Electrodermal predictors of functional outcome and negative symptoms in schizophrenia

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Abstract

The ability of electrodermal variables to predict negative symptoms and functional outcome over a 1-year period in schizophrenia was investigated in 78 young, recent-onset outpatients. Patients were stabilized on standardized medication and largely free of psychotic symptoms. Higher levels of both tonic (skin conductance level, nonspecific skin conductance response rate) and phasic (number of skin conductance orienting responses) activity were associated with more negative symptoms and with a combination of poorer social and occupational outcome at 1-year follow-up. This pattern was seen in both male and female patients, and in older and younger patients. Results are interpreted as suggesting that high levels of arousal and overreactivity to the environment may interfere with efficient cognitive processing in schizophrenia, contributing to poor outcome, and that negative symptoms might partially serve as a means of coping with overarousal.

Descriptors: Schizophrenia, Electrodermal activity (EDA), SCOR, EDA responders/nonresponders, Outcome in schizophrenia

Outcome is a central issue in the study of schizophrenia. Despite extensive research conducted to identify consistent predictors of good or poor outcome, poor consensus exists in the literature. Lack of consensus may be due to lack of standardized sample selection criteria, retrospective design, varied definitions of outcome, and the heterogeneity of patient populations (Westermeyer & Harrow, 1988), and to the fact that there are several domains in which outcome can be assessed, such as functional outcome (social relations, employment), symptomatic outcome, and duration of hospitalization (Bland, 1982; Strauss & Carpenter, 1972, 1974). Different aspects of outcome may reflect different biological, psychological, and social processes that may be largely independent despite bearing some relationship to one another (Nuechterlein et al., 1992; Strauss & Carpenter, 1974).

A number of variables in a number of different domains have been identified as possible predictors of outcome (e.g., premorbid adjustment, age of onset, gender). Psychophysiological variables, particularly electrodermal variables, have also been identified as possible predictors of outcome. Two prominent electrodermal abnormalities have been identified in schizophrenia. The first concerns skin conductance orienting responses to mild innocuous stimuli (e.g., moderately intense tones without task significance). It has frequently been reported that between 40% and 50% of schizophrenic patients (termed nonresponders) do not exhibit these responses to mild novel innocuous tones, compared with approximately a 10% rate of nonresponders in normal subjects (Bernstein et al., 1982; Dawson & Nuechterlein, 1984; Gruzelier & Venables, 1972; Öhman, 1981). The second abnormality involves a subgroup of patients who are responders who evidence abnormally high tonic arousal, indicated by a raised skin conductance response rate.) and phasic (number of skin conductance orienting responses) activity were associated with more negative symptoms and with a combination of poorer social and occupational outcome at 1-year follow-up.
conductance level, an elevated frequency of nonspecific skin conductance responses, and an abnormally slow decrease in skin conductance level across a test session (Dawson & Nuechterlein, 1984; Öhman, 1981). The two types of electrodermal abnormalities have been related to symptomatic and functional outcome in schizophrenia in concurrent and predictive analyses.

Electrodermal Activity and Symptomatic Outcome
Both high and low levels of electrodermal activity have been associated with poor symptomatic outcome. In particular, nonresponding to innocuous nontask stimuli and low levels of tonic activity primarily among chronic patients have been associated with the concurrent presence of negative symptoms (Bernstein et al., 1981; Straube, 1979). Fuentes, Merita, Miquel, and Rojo (1993) reported that increased global negative symptoms were associated with lower values of tonic electrodermal activity as well as nonresponding. Kim, Shin, Kim, Cho, and Kim (1993) found both positive and negative symptoms among chronic patients to be more severe among nonresponders. Alm, Lindstrom, Öst, and Öhman (1984) and Katzanis and Iacono (1994) obtained largely similar findings. Consistent with these studies that measured electrodermal activity and symptoms concurrently, Hultman et al. (1996) found that patients who were nonresponders and who were lower in tonic measures of electrodermal activity had longer hospital stays and shorter times to relapse, a finding particularly marked in their younger patients.

However, other investigators have found that higher levels of electrodermal activity were concurrently associated with higher levels of symptoms or longer hospital stays in schizophrenia (Frith, Stevens, Johnstone, & Crow, 1979; Straube, Wagner, Foerster, & Heiman, 1989; Zahn, Carpenter, & McGlashan, 1981). In more recent studies, Fuentes et al. (1993), in addition to finding that negative symptoms were concurrently greater among nonresponders, also found that some positive symptoms were greater among responders. Brekke, Raine, Ansel, Lencz, and Bird (1997) reported higher levels of tonic activity and phasic responding to be positively correlated with symptoms concurrently and Brekke, Raine, and Thomson (1995) found them to be predictive of greater disorganized symptoms at a 6-month follow-up. In an earlier article with a subset of young, recent-onset patients from the current project, Dawson, Nuechterlein, Schell, and Mintz (1992) reported that high levels of both tonic and phasic activity were concurrently associated with high levels of both positive and negative symptoms at an initial outpatient test. They also reported that high inpatient levels of electrodermal activity were predictive of greater persisting symptoms at the initial outpatient test approximately 3 months later.

These studies examining electrodermal activity while at rest and in response to nontask orienting stimuli or simple task stimuli are consistent with findings obtained when activity has been recorded while patients were socially interacting with relatives. Sturgeon, Turpin, Kuipers, Berkowitz, and Leff (1984) and Tarr and Barrowclough (1989) reported that higher levels of electrodermal activity were associated with greater relapse rates over a 9-month and 2-year period, respectively.

