Reduced Regional Brain Glucose Metabolism Assessed by Positron Emission Tomography in Electrodermal Nonresponder Schizophrenics: A Pilot Study

Erin A. Hazlett, Michael E. Dawson, Monte S. Buchsbaum, and Keith H. Nuechterlein

This pilot study examined whether electrodermal nonresponder and responder subgroups of schizophrenic patients differ in regional brain metabolism assessed by Positron Emission Tomography during a continuous performance test. In comparison to both normal controls \((n = 6)\) and responder schizophrenics \((n = 3)\), the nonresponder schizophrenics \((n = 3)\) showed about a 20% reduction in metabolic rate across the entire brain. Nonresponder schizophrenics tended to have lower absolute metabolic rates than responders in lateral and medial frontal, thalamic, and hippocampal areas. Nonresponders also had significantly lower relative metabolic rates in medial frontal and hippocampal areas as well as the right amygdala. These data suggest that electrodermal subgroups of schizophrenics differ in both regionally specific brain metabolic processes thought to be involved in electrodermal activity and in generalized brain metabolism.

One of the most consistent psychophysiological anomalies reported in schizophrenic disorders is a high incidence of skin conductance nonresponders (see reviews by Bernstein et al., 1982; Dawson & Nuechterlein, 1984; Holzman, 1987; Öhman, 1981). Between 40% and 50% of schizophrenic patients fail to exhibit any skin conductance orienting responses (SCORs) to mild stimuli, compared with only 5%–10% of normal controls. Furthermore, the remaining “responder” subgroup usually exhibits tonic electrodermal hyperarousal as indicated by abnormally elevated skin conductance levels and frequency of nonspecific skin conductance responses, whereas the “nonresponder” subgroup exhibits low to normal levels of electrodermal arousal. Unfortunately, the neurophysiological interpretation of these differences is not clear because the neural substrates of electrodermal activity are not well understood at this time.

Early research on the neuroanatomical substrate for the central nervous system control of the skin conductance response in animals implicated several key brain structures (see review by Venables & Christie, 1973). For example, it has been reported that most amygdalectomized rhesus monkeys produced diminished SCORs to tones (Bagshaw & Benzies, 1968; Bagshaw et al., 1965; Pribram & McGuinness, 1975). In addition, Kimble, Bagshaw, and Pribram (1965) found that a lesion in the lateral frontal cortex also markedly attenuated SCORs to initial and novel presentations of stimuli. In the Bagshaw et al. (1965) study, ablation of the hippocampus had no effect on SCORs or habituation. However, in an experiment with cats, Yokota, Sato, and Fujimori (1963) found that stimulation of the hippocampus produced inhibition of skin potential responses. Luria and Homskaya (1970) suggested a complex pathway between frontal cortex and limbic areas that is responsible for the regulation of the SCOR. Furthermore, they suggested the neocortex of the frontal lobes may mediate the highest form of this regulation. Gruzelier and Venables (1972) hypothesized that the skin conductance nonresponder and responder subgroups may have amygdaloid dysfunction and hippocampal dysfunction, respectively. Other key areas that have been implicated include the midbrain and thalamus (Lang, Tuovinen, & Valleala, 1964; Luria & Homskaya, 1970; Venables & Christie, 1973; Wang, 1964).

More recent work has applied the structural brain imaging technique of computed tomography (CT) to the study of the electrodermal nonresponder and responder distinction in schizophrenia. The hypothesis that enlargement of the third and lateral ventricles involves damage to excitatory centers of the autonomic nervous system and is associated with SCOR nonresponsiveness has been tested in several CT studies with varied results. Some studies have examined lateral and third ventricle size determined by CT scans and found no significant differences between SCOR nonresponder and responder schizophrenic subgroups (Alm, Lindstrom, Ost, & Öhman, 1984; Katsanis & Iacono, 1992; Katsanis, Iacono, & Beiser, 1989). Cannon et al. (1988) found a hypothesized association between lowered skin conductance response amplitude in adolescence and enlarged third ventricles in adulthood in a subsample of subjects from the Copenhagen Schizophrenia High-Risk Project. Others, however, have found SCOR responder
**Region of Interest Analysis**

