation of the cerebellum may be of therapeutic value in schizophrenia. Electrical stimulation of the cerebellar vermis in rats has been shown to increase the amplitude of acoustic startle responses, while increasing dopamine turnover and decreasing serotonin release within the nucleus accumbens (Albert et al. 1985). Thus, just as single neurotransmitter theories of schizophrenia are inadequate to explain the rich array of data, single locus

Figure 3. Effects of 50, 100, or 200 µg/kg LSD on tactile startle habituation in rats

Data are shown as % of saline control values for first and last blocks of 240-trial tactile startle test. LSD-impaired startle habituation as reflected by increased response magnitudes for last block in absence of significant effects on responses to initial trials. Detailed procedures and some of these data were first presented in Braff and Geyer (1980).
Theories are also probably too oversimplified to advance our knowledge of startle habituation.

Another productive approach to understanding the neurobiological substrates of LSD effects on startle habituation is to look at underlying neurotransmitter mechanisms of action. In contrast to the paucity of knowledge about the neurobiology of startle habituation, a great deal is known about the neuropharmacology of LSD. Clearly, the central nervous system effects of LSD are not limited to any particular neurotransmitter system or neuroanatomical structure. Nevertheless, current thinking about the substrates of the behavioral effects of LSD and related hallucinogens does provide some starting points from which to address our questions about the mechanisms underlying LSD effects on startle habituation and, by implication, possible alterations responsible for the deficit in startle habituation shown by schizophrenic patients.

Dopaminergic systems. Despite its predominant effects on serotonergic systems (see below), LSD appears to have some mixed agonist/antagonist actions at dopamine receptors (Creese et al. 1975) and can inhibit the firing of dopaminergic neurons (Walters et al. 1979). While such alterations in dopamine systems may contribute to the behavioral effects of LSD, it is unlikely that dopaminergic effects are responsible for the LSD induction of startle habituation deficits for several reasons: (1) Lisuride, a congener of LSD having even greater potency on dopaminergic systems, does not reproduce the habituation or other behavioral effects of LSD (Adams and Geyer 1985 and unpublished observations). Although relatively high doses of lisuride increase acoustic startle reactivity, this effect was successfully blocked by a serotonin receptor antagonist (Svensson 1985). (2) The more specific dopamine agonist apomorphine does not affect habituation but can increase or decrease startle reactivity. Reactivity effects are blocked by the dopamine antagonist haloperidol, implicating dopamine in reactivity but not habituation (Davis and Aghajanian 1976; Geyer et al. 1978). (3) Syntonic with the apomorphine results, fairly high doses >2.0 mg/kg) of the indirectly acting dopamine agonist amphetamine increase acoustic or tactile startle reactivity independently of any change in habituation (for review see Davis 1980).

Noradrenergic systems. Recent data suggest that norepinephrine contributes to the augmentation of responses to sensory stimuli associated with hallucinogens and such augmented responses might account for failure of habituation in schizophrenic patients. Aghajanian, McCall, and colleagues have found that hallucinogens potentiate the ability of norepinephrine (as well as serotonin) to facilitate the excitation of facial motor nucleus cells by glu-
tamate (McCall and Aghajanian 1980) and indirectly augment the reactivity of neurons in the noradrenergic locus ceruleus to phasic sensory inputs (Aghajanian 1980). Similarly, at a behavioral level, we have recently reported that selective depletions of brain norepinephrine induced by the neurotoxin xylamine effectively block the potentiating effects of LSD on the neophobic responses exhibited by rats when placed in a novel environment (Geyer et al. 1985). The possible relevance of noradrenergic systems in SCOR habituation abnormalities in schizophrenia has also been suggested by the finding of elevated norepinephrine metabolite levels in the cerebrospinal fluid of behaviorally hyperresponsive (SCOR) schizophrenic patients (Bartfai et al. 1984).

With specific regard to startle response measures, norepinephrine has often been considered to have a generally excitatory influence (Davis et al. 1984a). However, the specification of which noradrenergic systems are involved and the nature of the effect on startle have not been clearly established. We previously reported that 6-hydroxydopamine-induced lesions of the locus ceruleus in rats significantly accelerated behavioral habituation of tactile startle (Adams and Geyer 1981). This neurochemically specific lesion, shown in the fluorescence micrographs in figure 5, produces marked depletions of norepinephrine throughout much of the central nervous system, including the cortex, hippocampus, substantia nigra, and spinal cord. The fluorescence shown is derived from the reaction of formaldehyde with endogenous norepinephrine contained by these neurons. Details about this treatment and the specificity of its depletion of forebrain norepinephrine are provided in Adams and Geyer (1981). (The effects of this treatment on tactile startle habituation are shown in figure 6.) By most measures, however, the animals are behaviorally normal. Nevertheless, the effect of this lesion on startle habituation was reproduced at two different stimulus intensities and at two different times after the introduction of the lesion, as illustrated in figure 6. At 5 days postlesion, the initial trial block was not significantly affected by the lesion, although the treatment × trials interaction term confirmed the accelerated response habituation. The apparent acceleration of startle habituation induced by norepinephrine depletion can be most readily seen in the inset to figure 6, in which the data are plotted as percent of the first response. Thus, decreased noradrenergic tone creates a condition opposite that observed in schizophrenic patients, indirectly supporting the idea that increased norepinephrine levels may be implicated in the pathogenesis of schizophrenia.

