Neurobiological Studies of Sensory Gating in Schizophrenia

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Abstract

The sensory disturbance in schizophrenia is often described as an inability to filter out extraneous noise from meaningful sensory inputs. The neurobiological basis of this inability to filter has been examined using auditory evoked potentials, which are computerized averages of the brain's electrical response to sound. The sounds are presented in pairs to test the ability of the brain to inhibit, or gate, its response to a repeated stimulus. Schizophrenic patients lack the ability to gate the neuronal response shown by a particular wave, the P_{50} wave. The measurement of this deficit in human subjects and the exploration of its neurobiology in animals has produced evidence about several issues in the pathophysiology of schizophrenia: (1) the role of dopamine in improvement of sensory function in schizophrenic patients treated with neuroleptic drugs, (2) the interaction between familial or genetic deficits in sensory functioning in schizophrenic patients and possible abnormalities in dopamine metabolism, and (3) a mechanism by which noradrenergic hyperactivity in mania and other psychiatric illnesses might mimic some pathophysiological deficits in schizophrenia.

The enigma of schizophrenia seems only more puzzling in light of the plethora of research findings on its neurobiology. Family studies implicate genetic mechanisms, but exactly what is inherited is not clear. The efficacy of neuroleptic drugs implies a role for dopamine, but their failure to reverse the illness completely suggests that dopamine may not mediate all the symptoms. Mimicry of the symptoms of schizophrenia in acute mania suggests a related neurobiological dysfunction, but the similarities and differences require further explication. Data from studies on the neurobiology of sensory gating can be used to provide insight on these issues. The aim of such studies has been to use a relatively simple neurophysiological function, which can be examined in both human subjects and animal models, to answer questions about the pathophysiology of mental illnesses. This article will review electrophysiological evidence for an abnormality in sensory gating in schizophrenia, correlate modification of the abnormality during neuroleptic treatment with changes in dopamine metabolism, describe its familial pattern, and contrast its physiology during episodes of schizophrenia and mania. These investigations are primarily electrophysiological, and thus the perspective is limited to the data obtained with this technique. However, the results may be useful in constructing a more general framework in which to consider the interactions of catecholamines with genetic factors in psychosis.

Sensory Gating in Schizophrenia

Sensory disturbance has been an important element in many conceptualizations of schizophrenia (Venables 1964). It is not clear whether these disturbances are a cause of hallucinations and delusions or whether they are simply symptomatic of a generalized change in the brain's physiology, which is most easily observed in

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sensory areas. The sensory disturbance is often described as an inability to filter out extraneous stimuli with a correspondingly diminished ability to focus attention (McGhie and Chapman 1961). One mother described the problem in her schizophrenic son in these terms:

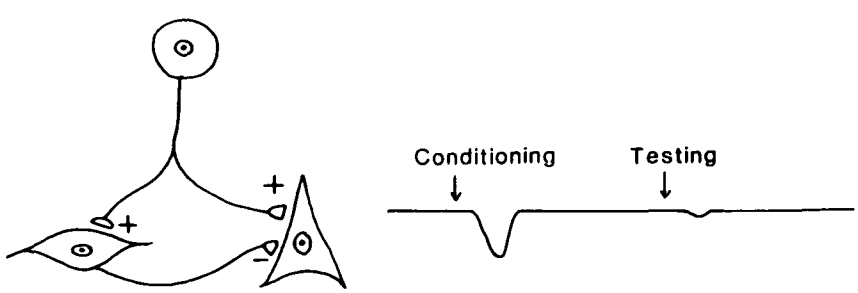
> If he isn't hallucinating, his hearing is different when he's ill. One of the first things we notice when he's deteriorating is his heightened sense of hearing. He cannot filter out anything. He hears each and every sound around him with equal intensity. He hears the sounds from the street, in the yard, and in the house, and they are all much louder than normal. [Anonymous 1985, p. 1]

The neurophysiological mechanism of this inability to filter has been the subject of numerous inquiries (Landau et al. 1975; Shagass 1976; Pfefferbaum et al. 1980; Patterson et al. 1986). One possible mechanism could involve the failure of an inhibitory gating pathway. Such pathways are known to exist in many brain areas, where their activity can block or "gate" the effects of a synaptic input on a target neuron.