**Cortical Peel Analysis**

- Superior frontal
- Middle frontal
- Inferior frontal

**Region of Interest Analysis**

- Medial superior frontal gyrus (1)
- Medial superior frontal gyrus (2)
- Medial superior frontal gyrus (3)
- Medial superior frontal gyrus (4)
- Medial superior frontal gyrus (5)

**Anterior thalamus**

- Medial thalamus
- Lateral thalamus
- Posterior thalamus

**Superior hippocampus**

**Amygdala**

**Inferior hippocampus**

**Midbrain**
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schizophrenics have significantly greater third ventricle width than nonresponder schizophrenics when measured cross-sectionally in adulthood (Schnur et al., 1989). One study to date (Raine, Reynolds, & Sheard, 1991) used magnetic resonance imaging to examine the neuroanatomical basis of electrodermal orienting in a group of normal control subjects and found that SCOR activity was associated with the size of both prefrontal and temporal structures.

The purpose of the present pilot study was to apply the functional brain imaging technique of positron emission tomography (PET) to the SCOR nonresponder and responder distinction. PET produces slice images of the metabolic activity of the brain of a cognitively active subject. The present study is the first to relate individual differences in PET-assessed brain metabolic activity with differences in electrodermal activity. The specific goal was to directly compare metabolic functioning of brain structures thought to mediate electrodermal activity in nonresponder and responder schizophrenic subgroups.

We hypothesized that SCOR nonresponder schizophrenics would have a lower rate of metabolic activity than responder schizophrenics in frontal cortex (lateral and medial areas), thalamus, midbrain, and amygdala, which are thought to be components of the neural substrates of electrodermal activity. Because the animal studies are mixed as to whether the role of the hippocampus in electrodermal responsiveness is inhibitory (Yokata et al., 1963) or insignificant (Bagshaw et al., 1965), we considered analysis of this structure exploratory. A nonpsychiatric control group was used only as a descriptive comparison group for glucose metabolic rates because electrodermal data were not available for them.

Method

Subjects

Six schizophrenic outpatients (24 to 30 years of age; M = 27.0; SD = 2.2; 5 men and 1 woman) recruited from an ongoing longitudinal study of recent-onset schizophrenia served as subjects (Nuechterlein et al., 1991). All patients met Diagnostic and Statistical Manual of Mental Disorders (3rd ed.; American Psychiatric Association, 1980) diagnostic criteria on the basis of an expanded version of the Present State Examination (PSE) and were unmedicated at the time of both their PET scan (M = 35.0 weeks off medication, SD = 40.1) and electrodermal test session. PET scans of 6 normal subjects matched for age and sex (M = 40.1; SD = 2.2, respectively) were used as a comparison group. In addition, the control group was matched to the patient group on years of education (M = 14.8, SD = 1.5; M = 13.5, SD = 2.2, respectively). The control subjects did not have electrodermal testing. Control subjects were screened by medical history and physical and neurological examination and were interviewed with a lifetime version of the PSE for history of psychiatric illness in self or first-degree relatives. All subjects were right-handed and were screened for significant head injury, substance abuse, and other confounding medical illness.

Design and Procedure

SCOR procedure. This study is a retrospective pilot analysis of all patients common to studies on the early longitudinal course of schizophrenia at the University of California–Los Angeles and a cross-sectional PET study of schizophrenia at the University of California–Irvine. For obvious fiscal and logistical reasons, not all patients and controls could enter both studies. Patients had repeated testing of SCOR as part of the longitudinal project in which they were participating. For purposes of this study, we selected each patient's off-medication SCOR test session that was closest in time to his or her PET scan. The time elapsing between the SCOR and PET tests was 28 days, 40 days, and 33 months for the 3 nonresponder patients and 2 days, 35 days, and 18 months for the responder patients. The delay between SCOR testing and PET testing is not ideal; however, any unreliability associated with the delay would only work against supporting the hypotheses. Nevertheless, the delay may not be critical given that reasonably high test-retest stability of SCOR nonresponding has been reported for both schizophrenic patients (Spohn, Coyne, Wilson, & Hayes, 1989) and normal college students (Simons, Losito, Rose, & MacMillan, 1983).