In concert with our lesion findings, clonidine, which inhibits the firing of locus ceruleus neurons (Svensson et al. 1975), is one of relatively few drugs that has been shown to accelerate startle response.

**Figure 5.** Fluorescence micrographs at 2 rostrocaudal levels of rat locus ceruleus after administration of vehicle or 6-hydroxydopamine

Fluorescence micrographs are shown at 2 rostrocaudal levels of the rat locus ceruleus from animal administered either vehicle (left) or representative animal infused with 6 μg/0.6 μl 6-hydroxydopamine bilaterally (right). Fluorescence is derived from reaction of formaldehyde with endogenous norepinephrine (NE) contained by these neurons. Treatment details and specificity of its depletion of forebrain NE are provided in Adams and Geyer (1981).
Figure 6. Effect of 6-hydroxydopamine-induced lesions of rat locus ceruleus on startle response amplitudes

Results are shown for first startle response and means (±SEM) for subsequent 12 blocks of 20 trials each. Inset depicts same data expressed as % of first response. Tactile (35 p.s.i. air puffs, 15-sec intervals) startle testing was conducted 5 days after introduction of the lesion. These findings were first presented in Adams and Geyer (1981).

habituation without affecting between-session habituation (Leaton and Cassella 1984). Despite the similarity between the effects on habituation of clonidine and locus ceruleus lesions, however, Davis et al. (1977) have shown that electrolytic lesions of the locus ceruleus do not preclude the effects of clonidine. Hence, it appears that clonidine does not act via its effects on cerulear cells. One alternative site of action for clonidine is the serotoninergic system, since systemic treatments with clonidine inhibit the firing of serotoninergic neurons in the raphe nuclei (Svensson et al. 1975). Another interesting possibility is suggested by our observation that the behavioral effects of our locus ceruleus lesions were better correlated with the lesion-induced depletion of norepinephrine within the dopaminergic substantia nigra versus the hippocampus (Adams and Geyer 1981). One could speculate that an interaction between noradrenergic and dopaminergic systems within the brainstem may be critical to these observed effects on startle habituation. By analogy, these complex monoamine interactions may be critical to understanding schizophrenia-related neurotransmitter abnormalities. Others have also considered such an interaction as possibly of importance in the mediation of drug effects on startle (Kehne and Sorenson 1978; Davis et al. 1985). The implication of norepinephrine effects for startle abnormalities in schizophrenia is that the dopamine theory, when stated as a single neurotransmitter hypothesis, is probably inadequate to account for these complex underlying mechanisms of action. One must hypothesize either complex variations in dopamine tone (Wyatt 1985) and/or a multiple neurotransmitter dysregulation hypothesis involving al-
Serotonergic systems. The effects of LSD on serotonergic systems have been extensively characterized largely because of the early finding by Aghajanian and associates of the remarkable sensitivity of serotonergic raphe neurons to LSD (Aghajanian et al. 1968; Aghajanian and Wang 1978). The effects of manipulations of brain serotonin levels on startle responding have also received considerable attention (Davis et al. 1984a). The available data suggest that whole-brain serotonin levels have an inverse relationship with startle reactivity (Davis 1980; Davis et al. 1984a). However, it is critical to note that serotonin appears to have different and even opposite effects on startle depending upon the specific region being manipulated. For example, direct infusion of serotonin into the cerebral ventricles or the hippocampus decreases both tactile (Geyer et al. 1975; Geyer 1976) and acoustic (Davis et al. 1980) startle reactivity. When infused onto the spinal cord, however, serotonin produces a dose-related increase in startle reactivity (Davis et al. 1980). Other studies using both electrolytic and neurotoxic lesions indicate that the forebrain inhibitory effect of serotonin on startle is primarily dependent upon the mesolimbic serotonergic pathway originating in the median raphe nucleus and innervating the thalamus, septum, and hippocampus (Geyer et al. 1976a, 1980; Geyer 1978; Vergnes and Kempf 1982). The much larger mesostriatal serotonergic pathway, which is more intimately related to dopaminergic systems, appears to have little if any effect on startle per se (Geyer et al. 1976b, 1980). Such findings have clearly indicated the need for regionally specific manipulations in virtually any attempt to relate the physiology of a neurochemically defined system to behavioral output. Still, in terms of understanding schizophrenic psychopathology, none of these studies provided any strong evidence for an inferred and widely hypothesized serotonergic involvement in startle habituation (versus startle reactivity) in the schizophrenic disorders. We therefore conducted the studies described below.