Electrodermal Activity and Social and Employment Outcome
The electrodermal activity correlates and predictors of functional outcome have been less well studied than have symptomatic correlates and predictors. Öhman et al. (1989) reported that skin conductance nonresponding and lower levels of tonic activity taken at the beginning of a follow-up period predicted poor social and employment outcome over a 2-year period in a subgroup of male schizophrenic patients. The participants included both inpatients and outpatients with varying levels of chronicity. Their outcome criteria combined the employment and social-contact outcome criteria developed by Strauss and Carpenter (1974) into one outcome index. To have a “good” outcome, patients had to simultaneously have at least a minimal social life (meet with friends at least once a month) and had to be employed or enrolled in school at least on a part-time basis. Consistent with these findings, Katsanis and Iacono (1994), who measured electrodermal activity and occupational functioning concurrently in their sample of chronic patients, reported that low skin conductance level and faster habituation to a set of loud tones were associated with poorer occupational functioning, and Brekke et al. (1997), also measuring electrodermal activity and functional state concurrently, reported poorer outcome among participants with lower levels of resting arousal and fewer orienting responses.

Conversely, Wieselgren, Öhlund, Lindström, and Öhman (1994), using an identical methodology to that used by Öhman et al. (1989), reported an opposite relation for female schizophrenic patients, with high tonic electrodermal activity predicting poor social and work outcome.

A number of individual difference factors may affect electrodermal activity in normal subjects and schizophrenia patients, such as gender and age (Boucsein, 1992), degree of chronicity (Kelly & Nuechterlein, 2001), medication (Kelly & Nuechterlein, 2001; Schnur, 1990), and symptomatic status at the time of testing (Dawson, Nuechterlein, Schell, Gitlin, & Ventura, 1994) and these may also affect symptomatic or functional outcome in schizophrenia (for a review, see Green, 2001). These factors may also affect the relationship between electrodermal activity and outcome. For instance, as mentioned, Öhman et al. (1989) and Wieselgren et al. (1994) found opposite relationships of skin conductance orienting responsiveness/nonresponsiveness with functional outcome using male and female patients, respectively, and Dawson, Nuechterlein, Schell, and Mintz (1992) found that high levels of tonic and phasic activity predicted poor symptomatic outcome for male, but not female, patients.

Of the studies cited above, most have included patients with varying degrees of chronicity or durations of illness, with varying medication status, and in various symptomatic states. Investigators who have found outcome to be poorer among hyperaroused nonresponders have generally (but not always) worked with older, more chronic patients and have suggested that nonresponding is associated with poor outcome because it is indicative of a reduced ability to allocate attentional resources to environmental stimuli or to a broader association between nonresponding and hypofrontality (Bernstein et al., 1982; for a review, see Kelly & Nuechterlein, 2001). Investigators who have found hyperaroused responders to have poorer outcome have generally (but not always) worked with younger patients, and have interpreted their findings as indicating that autonomic hyperreactivity may constitute a vulnerability characteristic for schizophrenia, and that states of autonomic hyperarousal may interact with environmental stressors in a way that produces an inability to focus attention on relevant as opposed to irrelevant environmental stimuli (Dawson & Nuechterlein, 1984; Nuechterlein & Dawson, 1984). As a result these investigators posit that hyper-
Electrodermal predictors of outcome in schizophrenia

It seems likely that both extremes of electrodermal activity in patients with schizophrenia (those hypoaroused and nonresponsive relative to normal controls and those hyperaroused relative to normal controls) may predict poor outcome. Whether a given study finds nonresponders or responders to have poorer outcome will depend upon the relative numbers of these two extreme groups in the patient sample, and thus on whether the sample of patients as a whole is less or more responsive and aroused than normals. Most of the studies cited above examining the relationship between electrodermal activity and outcome did not report data on normal controls. However, interestingly, Wieselgren et al. (1994), who found that patients with poor functional outcome had higher tonic activity and more skin conductance orienting responses than patients with good outcome, also found that the poor outcome patients had higher tonic activity and more frequent responses than normals, whereas the good outcome group did not differ from normals. Their patient group as a whole appears to have had higher tonic levels and was not less responsive in terms of skin conductance orienting responses than normals. Zahn et al. (1981), who found higher levels of tonic electrodermal activity and heart rate to be predictive of poor symptomatic outcome, also studied patients who as a whole were higher than controls on two of three autonomic arousal measures (heart rate and nonspecific skin conductance responses). Conversely, Öhman et al. (1984), who reported poorer functional outcome among nonresponders, had a sample of patients who were much more likely to be nonresponders than were controls (59% vs. 7%) and who as a whole appear to have been lower in skin conductance level.

The purpose of the present study was to determine the relationship between electrodermal activity and subsequent functional outcome in a group of young, recent-onset schizophrenic outpatients. Because the presence of negative symptoms has often been associated with poor functional outcome (Crow, 1980; Fenton & McGlashan, 1994; Pogue-Geile & Harrow, 1985), negative symptoms were also examined at follow-up. In this report, we adopted the combination of work and social outcome used by Öhman et al. (1989) as an index of functional outcome in order to parallel their analyses and used scores from the Scale for the Assessment of Negative Symptoms and the Anergia factor from the Brief Psychiatric Rating Scale as indices of negative symptoms.

We have previously found (Schell, Dawson, Nuechterlein, Subotnik, & Ventura, 2002) that these young, recent-onset patients were, as a group, higher in tonic electrodermal activity as outpatients than are normal controls, and that this heightened tonic activity was observed only among skin conductance orienting responders, whereas nonresponder patients did not differ from controls. We were also aware that in a group of patients largely overlapping with those discussed in the present study, nonresponsiveness was equally common among patients and controls (Schell et al., 2002). We have also previously reported that with these young, recent-onset patients, higher levels of electrodermal activity were predictive of higher levels of symptoms (Dawson, Nuechterlein, Schell, & Mintz, 1992). Therefore, we predicted that among these patients responder schizophrenics with higher levels of tonic activity would have higher negative symptom levels and poorer functional outcome at follow-up.