The normal role of such gating is probably to regulate the amount of sensory input to the brain. If a person needs to be aware of any sound, as in times of danger, then the gating pathways need to allow the brain to be very sensitive. If sounds have already been detected, or if the environment is very noisy, then the brain needs to filter more strongly to prevent distraction by irrelevant sounds. Schizophrenic patients have been characterized, particularly early in their illness, as hypervigilant. They are very sensitive to distracting sounds, as described above. At times, particularly during acute psychotic decompensation, their inability to gate stimuli makes them feel "flooded" by uncontrollable, overwhelming sensory stimulation (Venables 1964). It is therefore reasonable to examine whether the activity of sensory gating pathways is normal in schizophrenia. Figure 1 diagrams a common arrangement for such a pathway, which can be found in several areas of the brain such as the hippocampus, thalamus, and cerebral cortex (Eccles 1969). The activity of these pathways is often demonstrated using a conditioning-testing paradigm, in which paired stimuli are presented to the subject. The synaptic pathway carrying sensory information—in this example, the round neuron at the top of figure 1—makes an excitatory synapse on the pyramidal neuron at the lower right. The round neuron might be a sensory neuron which is activated when the subject hears a sound. The pyramidal neuron might be a hippocampal or cerebral cortical neuron which plays an important role in decisions about the significance of the sound. The pyramidal neuron, when activated by the excitatory synapse, produces electrical activity, which can be recorded by the investigator. At the same time, the stellate or oval neuron at the lower left is also excited by a branch of the same pathway. This stellate neuron provides an inhibitory input to the pyramidal neuron. If a second input comes from the round sensory neuron to the pyramidal neuron while this inhibitory input is active, then the pyramidal neuron will be less responsive. The response to the second stimulus will accordingly be diminished. This phenomenon is called conditioning-testing inhibition, because the first stimulus activates or conditions the inhibition, while the second tests its strength. The results of the sensory gating activated by this paradigm can be expressed as the conditioning-testing ratio, which is the electrical amplitude of the test response wave divided by the amplitude of the conditioning response.

The example in figure 1 is a simple model system, in which the activity of a single neuronal circuit could be monitored. In human subjects, there are many different types of circuits, each with different response parameters. None of these circuits can be recorded individually, since recording electrodes generally cannot be introduced into the brain itself to record selectively from single neurons. The technique that is used instead is computerized signal averaging, which produces an averaged evoked potential (EP). An EP is the brain's electrical response to a sensory stimulus. Recording

Figure 1. Model for excitatory and inhibitory neurons in conditioning-testing paradigm