New Experiments: Serotonin Manipulations and Startle Habituation

Interest in the behavioral effects of serotonergic systems has recently been sparked by ligand-binding studies showing the multiplicity of serotonergic receptors in brain tissue and leading to new and more potent serotonin (5HT) agonists and antagonists. These new studies indicate that many of the phenylethylamine-derived hallucinogens related to mescaline are fairly selective agonists at the 5HT2 binding sites (Glennon et al. 1984; Jacobs 1984), while LSD appears to be an effective agonist at both 5HT1 and 5HT2 sites (Janssen 1982; Glennon et al. 1984). Phenylethylamine hallucinogens appear primarily to affect startle reactivity (Bridger and Mandel 1967; Geyer et al. 1978); however, these drugs may also affect habituation. Illustrating such a complex pattern of results, phencyclidine increases reactivity at high doses and impairs habituation at lower doses (Geyer et al. 1984). Accordingly, we have recently begun to explore the effects of some of the newly developed serotonergic agonists and antagonists in a 201-trial tactile startle paradigm, using procedures and stimuli virtually identical to those used in our previous studies of the effect of LSD on startle habituation. This effort is designed to use drugs with more specific serotonergic actions than LSD to mimic the impaired habituation seen in schizophrenic patients. These more specific pharmacological probes will allow us to map out possible neurotransmitter abnormalities in the schizophrenic disorders.

Tactile Startle Habituation

Methods. Male Sprague-Dawley rats (250–300 g; Simonsen Laboratories) were tested in stabilimeter chambers during the light phase of the diurnal cycle. Typically, treatment groups consisted of 10–12 animals each. A microcomputer system was used to control the presentation of stimuli and to monitor startle responses, as previously described (Geyer et al. 1984). The background noise level was maintained at 70 dB(A) throughout testing. Each test session consisted of 25 p.s.i. air-puff (tactile) stimuli delivered through an 8-mm tube above the animal’s back at 15-sec intervals. Animals were placed in the stabilimeter 30 min after drug injection, with the first trial beginning 5 min later.

The effects of the 5HT2 antagonist ketanserin (Janssen Pharmaceuticals), the 5HT1A agonist 8-OH-dipropylaminotetralin hydrobromide (8-OHDPAT) (Research Biochemicals), the 5HT1B agonist m-trifluoromethylphenylpiperazine (TFMPP) (Aldrich Chemical Company, Inc.), the tryptophan hydroxylase inhibitor parchlorophenylalanine methyl ester hydrochloride (PCPA) (Sigma), and the 5HT reuptake inhibitor fluoxetine hydrochloride (Lilly Laboratories, Inc.) have been examined. All injections were given s.c. Controls were injected with equivalent volumes (1.0...
The data were reduced to the first response and 20 blocks of 10 trials each. For each experiment, a mixed-design ANOVA was done with the drug treatment as a between-subjects factor and blocks of trials as a within-subjects factor. The first response and the first and last 10-trial blocks were also analyzed in separate one-way ANOVAs. Differences in habituation trends were reflected by the drug × trials interaction term in the mixed-design ANOVA and/or the presence of a significant difference in the last trial block in the absence of a difference in the first trial block. Significant differences in the first trial block were considered evidence of an alteration in general reactivity, per our established methods and rationale (Braff and Geyer 1980; Geyer et al. 1984).

**Results**

**8OHDPAT.** We first examined the effects of the fairly specific 5HT$_1$ agonist 8OHDPAT (Hjorth et al. 1982). A fairly low dose of 0.1 mg/kg 8OHDPAT significantly decreased tactile startle reactivity (means ± SEM: saline 559 ± 15; 8OHDPAT 472 ± 23; F = 10.3; df = 1,22; p < .01). In a subsequent experiment, we found a similar effect with a dose of 0.3 mg/kg 8OHDPAT (means ± SEM: saline 524 ± 32; 8OHDPAT 401 ± 29; F = 8.2; df = 1,22, p < .02). We also found that this effect of the 5HT$_1$ agonist is similar even when less intense tactile stimuli are used. In all three experiments, the depression of startle reactivity produced by 8OHDPAT continued through to the last trial block. Incidentally, it should be noted that 8OHDPAT is considered to be a 5HT$_1$A agonist and that the 5HT$_2$B agonist TFMP (Fuller et al. 1981) (0.65–2.5 mg/kg) also produces a dose-related suppression of startle without affecting startle habituation (data not shown). However, this effect is very transient and is limited to only the initial trial blocks.

**Ketanserin.** As illustrated in figure 7, a 0.5 mg/kg dose of the 5HT$_2$ antagonist ketanserin (Janssen 1982; Laduron et al. 1982) accelerates habituation. The drug × trials interaction was significant (F = 1.69; df = 19,418; p < .05). While no significant differences were observed over the initial trials (F = 0.79; df = 1,22; NS), the last block was significantly reduced by ketanserin (F = 5.47; df = 1,22; p < .05). This result has since been replicated and extended to include a dose range from 0.5 to 2.5 mg/kg. In addition, other 5HT$_2$ antagonists have recently been found to produce a similar pattern of effects in this paradigm. These drugs include ritanserin, cinanserin, and cyproheptadine. With regard to cyproheptadine, we have also confirmed that, as in the case of LSD (Geyer et al. 1978), its effects on habituation are independent of the time after injection at which the series of startle trials is initiated. Such a finding is critical to the interpretation of acute drug effects on habituation when the testing session lasts, as in this case, for almost an hour.