One advantage of studying recent-onset schizophrenia outpatients is that they do not suffer from the confounding effects of a long history of medication and/or institutionalization. Another advantage is that, as outpatients, they are typically relatively stable in their clinical symptoms at baseline assessment and mostly free from severe psychotic symptoms. A final important advantage of studying the present group of patients is that they were taking a standardized type of antipsychotic medication and were, at the time of testing, on a similar maintenance dosage. Thus, many of the factors that may introduce variability into outcome and obscure the relationship between electrodermal activity and outcome were minimized in this study.

**Method**

**Participants**

Participants were 78 schizophrenia patients and 36 demographically matched normal controls who were included in Sample 1 of the Developmental Processes in Schizophrenic Disorders project, which involves a series of longitudinal follow-through studies of the early phases of schizophrenia (Nuechterlein et al., 1992). All participants gave informed consent for this particular study, and informed consent procedures and all research methods were approved by the Human Subject Protection Committee of the University of California, Los Angeles (UCLA).

The patient and normal groups were predominantly male (85% and 72%, respectively), and predominantly Caucasian (88% and 92%), with an average age of 23.4 years (SD = 4.3) and 24.4 years (SD = 3.8) and average years of education of 12.4 (SD = 1.8) and 13.4 (SD = 1.6). All patients received a diagnosis of schizophrenia (N = 68) or schizoaffective disorder, mainly schizophrenic (N = 10), using Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978), with their first psychotic episode within 2 years before entry into the longitudinal study. DSM-III-R and DSM-IV diagnoses were schizophrenia (N = 51), schizoaffective disorder (N = 6), or schizophreniform disorder (N = 21). For 61 patients the episode upon which they entered the study was their first episode (37 diagnosed with schizophrenia, 5 with schizoaffective disorder, and 19 with schizophreniform disorder) and for 17 patients it was a later episode (14 with schizophrenia, 1 with schizoaffective disorder, and 2 with schizophreniform disorder). Other inclusion and exclusion criteria for patient and normal participant selection can be found in Nuechterlein et al. (1992). All patients from this project for whom electrodermal data were available at the initial outpatient test and for whom social and employment outcome data were available at 1-year follow-up and all controls for whom electrodermal data were available at the initial outpatient test and 1-year follow-up were included in these analyses.

**Overall Design**

Patients were treated at the UCLA Aftercare Research Program, using a common starting dosage of 12.5 mg of injectable fluphenazine decanoate (Prolixin) every 2 weeks as soon as their clinical state stabilized. Dosage was decreased if intolerable side effects occurred and increased as clinically indicated if significant symptoms recurred. At the time at which the primary electrodermal data reported here were collected at an initial outpatient stabilization point, all but 6 patients were receiving 12.5 mg of injectable fluphenazine. Those 6 patients received doses ranging individually from 5 mg to 15 mg of fluphenazine decanoate. When clinically possible, if the patient was receiving antiparkinson medications with anticholinergic effects, these medications were discontinued for at least 24 h prior to electrodermal testing.
Only 8 patients were receiving such medications at the time of testing. Because the electrodermal measures of these patients did not differ even marginally from those of the remaining patients, their data were retained in the analyses described below. No patients were receiving any other medication with strong anticholinergic properties at the time of initial outpatient testing. Initial stabilization on medication was followed by at least 1 year of neuroleptic treatment. Individual case management, group therapy, and family education were also provided to all participants.

Participants were generally seen in the Aftercare Program at 2-week intervals. A battery of neurocognitive performance, psychophysiological, and other measures was administered on pre-specified occasions throughout the longitudinal procedure. The test occasions included (1) the initial test during inpatient treatment or immediately afterward, (2) a point at which the patient had been clinically stabilized on medication, usually about 3 months after hospital discharge (initial outpatient stabilization), and (3) a point approximately 1 year after the initial stabilization point (1-year follow-up). The time interval between the initial outpatient and follow-up tests was 12.3 months (SD = 1.2). Other tests were triggered by clinical state; these could include a test at a point of symptomatic remission or what appeared to be the best clinical state for the patient, and tests associated with psychotic or nonpsychotic symptom exacerbation or relapse.

Ratings of symptoms were completed every 2 weeks by specially trained case managers using an expanded version of the Brief Psychiatric Rating Scale (BPRS; Lukoff, Nuechterlein, & Ventura, 1986; Overall & Gorham, 1962) to provide monitoring of periods of remission, psychotic exacerbation, and relapse. Strauss/Carpenter Social Contact and Work Outcome ratings (Strauss & Carpenter, 1972) were completed every 3 months by the case managers. When approximately half of the patients had been entered into the study, the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) was added to the assessments done on test occasions. Therefore, for 44 patients, SANS data at the follow-up test were also available. Normal subjects were administered the same battery of tests at intervals comparable to those of patients. Written informed consent was obtained from each participant prior to participation. Participants were also provided with additional information orally to further enhance their understanding of the research project.

### Identification of Clinical States

The biweekly BPRS was used to identify the clinical state of the patients at both the initial outpatient and the follow-up test occasions. Remission was defined as being rated 3 or less (on a scale of 1 to 7) on all items on the standard 18-item BPRS (Overall & Klett, 1972) on the day of testing and on the biweekly BPRS for a period of at least 4 weeks preceding testing. Ratings of 3 or less comprise the nonpathological range of the BPRS (Lukoff et al., 1986; Ventura et al., 1993). For clinical state on the day of electrodermal testing, a psychotic state was defined as having one or more of the three BPRS psychotic items (Unusual Thought Content, Hallucinations, and Conceptual Disorganization) rated 4 or higher. Patients were classified as being in an Other Symptomatic State if they obtained a rating of 4 or higher on any nonpsychotic BPRS item.