Skin conductance was recorded from Beckman silver chloride cup electrodes filled with 0.05-molar NaCl electrode paste. The electrodes were attached to the solar surface of the distal phalanges of the first and second fingers of the patient's left hand using double-sided adhesive collars that permit a contact area of 1 cm in diameter. After a 5-min rest period, a series of 12 mild tones (78 dB (A), 1000 Hz, 1 s in duration, and 25 ms rise time) were presented binaurally through headphones. Patients were instructed before the tone phase that they would hear some tones through the headphones and that they did not have to do anything when they heard the tones. All patients were monitored throughout the session for compliance and movement artifacts.

Each patient was classified as either a SCOR nonresponder or responder based on reactivity to the innocuous tones. Following the standard criteria used in this area of study (Bernstein et al., 1982), a patient was classified a nonresponder if he or she failed to show a response of at least 0.5 μS to the first three innocuous tones. A patient was classified a responder if he or she exhibited a response to any of the first three innocuous tones. On the basis of this criterion, there were 3 nonresponder schizophrenic patients and 3 responder schizophrenic patients. These nonresponder and responder subgroups did not significantly differ on (a) total duration of illness measured from beginning of prodromal signs to the electrodermal test presented here (M = 48 months, SD = 15.9; M = 50 months, SD = 21.9, respectively), (b) age of onset of the illness (M = 22.7 years, SD = 2.5; M = 23.7 years, SD = 4.0, respectively), (c) years of education (M = 13.3, SD = 2.3; M = 13.7, SD = 2.5, respectively), (d) total scores on the 18-item Brief Psychiatric Rating Scale on the day of the PET scan (M = 25.0, SD = 6.6; M = 25.7, SD = 9.0, respectively), or (e) total scores on the 18-item Brief Psychiatr...
Table 1
Absolute Glucose Use (µmol/100 g/min) in Skin Conductance Orienting Response (SCOR) for Nonresponder and Responder Schizophrenics During a Continuous Performance Test

<table>
<thead>
<tr>
<th>Brain region</th>
<th>SCOR nonresponders (n = 3)</th>
<th>SCOR responders (n = 3)</th>
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<tbody>
<tr>
<td></td>
<td>Left</td>
<td>SD</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>19.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Middle frontal</td>
<td>19.3a</td>
<td>4.0</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>19.9c</td>
<td>4.7</td>
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</tbody>
</table>

Cortical peel analysis

<table>
<thead>
<tr>
<th>Region of interest</th>
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<tbody>
<tr>
<td>Medial superior frontal gyrus</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
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<td>Anterior thalamus</td>
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<td>1</td>
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<td>Lateral thalamus</td>
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<td>Superior hippocampus</td>
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<td>Middle hippocampus</td>
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<td>2</td>
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<tr>
<td>Inferior hippocampus</td>
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<td>2</td>
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<tr>
<td>Amygdala</td>
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<tr>
<td>Midbrain</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
</tr>
</tbody>
</table>

1 Significantly different from SCOR responder group by t test, p < .05, one-tailed.  
2 Significantly different from SCOR responder group by t test, p < .05, two-tailed. (Two-tailed tests were used only for exploratory hippocampal comparisons).  
3 No overlap between SCOR nonresponder and responder groups in rank order.  
4 The mean for the normal control group fell between the SCOR nonresponder and responder groups.

Overview of PET fluoro-deoxyglucose (FDG) method. Subjects were injected with the FDG tracer while seated in the sound-attenuated test room. The radio-labelled sugar analog was then taken up by the brain as a tracer of brain metabolic rate for a 32-min period during which the subjects were performing a Continuous Performance Test (CPT). At the end of this period, 80%–90% of the FDG had been taken up by the brain and converted to FDG-6-phosphate. This compound serves as the marker of metabolic rate and remains in place after the uptake period for the 60–90 additional minutes necessary to complete the subsequent scan procedure. Thus, the PET images reflect the metabolic rate during the 32-min uptake period, not the metabolic rate while the subject lies in the scanner.

PET procedure. All subjects performed the degraded-stimulus version of the CPT (Nuechterlein, Parasuraman, & Jiang, 1983) during the 32-min uptake period. These subjects were a subgroup of those described in a previous report (Buchsbaum et al., 1990). This CPT involved watching a series of single, blurred digits (0 to 9), each presented for 40 ms, at a rate of 1 every 2 s. The subjects were asked to respond with a button press each time they detected the digit "0." Schizophrenics show impaired vigilance level on CPT tasks (Nuechterlein & Dawson, 1984). The degraded-stimulus CPT also produces significant increases in electrodement arousal (as indexed by skin conductance level and nonspecific skin conductance response) compared with rest in normal controls (Munro, Dawson, Schell, & Sakai, 1987).

After the uptake period, the subjects were moved to the NeuroECAT scanner and a series of nine horizontal slices at 10-mm increments was obtained (parallel to the canthomeatal line with in-plane resolution of 7.6-mm full-width half-maximum [FWHM] and 9.9-mm resolution in the z axis). The scan slices were transformed to glucose metabolic rate according to the model of Sokoloff (1977). To perform the brain region analysis, each PET slice for each subject was then sorted to match the appropriate level in a stereotaxic atlas by a rater who was blind to both the diagnostic groups and SCOR responder status (Figure 1 shows the 10 atlas levels). For a more extensive description of the PET procedure, see Buchsbaum et al. (1989).

SCOR brain region analysis. On the basis of our review of the literature we selected a priori hypothesized brain regions in the size range assessable by PET. These regions included the lateral frontal cortex, medial frontal cortex, thalamus, hippocampus, amygdala, and midbrain.

The lateral frontal cortex was measured using a cortical peel technique (Buchsbaum et al., 1989). Specifically, the superior frontal, middle frontal, and inferior frontal gyrus areas were averaged across slices for both left and right hemisphere for each of the subjects as shown in Figure 1.

The medial brain regions of interest were assessed in both the left and right hemisphere using a stereotaxic atlas method described elsewhere (Buchsbaum et al., 1989). Five medial regions of the superior
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Figure 2. (Top Row) Histograms of absolute glucose metabolic rates in the left anterior thalamus and right medial superior frontal gyrus [area (3) in Figure 1] are shown for each of the electrodermal nonresponder and responder patients and normal controls. (Bottom Row) Using the same format as above, the relative glucose metabolic rates are shown for the left superior hippocampus and the right amygdala. (R = responder; C = control; NR = nonresponder.)

Frontal gyrus, four regions of the thalamus, three regions of the hippocampus, the amygdala, and the midbrain were assessed for each of the subjects (see Figure 1). Values for all brain regions were expressed as mean absolute metabolic rate (in micromoles glucose/100 g/min). In addition, for the cortical peel analysis, relative metabolic rate values were expressed as (metabolic rate)/(whole brain metabolic rate) and for the region of interest analysis as (metabolic rate)/(whole slice metabolic rate). Relative metabolic rate is particularly important because it corrects for generalized effects and allows inferences about regionally specific brain areas. Last, to determine whole brain glucose metabolic rate, a weighted mean was calculated across each subjects' nine PET slices, which took into account the number of pixels within each slice.

3 Among the schizophrenic patient group (responders and nonresponders combined), whole brain metabolic rates were highly correlated with whole slice metabolic rates (e.g., for the thalamus slice level: \( r = .94, p < .01 \); superior hippocampus slice level: \( r = .98, p < .01 \)). Therefore, relative metabolic rates for the regions of interest would yield very similar results whether the values were expressed as (mean metabolic rate)/(whole brain metabolic rate) or (mean metabolic rate)/(whole slice metabolic rate). To limit the number of comparisons made in the region of interest analysis, we chose the latter of these relative glucose use expressions.

7.6 mm and is an appropriate size. Furthermore, the stereotaxic method we used accounts for individual differences in head height, length, and width. Buchsbaum et al. (1991) has recently measured magnetic resonance imaging films on 29 other schizophrenic patients and specifies confidence limits for the accuracy of our stereotaxic method for the thalamus that are valid and reliable.
All of our hypotheses were tested by computing a series of between-group (nonresponder schizophrenic group vs. responder group) t tests with an alpha level of \( p < .05 \) on the mean absolute and relative metabolic rate values for the selected brain regions in both the left and right hemisphere. Because we hypothesized on the basis of previously established animal work that electrodermal nonresponder schizophrenics would have significantly lower glucose metabolic rates than responders in frontal cortex, thalamus, amygdala, and midbrain, one-tailed tests of significance were used. Given the conflicting findings regarding the role of the hippocampus in skin conductance orienting, exploratory two-tailed t tests were used in these comparisons. For descriptive purposes, we rank-ordered the glucose values for each brain region and determined whether overlap between the nonresponder and responder subgroups occurred and whether the mean of the normal control group fell between that of the two subgroups.

**Results**

As can be seen in Table 1, mean absolute glucose use was lower in the SCOR nonresponder schizophrenic group than in the responder group in 33 of the 34 brain areas we examined (the only exception being the inferior hippocampus in the left hemisphere). The brain regions that reached statistical significance included both left and right areas of the lateral middle frontal gyrus (cortical peel analysis), medial superior frontal gyrus, thalamus (all \( p < .05 \), one-tailed), and hippocampus (\( p < .05 \), two-tailed). Neither the amygdala nor the midbrain differences reached significance for absolute metabolic rate (see Table 1). For all brain areas that were statistically significant, with the exception of the right medial thalamus, there was no overlap between glucose metabolic rate values for SCOR nonresponder and responder subgroups. In addition, the mean for the normal control group fell between that of the two subgroups (see Table 1). Figure 2 illustrates examples of absolute and relative glucose metabolic rate values in key structures for all subjects in the three groups examined.

Because mean absolute glucose metabolism was lower in the SCOR nonresponder schizophrenic group compared with the responder group in all but one of the brain areas we examined, we decided to determine whether whole brain metabolic rate was also lower. The mean for the SCOR responder schizophrenics was similar to that of normal controls (\( M = 21.6, SD = 1.3 \) and \( M = 21.7, SD = 3.3 \), respectively). However, the SCOR nonresponder schizophrenics showed a 20% reduction in metabolic rate across the entire brain compared with responders and controls (\( M = 17.1, SD = 2.9 \)). However, the difference between nonresponder and responder subgroups failed to reach statistical significance.

The pattern for relative glucose use was similar to that observed for absolute glucose; however, overall slightly fewer brain areas reached significance. Specifically, nonresponders, compared with responders, showed significantly lower relative metabolic rate in the following areas: the left and right medial superior frontal gyrus (area 1 in Table 1 and Figure 1), the left anterior thalamus, and 3 of the 4 original areas in the hippocampus (the exception being the left middle hippocampus). In addition, relative glucose metabolism of the right amygdala was significantly lower in the nonresponders compared with the responders (0.79 and 0.98, respectively, \( t(4) = 2.63, p = .029 \)) and the normal control mean fell between the two groups (0.85).

The two schizophrenic SCOR subgroups showed similar task performance (\( \alpha \)) on the CPT. This finding implies that the glucose metabolism differences we observe in SCOR nonresponder and responder schizophrenic subgroups are not merely due to differences in their task performance. The mean \( \alpha \) scores for the nonresponder and responder subgroups were 2.57 (\( SD = 1.25 \)) and 2.53 (\( SD = 0.59 \)), respectively. CPT performance was better in normal controls (\( M = 2.94, SD = .83 \)) compared with both schizophrenic nonresponders and responders, but this difference did not reach statistical significance.

**Discussion**

To our knowledge, the present study is the first to directly compare metabolic activity of brain regions thought to be involved in electrodermal activity in schizophrenic nonresponder and responder subgroups. Consistent with early animal work (Kimble et al., 1965; Venables & Christie, 1973) that suggested that cortical control is likely to be the dominant influence in the regulation of electrodermal activity, we found nonresponders showed decreased glucose use in lateral and medial frontal cortex regions. We also found that the nonresponders had decreased relative glucose use in the right amygdala, which has been reported to be facilitory in SCOR regulation for the majority of subjects on the basis of animal models (Pribram & McGuinness, 1975).

When the absolute and relative glucose analyses are considered together, the areas that are consistently significantly different are located in the superior frontal gyrus and superior and middle hippocampus. As hypothesized, the SCOR nonresponder schizophrenic patients are lower in frontal areas compared with the responders. Kimble et al. (1965) found that rhesus monkeys with bilateral lateral frontal cortex lesions showed diminished skin conductance responding to initial presentations of novel stimuli. In the same study, they found that bilateral medial frontal cortex lesions did not significantly affect skin conductance orienting. However, their medial lesions included the anterior cingulate cortex; whereas our regions of interest in the medial frontal cortex were more localized and were limited to the superior frontal gyrus. Thus, our results, although preliminary, indicate that both lateral and medial regions of the frontal lobe may play an excitatory role in electrodermal activity in schizophrenia.

The results of early animal studies are mixed regarding the role of the hippocampus in SCOR mediation, and our findings do not simplify the picture. Yokata et al. (1963) found that stimulation of the hippocampus in anesthetized cats produced inhibition of skin potential responses. Yet Bagshaw et al. (1965), in their series of studies, demonstrated that monkeys with bilateral hippocampal lesions had normal SCORS. Contrary to both of these early reports, our finding that responder schizophrenic patients have significantly higher glucose metabolic rates in the hippocampus compared with nonresponders suggests a facilitory role in electrodermal regulation.

The extent that one can legitimately infer the role of any brain area in mediating electrodermal activity on the basis of
the present data is limited by the fact that brain metabolism and electrodermal activity were measured on separate occasions and in different stimulus conditions. We found that patients who were skin conductance orienting nonresponders and responders to mild stimuli on one occasion differed significantly and systematically in brain metabolism measures during a CPT on a later occasion. This finding does not necessarily indicate that the brain areas that differed in metabolic activity mediated the differences in skin conductance orienting. The differences between electrodermal nonresponders and responders are likely to be more general than just the fact that one subgroup orient to mild tones and another subgroup does not. Indeed, as stated previously, skin conductance nonresponders and responders usually differ in the tonic electrodermal arousal measures of skin conductance level and the frequency of nonspecific responses. Consistent with this relationship, we found that the electrodermal responders in the present study exhibited significantly more frequent nonspecific skin conductance responses (NS-SCRs) during the resting phase of the electrodermal test occasion than did the nonresponders (4.33 vs. 1.40 NS-SCRs/min, respectively, t(d) = 2.95, p = .042). Thus, nonresponders and responders differ in tonic electrodermal activation and activity, not simply in responsivity to mild tones. Hence, the terms and concepts of electrodermal stabiles and electrodermal labiles may be more appropriate than nonresponder and responder (Dawson, Schell, & Filion, 1990; Schell, Dawson, & Filion, 1988). Also, the skin conductance measures of tonic arousal are increased during performance on the degraded-stimulus CPT, especially in the more electrodermally labile subjects (Munro et al., 1987). Thus, the brain metabolic differences between nonresponders and responders observed during performance of this demanding CPT may be related to a generalized state of activation and not to orienting per se.

A striking feature of the present findings is the generalized nature of the brain metabolic differences between nonresponders and responders. Although significant regional specificity was observed in the superior frontal gyrus, amygdala, and hippocampus with the relative metabolic measure, the absolute metabolic differences between responders and nonresponders were quite generalized throughout the brain. The nonresponders, when compared with the responders, tended to have lower metabolic activity in the whole brain analysis, as well as significantly lower metabolism in the lateral and medial frontal cortex, thalamus, and the hippocampus. The generalized nature of the findings is consistent with the notion that the differences between electrodermal nonresponders and responders are related to general activation. Thus, the results suggest that electrodermal nonresponder and responder schizophrenic differences in regionally specific brain metabolic rates are superimposed on different generalized brain metabolism.

This is a preliminary pilot study that raises more questions than it answers. For example, we do not know if the brain metabolic differences observed between nonresponders and responders are specific to the continuous performance test or if they would also exist during rest or other tasks. Nor do we know whether the brain metabolic differences found between schizophrenic nonresponders and responders are specific to schizophrenia or whether they would also exist, and to the same degree, in normal nonresponders and responders. Nor do we know whether the brain metabolic differences between nonresponders and responders are state-related or trait-related. What we do know is that schizophrenic patients independently identified as electrodermal nonresponders and responders differ in brain metabolism during the continuous performance test. This we believe is an intriguing finding that suggests that electrodermal nonresponder and responder schizophrenic patients may differ in important underlying brain processes and that the electrodermal measures may prove to be useful noninvasive and inexpensive peripheral adjunct indices of these brain processes. Further exploration of the interrelationship of brain metabolism and electrodermal activity during attentional tasks among schizophrenic patients promises to lead to a better integration of neuroscience, cognitive science, and clinical science (Dawson, 1990).
dence of limbic dysfunction. *Journal of Nervous and Mental Disease*, 155, 277–287.