Given the observation that the 5HT$_2$ receptor antagonists, as defined largely by studies examining ligand binding (Janssen 1982) and the blockade of agonist effects (Lucki et al. 1983), consistently produce effects on tactile startle habituation that are opposite in direction to those of LSD, one would next like to confirm that other appropriate (i.e., 5HT$_1$) agonists would have an LSD-like effect. Unfortunately, with the exception of the phenylethylamine-derived hallucinogens such as mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM), no selective 5HT$_2$ agonists have yet been identified. LSD itself appears to be an effective 5HT$_2$ agonist, but it is not selective (Peroutka and Snyder 1979; Jacobs 1984). Quipazine is widely known to have a variety of effects in addition to being a 5HT$_2$ agonist (Schlicker and Gothert 1981; Schecter and Concannon 1982). We had previously shown, using similar stimuli and procedures (Geyer et al. 1978), that mescaline, DOM, and related phenylethylamine hallucinogens produce consistent and dose-related increases in tactile startle reactivity, an effect that precludes an unambiguous interpretation of any possible subsequent effects of the drugs on habituation. The effects of electrolytic or neurotoxic lesions are complicated by the apparent rapidity with which the central nervous system adapts to serotonin depletions (Davis 1980; Gately et al. 1986). Hence, lesion manipulations, which require surgical interventions, are difficult to compare directly with the effects of acute drug treatments.

**Fluoxetine.** On the basis of the above considerations, we opted next to study the effects of a selective blocker of serotonin uptake as a way to develop converging evidence for the presumed relevance of the endogenous serotonergic system to the effects of LSD and 5HT$_2$ antagonists on startle habituation. Fluoxetine is a relatively selective serotonin uptake blocker that has little affinity for 5HT$_1$ or 5HT$_2$ receptors (Wong et al. 1983). Since startle-eliciting stimuli induce bursts of firing of serotonergic neurons (Trulson and Jacobs 1979), we envision that, by blocking reuptake, fluoxetine should potentiate the actions of released serotonin and therefore act as an endogenous agonist only at serotonergic syn-
Figure 7. Effects of ketanserin on habituation to 201 air-puff stimuli (15-sec interstimulus interval)

Results are shown as group means for first startle response and subsequent 20 blocks of 10 trials each. Testing began 35 min after s.c. injections of either saline or ketanserin. Ketanserin caused animals to habituate significantly faster than controls.

Results are as follows:

- **SALINE**
- **KETANSERIN**

As illustrated in figure 8, we found that fluoxetine (10 mg/kg) mimics the effect of LSD by reducing startle habituation (drug × trials, $F = 2.58; df = 19,418; p < .001$). Fluoxetine produces a significant augmentation of startle in the last trial block ($F = 5.91; df = 1.17; p < .05$) without affecting startle on the initial trial block ($F = 0.65; df = 1.17; NS$). While higher doses of fluoxetine appear to produce some short-lived debilitating effects, we have found that a lower dose (5 mg/kg) of fluoxetine also impairs habituation (data not shown).

**Parachlorophenylalanine.** To provide more converging evidence as to the relationship between the effects of LSD and the 5HT, antagonists on startle habituation, we examined the effects of the serotonin synthesis inhibitor, parachlorophenylalanine (PCPA). As reviewed by Davis (1980), the effects of PCPA on startle and its habituation have been the subject of several studies, but with rather inconsistent results. However, when PCPA has been found to have an effect on startle, it has generally been one that emerges only after several trials (Carlton and Advokat 1973; Conner et al. 1970). Yet none of the studies had examined habituation of tactile startle over as many trials as we have found necessary to detect the effect of LSD on habituation reliably (Geyer et al. 1978). Hence, we administered 300 mg/kg PCPA 3 days before testing in our standard 201-trial paradigm. The results, illustrated in figure 9, revealed that this dose of PCPA appears to accelerate tactile startle habituation. Although the drug × trials interaction did not achieve significance ($F = 1.28; df = 19,361; NS$), the apparent acceleration of habituation was confirmed by the finding that the last trial...
block was significantly decreased by PCPA ($F = 6.34; df = 1,19; p < .02$) and the fact that the drug had no significant effect on the initial trial block ($F = 0.72; df = 1,19; NS$). Furthermore, we have recently replicated this effect and found that PCPA produces dose-related increases in startle habituation rates over a range from 100 to 300 mg/kg.

Conclusions. These new results enable us to consider more specific hypotheses about the possible substrates of the impairment of startle habituation induced by LSD and the similar deficit exhibited by schizophrenic patients. The pattern of results obtained with the postsynaptic serotonergic agonists and antagonists is consistent with the suggestion (Glennon et al. 1984) that the hallucinogenic drugs may exert many of their behavioral effects via their actions as 5HT$_2$ agonists. While the 5HT$_2$ agonists 8OHDPAT and TFMPP decreased reactivity without affecting habituation, ketanserin and related 5HT$_2$ antagonists significantly accelerated startle habituation and had no effect on initial levels of reactivity. That is, the 5HT$_2$ blockers produced effects opposite to those of LSD, suggesting that LSD may be exerting its effects as a 5HT$_2$ agonist.