The clinical states of the 78 patients at the initial outpatient assessment and at follow-up are shown in Table 1. As can be seen, psychotic symptoms in the clinical range (BPRS item ratings of 4 or above) were experienced by only 14% of patients on the day of the initial outpatient assessment and by 22% on the day of the follow-up assessment.

### Electrodermal Testing Procedures

Electrodermal testing procedures have been fully described elsewhere (Dawson et al., 1994), and recording procedures followed standard methods (see Dawson, Schell, & Filion, 2000); they will only be summarized here. Each test session began with the attaching of recording electrodes, followed by a 5-min rest period and three successive series of tone presentations. The first series measured skin conductance orienting responses to mild nonsignal tones (78 db, 1.0 s duration, 25 ms controlled rise and fall times) presented binaurally through headphones at intervals varying between 20, 25, and 30 s. The first 12 tones were 1000 Hz and the last three were 1200 Hz. These stimulus parameters were chosen to reproduce conditions under which skin conductance orienting and habituation abnormalities have been found previously in patients with schizophrenia (Bernstein et al., 1982; Gruzelier & Venables, 1972). The second series measured skin conductance orienting responses to 12 task-significant tones: The tones were 500 Hz, 1.0 s in duration, and presented monaurally, with participants being instructed to move their eyes toward the direction from which the tone was presented. The third auditory series involved presentation of 12 loud (98 db, 1.0 s duration) white noise bursts.

### Electrodermal and Outcome Variables

Three electrodermal summary variables were examined. These data were available for all 78 patients. The operational definitions of these variables are largely as found in Dawson et al. (2000). They were:

1. Nonspecific skin conductance responses: the average number of nonspecific skin conductance responses (0.05 μS or greater) per minute across the resting phase and during the intertrial intervals of the three stimulus sequences.
2. Skin conductance level: the average log skin conductance level in microSiemens during the experimental session, taken by averaging log skin conductance level during the resting phase (the average of the minute-by-minute levels read during the resting phase) and the log skin conductance level values obtained during the three auditory series. For each auditory trial series the average of the log skin conductance level values at stimulus onset were obtained.

<table>
<thead>
<tr>
<th>Clinical State Initially and at Follow-Up</th>
<th>Initial outpatient test</th>
<th>Follow-up test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully remitted</td>
<td>19 (24%)</td>
<td>29 (37%)</td>
</tr>
<tr>
<td>Symptom free on day of test</td>
<td>26 (33%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Psychotic state</td>
<td>11 (14%)</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Other state</td>
<td>22 (28%)</td>
<td>21 (27%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Fully remitted: rating of 3 or less on all 18 standard BPRS items on day of test and for at least 1 month previously.

Symptom free on day of test: rating of 3 or less on all 18 standard BPRS items on day of test but not for 1 month previously.

Psychotic state: obtained rating of 4 or greater on at least one BPRS psychotic item (Unusual Thought Content, Hallucinations, or Conceptual Disorganization).

Other symptomatic state: obtained ratings of 4 or higher on one or more BPRS nonpsychotic items.

### Electrodermal Summary

<table>
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<tr>
<td>Nonspecific skin conductance responses</td>
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</tr>
<tr>
<td>Skin conductance level</td>
<td>The average log skin conductance level in microSiemens during the experimental session, taken by averaging log skin conductance level during the resting phase (the average of the minute-by-minute levels read during the resting phase) and the log skin conductance level values obtained during the three auditory series. For each auditory trial series the average of the log skin conductance level values at stimulus onset were obtained.</td>
</tr>
</tbody>
</table>
3. Number of orienting responses: the total number of skin conductance responses elicited by the first 12 tones during the nontask series. In addition to treating number of responses as a continuous variable, we also (following Öhman et al., 1989) classified participants as Responders (number of responses >0) or Nonresponders (number of responses = 0).

Four outcome variables were examined, obtained at 1-year follow-up. They were:

1. Strauss/Carpenter Social Contact Outcome: a rating from 0 to 4 assessing for the preceding 3 months how often a patient meets with friends; 0 = does not meet with friends at all; 1 = does not meet with friends except “over the back fence;” at work, or at school; 2 = meets with friends about once a month; 3 = meets with friends two or three times a month; 4 = meets with friends on the average at least once a week. Strauss/Carpenter data were available at follow-up for all 78 patients.

2. Strauss/Carpenter Work Outcome: a rating from 0 to 4 assessing employment over the preceding 3 months, including “employment” as a student; 0 = no useful work; 1 = employed less than half the time in the last 3 months; 2 = employed part time or full time about half the time in the last 3 months, 3 = employed more than 1.5 months, but not continuously; 4 = employed continuously.

3. The BPRS factor score of Anergia, consisting of the sum of the item scores for Emotional Withdrawal, Motor Retardation, Blunted Affect, and Disorientation (Guy, 1976). BPRS scores at the 1-year follow-up point were available for 75 patients.

4. SANS score: the total of the subscales for Affective Blunting, Alogia, Avolition/Apathy, and Anhedonia/Asociality. SANS scores were available for only 44 patients at follow-up, as the SANS was added as a supplemental measure of negative symptoms during the course of this longitudinal study.

