AUTONOMIC FUNCTIONING IN SCHIZOPHRENIA:
ELECTRODERMAL ACTIVITY, HEART RATE, PUPILLOGRAPHY

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Abbreviations used in Text
ANS -- Autonomic nervous system
SC -- Skin conductance
EDA -- Electrodermal activity
HR -- Heart rate
FPV -- Finger pulse volume
OR -- Orienting response
SCR -- Skin conductance response
SCL -- Skin conductance level
SFs -- Spontaneous fluctuations (of skin conductance)
SCOR -- Skin conductance orienting response
FPVOR -- Finger pulse volume orienting response
CR -- Conditioned response
UCR -- Unconditioned response
PSE -- Present State Examination
CS+ (or CS) -- Conditional stimulus
CS- -- Differential stimulus (in the same conditioning paradigm)
UCS -- Unconditional stimulus
RT -- Reaction time
HRR -- Heart rate response
dB -- Decibel
CT -- Computed tomography
EE -- Expressed emotion
Measurement of the functioning of the autonomic nervous system (ANS) by peripheral indices in psychopathology research may be undertaken to test many different types of hypotheses as will be seen in this review. Regardless of the theoretical bases of a study, however, such measures can be regarded as potential empirical markers of various types (1). These measures, the most frequent of which include skin conductance (SC), frequently referred to as electrodermal activity (EDA), heart rate (HR), measures of vascular activity (finger pulse volume -- FPV), and pupil size, have a number of desirable features for this purpose not possessed in sum by other measures. First, they are noninvasive so that they can be repeated indefinitely without harm. This makes them suitable for studying the effects of treatments, drug challenges, clinical changes, etc. Second, measurement is continuous so the time course of such processes as stress and adaptation and the effects of challenges can be studied on a relatively fine time scale. Third, signal-to-noise ratio is high so that reactions to single stimuli can be measured. The effects of novelty, habituation, and changes in stimulus parameters are thus accessible to a degree not possible with event-related potentials, which require averaging many trials, or with measurements from periodic blood samples. Further, valid data can be gathered from relatively unrestrained subjects permitting their use in a wide range of situations. Finally, meaningful data can be obtained from severely impaired or minimally cooperative subjects, thus favoring representative sampling from schizophrenic populations.

Thus, ANS measures have a number of qualities that can make them useful tools in studying psychopathology. Most of the difficulties in using them come in interpretation of the data. Theoretically, ANS measures should help us understand the relationship between the basic biological substrates of psychopathology and their phenomenological expression in behavior, cognition, and experience. However, the physiological control of ANS measures is only partially understood, more so for peripheral than for central mechanisms, so it is seldom possible to make specific inferences about central neurophysiological or neurochemical functioning. Instead, generalizations about results are usually made in terms of psychological constructs.

Two general types of psychological constructs have been inferred from ANS measures -- affective and cognitive. The affective construct of choice has been that of 'arousal'. However for some time it has been realized that this concept has limited utility because different ANS measures are poorly correlated and frequently do not all change in the same direction in a given situation (2). The term 'arousal', however, may still be useful as a descriptive term, without reification, when several of its purported indicants do all change or differ in the same direction. As in the rest of psychology and psychophysiology, inferences about cognitive constructs have become widespread in psychopathology research. This has been reflected in a change in the dominant paradigm for studying schizophrenia from the effects of stressors to the ANS components of the orienting response (OR) and its habituation to innocuous stimuli, leading to inferences about attention and information processing.

By far, the most widely used of the ANS measures has been EDA. Skin conductance (SC) is typically recorded by passing a small constant voltage across electrodes on the palmar surfaces of the hands or fingers. SC responses (SCRs) are phasic increases in SC and may be evaluated as to frequency of occurrence, amplitude, onset latency from an eliciting stimulus, and recovery time (time for the SC to return halfway or fully to the prestimulus level). The aspects of EDA usually taken to index arousal are the tonic SC level (SCL) and the frequency of SCRs without regard to specific stimuli, referred to here as 'spontaneous fluctuations' (SF). SCRs may be elicited by a variety of
stimuli. We will use 'SCOR' to refer to those SCRs elicited by novel but otherwise innocuous stimuli. A feature of ORs is that they habituate with repeated stimulation. The speed with which this occurs (usually indexed by the number of trials before 2 or 3 consecutive stimulations which fail to elicit an OR) is an important measure.

Research in the last decade or so utilizing the OR paradigm has shown that 40 to 60 percent of chronic schizophrenics fail to exhibit skin conductance orienting responses (SCORs) to moderate intensity nonsignal auditory stimuli as compared to about 5 to 10 percent of controls (3). This would make the SCOR an excellent candidate for a diagnostic marker were it not that patients with major depression also show much SCOR nonresponding (4). However, Bernstein et al. (5) have shown that schizophrenics are as nonresponsive on the FPVOR, which is thought to be strictly adrenergic, as on the SCOR, but depressives have normal levels of FPVOR responding. Thus when both channels are measured, OR nonresponding as a marker for chronic schizophrenia has decent specificity as well as sensitivity.

Increased SCOR nonresponding has not been a prominent feature nor the only major finding in all studies of the OR in schizophrenia, however, and there are many valuable studies using other paradigms. This chapter will first explore the effects of pharmacological treatments and individual differences in symptoms on EDA and the psychological mechanisms involved. We will then deal with effects of the significance of stimuli and situations on ANS activity, the relationships of ANS activity to task performance and to other biologic markers, its relationships to prognosis, and its possible role in etiology as indicated in high-risk studies.

THE EFFECTS OF DRUGS ON EDA.

One of the few things we can be sure about is that the vast majority of schizophrenic patients will be receiving drug treatment. Furthermore this is likely to take the form of large doses of many different drugs. For example, the schizophrenic patient studied by Done et al. (6) was receiving "150 mg/week Depixol depot, and each night 800 mg lithium, 150 mg Amitriptyline, 30 mg Temazepam, 10 mg Nitrazepam, and 5 mg Procyclidine three times per day". Such a regime is not unusual. Obviously we study EDA in the hope that it will tell us something about schizophrenia rather than about drug effects. There is therefore, a strong motivation to believe that the effects of drugs on EDA are small.

Unfortunately, even before we examine the evidence about drug effects we have sufficient information to know that this is unlikely to be the case. Increases in EDA occur in response to a generalized sympathetic discharge which releases acetylcholine from the postganglionic neurones innervating the sweat glands. As a result local application of an anticholinergic such as atropine abolishes SCRs (7). Many schizophrenic patients will be receiving drugs with anticholinergic effects. In the example quoted above, the patient was receiving the anticholinergic Procyclidine to combat the side effects of neuroleptic treatment and Amitriptyline which also has anticholinergic effects to combat depression. Some neuroleptic drugs also have anticholinergic effects which are independent of their antischizophrenic potency. Snyder et al. (8) have shown that Haloperidol has very little anticholinergic effect. Chlorpromazine is 50 times as potent an anticholinergic and Thioridizine is 300 times as potent. Thus we would expect some neuroleptics to reduce SC responsivity because of their anticholinergic properties. The strategy of equating different neuroleptics by calculating chlorpromazine equivalents is irrelevant here since this equates for antischizophrenic effects and not for anticholinergic effects.
Before reviewing studies in which the effects of drugs on EDA have been examined directly, it is necessary to point out that statements about drug effects (or the lack of them) are often based on inappropriate experimental designs. In these studies EDA is measured in a large group of schizophrenic patients. Those who happen to be off drugs are then compared with those who are on. Since the allocation of drugs in these experiments is not random it is not possible to conclude that any differences between the groups are due to drugs. Equally, it is not possible to conclude that if there are no differences between the groups then there are no drug effects. It is very likely that the decision to give drugs to a patient was based on the observation that his symptoms were more severe or that he was more difficult to manage. Similarly the decision not to give drugs to a patient might be based on the observation that he had movement disorders. In order to study the effects of drugs on EDA it is necessary either to assign subjects to the treatment groups randomly or to study the same subject both on and off treatment.

**Anticholinergics**

Evidence of reductions in EDA from drugs with anticholinergic effects has been reported in a study on normals from a single acute dose of scopolamine (9), from a placebo controlled random assignment study of the tricyclic amitriptyline in neurotic outpatients (10), and a placebo controlled study of the tricyclic clomipramine in obsessive-compulsive patients (11). Recently Green et al. (12) have explicitly compared the EDA of chronic in-patient schizophrenics (who had been taken off of antiparkinson medication) who were taking neuroleptics differing in anticholinergic potency. Their data suggest that neuroleptics with strong anticholinergic properties reduce electrodermal tonic levels and responsivity. This was true both for SFs and for SCRs to nonsignal, signal, and aversive stimuli. These findings have been replicated by Spohn et al. (13) who studied SCORs to nonsignal tones, SCL, and SFs. These results are consistent with our expectations that anticholinergic drugs directly, and non-specifically, reduced EDA. The effects of anticholinergics in raising HR and reducing HR variability are well established (11,14).

**Neuroleptics**

The effects of neuroleptics on EDA are likely to be varied and difficult to interpret. We would expect to see effects due to anticholinergic properties, effects due to dopamine blockade, and with long term treatment direct effects on dopamine receptor sensitivity and also indirect effects consequent upon the patients recovering from their symptoms. Patterson and Venables (9), in the study already mentioned, found that chlorpromazine reduced, while haloperidol increased, SCR amplitude. This difference probably reflects greater anticholinergic effects of chlorpromazine. A number of other studies have found that EDA is reduced by chlorpromazine. Spohn et al. (15) compared treatment with chlorpromazine and placebo. They found no effect on SCL, but SCR amplitudes to signal stimuli were reduced and, to a lesser extent, the frequency of SFs. Gruzelier and Hammond (16) withdrew patients from treatment and then compared chlorpromazine and placebo. They observed that SCL on placebo was related to the patients' previous dose level. This result suggests that either there were long term effects of previous treatment or that dose level was determined to some extent by the patients untreated state. Chlorpromazine in this study lowered SCL, reduced the number of SFs and reduced the number of SCRs to a loud and unpleasant noise. Kugler and Gruzelier (17) reported that chlorpromazine also reduced EDA in 12 normal volunteers. Schneider (18) treated chronic schizophrenics with neuroleptics after a washout period. The treatment reduced OR magnitudes, reduced the number of SFs and the proportion of responders in the group. Recently Yannitsi et al. (19) found only 4 of 25 (16%) SCOR nonresponders in a group of newly admitted schizophrenic patients who had been
medication free for 15 days or more. After two weeks of low-dose chlorpromazine treatment 12 (48%) were nonresponders, and SCL had decreased as well. These studies consistently demonstrate that chlorpromazine reduces EDA, but it is not clear if this effect is due to the drug’s anticholinergic properties or to dopamine receptor blockade.