In this context, it is intriguing to note that one of the few other drugs known to accelerate startle habituation, clonidine, inhibits the firing of serotonergic raphe neurons, as discussed above (Svensson et al. 1975). Further indications of a potentially important interaction between catecholaminergic and serotonergic systems in the actions of hallucinogens come from the recent finding (Rasmussen and Aghajanian 1986) that the hallucinogen-induced potentiation of stimulus-elicited activity of locus ceruleus cells is
Figure 9. Effects of 300 mg/kg parachlorophenylalanine (PCPA) on startle habituation

PCPA was administered 3 days before testing, a time interval at which a largely selective depletion of serotonin is produced. PCPA significantly accelerated tactile startle habituation relative to controls. See note to figure 7.

PCPA was administered 3 days before testing, a time interval at which a largely selective depletion of serotonin is produced. PCPA significantly accelerated tactile startle habituation relative to controls. See note to figure 7.

While the decrease in reactivity induced by the 5HT₂ agonists may be consistent with the earlier literature suggesting an inverse relationship between limbic serotonin levels and reactivity (see above), the effects of the 5HT₂ antagonists reported here are more consistent with our new findings with fluoxetine and PCPA (figures 8 and 9). Like the action of the 5HT₂ antagonists, the acute depletion of serotonin induced by PCPA significantly accelerated startle habituation. Hence, both presynaptic and postsynaptic impairments of serotonergic functions seem to produce startle habituation abnormalities opposite to those exhibited by schizophrenic patients. Conversely, the potentiation of the action of synaptic serotonin presumably induced by the uptake blocker fluoxetine appeared to mimic the effect observed with LSD in the same paradigm. Taken together, these findings further corroborate the hypothesis that the serotonergic system is critically involved in the expression of startle habituation and that this involvement is mediated via 5HT₂ postsynaptic receptors.

An additional possibility raised by this set of results is that these behavioral phenomena may be reflective of an important interaction between serotonergic and catecholaminergic systems within the brainstem. Within this context, it is interesting to note that Stahl et al. (1985) have attempted the use of fenfluramine, a serotonin-depleting agent, to treat deficit or negative symptoms in schizophrenic patients. Their rationale was that negative...
symptoms in autistic patients may respond to fenfluramine treatment and that some autistic children and schizophrenic adults show hyper-serotoninemia (Freedman et al. 1981). In future studies, it will be of considerable interest to delineate the anatomical sites at which the serotonergic system exerts this effect and to examine the possible serotonergic correlates of the habituation deficits exhibited by schizophrenic patients.

Sensorimotor Gating of Startle in Schizophrenia

Braff et al. (1978) used Schaffer and Marcus’ (1973) unique self-stimulation, event-related potential (ERP) paradigm whereby a subject initiated the ERP-eliciting auditory stimulus using a key release. With increasing intervals between key release and stimulus onset, the $P_{300}$ ERP amplitude increased as the interval (and corresponding degree of uncertainty) increased. This self-stimulated ERP paradigm offered an opportunity to assess the time linkage of information-processing dysfunction in schizophrenia. Results showed that schizophrenic patients had relatively increased $P_{300}$ ERP waves at the 250 ms delay between key release and stimulus onset, as reflected by a lack of amplitude increase between the 250 and 500 ms delay conditions. At the 250 ms delay condition, controls were relatively certain that a stimulus would be arriving and their ERP amplitudes were relatively smaller (reflecting less uncertainty) than the schizophrenic patients in the 250 ms delay condition. The schizophrenic patients’ larger 250 ms ERP was interpreted as reflecting relatively greater uncertainty that the stimulus was arriving. The implication of this finding was that schizophrenic patients were unable to maintain their attentional set for 250 ms, whereas controls were able to do so. This study helped to quantify the time base of the schizophrenic deficits in attention/information processing. The critical period of dysfunction seemed to occur in the range of 250 ms after the subject initiated the key release. Later studies have repeatedly implicated this time base (i.e., < 500 ms of processing time) as being important in the information-processing dysfunction in schizophrenia (Schwartz et al. 1983; Green and Walker 1984; Braff and Saccuzzo 1985; Merritt and Balogh 1985).

The self-stimulated ERP paradigm shares features with both the sensory gating ERP paradigm of Freedman et al. (1983) and the prepulse inhibition acoustic startle reaction paradigm described in detail below. Specifically, these paradigms all use two time-dependent events (key release-stimulus or weak prestimulus-startle stimulus), and then measure the modulating effects of the first event on the response to the second event. Although this process has been variously labeled, Freedman and associates’ use of the term and concept of sensory (or sensorimotor) gating is perhaps most theoretically descriptive and informative.

Freedman et al. (1983) have advanced our understanding of sensorimotor gating deficits in schizophrenia by the use of a unique two-stimulus, conditioning/testing, cortical ERP paradigm in a thematic and interesting series of studies. Freedman’s work builds on prior studies by Shagass (1977), who noted decreased ERP “recovery curves” in schizophrenic patients which were interpreted as representing an underactivation of cortical filtering mechanisms. When two auditory stimuli are presented at a variable and fairly brief (i.e., 500 ms) inter-stimulus interval, the second stimulus-evoked $P_{50}$ wave is normally inhibited or gated by the effects of the first stimulus.