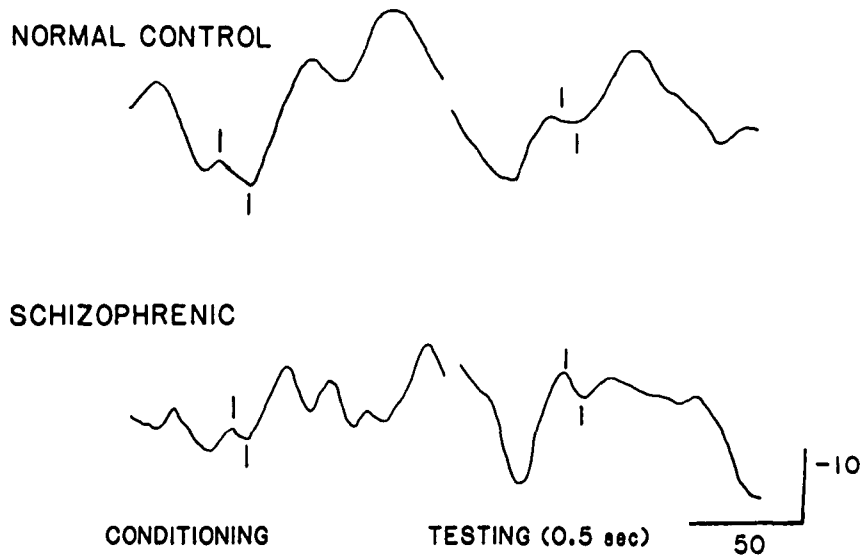


electrodes are standard electroencephalographic (EEG) electrodes pasted to the scalp surface. The EEG activity is amplified and led to a digital computer. Technical details have been described elsewhere (Siegel et al. 1984). The subjects hear a series of loud clicks. The EEG response to the clicks is summed by the computer in registers that are synchronized to the stimulus, so that waves that occur at fixed intervals after the stimulus are summated and thus enhanced. Waves that are not directly related to the stimulus and, thus, not time-linked to it tend to cancel themselves out. The use of the computer allows detection of a series of waves that represent the activation of various brain areas by the sound. The individual waves of the averaged EP are described by the location of the electrode, their electrical polarity, and the time after the stimulus at which they occur.

The wave to be described here is the P_{50} wave, recorded at the vertex; i.e., a positive wave recorded at the top of the head that occurs 50 ms after the click. Although all EP waves can vary with attention, the P_{50} wave was chosen for this study because it depends less than other waves on the subject's maintaining interest in the task, so that lack of motivation in psychotic subjects is a less critical issue (Hillyard et al. 1973). The clicks are given in pairs for the conditioning-testing paradigm, with 0.5 sec between the conditioning and testing stimuli. After the computer has determined P_{50} amplitude in both the conditioning and test responses, it computes the ratio of the test amplitude of the conditioning amplitude. Low values indicate that the test response has been suppressed by sensory gating mechanisms. High values indicate failure of these mechanisms. The subjects hear a train of 32 pairs of clicks, each pair 10 sec apart. The train is repeated three to five times. Averages of each train that are free of apparent artifact are then summed together into a larger average, which the computer analyzes. The averages are recorded using techniques designed to enhance the P_{50} wave. The sound is loud (peak 90 dB(A) sound pressure level). The subject is supine, to minimize myogenic artifacts that occur 30 ms after the stimulus. The signal is amplified and filtered at 1–300 Hz and then further digitally smoothed after averaging, so that amplitudes below 10 Hz and above 200 Hz are diminished by 33 percent. This smoothing distorts the later, larger waves in the potential. The computer identifies the P_{50} wave as the most positive wave between 40 and 80 ms, and determines its amplitude relative to the most negative preceding peak. (Positive is down going in the figures.) This preceding negative peak is generally small, except when the subject makes neck movements in response to the sound. Trials with such artifacts are discarded. Eye movements are also monitored simultaneously to ensure that eye deflections do not contaminate the EEG activity.

The performance of normal subjects and schizophrenics in the conditioning-testing paradigm is shown in figure 2. The potentials are grand averages of the potentials from 12 normal and 20 schizophrenic subjects. The normal subjects had no personal or family history of mental illness. The schizophrenic subjects were all on neuroleptic medication and had Research Diagnostic Criteria diagnoses of schizophrenia,

Figure 2. Grand averages of evoked potentials of 12 normal control and 20 schizophrenic subjects to auditory stimuli in conditioning-testing paradigm



The auditory stimulus occurred at the beginning of each tracing. The vertical tic below the tracing is the peak of the P_{50} wave; the vertical tic above each wave is the point from which the amplitude of the peak is measured. Vertical calibration is 10 μV, positive down; horizontal is 50 ms.

made following an interview using the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1979). Schizophrenic subjects showed significantly less suppression of the response to the test stimulus than did the normal subjects. Less suppression means that the conditioning-testing ratio is higher. The mean conditioning-testing ratio was 84 ± 11 percent (mean ± SEM for schizophrenic subjects, but only 34 ± 17 percent for the normal subjects. Of 20 schizophrenic subjects, 18 had ratios over 40 percent, while only 2 of the 12 normal subjects had ratios that high.