Results

Functional Outcome

Good versus poor functional outcome groups. Following the approach of Öhman et al. (1989), the most similar prior study, we divided patients into those who showed both good social outcome and good work outcome at the 1-year follow-up assessment and those who did not. Good social outcome was defined as a score of 2 or above on the Strauss-Carpenter Social Contact scale and good work outcome was defined as a score of 2 or above on the Strauss-Carpenter Work Outcome scale. Thus, consistent with Öhman et al. (1989), to be classified as having good functional outcome, a patient both had to meet with friends at least once a month and had to be able to work at least part time the majority of the 3 months preceding the follow-up test. Interestingly, social and work outcome scores had a negligible correlation at follow-up ($r = .08, df = 76$). Seventy-two percent of the patients had good social outcome whereas only 37% had good work outcome. When the dual criteria were employed, 19 patients (24%) were found to have both good social and work outcome (the good functional outcome group), whereas 59 patients (76%) did not, having either poor social outcome, poor work outcome, or both (the poor functional outcome group).

The good and poor functional outcome groups did not differ initially or at follow-up on the BPRS Thought Disturbance factor (consisting of items for Unusual Thought Content, Grandiosity, Hallucinations, and Conceptual Disorganization) or on the BPRS 18-item total score. Means for Thought Disturbance were 1.26 for the good outcome group and 1.29 for the poor outcome group initially and 1.53 and 1.56 for good and poor outcome groups, respectively, at follow-up, and means for the total BPRS score were 25.16 and 26.39, respectively, initially and 28.32 and 31.19 at follow-up. Psychotic symptoms were thus not prominent at either time point, and the failure of the poor functional outcome group to function better socially and/or occupationally cannot be laid to a global failure to respond to treatment. The outcome groups also did not differ significantly with respect to gender, age, or first versus later episode status (see Table 2).

Electrodermal predictors of functional outcome. The good and poor functional outcome groups were compared on electrodermal variables obtained at the initial outpatient test approximately 1 year before the outcome assessment: the number of nonspecific skin conductance responses and skin conductance level, which reflect tonic arousal, and the number of orienting responses, which reflects responsiveness to innocuous nontask related stimuli in the environment. These electrodermal variables are generally reported to be positively intercorrelated, with participants higher in tonic arousal showing greater responsiveness as well (Dawson et al., 2000). In this group of patients, these variables were all significantly intercorrelated: $r$ (number of nonspecific responses, skin conductance level) = .61, $r$ (number of nonspecific responses, number of orienting responses) = .72, $r$ (skin conductance level, number of orienting responses) = .55, all $df$s = 76, all $p$s < .01.

To determine which if either of our two functional outcome groups differed in tonic or phasic electrodermal activity from normal controls, we compared both outcome groups to the normal controls on responder/nonresponder status and on nonspecific responses, the tonic arousal variable best distinguishing the two functional outcome groups (see Table 2). $\chi^2$ analyses indicated that neither outcome group differed from the control group in percentage of nonresponders. Dunnett’s tests revealed that the poor outcome group had a significantly higher number of nonspecific skin conductance than the controls, $t = 3.12, df = 111$, $p < .01$, whereas the good outcome group did not differ from the

| Table 2. Functional Outcome Group and Control Group Means and Standard Deviations on Initial Age, Gender, Episode, and Electrodermal Variables, Anergia, and SANS at Follow-Up |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Good outcome    | Poor outcome    | Control         |
| N                               | 19              | 59              | 36              |
| Male/female                     | 15/4            | 51/8            | 26/10           |
| Age (years)                     | 23.32 (4.07)    | 23.47 (4.38)    | 24.4 (3.80)     |
| First/later episode             | 16/3            | 45/14           |                 |
| Nonspecific skin conductance    | 0.49 (0.70)     | 2.05 (2.12)     | 0.87 (0.97)     |
| responses (per minute)          |                 |                 |                 |
| Skin conductance level          | 0.61 (0.18)     | 0.76 (0.23)     | 0.69 (0.18)     |
| (log microSiemens)              |                 |                 |                 |
| Number of orienting responses   | 0.68 (1.49)     | 1.97 (1.94)     | 1.31 (1.47)     |
| SANS                            | 5.10 (2.51)     | 10.50 (4.70)    |                 |
| Anergia                         | 1.42 (0.48)     | 1.81 (0.90)     |                 |
controls. The poor outcome group thus shows electrodermal hyperarousal relative to normal controls (see Table 2).

Significant outcome group differences were found for all three electrodermal variables (see Table 2). Good functional outcome patients had fewer nonspecific skin conductance responses than poor functional outcome patients at the first outpatient test, \( t = 3.13, df = 76, p < .003 \), lower skin conductance levels, \( t = 2.74, df = 76, p < .01 \), and fewer orienting responses, \( t = 2.64, df = 76, p < .01 \).

To determine the relative predictive power of the three electrodermal variables and to investigate whether they discriminated good from poor outcome patients differentially depending upon gender, age, and first episode/later episode status, we centered all variables using the method of Kraemer and Blasey (2004) and entered the electrodermal variables, gender, age, first versus later episode information, and the nine two-way interactions of the gender, age, and episode variables with the electrodermal variables into a logistic regression analysis. To arrive at the most parsimonious predictive model, interactions that were clearly nonsignificant were dropped from the model, basing the decision to eliminate interactions on a series of omnibus tests, each of which evaluated the three interactions of each electrodermal variable with the three demographic variables as a set to reduce the number of statistical tests.

The variables remaining in the model were nonspecific skin conductance responses (log likelihood ratio \( \chi^2 = 4.65, df = 1, p < .04 \)) and the interaction between number of orienting responses and age (log likelihood \( \chi^2 = 5.84, df = 1, p < .02 \)). The interaction reflects the fact that the number of orienting responses discriminated the outcome groups highly significantly among subjects below the median age of 22.0 years, \( t = 2.84, df = 38, p < .01 \); means .30 for the good outcome group and 2.17 for the poor outcome group, but did not discriminate the groups among subjects above the median age, \( t = 0.37, df = 38, p = 1.22 \) and 1.48, respectively. Gender and first versus later episode status did not interact with the electrodermal variables in predicting outcome.

Although the electrodermal variables obtained at the outpatient stabilization test were the primary focus of this study, these same variables were also recorded as part of the initial inpatient evaluation and at the 1-year follow-up test for most patients. Because the findings of Ohman et al. (1989) were based on an inpatient assessment and were in the opposite direction as those from our outpatient assessment, we also compared the good and poor functional outcome groups on our electrodermal variables obtained during the inpatient test. None of these variables differed significantly between the outcome groups. Moreover, although the number of nonspecific skin conductance responses and skin conductance level obtained at follow-up continued to differentiate the groups, with higher arousal being seen in the poor outcome group, the differences did not reach as high a level of significance as did the differences obtained from the first outpatient test, and at follow-up the number of orienting responses did not significantly differentiate between the groups.

**Skin conductance orienting responder versus nonresponder status.** In keeping with Ohman et al. (1989), we examined the relationship between good versus poor functional outcome and skin conductance orienting responder versus nonresponder status. Responders were those who produced at least one skin conductance orienting response to the first 12 tones in the innocuous tone series at the initial outpatient test; nonresponders were those who demonstrated no orienting responses during these tones. Of the 78 patients, 48 were responders and 30 were nonresponders. A \( \chi^2 \) test revealed a significant relationship between good versus poor functional outcome and responder versus nonresponder status, \( \chi^2 = 9.53, df = 1, p = .002 \); 12\% (6 of 48) of responders were in the good functional outcome group and 88\% (42 of 48) were in the poor outcome group, whereas 43\% (13 of 30) of nonresponders were in the good outcome group and 57\% (17 of 30) were in the poor group. Of patients with good outcome, 68\% were nonresponders and 32\% were responders.

In this sample of patients, stability in responder versus nonresponder status over the 1-year follow-up period based on number of orienting responses to the innocuous stimuli was 64\%, \( \kappa = .28, p < .01 \) (Schell et al., 2002); 39\% were responders both at the initial outpatient test and at follow-up, 25\% were stable nonresponders, and 35\% were responders on one occasion and nonresponders on the other. To evaluate the importance of stability of responding/nonresponding, stable nonresponders, stable responders, and patients unstable in classification were compared for outcome status. Electrodermal data were available for 65 of the 78 patients at both time points. Of the 18 stable nonresponders, 9 (50\%) had a good functional outcome; of the 21 unstable responder status patients, 5 (24\%) had a good functional outcome; and of the 26 stable responders, 3 (12\%) had good functional outcome, \( \chi^2 = 8.24, df = 2, p < .02 \). Clearly, functional outcome is best among stable nonresponders.

**Negative Symptom Outcome**

Correlations between electrodermal variables and negative symptom outcome variables. We next examined the relationship between initial outpatient electrodermal variables and indicators of negative symptoms at follow-up. The BPRS Anergia factor score at follow-up was significantly positively correlated with all three electrodermal variables (\( r = .24, .34, \) and .49 for skin conductance level, number of nonspecific skin conductance responses, and number of orienting responses, respectively, \( df = 73, p < .05, .01, \) and .01). Following the same procedures as for functional outcome, we entered the three electrodermal variables and gender, age, and episode and their interactions with the electrodermal variables into a multiple regression analysis to predict Anergia at follow-up. The only variable selected was the number of orienting responses, \( F = 22.54, df = 1, 73, p < .001 \).

SANS global scores were also significantly positively correlated with initial skin conductance level, nonspecific skin conductance responses, and number of orienting responses, \( r = .34, .47, \) and .34, respectively, \( df = 42, p < .05, .01, \) and .05. When the three electrodermal variables, gender, age, episode, and their interactions with the electrodermal variables were entered into a regression analysis to predict SANS at follow-up, variables selected were nonspecific skin conductance responses, \( F = 10.88, df = 1, 41, p < .001 \), and gender, \( F = 4.62, df = 1, 41, p < .04 \). Women had lower SANS scores than men, \( t = 2.28, df = 42, p < .03 \). Gender, age, and the episode status variable did not interact with the electrodermal variables in the prediction of Anergia or SANS scores.

Although the number of orienting responses and nonspecific skin conductance response values obtained at follow-up continued to correlate significantly positively with SANS and BPRS Anergia scores at follow-up, the correlations were generally not as high as those of the symptom measures with the initial outpatient electrodermal variables.
Anergia and SANS scores at follow-up differed significantly between good and poor functional outcome groups (see Table 2), with the poor outcome group having higher scores. For Anergia, $t = 2.47$, $df = 76$, $p < .02$, and for SANS, $t = 3.47$, $df = 42$, $p < .01$.

**Responder versus nonresponder status.** $T$ tests were carried out comparing electrodermal responders and nonresponders to the innocuous tones with respect to the BPRS Anergia factor scores and SANS global scores at follow-up. Consistent with the correlation observed between the number of orienting responses and negative symptoms, responders had significantly higher Anergia factor scores than nonresponders; means were $2.14$ ($SD = 1.09$) and $1.61$ ($SD = .63$), $t = 2.44$, $df = 73$, $p < .02$. Responders also had significantly higher SANS scores at follow-up than did nonresponders; means were $10.62$ ($SD = 5.01$) for responders and $7.33$ ($SD = 3.97$) for nonresponders, $t = 2.32$, $df = 42$, $p < .03$.

**Discussion**

Our findings strongly indicate that, for this group of young, recent-onset schizophrenia patients with medications held relatively constant, heightened electrodermal responsiveness to innocuous stimuli and higher tonic electrodermal arousal were predictive of poorer functional outcome (combined social and work outcome) and greater negative symptoms at 1-year follow-up. Patients with both good social and good work outcome were more likely to be nonresponders and to demonstrate lower skin conductance levels and fewer nonspecific skin conductance responses at their initial outpatient test, and also, although to a lesser extent, at their follow-up test, and did not differ from normal controls on electrodermal variables. Patients with poor outcome, on the other hand, showed higher tonic levels than did controls.

It is noteworthy that electrodermal activity in this study was measured in outpatients while most were free of psychotic symptoms at the stabilized outpatient assessment and the one-year follow-up assessment. Furthermore, these outpatients were on the same type of antipsychotic medication and, at the initial outpatient assessment, generally were prescribed similar maintenance dosages. In contrast to the outpatient test, electrodermal variables measured at an earlier initial outpatient test did not significantly discriminate the two outcome groups, although observed nonsignificant differences were again in the direction of patients with good outcome being less electrodermally responsive and less tonically aroused. The lesser ability of the inpatient electrodermal activity to predict outcome is likely due to the fact that at the inpatient test, the electrodermal measurements are likely to be influenced by the greater variability in symptomatic state and medication status. The best functional outcome was seen among participants who were consistent nonresponders at both the first outpatient test and at follow-up 1 year later.

The same pattern was seen with respect to prediction of negative symptoms. The number of orienting responses, the number of nonspecific skin conductance responses, and skin conductance level at the initial outpatient test were positively correlated with the BPRS Anergia factor score and with SANS total score at follow-up, and skin conductance orienting responders had higher BPRS Anergia and SANS scores than nonresponders. Negative symptoms, which have often been reported to be associated with poor functional outcome (Crow, 1980; Fenton & McGlashan, 1994; Pogue-Geile & Harrow, 1985), were found to be greater for the poor social and work outcome group in the present study.

These findings are consistent with our previous report that high levels of tonic electrodermal activity among a sample consisting primarily of these same patients are concurrently correlated with higher symptom levels (including negative symptoms) and that high levels of inpatient electrodermal activity are predictive of poor symptomatic outcome over a 3-month period (Dawson, Nuechterlein, Schell, & Mintz, 1992). They also concur with those of Katsanis and Iacono (1994), who found higher electrodermal activity to be associated with anhedonia and asociality, but not with those of Bernstein et al. (1981), Fuentes et al. (1993), and Straub (1979), who found higher negative symptoms among less electrodermally active participants, those who are lower in arousal. Our results are also consistent with the functional outcome findings of Weiselgren et al. (1994). In fact, our percentage of good functional outcome patients (24%) is exactly that of Weiselgren et al.

In this study, the better outcome associated with lower levels of tonic and phasic electrodermal activity was generally similar in both male and female patients, in younger and in older patients, and in both first episode and later episode patients. It thus appears to be a very robust relationship in this group of patients.

These results suggest that, when arousal increases well beyond the level needed to initiate attention and problem solving, interference with cognitive processing may begin as the range of attention becomes narrowed and the ability to discriminate between relevant and irrelevant information is impaired (Broadbent, 1971; Dawson & Schell, 2002; Easterbrook, 1959; Gjerde, 1983; Kahneman, 1973; Nuechterlein & Dawson, 1984). We have previously proposed (Dawson et al., 1994; Dawson, Nuechterlein, & Liberman, 1983; Dawson & Schell, 2002; Nuechterlein & Dawson, 1984) that patients with schizophrenia have fragile arousal modulation mechanisms, so that stressors may produce hyperarousal that then causes the patient to further misinterpret stimuli and to interact with the environment in ways that contribute to the return of symptoms, particularly as hyperarousal exacerbates vulnerabilities in the areas of social competence and coping deficits (Dawson, Nuechterlein, & Schell, 1992; Nuechterlein & Dawson, 1984; Nuechterlein et al., 1992). This may be particularly likely in a highly stimulating major urban environment such as that experienced by the patients in the present study.

This formulation is consistent with the suggestion by Brekke et al. (1995) that both disorganized symptoms and continued skin conductance orienting responsiveness are associated with excessive frontaltemporal activation, and with formulations by Bellack (1992) and Brenner, Hodel, Roder, and Corrigan (1992) regarding the role that heightened reactions to social and environmental stimuli may play in social functioning in schizophrenia. Although there is a general view that schizophrenia is associated with lowered activity in the prefrontal cortex (Andreasen et al., 1992; Andreasen, 1999), there is evidence that in the group of patients we studied, electrodermal responders show higher frontal cortical activation than do normal controls, whereas nonresponders show lower levels than controls (Hazzlett, Dawson, Buchsbaum, & Nuechterlein, 1993). Moreover, Callcott et al. (2000, 2003) reported that schizophrenia patients who perform as well as normal controls on working memory tasks show increased prefrontal activation relative to controls, and concluded that abnormalities of the prefrontal cortex in schizophrenia “are not reducible to simply too much or too little
activity but, rather, reflect a compromised neural strategy for handling information mediated by the dorsolateral prefrontal cortex.” (Callicott et al., 2003, p. 2209).

Although increased frontal activity would be expected to produce greater electrodermal responsiveness and higher levels of tonic activity (Boucsein, 1992), hypofrontality may also have the same effect. Thayer (2005), in a review of the role of inhibitory processes in sculpting neural action, points out that the prefrontal cortex exerts inhibitory control over subcortical structures, particularly the amygdala, to modulate emotional responses, including their autonomic nervous system components, and to increase stress tolerance. The failure of such inhibition, according to Thayer, would have marked consequences for behavior and functioning, leading to hypervigilance and a defensive behavioral disposition. In the context of schizophrenia, this would suggest withdrawal and poor functional outcome. LeDoux (1994, 2002), in extensive investigations of neural circuitry involved in fear learning and emotion, also points out that the prefrontal cortex may act on the amygdala to prevent emotional responses when they are no longer useful and to allow cognitive processing to regulate emotional processing. Although we cannot conclusively identify the mechanism for the relationship between heightened autonomic arousal and negative symptoms seen in the present study, we suggest that it might result from patients withdrawing from social interactions and attempting to suppress visible reactions to stimuli because of overreaction and/or defensive responses by others to the patients’ high arousal and overresponsiveness.

Wing (1989) suggested that in some cases negative symptoms might result from attempts by patients to cope with what is for them an overstimulating environment. Green, Nuechterlein, Ventura, and Mintz (1990) and Ventura et al. (2004), studying patients from this same longitudinal project, have suggested that some negative symptoms could result from social withdrawal as a result of oversensitivity to stress or preoccupation with positive symptoms. If so, these negative symptoms during the initial course of schizophrenia may sometimes be so-called secondary negative symptoms rather than the primary negative symptoms that characterize the deficit syndrome (Carpenter, Heinrichs, & Wagman, 1988). Ventura et al. (2004) also point out that in young, recent-onset schizophrenia patients, negative symptoms would not be a result of prolonged exposure to antipsychotic medication or to other aspects of chronicity. Thus, in this group, negative symptoms could more likely be associated with high arousal rather than with low arousal. Our results are consistent with the suggestion of Brekke et al. (1997) that the employment of stress management techniques to regulate autonomic arousal and reactions to stress may be useful in the improvement of social functioning.

Although heightened tonic arousal and electrodermal responsiveness are linked to poor functional and negative symptom outcome in the present population of patients, it may be that both hyperarousal/responsiveness and hypoarousal/nonresponsiveness relative to normal controls may be predictive of poor outcome. It is often thought that there is a subgroup of schizophrenic patients characterized by nonresponsiveness, negative symptoms, cognitive deficits, and poor functional outcome (see the review by Kelly & Nuechterlein, 2001). Such patients are thought to have diminished cognitive processing resources and to be unable to allocate attentional resources to processing environmental stimuli (Bernstein et al., 1982). This pattern, which is descriptive of deficit syndrome (Buchanan et al., 1997; Carpenter et al., 1988; Fenton & McGlashan, 1994) has been linked with hypofrontality (Kelly & Nuechterlein, 2001), as has electrodermal nonresponding (Hazlett et al., 1993; Kelly & Nuechterlein, 2001). However, those conclusions were largely based on samples of older patients further advanced in the disorder and having longer institutionalization histories than the patients of the present study, where deficit syndrome is less common. Such patients are more likely to have negative symptoms arising from biological processes associated with chronicity and possibly also from lack of social stimulation associated with institutionalization than are our young, recent-onset schizophrenia patients, studied as outpatients. Interestingly, Olman et al. (1989), who found that nonresponder first-episode patients had poorer functional outcome than responders, reported that nonresponders were older than responders (mean age = 29.3 years vs. 25.5), and their responder patients appeared to be equivalent in tonic electrodermal activity to controls, whereas the nonresponders were hypoaroused.

The findings that both schizophrenia patients who are hyperaroused with respect to normals (who tend to be younger patients) and those who are hypoaroused (who tend to be older patients) both have poorer functional outcome than do normally aroused patients raises an interesting question. If patients decline in arousal and responsiveness relative to normal controls over time during the first few years of their illness, do the same patients continue to have good versus poor outcome, or does outcome shift with arousal? Is it possible that patients who are initially hyperaroused will decline to normal levels and begin to function at a better level, whereas patients who were initially within the normal range will descend into hypoarousal and function less well? Longitudinal follow-up research extending over a longer period of time will be needed to pursue this issue.

The attempt to identify the relationship between electrodermal responsiveness and tonic arousal on the one hand and symptomatic and functional outcome in schizophrenia on the other exemplifies many of the difficulties often faced by those engaged in clinical research. In most of the earlier studies cited above, researchers had available a very mixed group of patients, with varying gender, age, duration of illness (recent onset vs. chronic), medication status (medicated vs. unmedicated, type of medication, degree of compliance), and/or symptom status at time of testing (in an acute episode and highly symptomatic vs. remitted). Many of these variables may affect functional outcome and most, if not all, may also affect electrodermal activity. They may also affect the relationship observed between electrodermal activity and outcome. The present study has the advantage of having participants who were all recent-onset patients, diagnosed by uniform criteria, seen at twice-weekly intervals, treated with the same medication with a similar starting maintenance dose for which compliance was maximized by using an injectable form, and in a less heterogeneous state with respect to symptom level than has often been the case.

Nearly all previous studies have assessed patients while they were medicated, as did we. However, it seems clear that the patients in the present study were generally less symptomatic than patients in past studies, who were more likely to be assessed while inpatients, or were outpatients with higher levels of chronic symptoms. At the initial outpatient test during which predictive electrodermal activity data were obtained, 86% of our patients were without psychotic symptoms, with no BPRS psychotic item in the clinical range, and the average 18-item BPRS score was for the group was 27.3 (minimum possible score = 18). Interestingly, it was the data obtained during this outpatient test, when symptom levels were low, that were most predictive (compared to data
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