Schizophrenic patients exhibit a lack of these normal inhibitory or sensorimotor gating influences, leading to increased $P_{50}$ ERP’s to the second stimulus (Adler et al. 1982; Franks et al. 1983; Freedman et al. 1983). This schizophrenic deficit is most demonstrable when the inter-stimulus interval between the two stimuli is about 500 ms. In more neurophysiological terms, Franks et al. (1983) noted that neurophysiologists have used the paradigm “to examine inhibitory neuronal feedback and feedback pathways in many brain structures, including cerebellar cortex, hippocampus, and neocortex” (p. 990). This effect is not merely an artifact induced by antipsychotic medications since family members of schizophrenic patients showed similar deficits (Freedman et al. 1983). Adler et al. (1982) proposed that these deficits are caused by a state of hyperarousal with hypereexcitable neurons causing a defect in “normal cortical and subcortical inhibitory mechanisms” (p. 640). We have recently replicated the Freedman et al. (1983) finding of the $P_{50}$ conditioning/test deficit in sensorimotor gating in a population of schizophrenic patients (Braff and Judd 1986).

Prepulse Inhibition of Startle in Schizophrenia. To assess “inhibitory failure” or the loss of sensorimotor gating in schizophrenia, we applied a “weak prestimulation” startle paradigm to schizophrenic and control patients (Graham 1975; Lison and Hoffman 1983). We first confirmed in normal human subjects that when weak acoustic prestimuli precede the loud startle-eliciting tones by 60 or 120 ms, there are dra-
matically "gated" or inhibited startle (blink) reflex amplitudes and concurrent blink latency facilitation (i.e., shortening of latency-to-onset).

In applying this paradigm to schizophrenic patients, we reasoned that schizophrenic patients would show decreased inhibition of the blink reflex in the 30, 60, or 120 ms inter-stimulus-interval condition. Such time-linked inhibitory failure would "theoretically be correlated with loss of preattentive filtering" and would produce "stimulus 'flooding' and miscoding due to this gating mechanism dysfunction." Twenty normals were compared with 12 schizophrenic patients using standard measures for eliciting and measuring the blink reflex, the major measurable component of the startle response in humans (Landis and Hunt 1939). The prestimulus was a continuous, 1,000 Hz, 71 dB(A) tone and the startle stimulus was a 50 ms, 104 dB(A) burst of white noise.

Using topographic criteria to detect and delete voluntary eyeblinks, we analyzed and sorted reflexive blinks. As predicted, schizophrenic patients exhibited less amplitude inhibition and less latency facilitation than normals. Specific ANOVAs confirmed that schizophrenic patients exhibited a loss of prepulse inhibition and latency facilitation in the 60 ms condition (see figure 10).

The prepulse data were consistent with the idea that in schizophrenic patients there is a loss of reflex amplitude inhibition and less latency facilitation than normals. Specific ANOVAs confirmed that schizophrenic patients exhibited a loss of prepulse inhibition and latency facilitation in the 60 ms condition (see figure 10).

Graham (1975) has pointed out that normal inhibition of the blink occurs in many species and, in humans, maximal inhibition is seen with 60 to 120 ms of prestimulation. Graham calls this inhibitory process "a wired-in negative feedback which reduces the distraction produced by reflexes such as startle, and thus protects what has been called preattentive stimulus processing" (1975, p. 246).

Graham (1975) links this inhibitory process with Massaro's (1975) description of auditory backward masking and further notes that Eccles (1965) invoked the concept of widespread presynaptic inhibition of flexor reflex afferents that provides the first stage in suppressing all concurrent inputs into the central nervous system. Graham (1975) also cites the short and long time constant neurons that Gersuni (1971) has identified at all levels of the central nervous system. The short time constant neurons respond to brief energy pulses (6–15 ms), and thus are sensitive to rapid rise-time stimuli, have low detection thresholds, have rapid recovery, and use spatial but not temporal integration. In contrast, long time constant neurons respond to longer energy pulses, have higher thresholds, slower recovery times, and more opportunity for achieving temporal integration due to slower responses. According to Graham's initial formulations, at prepulse intervals ≤ 240 ms, reflex inhibition is dependent on hard-wired, inhibitory effects mediated...
by short time constant neurons. At longer prepulse intervals, reflex modification is due to a combination of long time constant neuron mediated activation and orienting effects.

Prepulse Inhibition in an Animal Model of Schizophrenia. Since mesolimbic dopamine overactivity had been repeatedly implicated in the pathophysiology of schizophrenia (Randrup and Munkvad 1967; Stevens 1973, 1979; Matthysse 1978), we hypothesized that rats with nucleus accumbens dopamine overactivity would lose their normal prepulse inhibition of the acoustic startle response. In our human studies, the relationship of increased central dopamine activity to information-processing dysfunction and psychosis was clouded by many factors, including chronic dopamine blockade by neuroleptics (Creese and Sibley 1981; Cross et al. 1981) and subtype differences among schizophrenic patients (Angrist et al. 1980; Crow 1980; Carpenter and Heinrichs 1981). Recent post-mortem evidence in psychiatric patients indicates that increased dopamine concentration (decreased turnover) in nucleus accumbens is associated with cognitive impairment (Bridge et al. 1987), supporting the link of dopamine overactivity with attentional and cognitive deficits. As with most animal models of psychopathology (McKinney 1977), animal model studies of information processing are also typically confounded since they are not easily generalized to human cognitive functioning. This difficulty is due in part to the complexity of most measures of schizophrenic patients' cognitive deficits relative to the simpler measures obtained in animal behavioral studies. However, we felt that a model based on the prepulse inhibition of startle would offer a unique opportunity to examine attentional/information-processing deficits in an animal model of schizophrenia, since the plasticity of startle responding is so similar in humans and animals.