A recent study (13), however, in which a random group of patients were withdrawn from medication and compared two and four weeks post-withdrawal with a continuously medicated control group, found minimal effects on EDA including the incidence of SCOR nonresponding to nonsignal tones. The only positive finding was an increase in SCL in patients tested near the time of relapse. This study points out a difficulty in withdrawing drugs from long-term medicated patients in that the direct effects of the drug diminish patients may become untestable due to an exacerbation of psychotic symptoms and need remedication. Therefore additional strategies may be needed to address the problem.

A few studies have attempted to look specifically at the role of the dopamine system in EDA. Frith et al. (20) compared the effects of a-flupenthixol, b-flupenthixol and placebo in schizophrenic patients who were randomly assigned to treatment. Any differences in the effects of these two isomers can with reasonable confidence be ascribed to blockade of dopamine receptors since the alpha isomer is more than 1000 times more potent in this respect (21). A-flupenthixol significantly reduced the probability of ORs and to a lesser extent reduced SCL and number of SFs. This effect was independent of the degree of recovery from symptoms. This result suggests that dopamine blockade which is the common feature of neuroleptic drugs also tend to reduce EDA. Stimulation of the dopamine system has the opposite effect. Horvath and Meares (22) found that treatment with L-DOPA (which increases the amount of available dopamine) increased the number of SFs and slowed habituation. Similar results were reported for dextroamphetamine (23).

Benzodiazepines

As in the example quoted above, schizophrenic patients often receive benzodiazepines, either as hypnotics (e.g. Nitrazepam) or as an aid to ward management (e.g. Diazepam). Although their mode of action is entirely different, benzodiazepines have similar cognitive effects to anticholinergic drugs impairing long term memory. This effect is probably due to a reduction of stimulus processing. For this reason alone we might expect these drugs to reduce ORs. Farhoumand et al. (24) found that Lorazepam reduced SCL and SFs. Frith et al. (1984) found that chronic treatment with Diazepam reduced responding to “irrelevant” stimuli, suggesting that its action was centrally rather than peripherally mediated. Molander (25) found that diazepam reduced the number of ORs (both CRs and UCRs) in a conditioning task but did not alter the rate of habituation.

Conclusions

It is clear from this brief review of the literature that all the drugs commonly given to schizophrenic patients tend to reduce EDA. There is less consistency about whether some components are affected more than others. For example, in some studies response amplitude is reduced, but habituation status is not changed. However, these are minor differences that could be the consequence of floor and ceiling effects. It is also clear that this reduction in EDA is consequent upon different modes of action. Thus drugs with anticholinergic properties may well act directly upon sweat gland activity, Dopamine blockers and benzodiazepines on the other hand probably produce their effects by centrally mediated alterations of information processing.
Given this conclusion we have to ask whether the reduction in EDA, and in particular a high incidence of SCOR nonresponding, observed in the majority of studies of schizophrenic patients (3) is a consequence of drug treatment. This review of research makes clear that drugs do play a role in the reduction of EDA in at least some schizophrenic patients. However, not all studies have observed reduced EDA in schizophrenia; some studies have found excess activity and some studies have found both, notably Gruzelier & Venables (26). It is striking that most of those studies in which reduced EDA has not been observed have concerned acute, unmedicated schizophrenic patients. Horvath and Meares (27), Frith et al., (28), Zahn et al., (29), Toone et al., (30), and Bartfai et al., (31), all observed slower habituation and more SFs in such patients. Similar conclusions can be drawn from recent studies by Straube et al. (32) and Yannitsi et al. (19). Nevertheless there are studies in which drug-free patients did show reduced EDA (e.g. 33) and studies on acute, but medicated, patients with only a modestly elevated incidence of nonresponding (28%) (34) so that the results cannot be entirely explained by the effects of treatment. In the next section we shall suggest an explanation for these discrepant results.

Elevated HR and reduced HR variability are very common findings even in unmedicated schizophrenics (4,35), but the value of these variables as markers is weakened not only by the frequent use of drugs with anticholinergic effects but by a sedentary life-style and heavy nicotine use by many patients. There is evidence that dopamine receptor blockade per se has little effect on HR or its responsivity, however, but chlorpromazine, which has anticholinergic effects, increases both parameters (36).

EDA AND SUBGROUPS OF SCHIZOPHRENIA

In order to account for these differences we need to compare studies conducted at different times and in different locations. One of the major problems with studies of schizophrenia is that definitions of this disorder have varied with time and place. However, these variations provide us with a clue for understanding the differences in EDA. The early studies carried out in the USA tend to have classified the patients in terms of DSM II. This provides a wide definition of schizophrenia permitting affective components and residual symptoms. In Europe narrower definitions were being used which required the presence of first rank symptoms (e.g. the CATEGO classification system associated with the Present State Examination [PSE]). In the most recent studies in both Europe and the USA the narrowest definition of all has been used (DSM III) which depends on the presence of first rank symptoms, the absence of affective components and a degree of chronicity. The studies in which overactivity is observed are those more recent studies in which first rank symptoms have been necessary for a diagnosis of schizophrenia. Horvath and Meares (27) studied schizophrenics with Schneiderian symptoms. Frith et al. (28) and Toone et al., (30) studied patients classified NS+ on the PSE. Bartfai et al. (31) studied patients with hallucinations, delusions, or thought disorder, none of whom had negative symptoms. Zahn et al. (29) used DSM II, but state that the majority of their patients had "flagrant" symptoms. Most of the patients in these studies have been acute, or, if chronic, have recently been admitted because of an exacerbation of their symptoms (19,32,34).

In contrast, those studies in which schizophrenic patients have been shown to have reduced EDA or a mixture of underactivity and overactivity have tended to be of chronic, institutionalized patients (see 3). Mirkin (37) explicitly examined the difference between acute and chronic patients and confirmed that the acutes tended to be hyper-responsive whereas the chronics tended to be hypo-responsive. The exception to this finding is the study of Straube (33) in which some of his acute patients were hypo-responsive. However, Straube's diagnostic criteria resulted in the inclusion of patients
with affective components and withdrawal, and he found a significant relationship between low EDA and withdrawal and cognitive disorganization. Other studies have also observed this relationship between hypo-responsiveness and emotional withdrawal (38-40). Thus hypo-responsivity seems not to be directly associated with chronicity, but with the signs and symptoms that usually, but not necessarily, appear in the chronic stages of the illness. Hyper-responsiveness, and particularly a high frequency of SFs, has been observed to be associated with auditory hallucinations during the recording session (30,41).

We would propose that the two different kinds of abnormal EDA observed in schizophrenia are associated with two different syndromes. These syndromes correspond partially, but not completely with the acute/chronic dichotomy interpreted as duration of the illness. Venables (42) has made a similar distinction. He considers that the acute/chronic dichotomy is important, but modifies it by the suggestion that process patients are always chronic, while reactive and paranoid patients never cease to be acute. Clearly a distinction is sought which is not solely determined by length of illness. Crow (43) has described two syndromes on the basis of considerations which are quite independent from psychophysiological results, but which correspond quite well with differences discussed above. Type I schizophrenics have "positive" signs and symptoms (hallucinations, delusions and thought disorder) and are usually acute. Type II schizophrenics have "negative" signs and symptoms (flattening of affect and poverty of speech). They tend to have cognitive impairments and movement disorders and are usually chronic. These two syndromes are not identical with the acute-chronic dichotomy since it is possible for chronic patients still to show florid, positive symptoms or to have episodes of such symptoms. It is also possible for a patient to present for the first time (thus being acute) with only negative symptoms. However, many modern diagnostic systems (such as those based on the PSE) would not allow the diagnosis of schizophrenia in such cases. Thus Type II patients tend to be chronic patients who originally presented with positive symptoms. Gruzelier (44) and Gruzelier and Manchanda (45) have proposed a somewhat similar distinction based on a post hoc comparison of subgroups defined in terms of psychophysiological measures.

To investigate this hypothesis in relation to EDA it would be necessary to measure the current mental state of the patient. Those studies that have investigated subgroups of schizophrenic patients tend not to have taken the appropriate measures. It would also be crucial to take into account drug treatment since this could well mask the underlying individual differences.

In conclusion we suggest that electrodermal overactivity (slow habituation, many SFs) is associated with the positive symptoms of schizophrenia, while electrodermal underactivity is associated with the negative symptoms. This conclusion is, of course, entirely consistent with the definition of positive and negative symptoms. Positive symptoms imply the occurrence of something abnormal (i.e. overactivity), while negative symptoms are present when there is a lack of something normal (i.e. underactivity). In the next section we shall consider how the two kinds of abnormal EDA relate to underlying psychological processes.

Since writing this conclusion several essentially negative reports of the relationship between EDA and symptoms have appeared. Olbrich & Mussgay (46) performed a multiple regression of the symptomatic predictors of SFs in 48 medicated inpatients. Ratings of Activation, thought to reflect 'central arousal', correlated positively with SFs as expected, but a measure of hallucinations correlated negatively. Öhman et al. (34) do report that their more responsive patients reported themselves to be more anxious, but ratings on a standardized scale of specific symptoms did not relate to EDA.
In the Green et al. (12) study mentioned earlier, patients with negative symptoms had lower SCL, but there was a very weak tendency for SCOR nonresponders to show both more negative and more positive symptoms. Similarly Öhman et al. (47) reported a nonsignificantly larger total score on a symptom rating scale in nonresponders, but individual items were as likely to be positive as negative symptoms. Since most of the patients in these studies were on one or more of a variety of medications, it is possible that this affected symptoms and EDA differently, thus destroying a potential relationship. However it is more likely that existing rating scales do not tap the type of clinical symptomatology that is associated with differences in EDA.

This distinction can help account for some seemingly conflicting data described in the preceding section. There were effects of neuroleptic drugs on EDA (apart from anticholinergic effects) in acute patients with elevated EDA (20), but not in chronic nonresponders (13). This is consistent with idea that neuroleptics are effective in reducing the positive symptoms in acute patients (43), and thereby reducing the correlated EDA, but they do not affect negative symptoms in the EDA nonresponsive Type II patients (43). In later sections we will see that the positive/negative symptom distinction, or something like it, is also of value in accounting for the results of various studies.

**PSYCHOLOGICAL MECHANISMS UNDERLYING ABNORMAL EDA IN SCHIZOPHRENIA.**

The most obvious interpretation of the two types of abnormality discussed in the previous section would be in terms of arousal. Thus the non-responsive chronic schizophrenics would be underaroused whereas the hyper-responsive acute schizophrenics would be overaroused. This simple interpretation, however, has been considered inadequate for some time. In part this is because of the well documented failure of the unitary concept of arousal; different measures of arousal simply do not relate well to one another. These discrepancies may occur even within the skin conductance system. Thus different indices of arousal (SCL, habituation status, rate of habituation and number of SFs) do not necessarily correspond (27-29,34). A more serious problem for this interpretation comes directly from studies of attention and perception in schizophrenia. On the basis of a thorough review of such studies, Venables (42) concluded that chronic schizophrenics were over-aroused whereas acute schizophrenics were under-aroused. This conclusion is clearly totally incompatible with our simple-minded interpretation of the EDA results. It is convenient to characterize two competing explanations of schizophrenia: One in terms of abnormalities of arousal, the other in terms of abnormalities of information processing. In Venables' seminal review abnormalities of information processing were seen as consequent upon abnormalities in arousal. However, since then, abnormalities of information processing have been seen as sufficient explanations on their own. This is true even in the domain of psychophysiology (e.g. 46).

The role of information processing in the SCOR was theorized to be critical by Sokolov (49). In order to habituate the subject must recognize that the stimulus has been presented before. This necessitates an "internal model" of the stimulus and some sort of matching process. Abnormalities in these purely cognitive processes would result in abnormalities of habituation in the absence of any abnormalities in arousal. Groves and Thompson (50) use this model to distinguish explicitly between two independent processes that can alter the amplitude of the OR. One is "sensitization": A subject in a sensitized state (high arousal) will give larger responses. The other process is to do with the matching procedure: If the subject observes a stimulus mismatch then a larger OR amplitude will occur. These processes can be distinguished by studying the effects of a
novel or "dishabituating" stimulus presented late in the series. Horvath and Meares (27) used this technique in their study of acute, drug-free schizophrenic patients. In this study the paranoid patients habituated normally. However, their response to a dishabituating tone at the end of the sequence was abnormally small in comparison to controls. This result was replicated by Frith et al. (28) who also studied acute drug free patients. In this study the novel tone did not actually produce any dishabituation since responses to subsequent familiar tones were not enhanced. In terms of Groves and Thompson's model this result suggests that no sensitization was occurring and thus differences in the response to the dishabituating tone may be attributed to the perceived mismatch. Thus the relatively smaller responses to the dishabituating tone given by the schizophrenic patients in these studies indicate that they were making less of a distinction between novel and familiar tones. These results therefore confirm those from outside psychophysiology in suggesting that the abnormalities found in schizophrenia are to do with abnormalities of information processing rather than arousal.

Öhman (51) has suggested that an orienting response occurs when a stimulus appears which requires "controlled" rather than "automatic" processing and thus necessitates the use of the limited capacity central processing system. This typically occurs when a stimulus is novel. Callaway and Naghdi (52) and Koukkou (53) have suggested that it is controlled processing that is impaired in schizophrenia, while automatic processing remains intact. Thus we would expect to see abnormal orienting. This abnormality could take two forms. Either orienting occurs even to familiar stimuli or orienting does not occur to novel stimuli. It would be tempting to assume that these two possibilities correspond to the hyper-responding and the hypo-responding subgroup of schizophrenia respectively. The effect of a dishabituating stimulus does not distinguish between the two possibilities because in both cases there is a reduction in the distinction between the novel and the familiar. However, in both the studies discussed above, it was the response to the novel stimulus that was smaller rather than the response to the familiar stimulus that was larger. This suggests that the schizophrenic patients were failing to respond to novelty.

At first sight this seems incompatible with these patient's status as hyper, or at least normal responders since clearly a failure to respond to novelty should result in a reduction of responsiveness. In fact, this inconsistency is typical of schizophrenic patients. As we discussed above different skin conductance measures often appear to tell a different story. Thus Zahn et al. (29) observed schizophrenic patients to have more SFs, but lower SCL, a result recently replicated by Öhman et al. (34); slower habituation rates, but less reactivity to tones. In particular Zahn et al. note that the patients had "disproportionately more spontaneous than elicited SC activity" (29, p. 251). This finding was a replication of an earlier one (54), and in turn has been recently replicated again (34). Given that response to novelty must be elicited, these results suggest that schizophrenic patients are more responsive, while responding less to the novelty. This is because their responsiveness is largely due to SFs. Bartfai et al. (31) also found apparent inconsistencies since their schizophrenic patients habituated in the same number of trials as controls, but showed significantly more SCORs. This was due to a greater irregularity in the course of habituation, a result also obtained previously (29,54,55). Likewise Frith et al. (28) found that schizophrenics did not differ from controls in terms of a trials-to-habituation criterion, but habituated faster in terms of response amplitudes.

Thus these studies, mostly of drug-free acute (type I) patients, concur in finding apparently inconsistent patterns of responding. Frith et al. (28) suggested that this might be an artifact due to the difficulty of distinguishing between ORs and SFs particularly when there is a very high rate of the latter. They observed a strong relation between number of SFs and habituation status when habituation was defined in the traditional way
SCRs occurring in a 1-5 sec response window and 3 successive zero responses for habituation). When SCRs were redefined such that they had to be larger than the surrounding SFs, then the discrepancies disappeared and the schizophrenics habituated faster both in terms of trials to criterion and in terms of response amplitude. It was concluded that the apparently slow habituation was due to SFs being mistaken for SCRs. The same conclusion was reached by Levinson et al. (56,57) who also showed that different indices of habituation were inconsistent when SCRs were defined rather liberally (1-5 sec response window). When a narrow definition was used the patients were seen to habituate rapidly and it was concluded that the liberal definition was erroneously categorizing SFs as SCRs. The conclusion is, therefore, that schizophrenic patients who are "responders" in terms of EDA habituate abnormally fast, but show many SFs. This conclusion would also be consistent with the results of Zahn et al. (29) and Bartfai et al. (31) who used 4 sec and 5 sec latency cutoffs respectively. The latter authors concluded that SCRs were not being confused with SFs in their study since correlations between number of SCRs and number of SFs were not significant. However, in view of their liberal latency criterion it might well be the case that alternative definitions of SCRs in their study would have lead to different results.

We would conclude therefore that schizophrenic patients who are responders or hyper-responders in terms of EDA are characterized by rapid habituation to nonsignal stimuli and have a high rate of SFs. By definition SFs are responses to stimuli other than those presented by the experimenter. Assuming that the experimenter has complete control over external sources of stimulation then these SFs must be responses to internal events spontaneously generated by the subject in terms of information processing we would therefore conclude that these schizophrenic patients are attending more to internal events than external stimuli. As a consequence they habituate more rapidly to irrelevant tones and respond less to novel tones. It would seem reasonable to relate the internal events which generate the many SFs to positive symptoms. The majority of these symptoms are weird experiences such as hearing voices and discovering meanings which are not actually present. It would seem likely that these experiences would give rise to ORs. In the absence of an identifiable stimulus the experiment would have to label these SFs. We have already suggested that responders and hyper-responders among schizophrenic patients are likely to be those with positive symptoms. There is also evidence that SFs may be specifically associated with auditory hallucinations (30,41). We would therefore conclude that if schizophrenic patients are observed to be responders or hyper-responders in terms of EDA, then this is because they are experiencing positive symptoms which in turn give rise to many apparently SFs. Because of the difficulty in separating out the effects of SFs on ORs described earlier, the best empirical EDA marker for Type I schizophrenia would be a high rate of SFs.

The SCRs of non-responders cannot be analyzed in terms of information processing since there are none to analyze. However, it would seem plausible that these subjects are showing, in more exaggerated form, the same defect that has been demonstrated in responders. That is a failure to respond to novel stimuli which leads to extremely rapid habituation or a general lack of response to nonsignal stimuli. This is, of course, consistent with our suggesting that these patients will correspond to Crow's (43) Type II syndrome; schizophrenics who no longer have positive symptoms, but only negative signs. Thus they no longer experience the internally generated events that lead to SFs. The best empirical marker for chronic schizophrenia, then, would be speed of habituation. This analysis also suggests that the EDA of a Type II patient who undergoes an exacerbation of acute or florid (Type I) symptoms would be characterized by many SFs but marked hyporesponding to novel stimuli. It is of interest that all three studies that have examined the ratio of SCRs to SFs have found it to be the best discriminator
of schizophrenics from controls of their EDA variables (29,34,54), probably because both acute and chronic patients are low on it.

We have suggested that both acute and chronic schizophrenic patients are characterized by deficits in orienting to novel external stimuli. If we wish to speculate on why this should be then we clearly need to consider evidence from many sources in addition to EDA. This chapter is clearly not the place for such speculation. We shall therefore content ourselves with only a brief comment. If we accept Öhman's (51) suggestion that the OR reflects the onset of controlled or strategic processing, then the data from skin conductance studies is consistent with the proposals by Callaway and Naghdi (52) and Koukkou (53) that controlled processing is impaired in schizophrenia. However, by definition, controlled processing is not a passive perceptual process elicited by stimuli. It is an action taken by the organism in response to the unexpected. Thus the reduction of SCORs in schizophrenia is part of a general reduction of action. We have suggested that the many SFs observed in some acute patients are responses to internal events. Since these events must in some sense be self generated they ought to be expected and thus should not elicit ORs. This result can therefore be seen as consistent with the suggestion that acute schizophrenic patients have lost the ability to distinguish between externally generated and internally generated events (58).

EFFECTS OF STIMULUS SIGNIFICANCE ON AUTONOMIC RESPONDING.

Novelty can be considered as a property of a stimulus that increases its significance for the subject. Another way of increasing the significance of a stimulus is to make it a signal for some action by the subject or for another stimulus which itself has significance for the subject as in the classical or Pavlovian conditioning paradigm. Studies using a differential conditioning method have found consistently that schizophrenics do not give larger ANS responses to conditional stimuli (CS+) which precede an aversive or imperative stimulus (UCS) than to differential (CS-) stimuli which do not precede an UCS, while normal subjects usually show clear ANS discrimination (59-62). However, in such a paradigm subjects need to learn and remember the stimulus contingencies in order to produce discriminative conditioning. The schizophrenic subjects in the above studies in contrast to the controls, generally could not verbalize the contingencies when questioned about them. Thus these studies do not provide a test of the ANS response to meaningful stimuli.

When subjects were given pretest information and training about the contingencies (63), significant differential SCR conditioning was obtained in both schizophrenic and normal groups. The patients, however, were significantly less reactive to both the CS+ and CS- during the conditioning trials but not during the adaptation trials prior to the introduction of the UCS. Rist et al. (62), did not obtain differential conditioning in chronic, process, inpatient medicated women but, in a second experiment which excluded subjects with low SC responsivity to the UCS, patients showed unimpaired SCR conditioning and even enhanced HR conditioning compared to controls. Öhman et al. (64) found differential SCR responding in both schizophrenics and controls only for those with RTs faster than the median RT for their respective groups. However, for the schizophrenics the enhanced responding to the CS+ habituated within 20 trials. Overall responding to all stimuli including the imperative RT stimulus was markedly reduced in the schizophrenic group. The schizophrenics as a whole did show differential FPV
responsivity but its magnitude and the overall responsivity was markedly and significantly less than that for the controls. In contrast to this evidence of lower ANS responding to significant stimuli, Öhman et al. report that in responding to irrelevant lights the schizophrenics evidenced slower SC habituation and that there were no group differences in responding to nonsignal tones given in another session.

In summary, when given information about contingencies some schizophrenic subjects show differential ANS conditioning but they have generally shown less autonomic discrimination, lower overall responsivity to all significant stimuli, and more rapid habituation than controls.

Other studies of the effects of significance have been done from other perspectives. A nondiscriminative warned RT method has been used by Zahn (29,65,66) whose studies have shown unmedicated schizophrenic subjects to be low in SC and FPV reactivity to the RT stimuli but not in ANS reactions to an untimed motor response to a tone, to ready signals, and to nonsignal tones. The conclusion of poor ANS discrimination between more and less important stimuli in schizophrenia is the same as that drawn from the conditioning studies. However, since different motor responses are required for the untimed response and ready signal (depress a Morse key) and imperative stimulus (release the key as quickly as possible) and no responses were required for the nonsignal tones, the effective stimuli for the ANS reactions are dissimilar across conditions and may be different between groups. Indeed, greater pressure on the key in schizophrenics has been reported (65).

Some studies have found no schizophrenic deficits in responding to signal stimuli. With a warned RT paradigm requiring a key-press RT response, Gray (67) did not find significant differences between unmedicated schizophrenics and controls in either SCRs or HRRs to either 70 dB or 110 dB tones when they were either nonsignal or signal stimuli. Similarly Spohn, et al. (68) in a study which probably controlled adequately for drugs, reported no differences between schizophrenics and controls in SCRs or HRRs in a span of apprehension task where the stimulus complex was fixating, perceiving a flashed stimulus, and writing a series of letters.

Some studies have independently varied signal value and motor response requirements. Gruzelier and Venables (69) required schizophrenic and nonschizophrenic patients to give an untimed button-press to one of two tones. It had just been presented in an habituation series. Schizophrenic SCOR nonresponders to these tones were mostly also nonresponders to the nontarget tone in the discrimination procedure but almost all responded to over half of the tone-key press combinations. SC responders tended to respond to all stimuli but more so to the signal stimuli. Spontaneous voluntary key depressions did not produce SCRs in schizophrenic nonresponders. Thus it was not signal value or the motor response alone but their combination that made responders out of nonresponders. In a study with unmedicated schizophrenic adolescents Bernstein and Taylor (70) used a discriminative RT paradigm and two nontarget stimuli varying in information content. The schizophrenics gave nonsignificantly smaller SCRs to the target stimulus-response than controls or nonschizophrenic patients but were very unresponsive to nontarget stimuli, and they alone failed to differentiate these stimuli from nonsignal stimuli. Bernstein et al. (71) reported that electrodermal reactivity to verbal stimuli was abnormally low in medicated schizophrenics when they just listened to the stimuli, but was at essentially normal levels when the stimuli were signals in a recall task. These studies agree in finding only modest schizophrenic impairment in ANS responding to a stimulus which elicits a motor response, but attenuated responding to nontarget stimuli having signal value.
Bernstein et al. (72), reported a similar study designed to study the habituation of ANS responses to signal stimuli. One subgroup each of schizophrenic and nonschizophrenic patients and normal controls just listened to a series of sixty 60 dB tones while another received a discrimination RT paradigm involving the same tone series. The schizophrenics had many nonresponders (60%) to the nonsignal tones, fewer (40%) to the nontarget tones, marginally less than controls, and very few (15%) to the imperative tones. However in contrast to both control groups they habituated rapidly to the imperative stimulus and were significantly hyporeactive from the second block of 10 trials on. The groups were generally the least different, overall, in responding to the nonsignal stimulus. The frequency and amplitude of both SC and FPVR all showed the same differences.

What have we learned from these studies? First, the consistent and marked reduction in ANS nonresponding by signal stimuli when they elicit a motor response in the schizophrenic groups which exhibit much nonresponding, shows that this is not due principally to peripheral factors.

Second, although nonresponding to significant stimuli in schizophrenia is rare attenuated ANS responding compared to control subjects is a frequent finding. However, it is by no means universal. The conditions determining this are obscure partly because of lack of control over many of the sources of variation in these studies. For example, minimal impairment in schizophrenics' ANS responses to elicited motor responses might be due in part to their use of more force in these responses (65) thereby increasing the effective intensity of the stimulus. In ANS responses to more complex task stimuli such as those involving verbal recall the task may be more difficult or require more effort in many schizophrenic patients than in controls. Green et al. (12) reported that when a tone was made to elicit an eye movement response (used to eliminate movement artifacts in EDA) there was no increase in responding in schizophrenics compared to that to nonsignal tones. Increasing the information content or significance of stimuli without motor involvement as in the CS in the conditioning studies and "no-go" stimuli in discrimination paradigms also is relatively ineffective in increasing schizophrenic responding.

The hypothesis of increasing schizophrenic deficit in responding as a direct function of stimulus significance advanced some years ago (65) has received only limited support from these studies. The opposite hypothesis and a hypothesis of no difference are also supported. However the disconfirming evidence is due as much to the presence of nonresponding to insignificant stimuli as in responding to significant stimuli. Nevertheless there are still studies in which hyporesponsivity to signal stimuli distinguishes schizophrenics from controls while responding to nonsignal stimuli does not (29,64).

Anticipatory Activity

A number of the studies described in the previous section focused specifically on ANS activity occurring just prior to a temporally predictable significant stimulus–either aversive or imperative. These studies all use a conditioning or fixed foreperiod RT paradigm with an inter-stimulus interval (CS-UCS) of 5 sec or more. Anticipatory ANS activity typically includes increased EDA, vasoconstriction in the FPV, and HR deceleration. It will be recalled that this type of study produces definitive data for the question of ANS responsivity only when subjects are aware of the stimulus contingencies.
Fuhrer and Baer (63) observed unimpaired differential anticipatory SCRs ("second interval CRs" in the traditional terminology) in schizophrenic women, but they had smaller SCRs than controls on test trials in which the UCS was omitted. In the Rist et al. (62) study when only subjects who produced consistent SCRs to the UCS were included, schizophrenics had even larger anticipatory HR decelerations than controls when the UCS was an imperative (RT) stimulus. Öhman et al. (64) also reported that schizophrenics showed some evidence of significant differential FPV and HR anticipatory responding, but the magnitude of vasoconstriction and deceleration was significantly greater in controls. These results were not affected by the level of RT performance. Similarly, a recent study of Steinhauer et al. (submitted), whose subjects silently counted critical stimuli but ignored others, found that when the upcoming stimulus was uncertain controls had a significant anticipatory deceleration (and showed acceleration following critical stimuli) whereas schizophrenics did not, even though they counted accurately and were able to verbalize the stimulus contingencies.

Studies using nondiscriminative RT paradigms have rather consistently found impaired anticipatory ANS responding in schizophrenics. Gray (67) compared EDA and HR slowing prior to warned tones varying both tone intensity (70 dB vs 110 dB) and a RT response requirement. Both of these variables tended to increase the anticipatory activity of controls as expected. However, unmedicated schizophrenics showed overall lower and undifferentiated anticipatory responding and paradoxical decreases in EDA and HR responses preceding the loud stimuli. In partial agreement with these results, Waddington et al. (73) reported an absence of HR deceleration in schizophrenics preceding an aversive stimulus for a RT response. Similarly, Zahn (65) reported an increase in SC and FPV responsivity during the course of 15 sec. RT foreperiods in controls but absent or greatly reduced trends in schizophrenics. A similar finding was reported in a later study also using unmedicated patients (29). In addition, significantly attenuated HR slowing during the foreperiod occurred in the patients compared to controls.

In conclusion, most of the studies just reviewed have found attenuated physiological activity in schizophrenics preceding predictable, important stimuli. The exceptions might be accounted for by patient selection. Fuhrer & Baer (63) tested outpatients and Rist et al. (62) obtained their "good" results in SCR responders. In addition Zahn et al. (74) reported normal HR deceleration in a subgroup of patients whose psychosis remitted within 3 months after the test although they did not differ from the poor prognosis group in current clinical state. Similarly, a study of HR responses in a 'sensory intake' procedure (75) found greater deceleration during a 6 sec viewing period in schizophrenics, who were mainly good premorbid acutes, compared to an alcoholic control group. Thus a relationship between prognosis or clinical state and anticipatory ANS activity is suggested.

The demonstration of generally impaired anticipatory activity in most schizophrenics can be considered relevant to Shakow's (76) theory that slow RT in schizophrenia is due to their faulty preparatory set to respond. The ANS data provide support for this hypothesis in a direct way not attainable with purely behavioral measures. Support comes also from the observation of Zahn et al. (74) that the subgroup with normal HR deceleration also had relatively fast RT (although still slower than controls). It is conceivable that this failure to anticipate predictable environmental events plays an important role, generally, in the cognitive and social impairments in schizophrenia. Contrasting psychophysiological interpretations of anticipatory cardiac slowing have been proposed (77,78), but it is agreed that it is accomplished by means of a parasympathetic response of increased vagal tone and that it accompanies sustained attention. Another vagally mediated cardiac reflex, called "primary
bradycardia” (77), is manifested by a delay of the next systole by stimuli occurring early in cardiac cycle (interbeat interval) or by a lengthening of the next cycle by stimuli occurring late in the cycle. Steinhauer et al. (submitted) found significant bradycardia in controls only for uncertain stimuli, confirming that this response is influenced by cognitive factors, but no significant bradycardia in schizophrenics under any condition. Thus deficiencies in parasympathetically as well as sympathetically mediated responses are observed in a significant proportion of schizophrenics.

**Tonic ANS Responses to Task Performance and Stress**

The earlier literature on this topic has been reviewed elsewhere (66), where it was pointed out that generally low physiological reactivity in schizophrenics (mainly chronic) to a variety of psychological, physiological, and physical challenges was a very common observation (79). In contrast, an influential study by Malmo and Shagass (80,81) found equal or greater cardiovascular responses to pain-stress and to two tasks in chronic schizophrenics compared to controls. However, the tasks used, size discrimination and mirror drawing, both require externally directed attention which is now thought to be facilitated by HR slowing thus making the interpretation of these findings ambiguous. Recent studies, for the most part, have confirmed the low tonic ANS reactivity findings. Kelly (82), whose patients were candidates for psychosurgery, and thus chronic nonresponders to pharmacologic treatment, found them to have sluggish cardiovascular reactions to a mental arithmetic task. The measures were HR, forearm blood flow, and blood pressure, and the schizophrenics were the least reactive of the several diagnostic groups tested. Similarly, Albus et al. (83,84) reported a decreased HR response to doing mental arithmetic in drug-free acute paranoid schizophrenics with positive symptoms compared to controls. Other stressors (cold-pressor, noise) and a variety of other measures (electrodermal, vascular, etc.) did not produce significant group differences. Zahn et al. (29) reported low ANS reactivity to a mental arithmetic task in acute unmedicated schizophrenics, manifested by SCR frequency, SCL, HR, and finger temperature.

In contrast to this set of similar findings, studies using other tasks have produced more conflicting results. In a complex study which tested many schizophrenic groups on a discrimination task, Magaro (85) found greater-than-normal increases in SCL in most patient groups, the exception being nonparanoid schizophrenics with poor premorbid histories, but no statistical analysis specifically directed at this point is presented. However, Spohn et al. (68) reported increases in SCL or HR to the initiation of a task in normals but not in schizophrenics, and Zahn (65,66) observed attenuated SCL increments to RT task performance in u of a task in normals but not in schizophrenics, and Zahn (65,66) observed attenuated SCL increments to RT task performance in unmedicated samples were small, it does suggest that drugs might influence the tonic levels more under passive or nonsignal conditions than under task conditions.

In summary, with one exception (85) these studies have found lower or equal ANS responses to psychological stress or task performance in schizophrenics than in controls. The low responsivity of HR to psychological stress contrasts with two reports of greater HR increases in schizophrenics to a change in posture from supine to standing than in controls (36,86), independent of medication.
Summary and Conclusions of Significance Studies

Most of the studies reviewed in the last three sections have shown lower phasic and tonic ANS responsivity to significant stimuli and situations or in anticipation of important stimuli. However, there are many exceptions to this generalization which cannot be ignored. Most of the exceptions can be lumped empirically into two general categories: one having to do with the nature of the task, and one with the selection of subjects.

First, several studies with nondifferential ANS responding have involved an untimed motor response to a stimulus. This response frequently, but not always, has been a button press (65,66,68,69,71). Greater HR anticipatory slowing under similar conditions in schizophrenics was also reported (75). At this point the specific attributes of the situation responsible for these conflicting results are not clear. More studies are needed which compare timed and untimed responses in the same subjects to confirm the reality of the effect and to further delineate what stimulus characteristics are critical in producing differential responding.

The second major source of nonimpairment in these studies seems to be some favorable clinical attribute. These have included being in remission (63), acute, and/or good premorbid status (75,83-85), or having a quick remission (74). It is possible that a common characteristic of these subjects is a relative preponderance of positive symptoms or, perhaps better, a paucity of negative symptoms. The hypothesis that this symptom pattern is related to ANS reactivity to significant stimuli and situations might also account for the favorable effects of having relatively fast RT (64) or SCOR responder status (62) in differential conditioning paradigms.

However, this conclusion may be oversimplified. The good and poor outcome groups of Zahn et al., (74) did not differ clinically yet showed marked differences in ANS baselines and responses to significant stimuli. At a followup test when there were marked clinical differences the ANS differences remained essentially the same. Therefore, the ANS differences were independent of the clinical differences, and they were also better predictors of short term outcome than symptoms. Similar conclusions can be drawn from studies which have used differences in the OR as predictors which will be reviewed in a later section. As we saw earlier with differences in responding to nonsignal stimuli the clinical differences indexed by adequate vs inadequate response to task demands may be distinct from those indexed by existent rating scales but nevertheless important.

Low motivation is frequently given as an explanation of the low ANS response (and behavioral impairments) to tasks in schizophrenia. This implies a voluntary lack of cooperation. While this explanation may have some merit in terms of parsimony and simplicity, there is little direct evidence for it, and the fact that ANS impairments seem about as likely in studies using aversive stimuli as those using voluntary "imperative" stimuli would weigh against it. In addition, in our experience the great majority of patients seem to be trying hard to perform well. It might be more fruitful to think of the ANS deficits as reflecting an inability to bring attentional resources to bear on the task. Perhaps this is partly the result of the competition for attention by internal and external stimuli as suggested earlier. The greater likelihood of such impairments in chronic schizophrenics and those with poor prognosis suggests that they are related to the cause of the illness, but whether they just correlated with this or play a causal role in the failure to respond to treatment cannot be determined at present.

ANS ACTIVITY IN RELATION TO OTHER MARKERS
Task Performance Deficits  Because of the frequent early reports of elevated physiological levels in schizophrenics, the concurrent acceptance of the unitary arousal concept, and the idea of an inverted-U relationship of performance to arousal, the hypothesis that schizophrenics' impairment on task performance was causally related to their high arousal levels was advanced (e.g. 87). As pointed out in earlier reviews of this topic (4,66) the evidence for high arousal in schizophrenia comes mainly from observations of baseline or resting conditions. However, because of the sluggish tonic response to task performance usually observed in schizophrenics, ANS levels are frequently not much different from normal under task conditions. This suggests that a "strong" form of the inverted-U hypothesis--one curve for both schizophrenics and controls--does not fit the data. However, a weaker form of the hypothesis, with a schizophrenic inverted-U curve displaced to the left (indicating a lower threshold for disruption of behavior by arousal than that for normals), would not be incompatible with the group-difference data, and would be testable by manipulating arousal experimentally or by correlating arousal with performance.

The hypothesis of impairment due to high arousal received major support from Spohn et al. (15) whose well-controlled study showed that neuroleptic medication reduced SCL under both baseline and task conditions and also improved performance on tasks of attention and information processing.

Correlational studies have not produced very consistent results, and in addition are not always unequivocally interpretable in terms of a direct effect of arousal on task performance. Spohn et al. (68) found that performance on a span of apprehension task had positive relationships a with small declines in SCL during the task and with high HR variability, which they interpret as reflecting a factor of alertness or attention, but there were no effects of SCL or HR levels. Zahn (66) reported that there were significant negative correlations of baseline SCL and HR with speed of response in an RT task, similar correlations with levels during the task itself were lower. High positive correlations were obtained between speed and specific responses to the task stimuli. Similar conclusions can be drawn from Zahn et al. (74) in which the schizophrenics with faster RT had lower baseline arousal measures and greater responsivity to the task stimuli but were not different on arousal during the task itself than those with slow RT.

These observations are not completely consistent with even the weak inverted-U model. However, the fit is improved if it is assumed that only nonspecific (66) or endogenous (88) arousal has an inverted-U relationship to performance but that specific or exogenous arousal has a direct relationship. Thus the resting data provide a better estimate of endogenous arousal than task levels do and, therefore, should be more highly related to performance.

There are several studies of task performance in patients separated in terms of SCOR responsivity. Although this variable is correlated with arousal indices, we saw earlier that it may reflect an underlying attentional or information-processing parameter. The significant findings with this variable show that both the type of deficit and drug status influence the results. Two studies on medicated patients have shown more deficient signal detection (errors of omission) in SCOR nonresponders than in responders (16,33) and one (89), using subjects selected to be on low levels of neuroleptic medication, reported poorer signal detection in nonresponders than in fast habituators and normals, but not compared to responders with slower habituation. Bartfai et al. (90) also found better task performance in an intermediate group of patients whose SCOR habituated than in nonresponders or nonhabituaators although Ns are small and only one of several differences (left hand finger tapping) was significant. A study on event-related potentials (91) showed the N220 wave to clicks was reduced in SCOR nonresponders and
increased in nonhabituated compared to habituators when counting the clicks compared to counting interspersed visual stimuli. This was interpreted as excessive interference by counting in the nonresponders. In the same patients, latency of wave V of the brainstem auditory evoked potential to click trains was reduced when attention was directed away from the clicks in the nonresponders but not in responders (92). This was interpreted as a sign of excessive selective filtering of auditory stimuli in the nonresponders.

Conversely, in unmedicated patients, responders (who were slow habituators) were more impaired than nonresponders under conditions of fast stimulus presentation and made more false positive errors (16). Similarly Alm et al. (93) found marginally more disruptive effects of distraction in unmedicated SCOR responders than in nonresponders and Bartfai et al. (94) reported poorer eyetracking in unmedicated nonhabituated than in habituators.

In terms of the inverted-U hypothesis the findings that in medicated patients those with low arousal, at least as indexed by SCORs, show the most impairment, and in unmedicated patients those with high arousal are most impaired suggests that antipsychotic drugs shift patients from the right side of the inverted-U, where they are distributed along the descending limb, to the left or ascending side. This hypothesis was able to reconcile most of the apparently conflicting data from a number of studies relating the two-flash threshold to arousal indices (usually SCL) in schizophrenia (4). The hypothesis is also consistent with a recent report that neuroleptic dose level is negatively correlated with both EDA and performance of attention and information processing tasks (95).

However, many of the findings presented in this section can be accounted for better by the model based on two general types of schizophrenia discussed earlier. Thus Type I patients (responders, nonhabituated) especially when unmedicated, seem prone to types of errors attributable to overactivity or interference from internal stimuli while Type II patients (nonresponders) are prone to errors attributable to failures to activate central processing. More information might be gained from future studies in this area by using tasks which permit a differentiation of error types and a stages of information processing approach.

Biological Markers

The study of ANS activity in relation to other biologic variables has been neglected but there are a few studies emerging concerning brain imaging. Alm et al. (93) did not find SCOR responder status associated with size of lateral ventricles. However Zahn, et al. (96) reported that cortical atrophy rated from CT scans was significantly associated with diminished SCR amplitudes and small tonic SC and HR increases to task performance in chronic unmedicated patients. If SCOR nonresponding had been the selection variable in this study negative results would have also been obtained. In contrast Bartfai et al. (90) found marginally significantly larger third ventricles in acute medicated SCOR nonhabituated compared to habituators and nonresponders. A similar result was obtained by Schnur et al. (97). Responders had significantly larger third ventricles and marginally larger sulci than nonresponders. The results of these latter two studies are somewhat surprising since it might be expected that both low EDA and brain atrophy would be related to negative symptoms.

Relationships of EDA to ventricular enlargement in subjects at genetic risk for schizophrenia has recently been reported by Cannon et al. (98). The subjects were part of a long term high-risk project and had had their EDA recorded when they were children or adolescents some 18 years before the CT scans. Subjects whose third ventricle width
was greater the median had lower EDA responsiveness to a variety of stimuli in an aversive conditioning paradigm in terms of both frequency and amplitudes of SCRs. The results were independent of current diagnosis.

It is difficult to find a common pattern in the above findings. More data on this problem is needed and will certainly be forthcoming, along with data relating these types of measures to information from other brain imaging techniques. An exciting preliminary report by Dawson (99) using positron emission tomography in schizophrenics revealed that three SCOR responders had markedly and generally higher brain glucose utilization that three nonresponders, particularly in some portions of the frontal lobes, thalamus and limbic system.

ANS ACTIVITY AND CLINICAL COURSE

There are significant individual differences in the course of schizophrenic illness, and various typologies and correlates have been proposed to deal with this over the years such as the process-reactive or good-poor premorbid adjustment dichotomies. Studies of ANS activity in relation to those predictors have not generally been successful (4), but several studies which have related ANS activity to actual outcome have been illuminating. Frith et al. (20) tested unmedicated schizophrenics in the early stages of an episode in an OR paradigm which was repeated after treatment with either a dopamine receptor blocker or an inactive drug. The SCOR of about half of the patients failed to habituate on the initial test, and this group showed less clinical improvement, irrespective of drug treatment, than the habituators. Habituation was a better predictor of outcome than type of treatment or insidiousness of onset. Several other indicators of EDA were higher in the nonhabituators as well. On the repeat test, although habituation was increased by the active drug, this increase was not related to clinical improvement. Thus the ANS variable was better as a predictor than as an indicator of clinical change.

Similar results were reported by Zahn et al. (74) who tested drug-free acute schizophrenics. On the before trial, patients who were later determined to have shown minimal improvement after a 3 month hospitalization were higher in EDA and HR under resting conditions, had slower habituation rates and smaller phasic and tonic reactions to significant stimuli than did those patients who remitted within 3 months despite equally bad clinical ratings at time 1. On the second test there were only minimal ANS changes compared to the first test in either group, showing again that the ANS pattern predicted clinical change but did not accompany that change.

Another replication of this type of result has been reported by Straube et al. (32) who studied ANS activity in newly admitted paranoid schizophrenic patients who were then given a 28 day trial on the neuroleptic perazine and rated for clinical improvement. Those showing the most improvement had faster habituation of the FPVOR, lower resting HR, but higher SCL under task conditions than patients showing minimal improvement. A discriminant function using those variables correctly predicted the improvement status in 16 out of 19 patients.

However two other predictive studies have produced quite different results from the three just reviewed. Schneider (100) tested very chronic schizophrenics 55 to 67 years old after a drug washout period. Eighteen patients who showed improvement on a subsequent 6-month controlled neuroleptic drug trial had higher EDA and slower SCOR habituation than 8 patients who worsened on treatment. Öhman et al. (47) studied the SCOR in 37 recently admitted patients, 15 of whom were first admissions, but evaluated them in terms of long-term (2 year) outcome. They found that 5 out of the 6 new admissions who were SCOR responders subsequently had a good outcome while all 9 of
the nonresponders had poor clinical outcomes. Twenty out of the 22 readmissions had poor outcomes but 9 of these patients were SCOR responders so the predictive value of the SCOR was good only for the new admissions. Number of SFs and SCL was highly related to habituation status.

Although the latter two studies obtained results that were the opposite from the first three studies cited in this section, the conflict is probably more apparent than real due to differences in the criteria for outcome. In Schneider's (100) very chronic patients low EDA was probably predictive of the severity of negative symptoms which did not improve from neuroleptic treatment. Öhman et al. (47) point out that only social and employment outcome were predicted by the SCOR in their study, not hospitalizations or medication usage. Therefore nonresponding seems to be predictive of the negative symptom of social withdrawal. In the short-term outcome studies, fast habituation was predictive of a quick recovery from the (presumably mostly positive) symptoms of an acute episode. An interesting group of studies has concerned the ANS correlates of environmental conditions conducive to relapse in outpatients. Patients with relatives who have high 'expressed emotion' (EE -- critical or overinvolved) have been shown to be more likely to relapse than those with low EE relatives. Tarrier, et al. (101) recorded ANS measures from schizophrenic outpatients, who were classified in terms of EE ratings of a close relative, when talking with that relative or just with the experimenter. Both schizophrenic groups showed more EDA than controls to about the same extent while interacting with the experimenter, but only the high EE group maintained the elevated EDA when talking to the relative. Systolic blood pressure also showed a differential response in the same direction for the EE groups.

A study using a similar procedure comparing EDA in hospitalized high and low EE patients after a relapse (102) showed generally elevated EDA in high EE patients whether or not they were interacting with a relative. A similar followup test some months after the patients had been discharged produced similar results. This study also found that EE and EDA in the initial testing were independently related to future relapse, and that in high EE, but not low EE patients, those who responded with increased EDA to interacting with their relative were more likely to relapse than those who did not.

However a similar study on new admissions (103) found differences in SFs between patients with high and low EE relatives only when they were talking to that relative, due to habituation in just the low EE group. However SCL was higher in high EE subjects throughout the session. Thus the evidence is somewhat inconsistent as to whether patients with high EE families have generally elevated EDA, but it is consistent that they have elevated EDA when interacting with the high EE relative.

Another environmental condition which is conducive to relapse, the recent experience of a significant 'life event' (104), has also been shown to be related to elevated EDA in schizophrenic outpatients when talking to a relative (101). This finding has recently been replicated by Nuechterlein et al. (105) who measured SFs during a protocol which involved presentation of simple nonsignal and signal stimuli (without a relative present). These studies are consistent with previously described findings in episodic patients that elevated ANS activity is predictive of poor clinical course and extends this general idea to prediction of future relapse and to patients on their usual clinical medication regimens. Since relapse in such cases would be expected to involve an increase in positive symptoms, these findings support the association of elevated EDA with positive symptoms. They also suggest that the greater relapse rate observed in unmedicated patients in remission may be mediated through elevated ANS activity.
In addition to this evidence of EDA in remission as a predictor of relapse, is a recent report indicating state-related changes in EDA by Dawson (99). In this study young recent-onset medicated patients were tested on EDA and rated every two weeks. When ratings indicated that they were truly in a state of remission they had very low EDA (SCORs and SCL) compared to controls. After they had relapsed, there was a marked increase in EDA to above normal levels on both measures. Moreover, preliminary data on a few patients suggest that an increase in EDA predates actual clinical worsening. If confirmed, this suggests that periodic ANS studies of remitted schizophrenics might well have an important clinical value as an 'early warning system' to allow clinical intervention at an appropriate time before an actual relapse occurs.

Although these data are not in direct conflict with the data presented at the beginning of this section on the lack of relationship between changes in psychophysiology and changes in clinical state in hospitalized patients there seems to be a conceptual mismatch. Other data have also been interpreted as indicating low correlation between the two domains. Iacono (106) studied medicated outpatients who were in remission. Similar to studies of hospitalized inpatients, almost half of his group were SCOR nonresponders (although his method produced a high rate of nonresponding in the controls -- 18%), and the responders were higher than responder controls on SCL and SFs and marginally so on HR. Although there were no data on the same patients when hospitalized the conclusion that the data were not much different than the typical study on hospitalized patients seems reasonable. However, this does not mean that the ANS variables would not change with an impending relapse.

Along somewhat different lines, Hommer et al. (107) reported that a clinical trial of prazosine, a specific alpha1-noradrenergic receptor antagonist, but which has been found to raise plasma norepinephrine, increased SFs and SCOR frequency and amplitude but did not produce any clinical changes compared to placebo treatment, thus demonstrating a lack of a cause-and-effect relationship between ANS and clinical variations. Of course, the evidence on drug effects presented in an earlier section suggests the same conclusion. There seem to be greater effects of anticholinergic drugs on EDA and HR than those of neuroleptics, yet the latter are what effect the clinical changes. Although the altered ANS activity from both prazosine and anticholinergics may be due to their peripheral rather than their central effects, caution is indicated in accepting a direct causal role of ANS activity on clinical state.

HIGH-RISK STUDIES

ANS measures have been included in several studies on the offspring of schizophrenic parents, usually studied before they have reached the risk period for schizophrenia. The earlier results from these studies, most of which concern comparisons between high-risk and control subjects in childhood, have been reviewed extensively elsewhere (4,48,108,109). To summarize these, the exciting early results of Mednick & Schulsinger (110) of greatly elevated EDA in children and adolescents (mean age of 15) with a schizophrenic mother, were partially replicated in some later studies (111,112) and not in others (113,114). There are many methodological differences among the studies, but it has not been possible to attribute the differences in results to any of these, although the negative results have been mainly in younger subjects (4). In clinical followups Mednick (115) reported that high risk subjects who 'broke down' (any diagnosis) in the early part of the risk period had especially elevated EDA compared even to high-risk subjects who did not break down, but in a later followup (116), while the results were generally in the same direction, they were much less general both as to the variables and the subjects (males only) showing the effect.
Results in conflict with the original findings have been reported by Erlenmeyer-Kimling et al. (117) who compared offspring of schizophrenics, nonschizophrenic psychiatric patients, and normal controls on EDA during a differential conditioning paradigm with a loud noise as the UCS. The only significant overall group result was that SCR latencies were longer in the high risk group. However there were trends for the high risk subjects whose global adjustment was impaired or who broke down, to have had faster recovery times in the earlier test than non-high-risk subjects of equivalent clinical status (but not compared to other high risk subjects). Interestingly, offspring of high risk mothers had faster recovery times than offspring of high-risk fathers. A serious problem with this study is that the electrodermal recording was insensitive compared to state-of-the-art methods by a factor of 5-10, but it is not clear how much this affected the results.

Conflicting results were also reported by Kugelmass, et al. (118) from a high risk study of Israeli children (mean age of 11.3). EDA was recorded to nonsignal and signal tones, loud noises, and during an information-detection procedure in offspring of 50 schizophrenics and 50 matched normal controls. Half of each group was born and raised on a Kibbutz thereby lessening their direct contact with their parents. Two significant overall group effects were found: Index cases had slower recovery rates to innocuous tones and lower scores on a complex index which reflected responsivity to significant names versus neutral names. Both of these effects were stronger in the Kibbutz group. Index subjects raised on a Kibbutz also had significantly longer SCOR latencies and nonsignificantly lower SCOR amplitudes and lower SCL than the other groups. It may be of note that on a 15 year followup of these cases (119) the Kibbutz-reared index group had an unexpectedly high incidence of affective disorders (9 of 23 cases) in addition to schizophrenia (6 of 23 cases).

Some of the confusion in the preceding reports may be clarified in emerging new data on the relationships of earlier ANS data to later clinical outcome. The latest report from the Mednick & Schulsinger (110) study (120) indicated a quite different result from those reported earlier. Subjects with a diagnosis of schizophrenia were compared with those with schizotypal personality disorder and well subjects. EDA nonresponding on the original test occurred significantly more in subjects who became schizophrenic (7 of 15) compared to the other subjects (9 of 51). In addition, schizophrenics who were responders had a preponderance of positive symptoms at both adolescence and adulthood whereas nonresponders had more negative symptoms at adolescence and when adults were higher on a scale of 'anergia-retardation' (but not significantly on other negative symptoms) than responders.

A recent clinical followup from the Israeli high-risk study (Kugelmass, et al., unpublished) shows that high-risk subjects with diagnoses of both schizophrenia and affective disorder, particularly the latter, had lower EDA in childhood compared to both high-risk and control subjects without a diagnosis. The most significant measure was SCR latency. This study can be seen as partially confirmatory of Cannon & Mednick (120), in associating abnormally low EDA with risk for schizophrenia, but because of methodological differences the two studies are not directly comparable.

A final study in this area was done from a family-interaction rather than a genetic perspective (121). This group had shown that in nonpsychotic adolescents seen at a clinic, those whose families had high expressed emotion (EE) were more likely to develop a schizophrenia spectrum disorder than patients from low EE families. Skin conductance was recorded from both adolescents and parents during a laboratory confrontation. Results showed significantly greater EDA in high EE subjects and parents compared to the low EE families in parts of the interview. Thus, it is possible that elevated EDA is indexing a familial emotional climate which may be predisposing for
schizophrenic disorders. Alternatively, both EDA and EE may be related to some other (genetic?) predisposing factor.

In conclusion, the followup tests to date suggest that low EDA in genetic high-risk children or adolescents may be a reasonable candidate for a genetic marker for one type of schizophrenia at least. These results are also consistent with those of Alm et al. (93) who found 11 nonresponders in 12 chronic patients with a family history of schizophrenia, contrasted to 50% nonresponders in those without a family history. However, the Israeli data (Kugelmass, unpublished) suggest that low EDA might not be specific to schizophrenia, and in that light it is interesting that the negative symptom that was discriminating in the Cannon & Mednick data is also a symptom of depression.

These results do not invalidate the earlier findings of high ANS activity in high-risk adolescents. Since only 9-13% of the offspring of schizophrenic parents develop schizophrenia (122), and only a proportion of these cases will end up having the type of schizophrenia that is indexed by EDA nonresponding, then it is quite possible for that marker to be hidden in the larger sample -- for the high-risk group as a whole to show different results from the small subgroup who develop (Type II?) schizophrenia.

Since neither of the followup studies have found that abnormally elevated EDA is a predictor its role is unclear. It is possible to speculate that the reason for the finding of high EDA in the diagnosed cases in the first followup from the Mednick study (115) is that it is related to positive symptoms which are more likely to produce disruptive and troublesome behavior and attract attention than are negative symptoms. For this reason the Alme et al. (121) strategy may be preferentially selecting potential Type I schizophrenics. Whether or not there is a role for high EDA as a predictor should emerge with continued followup evaluations using both types of strategies. Since we saw earlier that the rate of SFs may be the best marker for Type I schizophrenia, it might be well to target this variable for particular attention.

**PUPILLARY RESPONSES IN SCHIZOPHRENIA**

The pupil of the eye is responsive to virtually all psychosensory stimuli. Throughout the centuries, the ability to observe large changes without special instrumentation has made it, along with such other overt autonomic reactions as blushing and sweating, a focus for monitoring reactions to highly emotional situations.

Under two conditions, the pupil exhibits constriction: after presentation of light, and during accommodation to near objects. While the afferent central pathways of these responses differ, they converge at the Edinger-Westphal nucleus of the oculomotor complex, where efferent parasympathetic fibers travel along the third cranial (oculomotor) nerve, synapse at the ciliary ganglion, and a final pathway leads to the sphincter pupillae, a ring of smooth muscles of the iris surrounding the pupil.

Other stimuli, including sound, touch, painful stimuli, as well as psychologically stimulating events, produce dilatation of the pupil. A variety of inputs descending from cortical, thalamic, and limbic regions converge at the hypothalamus, where the sympathetic chain has its innervation. Descending fibers from the posterior and lateral hypothalamic nuclei then synapse at the ciliospinal center of Budge, with a final synapse at the superior cervical ganglion, before they reach the dilator pupillae, a series of radial muscles which, when constricted, increase pupil diameter. Initially, it would appear that the pupil is a reflection of simple parasympathetic and sympathetic impulses, with increased activity among one branch of the autonomic chain simultaneously contributing to reciprocal inhibition of the other. Loewenfeld (123), for example, noted that a small
component of reflex dilatation can be attributed to relaxation of the sphincter muscles. More complexly, there are also several direct influences that serve to decrease the cholinergically mediated parasympathetic pathway. Inhibitory influences from such diverse areas as cortex, thalamus, and hypothalamus impinge on the Edinger-Westphal nucleus (124,125), resulting in a "supranuclear" or "central" inhibition of the parasympathetic outflow to the iris under conditions of arousal or stress.

Early Studies

Deviations of pupillary movements have been associated with schizophrenia from the beginning of the century (for reviews, see 127,128). The catatonic pupil described by Westphal (128) was characterized by a dilated pupil and a range of deviant responses from prompt reactions to absolute rigidity. Sluggish contractions to light were noted by Lowenstein and Westphal (129) as characterizing psychiatric patients. Levine and Schilder (130) reported a series of investigations in schizophrenics in which pharmacological effects were investigated in the patients. However, more systematic studies could not be undertaken until the 1960's, when electronic scanning pupillometers, and later, infra-red based video pupillometers, as well as computerized methods of analysis, became available to study changes that could average as little as several hundredths of a millimeter (131,132).

Pupillary Reactions to Light Stimuli

In a study of pupillary constriction to light pulses in unmedicated acute and chronic schizophrenics and normal subjects, Hakerem, Sutton and Zubin (133) observed smaller initial pupillary diameters in darkness for the acute patients. Latency to maximal contraction was shorter for both patient groups than for normals, though no clear differences in extent of contraction were observed among groups. Lidsky, Hakerem and Sutton (134) found slightly smaller initial diameters among unmedicated, recently admitted schizophrenic patients than controls, and a clearly attenuated response to 30 msec flashes of light, with a median constriction of .9 mm for the patients and 1.79 mm for controls. Using a cutoff of 1.7 mm, they correctly identified 86% of the patients. Moreover, when they matched pairs of patients and controls on initial pupillary diameter, it was possible to determine that the decreased constriction of the patients was unrelated to initial pupil diameters. The reduced pupillary constriction to light stimuli appears to be separable from constriction due to accommodation, which has been reported normal even among patients with reduced constriction amplitudes (135). Abnormally reduced constrictions were reported for 37% of acutely ill schizophrenics and 44% of remitted patients, including those who were drug-free. Even greater proportions of patients (78% of the acutely ill and 63% of remitted patients) showed reduced reflex dilation during 10 sec dark periods (136). Rubin, over a period of several years (for example 136-139), attempted to develop a model for describing autonomic deviations in psychiatric groups based on the notion that specific deviant autonomic patterns could be detected among schizophrenic and other psychiatric patients. Typical responding is indicated by normal autonomic levels at rest, with stress producing increased sympathetic (adrenergic) and decreased parasympathetic (cholinergic) levels. Thus, Rubin suggested that any other combination of abnormally heightened or decreased autonomic activity would be related to pathological central autonomic activity. The pupil was presented as an ideal model for testing these distinctions (139). Using light stimuli to elicit constriction, or light offset or the cold-pressor test to evoke dilation, the relative responsivity of a variety of patients could be assessed.

The most radical aspect of this conceptualization was that the imbalances indicated by the autonomic laboratory results should then be corrected by the
administration of combinations of adrenergic or cholinergic stimulants, or by adrenolytic and anticholinergic compounds. While this formulation has served to stimulate additional research (140), several studies (141,142) were unable to replicate the high rates of classification of pupillary abnormalities indicated by Rubin, especially for over-reactive patients. Rubin & Barry (143) noted critical methodological differences among these studies which, they suggested, accounted for the differences. A further problem for Rubin's model involves the primarily cholinergic nature of the central autonomic pathways: it is the final neuromuscular junctions of the pupillary system which show the major differentiation of adrenergic and cholinergic activity (144).

Several studies have indicated an association between pupillary reflex activity and EDA in schizophrenics. Patterson (145,146) reported both decreased constriction to light and decreased reflex dilation to darkness among medicated schizophrenics. This finding could be attributed to those patients who also showed a reduced SCOR, suggesting overall reduced autonomic responsivity in these patients. Similarly, Straube (147) reported that patients who gave few SCORs also had reduced constriction amplitudes.

**Pupillary Reactions to Non-Visual Stimuli in Schizophrenia**

Reactions to non-visual stimuli were reported to be deficient among schizophrenics as early as 1904 by Bumke (148), who associated a decreased dilation to painful stimuli with a poor prognosis. May (149) reported that schizophrenics were less likely than control subjects to exhibit dilation either when exposed to painful stimuli or when muscular effort was required. Decreased pupillary dilation in schizophrenics during the cold-pressor test has been presented as further evidence of autonomic dysfunction (150,151). The nature of the deficits observed in schizophrenic subjects has been examined with regard to possible interactions of the sympathetic and parasympathetic systems as well as non-autonomic central activity. Reduction in the light reflex may be due to increased supra-nuclear inhibition at the level of the oculomotor nucleus, and Hakerem and Lidsky (127) suggested that this inhibition might be a result of a greater tonic arousal in patients. Rubin and Barry (152) noted that hyperarousal would be expected to lead to larger initial diameters in patients, yet initial diameter has often been reported to be smaller for schizophrenic groups. They argue, therefore, that arousal cannot be implicated as being the source of inhibition of the light reflex. However, the question of decreased constriction due to central inhibition was not resolved, because Hakerem and Lidsky (127) demonstrated that matching patients and controls for initial diameter still resulted in smaller constrictions in patients. Furthermore, they noted Loewenfeld's finding that amphetamines, though related to arousal, did not change initial diameter but did reduce the amplitude of constriction to light. This, they suggested, indicated a dissociation of central sympathetic activity from peripheral sympathetic activity, and suggested that aspects of the dilation response be studied more carefully in patients.

Across studies, the least consistent findings have involved differences between schizophrenics and controls in initial diameter. More consistent findings include patient's decreased constriction to light and faster constriction or shorter latency to the end of the constriction process. Reflex dilation to light offset and the dilatory response to stress (primarily the cold-pressor test) are also reduced in schizophrenics. It is somewhat surprising that little mention appears of the pupillary response to tones in the orienting paradigm so typical of EDA studies in schizophrenia, even though the primary involvement of pupillary dilation in the orienting situation is well known (49). **Pupillary Dilation During Cognitive Activity**
There has been less of an emphasis on pupillary dilations elicited under conditions requiring task performance. A variety of cognitive tasks has been investigated which lead to reliable dilations in normal subjects, making the pupillary response a valuable tool for cognitive psychophysiology (153-155). Auditory tasks which are typically employed for the generation of the P300 component of the event-related potential (see Friedman, this volume) are especially appropriate for eliciting pupillary dilations, as revealed in the averaged pupillary responses. Inpatient schizophrenics were found to show greatly reduced dilations compared to controls when performing in a guessing task (156), similar to one employed originally for investigations of ERPs and schizophrenia (e.g. 157). Steinhauer and Zubin (158) reported that both pupillary dilations and P300 amplitudes, recorded simultaneously, were significantly reduced for medicated inpatient schizophrenics as compared to controls. In addition to amplitude reduction, however, a qualitatively different pattern of responding among experimental conditions was also observed. Controls showed larger dilations depending on the sequential conditional probabilities of events, while patients showed significantly larger dilations when the previous stimulus (three sec before) differed physically from the current stimulus, as compared to a repeated stimulus. In particular, the dilation was observed in conditions in which the stimulus change was perfectly predictable, and to which controls showed little relative change. Similarly, P300 amplitude was associated with stimulus change in these patients. The data were interpreted as indicating that the patients were at least attending to the physical differences among stimuli, even though irrelevant to task requirements.

One interpretation of these two studies suggests that pupillary dilations may merely indicate reduced autonomic reactivity overall. However, during performance of a digit span task, Straube (159) observed larger dilations among schizophrenics than controls. Pupillary dilation during the digit span has often been used as a measure of workload (160). Thus, the differences among the latter studies suggest that the pupillary response in one case may reflect excessive effort used by patients in trying to perform a difficult task, while in the other case it is indicative of a deviation in the utilization of information where the task is easy, but complexity of the information is high.

Pharmacological Investigation of Pupillary Reactions in Schizophrenics

The sensitivity of the pupil to pharmacological variables is well recognized (144,161). This becomes especially problematic in trying to examine patients who have received anticholinergics, such as scopolamine, which both dilate the pupil and reduce or eliminate constriction (9). Single doses of haloperidol seem to have a minimal effect on the pupil (9), while single doses of chlorpromazine produce a slightly miotic (constricted) pupil that recovers within a day (162). However, single doses of chlorpromazine have also been associated with slight reduction of constriction to light and decreased redilation in darkness (9).

Long-term administration of neuroleptics does not appear to normalize the decreased light reactions of schizophrenics (135,163), and no differences between medicated and unmedicated patients in remission have been observed (136,164). Moreover, several of the earlier studies included unmedicated patients (133). The prolongation of decreased reactions to light, even during remission, suggests that at deviations in the pupillary constriction to light may be more of a long-term trait, or vulnerability marker, than a specific indicator of state (episode) in schizophrenics (1).

SUMMARY AND CONCLUSIONS
Many studies in the past decade or two have observed an absence of SCORs to innocuous stimuli in close to half of chronic schizophrenics but in relatively few normal persons. Schizophrenics can be distinguished from endogenous depressives if FPV is also measured. Thus a profound reduction in or absence of autonomically mediated ORs may be a reasonably good biologic marker for chronic schizophrenia. However most of this evidence comes from studies in which patients were medicated. Examination of medication effects shows that drugs with anticholinergic properties lower EDA, including the incidence of SCORs, and raise HR. There is evidence that neuroleptics without anticholinergic activity affect EDA in acute schizophrenics, but their effects on chronic patients is less certain. Their effects do seem less than that of anticholinergics, and they probably do not greatly affect the incidence of OR nonresponding in chronic patients; also, they may work on central rather than peripheral mechanisms. However, more careful research on neuroleptic effects on EDA is needed.

In addition to the studies finding many SCOR nonresponders are studies finding equal or slower habituation in a large number of schizophrenics, mostly on acute or episodic unmedicated patients in the early stages of an episode. Some studies have found both hypo- and hyper-responsiveness. Medication effects cannot account totally for these differences. There is evidence that schizophrenics who are SCOR nonresponders are generally those with negative or defect symptoms and that responders and hyperresponsive patients have few negative symptoms but may have positive symptoms. This latter group may be best distinguished by a high rate of SFs. However, recent attempts to correlate symptoms with EDA have produced equivocal results.

Many reports of retarded habituation in schizophrenia may be due to confusing SFs with SCORs due to excessively wide latency criteria. With a stringent definition of an SCOR, fast habituation occurs in all types of schizophrenia particularly in relation to SFs. The reduction in responding to novel stimuli may reflect a deficit in controlled processing, most severe in chronic patients. Acute patients may not be able to distinguish between internally generated and external stimuli.

Schizophrenics are also impaired in responding to stimuli which are made significant by task relevance or by being paired with a significant stimulus. Patients who are OR nonresponders may respond to significant stimuli but habituate rapidly. Those who do respond to nonsignal stimuli generally do not increase their responsivity to significant stimuli as normals do. Deficits in ANS indices of anticipation of significant stimuli are consistently found as well. Less cognitively impaired schizophrenics may show minimal impairment in ANS responding to or anticipating significant stimuli, however. Lack of control over motor responses creates some variability in results using this method. Increases in tonic ANS levels during task performance are also reduced in schizophrenia.

Especially poor performance on cognitive tasks occurs in chronic medicated patients who have low baseline ANS activity and in acute unmedicated patients with high baseline ANS activity. This fits an ‘inverted-U’ model relating nonspecific arousal and performance under certain assumptions, but evidence that the two groups have different types of deficits suggests that different processing stages are affected in each group. Therefore a more cognitively differentiated model will have more predictive power.

Results from a few studies attempting to relate brain morphology to EDA are equivocal at present, but studies of structural and functional brain imagery in relation to ANS activity are potentially quite valuable.
Slow habituation and elevated ANS base levels in acute unmedicated patients seem to be predictive of poor short-term outcome independent of treatment. However, chronic responders may have a better response to neuroleptics than nonresponders, and SCOR responding in acute patients may be predictive of better long-term social outcome on medication. Patients in remission who are exposed to environmental factors associated with early relapse (critical or hostile families and significant life events) have elevated EDA. There is evidence that ANS changes predate clinical changes -- either improvement or relapse. However changes in EDA per se are not necessarily accompanied by clinical changes.

The role of ANS activity in the etiology of schizophrenia in high-risk subjects is unclear at present. Earlier reports of greatly elevated EDA in children and adolescents with schizophrenic mothers compared to controls have not generally been confirmed by later studies. Elevated EDA in adolescents at risk may be conducive to an early breakdown with a schizoid disorder. However, recent followup studies suggest that unusually low premorbid EDA responsivity is associated with future schizophrenia characterized by negative or depressive symptoms but few positive symptoms. Subjects who develop positive symptoms do not necessarily have unusual premorbid EDA.

Like other indices of ANS activity pupillary responses to external stimuli are reduced in schizophrenia. This holds for both sympathetic and parasympathetic reactions, mostly elicited by biologically significant stimuli. This confirms similar findings with HR reactions to psychogenic stimuli. A report of enhanced dilation during work load in schizophrenics needs replication.

It can be concluded that autonomic hyporesponsivity to external stimuli is a very general and pervasive feature of schizophrenia which may reflect a core deficit in controlled information processing. In addition, individual differences in EDA, especially, have suggested a discrimination between two major types of schizophrenia which may differ more in cognition, prognosis, and treatment effects than in current symptomatology, at least as assessed by contemporary methods. This distinction has helped account for apparently conflicting results concerning neuroleptic effects on EDA, relationships of ANS activity to task performance, and the autonomic predictors of outcome, and it may have implications for etiology. The difficulty in discovering replicable symptomatic correlates of the two types defined by EDA thus may indicate not that it is an invalid distinction, but rather that EDA provides somewhat different information than symptoms.

Much evidence is consistent with the hypothesis that a patient's ANS responsivity is a trait, but some newer longitudinal data dispute this. An important question is whether those acute or episodic patients who have elevated EDA when they are ill (Type I) become normalized or hyporeactive when in remission. Similarly, what is the longitudinal course of ANS activity in chronic (Type II) schizophrenia. Patient cohorts need to be followed over a considerable length of time to answer some of these questions. In addition, the meaning of variations in spontaneous and elicited ANS activity need further investigation by studying the cognitive, clinical, and biologic attributes of the same patients over the same time periods.
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