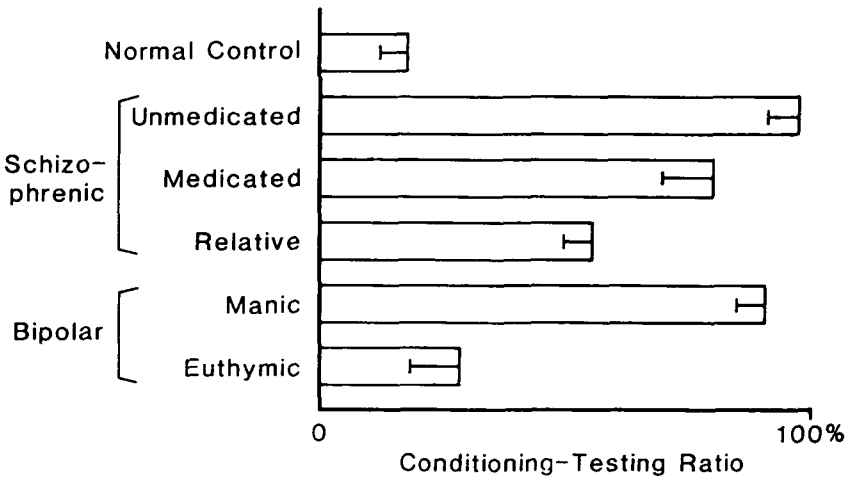
The results suggest that schizophrenic patients are deficient in a gating function that is present in normal subjects. Such a deficit might be part of the neuronal substrate of their inability to filter sensory information. It might also underlie the inability to inhibit the startle response, which Braff and his associates have described (Braff et al. 1978; also, this issue). The abnormality is observed in both unmedicated and medicated schizophrenic patients. However, the abnormality is not diagnostically specific; it can be seen in a variety of other psychiatric patients when they are acutely ill, especially manic patients. Abnormal values can also be found in many of the relatives of schizophrenic patients (figure 3). Each of these points will be considered further below.

Effects of Neuroleptics on Sensory Gating and Dopamine Metabolism

A comparison of acutely ill, unmedicated schizophrenic patients with patients on maintenance neuroleptics shows little difference in the conditioning-testing ratio (figure 3; Freedman et al. 1983). Since neuroleptic drugs clearly improve sensory functioning in schizophrenic patients (Spohn et al. 1977), other aspects of the P_{50} wave were examined to determine if they reflected an effect of neuroleptic drugs. Neuroleptics were found to change the amplitude of both the conditioning and the testing wave, unrelated to the conditioning-testing ratio, which did not change (Freedman et al. 1986). This phenomenon is illustrated in figure 4, which shows the EPs of a patient who was recorded after he had been off neuroleptics for 6 weeks and then 3 weeks after resumption of drug therapy. Both waves increased in size after initiation of neuroleptic treatment, but the conditioning-testing ratio did not change. A similar change in P_{50} amplitude has been reported by Straumanis et al. (1982). The increase in P_{50} represents a normalization of the amplitude of P_{50}, which is lower in unmedicated schizophrenic patients than in normal controls. Thus, unmedicated schizophrenic patients differ in two ways from normal controls: the P_{50} response is smaller, and it is not gated. The neurobiological and functional significance of a smaller P_{50} is further described below.

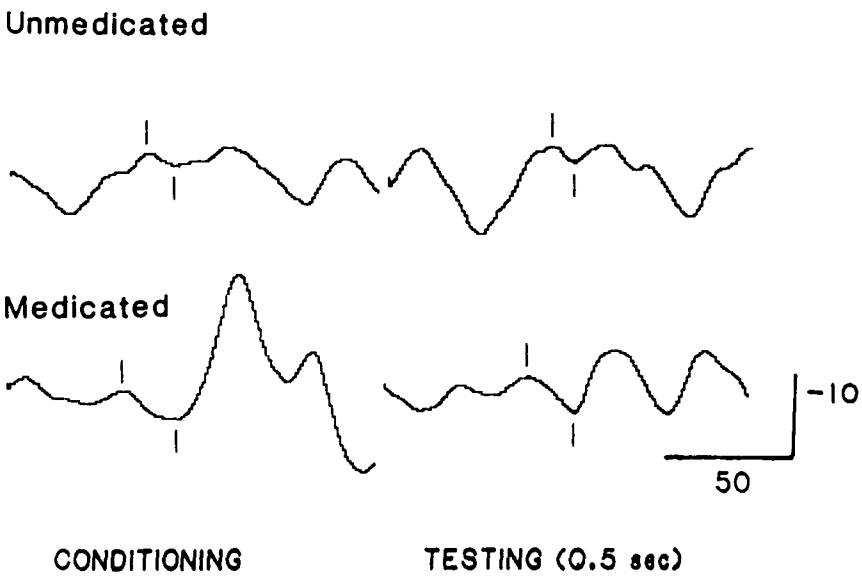
Since the size of the P_{50} wave is normalized by neuroleptics, which block dopaminergic neurotransmission, we decided to determine if small P_{50} waves were caused by dopamine in the unmedicated schizophrenic patients. We recorded patients both before and after treatment with neuroleptic medication, and monitored the effect of neuroleptic treatment on dopamine by measuring the dopamine metabolite, plasma free homovanillic acid (HVA), which decreases during neuroleptic treatment (Pickar et al. 1984; Davis et al. 1985). In six subjects we found that normalization of P_{50} amplitude is related to the fall in HVA levels. This finding suggests that dopamine is responsible for the smaller waves in unmedicated schizophrenic patients. Some stud-

Figure 3. Conditioning-testing ratios (mean and SEM) for various subject groups



Normal controls (n = 35), unmedicated schizophrenics (n = 13), neuroleptic-treated schizophrenics (n = 43), first-degree relatives of schizophrenics (n = 44), acutely ill manics (n = 21), and euthymic bipolars (n = 10) are shown

Figure 4. Auditory evoked potentials of a schizophrenic patient off medication for 6 weeks (top) and after treatment with neuroleptic medication for 3 weeks (bottom)



Treatment with medication did not change the ratio of the P_{50} test response (right) to the conditioning response (left), but it did increase the overall amplitude of the P_{50} waves. This patient's plasma homovanillic acid level decreased from 14 2 ng/ml while he was unmedicated, to 9.3 ng/ml during medication treatment. The change in neurobiological parameters was accompanied by clinical improvement. His rating on the Brief Psychiatric Rating Scale fell from 27 to 17.

ies have shown that schizophrenic patients have an increased number of dopaminergic receptors in the brain, which would make their neurons hypersensitive to dopamine (Seeman et al. 1984).

To produce normal amplitude P_{50} waves, it is necessary that the group of neurons that give rise to the wave respond to the stimulus together, to produce a potential large enough to be recorded through the skull and scalp. A smaller wave may indicate that the necessary synchrony of response is lost. How dopamine might cause this loss of synchrony is not known. However, one of its actions is to make neurons hyperresponsive to their synaptic inputs, which could cause a lack of synchrony (Johnson et al. 1983). Dopamine thus causes a second type of increased sensitivity to auditory stimuli in schizophrenic patients. To test this hypothesis, we have used the auditory EP in laboratory rats as a model for the human auditory EP. With this model, we can use drugs to manipulate the level of activity of the dopamine synapses. Increase of dopamine release caused by administration of amphetamine produces smaller auditory EP waves in these animals. Haloperidol, a neuroleptic that blocks the actions of dopamine, also blocks this effect of amphetamine. These experiments provide further evidence for dopamine's role in the alteration in P_{50} size (Adler et al. 1986*a*).

The functional significance of this aspect of the study of sensory gating is that there may be two different dysfunctions in the neuronal processing of auditory inputs in acute schizophrenia: one, the reversible change in P_{50} amplitude, which is dependent on dopamine, and the other, the fixed deficit in gating, which is independent of dopamine. Both abnormalities may have synergistic effects on auditory perception, which leave schizophrenic patients hypersensitive to stimuli and unable to filter them. The dopamine-dependent mechanism may account for much of the change in psychotic symptoms during acute episodes, whereas the dopamine-independent mechanisms may account for more chronic, neuroleptic-resistant psychotic symptoms.

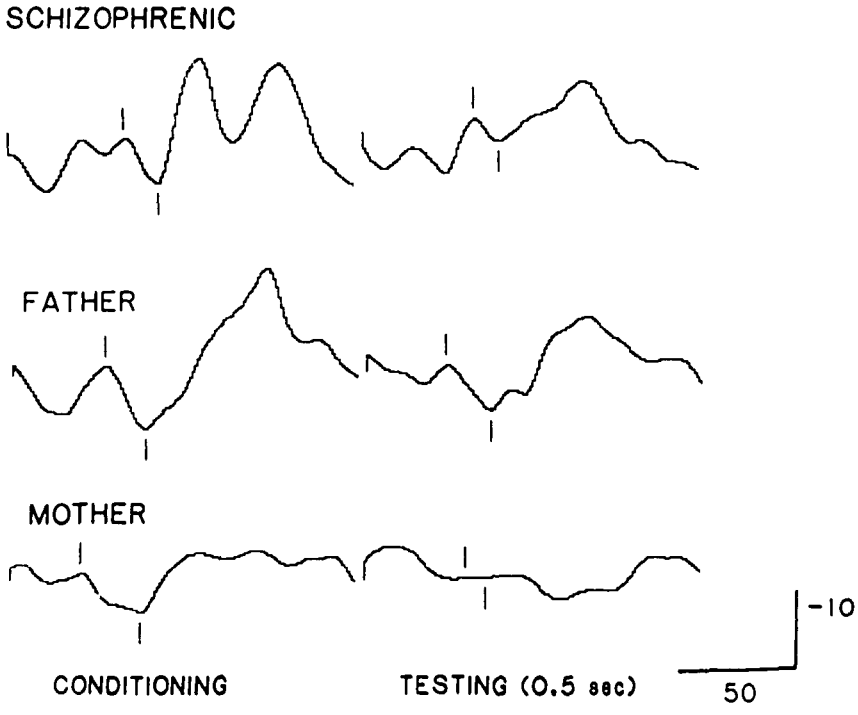
Familial Distribution of Deficits in Sensory Gating

The deficits in sensory gating demonstrated by the conditioning-testing paradigm in schizophrenic patients are also found in many of their first-degree relatives (Siegel et al. 1984). Figure 3 shows that the mean conditioning-testing ratio for these relatives is midway between the lower value found for normal controls and the higher value found for schizophrenic patients. This mean value actually represents the average of two patterns, as shown by the example in figure 5. About half the relatives have conditioning-testing ratios in the normal range, while the other half have ratios in the range seen in the schizophrenic patients themselves. In the families examined, generally one parent and half the siblings, including the schizophrenic patient, had the abnormal pattern. The parent with the abnormality also was more likely to have a family history of possible schizophrenia than the parent with the normal conditioning-testing

ratio. Family members with abnormal ratios also had significantly higher schizophrenia subscale scores on the Minnesota Multiphasic Personality Inventory than relatives with normal ratios.

There was a significant difference between relatives with abnormal sensory gating and schizophrenic patients: the relatives with abnormal sensory gating had normal P_{50} amplitude. This finding suggests that dopamine-mediated neuronal hypersensitivity, as reflected by small P_{50} waves, may be a critical mechanism in the production of schizophrenia. The abnormality in sensory gating may be a necessary substrate, which itself can produce schizotypal features, but not schizophrenia, unless coupled with another abnormality. The dopaminergic mechanism may represent that second abnormality, but plasma measurements of HVA in the relatives with abnormal sensory gating need to be performed to provide further evidence for that hypothesis. Other factors that could also account for the expression of schizophrenia in only some members of a family might include brain atrophy (Weinberger et al. 1980) or even common viral illnesses. Whether the abnormality in P_{50} gating represents a genetically determined schizotaxic factor, as forecast by Meehl (1962), is also not yet definitively determined by genetic linkage analyses. However, a simple mechanism such as abnormal sensory gating might be a better candidate for a genetically derived dysfunction than the symptoms of schizophrenia itself, which may result from the interaction of genetic and nongenetic factors.

Figure 5. Auditory evoked potential of a schizophrenic patient and her father and mother in the conditioning-testing paradigm

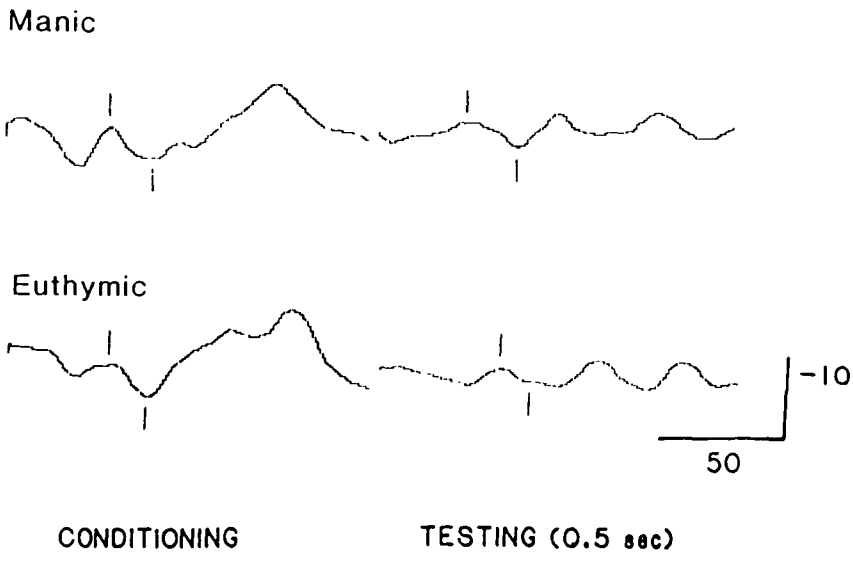


Like his schizophrenic daughter, the father shows little suppression of the test response. The mother, however, shows nearly complete suppression, which is the normal pattern.

Sensory Gating in Mania and Other Psychiatric Illnesses

The lack of diagnostic specificity of biological abnormalities found in patients with schizophrenia discourages many researchers and perhaps obscures the significance of many findings. The overlap between the phenomenology of schizophrenia and mania is considerable (Abrams and Taylor 1981), so that common neurobiological dysfunctions are to be expected. Abnormal sensory gating is found not only in schizophrenia, but also in mania and in acutely ill psychiatric patients with a wide variety of illnesses (Baker et al., in press). There is an important difference, however, in the abnormality in schizophrenia and in these other illnesses. In schizophrenia, the conditioning-testing ratio does not change during various phases of illness. In mania, the ratio normalizes when the patient becomes euthymic (Franks et al. 1983; figure 6). In fact, even during the acute phase of manic illness itself, the conditioning-testing ratio is correlated with ratings of the severity of mania. In contrast, there is no correlation with any ratings of psychopathology in schizophrenics. Thus, this type of abnormal sensory gating appears to be a fixed trait in schizophrenia, but a variable state-dependent abnormality in mania. A similar distinction has been made for smooth pursuit eye movement, another common physiological dysfunction in schizophrenia and mania, which is also a fixed trait deficit

Figure 6. Auditory evoked potentials of a manic patient, initially untreated (top) and then treated with lithium carbonate (bottom)



Clinical ratings on the Brief Psychiatric Rating Scale fell from 27 to 14, indicative of significant clinical improvement toward euthymia. This improvement was accompanied by suppression of the test response. The conditioning-testing ratio fell from 81 to 41 percent, while plasma MHPG level decreased from 4.9 ng/ml to 2.9 ng/ml

in schizophrenia and a reversible state deficit in mania (Holzman et al. 1973).

The role of norepinephrine in mania is not completely established, but much evidence points to increased noradrenergic neurotransmission during manic episodes (Bunney et al. 1972). Acutely manic patients have been found to have elevated levels of the plasma norepinephrine metabolite free 3-methoxy-4-hydroxyphenylglycol (MHPG), which correlated with the conditioning-testing ratio (Freedman et al. 1986). Plasma MHPG and plasma HVA were measured simultaneously by an assay described elsewhere (Gerhardt et al. 1986). As mania subsided, the levels of MHPG dropped, as did the conditioning-testing ratio. The conditioning-testing ratio and plasma MHPG levels were significantly correlated in these manic patients. Plasma MHPG levels did not correlate with the conditioning-testing ratio in schizophrenics. Plasma HVA, a dopamine metabolite, which correlated with P_{50} amplitude in schizophrenic patients, and which normalized in these patients in concert with the normalization of amplitude during neuroleptic treatment, did not correlate with the P_{50} amplitude in manic patients. Thus, the two catecholamines appear to have different relationships to altered sensory processing in the two illnesses.

A possible criticism of the use of plasma metabolites in studies of brain physiology is that these metabolites do not entirely result from neurotransmitter release in the brain, but are also derived from neurotransmitters released from peripheral sympathetic nerves. We therefore also measured plasma free vanillylmandelic acid (VMA), which is produced from norepinephrine entirely outside the brain. Plasma VMA decreased significantly in both manic and schizophrenic subjects during their treatment, but this decrease was not related to changes in any EP parameters (Freedman et al. 1986).

The experiments in animals showed that when amphetamine caused release of dopamine, auditory EP amplitude decreased as it does in acute schizophrenia. Amphetamine also releases norepinephrine, which caused an increase in the conditioning-testing ratio, as it does in mania. The effect of amphetamine on norepinephrine was blocked by a selective neurotoxin, DSP4, which lesions brain noradrenergic terminals (Jonsson et al. 1981). After this lesion, amphetamine altered only the EP amplitude. The conditioning-testing ratio was unchanged (Adler et al. 1986*b*). Thus, the animal model experimental results are in agreement with the human data, which indicate different roles for norepinephrine and dopamine in the regulation of the responsiveness to auditory stimuli.

Comment

This article has attempted to present an overview of a decade of study of the effects of catecholamines on sensory processing in animal models and in psychiatric patients. Much of the experimental methods and results has been referenced rather than described in detail. It was our intent to present a conceptual framework for understanding the possible interactions between psychophysiological, genetic, and biochemical abnormalities in schizophrenia and their overlap

with similar abnormalities in mania and other psychiatric illnesses. The P_{50} wave conditioning-testing paradigm shows an apparent abnormality in auditory sensory gating that may be a genetic trait in schizophrenia, since it appears in many family members and changes little with treatment in schizophrenic patients. This abnormality may underlie some of the problems in sensory perception noted in schizophrenia. Activation of dopaminergic neurotransmission in acute schizophrenia may be an important additional factor in producing more severe sensory disturbances and ultimately acute psychotic decompensation. The electrophysiological data so far suggest that relatives with abnormal sensory gating who are not schizophrenic may not have increased dopaminergic neurotransmission. However, direct measurement of dopamine metabolites in relatives with abnormal sensory gating is still in progress. The electrophysiological perspective thus provides a hypothesis that dopaminergic activation, plus a genetic predisposition, may be necessary for the production of schizophrenia. Whether dopamine hyperactivation itself is a second genetically determined abnormality or whether it is environmentally determined is unknown. In addition, the role of other factors, such as brain atrophy, needs clarification.

While there is clearly overlap between the abnormalities observed in schizophrenia and those observed in mania and other psychiatric illnesses, the combined biochemical and electrophysiological data suggest that there are important differences in the neurobiological mechanisms involved. Norepinephrine plays a more central role in abnormal gating in mania, but the effect is transient. The differences between the role of norepinephrine and dopamine receive confirmation from experiments on effects on auditory EPs in animals.

The diagram in figure 1 thus requires modification to act as a model for our current hypothesis of the role of dopamine and norepinephrine in sensory gating in psychotic illness. Dopamine's role in producing hypersensitivity to sensory stimuli might reflect a modulatory role on the round sensory neuron at the top of the picture, making it more hypersensitive to auditory stimuli, diminishing the synchrony in the pathway to the pyramidal neuron at the right. Norepinephrine's role might be to cause temporary dysfunction of gating neurons, like the stellate cell at the left, by inhibiting their response to auditory stimuli. Both roles are within the known capabilities of these catecholamine neurotransmitters (Freedman 1977), but further work must be done to establish the identity of each neuron and the synaptic basis of the modulatory role of catecholamines in sensory gating. It is also possible that other neuronal mechanisms, such as changes in facilitation, are responsible for gating of P_{50} waves. Impairment of facilitation has been shown in schizophrenia (Shagass 1976). Clearly, the neuronal basis for the sensory deficits of schizophrenia requires further investigations in both patients and animal models.

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Providing a forum for a lively exchange of ideas ranks high among the *Schizophrenia Bulletin*'s objectives. In the section **At Issue**, readers are asked to comment on specific controversial subjects that merit wide discussion. But remarks need not be confined to the issues we have identified. **At Issue** is open to any schizophrenia-related topic that needs airing. It is a place for readers to discuss articles that appear in the *Bulletin* or elsewhere in the professional literature, to report informally on experiences in the clinic, laboratory, or community, and to share ideas—including those that might seem to be radical notions. We welcome all comments. —*The Editors*

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