To create dopamine overactivity, rats received bilateral injections of 6-hydroxydopamine (6OHDA) into frontal cortex, nucleus accumbens, or substantia nigra using stereotaxic procedures that yield selective regional dopamine depletion as established by our collaborators Swerdlow and Koob (Koob et al. 1984). In time, this depletion presumably causes a proliferation of postsynaptic dopamine receptors in the denervated region. One week later, animals were placed in the startle chambers and treated with apomorphine or saline/ascorbic acid vehicle before testing. Trials consisted of a single 118 dB(A) noise burst (pulse condition) or an 80 dB(A) prepulse followed 60, 120, 480, or 2,000 ms later by the 118 dB(A) noise burst (prepulse conditions). A total of 121 trials were presented, with the pulse and prepulse conditions being given in a pseudorandomized order. This procedure was repeated 1 week later with drug treatment (apomorphine or vehicle) reversed for each animal. The low dose (0.1 mg/kg) systemic apomorphine was designed to have no generalized effects, but to cause preferential activation of the regionally specific increased numbers of postsynaptic dopamine receptors. All prepulse condition values were represented as percent of baseline (pulse) amplitude for each treatment and lesion condition, and analyzed by two-way ANOVAs with repeated measures on treatment and prepulse condition.

As can be seen in figure 11, apomorphine treatment significantly attenuated prepulse inhibition in nucleus accumbens in 6OHDA-injected animals and, to an apparently lesser degree, in nigral 6OHDA animals compared with the sham-injected control groups. In contrast, no such difference was detected between frontal cortex 6OHDA vs. vehicle-injected animals. This apomorphine-induced attenuation of prepulse inhibition was most pronounced at the 60 and 120 ms intervals in nucleus accumbens-lesioned animals and at the 120 ms interval in the nigral-lesioned animals, supporting the idea that the nucleus accumbens dopamine overactivity closely mimics the loss of sensorimotor gating found in schizophrenic patients. Apomorphine produced a robust potentiation of locomotor activity in nucleus accumbens but not nigral or frontal cortex 6OHDA-injected animals. In contrast, 0.1 mg/kg apomorphine produced robust stereotyped oral behavior in nigral 6OHDA-injected animals but not in nucleus accumbens or frontal cortex 6OHDA-injected animals, supporting the idea that the nigral lesions most closely approximate certain dopamine-mediated motor disturbances. Regional assays of dopamine and its metabolites confirmed the relative anatomic specificity of the depletions produced by the 6OHDA (Swerdlow et al. 1986).

These results were discussed from several perspectives. First, the 6OHDA lesions cause denervation supersensitivity with increases in the number but not binding affinity of D2 dopamine receptors (Creese 1977; Seeman 1980). Increased numbers of dopamine receptors have been reported in schizophrenia using a variety of techniques including positron emission tomography scans, evidence which supports this animal model of schizophrenia (Mefford 1981; Reynolds et al. 1981;
Injections were into the nucleus accumbens (NAcc), substantia nigra (SN), or frontal cortex (FC). Animals were treated with saline or 0.1 mg/kg apomorphine immediately before testing. Asterisk indicates significant difference by Student's t test following significant analysis of variance lesion × drug interaction. These data were presented in detail in Swerdlow et al. (1986).

Mackay et al. 1982). It is well known that clinical efficacy of antipsychotics is directly correlated to their D₂ receptor affinities (Creese et al. 1976; Seeman et al. 1976), so we next hypothesized that antipsychotic medications should block the putatively dopamine-mediated loss of prepulse inhibition of acoustic startle. As summarized elsewhere (Braff et al. 1985), we have reported that the antipsychotic haloperidol effectively blocks the loss of prepulse inhibition induced by 0.1 mg/kg apomorphine in nucleus accumbens-lesioned animals.

We have more recently found that somewhat higher doses of apomorphine ranging from 0.25 to 4.0 mg/kg induce similar and dose-related decreases in sensorimotor gating, even in rats having intact dopaminergic systems. Our recent experiments have revealed that systemic apomorphine produces a virtually total elimination of prepulse inhibition of the acoustic startle response at doses as low as 0.5 mg/kg. Furthermore, as with nucleus accumbens-lesioned rats treated with apomorphine, a dose of haloperidol that has no effect by itself (0.1 mg/kg) reverses the apomorphine effect. This finding further validates our animal model of schizophrenia based on the loss of sensorimotor gating (inhibitory failure) in catecholaminergically overactivated animals. It is of some interest to note that haloperidol by itself also has no effect and, in particular, does not potentiate prepulse inhibition, even when parameters of stimulation are used which produce submaximal levels of prepulse inhibition. In addition to our studies of the directly acting dopamine agonist, we have also found that amphetamine, an indirectly acting catecholamine agonist, significantly attenuates prepulse inhibition of acoustic startle even at doses that have no sig-
nificant effect on acoustic startle reactivity per se. This effect is evident following a single injection of amphetamine, and it appears that neither tolerance to nor sensitization of the effect occur when the drug is administered repeatedly over a period of 7 days.

In summary, both schizophrenic patients and rats with mesolimbic dopamine overactivity exhibit a deficit in the normal sensorimotor gating of startle when a prestimulus is presented 60–120 ms before an acoustic startle stimulus. Thus, these results form a bridge between hypotheses of mesolimbic dopamine overactivity and information-processing/sensorimotor gating abnormalities in schizophrenia (Matthysse 1978; Braff 1985). Sensory gating or inhibition of startle provides a useful model for studying the neural mechanisms underlying the specific, time-dependent deficits in information processing that occur in schizophrenic patients. This paradigm has also allowed us to specify the dynamic functional significance of dopamine overactivity in a cross-species model of schizophrenia.

Discussion and Synthesis

The studies discussed above demonstrate the utility of operationally defined measures of preattentive processes in the study of the group of schizotypal disorders. In particular, this work illustrates the potential power inherent in the development and use of animal models of specifiable behaviors exhibited by schizophrenic patients. An advantageous characteristic of startle response measures is their applicability to a variety of species. As exemplified by the studies described here, important examples of behavioral plasticity can be readily defined and quantitated using very comparable test paradigms in animals such as rats and in both normal and psychotic human subjects. Although the startle reflex itself appears to require only a small number of synapses and brainstem structures for its expression, it is evident from the foregoing review that the plasticity of the response is likely to be due to the modulatory influences of higher brain centers. It is also evident that, in addition to specifying neuroanatomic and neurotransmitter changes, animal model and human startle studies must address the functionally important issue of the timing pattern of any observed deficits. Accordingly, one of the important lines of future research will involve the specification of the anatomical pathways by which, for example, forebrain dopamine activity can induce such a profound loss of normally robust prepulse inhibition or serotonergic drugs can interfere with so fundamental a process as habituation.

The use of parallel startle responses in animal models of schizophrenia and humans affords a unique opportunity to explore the neurobiological basis of the schizophrenic disorders. For example, habituation and sensory gating abnormality profiles can be obtained for positive versus negative symptom schizophrenic patients. It can then be seen whether forebrain dopamine overactivity in an animal model selectively mimics the profile of positive versus negative symptom patients. If specific 5HT2 agents or D2 antagonists selectively block the habituation and/or sensorimotor gating deficits of dopamine overactivated rats, we would be able to use this animal model as a functionally significant and meaningful screening mechanism for antipsychotic medications in positive symptom patients. Via parallel human and animal studies, we will be better able to understand the complex interactions of multiple neurotransmitter systems, neuroanatomical sites, and temporal relationships of observed abnormalities that are involved in the pathogenesis of schizophrenia.

The work discussed in this article has focused on habituation and sensorimotor gating abnormalities exhibited by schizophrenic patients in test paradigms that use measures of the startle response. In both instances, schizophrenic patients exhibit abnormally reduced behavioral plasticity in response to changes in the sensory environment. In the habituation paradigm, the sensory events involve a time base on the order of many seconds to minutes. With prepulse inhibition of startle or similar two-event ERP paradigms, the antecedent event’s time base is on the order of several hundred milliseconds. We have not examined the prepulse inhibition of startle in the same patients in which startle habituation has been characterized. However, it is important to consider the possibility that these two paradigms have revealed some common deficit in schizophrenia. Such a possibility is suggested indirectly by an experiment on individual differences in the behavior of rats (Harrison-Read 1979), in which animals exhibiting little inhibition of the second response in a two-stimulus ERP paradigm also exhibited less habituation on various measures of exploratory behavior. Thus, on both measures, these animals were similar to our schizophrenic patients.

Startle responses offer a unique bridge between human schizophrenia and animal model research and provide an opportunity to specify the neurobiological foundations of information-processing abnormalities in schizophrenic patients.
As discussed in a thought-provoking and imaginative review by Callaway (1973), there is ample reason to consider the possible mechanistic relationships between the within-session habituation of responses like startle and the inhibitory phenomena reflected in two-stimulus paradigms. These latter phenomena are generally discussed as recovery cycles or refractory periods, while habituation is typically considered to reflect an active inhibitory process. However, partly on the basis of Gogan’s (1970) studies of human startle habituation, Callaway (1973) concludes that the "point here is that habituation may be considered a recovery cycle phenomenon when the refraction period is related to loss of novelty because of stimulus repetition, i.e., because the similarity between repeated stimuli is remembered" (p. 166). In concert with Callaway, we would argue that it remains for future studies to clarify the relationship, if any, between deficits in habituation and deficits in prepulse inhibition exhibited by schizophrenic patients.

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**The Authors**

Mark A. Geyer, Ph.D. is Associate Professor, and David L. Braff, M.D., is Associate Professor, Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA.