Attentional and eye tracking deficits correlate with negative symptoms in schizophrenia

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Abstract

Thirty patients with a DSM-III-R diagnosis of schizophrenia were assessed for severity of schizophrenic symptoms using the Brief Psychiatric Rating Scale (BPRS) and were tested on a Continuous Performance Test (CPT) and a smooth pursuit eye tracking task. Negative symptoms were significantly correlated with eye tracking impairment (r = 0.43, p < 0.01) and CPT deficits (r = 0.67, p < 0.001), but performance on neither task was correlated with positive symptoms. CPT performance and eye tracking performance were modestly correlated with each other (r = 0.39, p < 0.01) and CPT performance was found to be a stronger predictor of negative symptoms than eye tracking performance. These data indicate that neurocognitive markers of vulnerability to schizophrenia are associated with negative rather than positive symptoms. © 1997 Elsevier Science B.V.

Keywords: Schizophrenia; Continuous Performance Test; Eye tracking; Attention; Positive and negative symptoms

1. Introduction

Information processing measures such as attentional and eye tracking tasks may represent potential indicators of membership in the schizophrenia spectrum (Siever, 1992) and markers of genetic vulnerability to schizophrenia (Nuechterlein, 1991). Abnormalities on the Continuous Performance Test (CPT) and smooth pursuit eye movement (SPEM) task have been found in schizophrenic patients (Nuechterlein et al., 1986; Holzman et al., 1973), individuals with schizophrenia-related personality disorders (Siever, 1992, 1994; Lenzenweger et al., 1991) and biological relatives of schizophrenic probands (Keefe et al., 1997). Schizophrenic patients have shown deficits on information processing tasks such as eye tracking and continuous performance tests when compared to normals (Asarnow and MacCrimmon, 1978; Holzman et al., 1973; Iacono and Koenig, 1983; Grove et al., 1991; Friedman et al., 1991) and other psychiatric patients (Amador et al., 1991; Cegalis et al., 1983; Cornblatt et al., 1989). Impaired performance on these tests has consistently been found in schizophrenic patients during psychotic states (Asarnow and MacCrimmon, 1981; Walker, 1981) as well as while in remission (Asarnow and MacCrimmon, 1978; Levy et al., 1994; Lenzenweger et al., 1991). Schizophrenic patients have shown deficits in attentional and eye tracking tasks when compared to normals (Asarnow and MacCrimmon, 1978; Holzman et al., 1973; Iacono and Koenig, 1983; Grove et al., 1991; Friedman et al., 1991) and other psychiatric patients (Amador et al., 1991; Cegalis et al., 1983; Cornblatt et al., 1989). Impaired performance on these tests has consistently been found in schizophrenic patients during psychotic states (Asarnow and MacCrimmon, 1981; Walker, 1981) as well as while in remission (Asarnow and MacCrimmon, 1978; Levy et al., 1994; Lenzenweger et al., 1991).
Furthermore, while schizophrenic patients on anti-psychotic medication show some improvement on attentional tasks, their performance remains impaired compared to normals (Epstein et al., 1996; Harvey et al., 1990; Serper et al., 1990; Holzman et al., 1974). These studies suggest that CPT and eye tracking dysfunctions are stable deficits which occur independent of state of illness and are present more often in schizophrenia-spectrum disorders than in other psychiatric illnesses, thus making them potential neurocognitive indicators of schizophrenia-related disorders.

The present study was designed to determine which aspects of the schizophrenia syndrome are most closely related to the neurocognitive deficits measured by the CPT and smooth pursuit eye tracking task. Previously, Nuechterlein et al. (1986) reported a relationship between CPT performance and the severity of the Brief Psychiatric Rating scale (BPRS) Anergia subscale, whereas Strauss et al. (1993) did not find a relationship between attentional deficits on the CPT and BPRS negative symptoms in schizophrenic patients. Using root mean square error (RMS) as a measure of eye tracking performance, Katsanis and Iacono (1991) found a significant correlation between eye tracking impairment and negative symptoms as measured by the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1981). Each of these studies only looked at a single informational processing task. Our own previous work (Keefe, 1990) indicates that CPT and SPEM performance are only modestly correlated in schizophrenic patients, which suggests that there may be an advantage to measuring both variables within the same individuals. Because of the importance of the distinction made between positive and negative symptoms (Crow, 1980; Andreasen, 1982; Strauss et al., 1974), we have, in the current study, examined the correlations of CPT and eye tracking performance with positive and negative symptoms.

2. Methods

2.1. Subjects

The sample consisted of 30 male patients who met DSM-III-R (American Psychiatric Association, 1987) criteria for schizophrenia. Some of these patients participated in studies reported previously from our laboratory (Harvey et al., 1990; Friedman et al., 1995). Relevant demographic information is presented in Table 1. All the patients participated in this study as part of ongoing biological research protocols at the inpatient and outpatient units of the Bronx VA Medical Center and were stabilized on a typical neuroleptic medication for at least 2 weeks before assessment and testing. Twenty subjects were also on anticholinergic medication. Informed consent was obtained from all subjects prior to their participation in the study. Subjects were evaluated for drug and alcohol use; subjects showed no evidence of drug or alcohol abuse within the past year. Patients with other psychiatric or neurologic disorders that could possibly contribute to difficulties on either task were excluded from the study.

Table 1
Demographic characteristics of sample (n = 30)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.13</td>
<td>9.46</td>
<td>25–63</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>12.25</td>
<td>2.05</td>
<td>6–16</td>
</tr>
<tr>
<td>WAIS-R Vocabulary scores</td>
<td>9.47</td>
<td>2.26</td>
<td>6–14</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>7.08</td>
<td>5.23</td>
<td>1–20</td>
</tr>
<tr>
<td>Age of onset</td>
<td>22.58</td>
<td>3.63</td>
<td>18–29</td>
</tr>
<tr>
<td>Total of BPRS positive symptoms</td>
<td>8.80</td>
<td>3.24</td>
<td>3–13</td>
</tr>
<tr>
<td>Total of BPRS negative symptoms</td>
<td>7.37</td>
<td>2.49</td>
<td>3–15</td>
</tr>
<tr>
<td>Clinical global impression (BPRS)</td>
<td>3.91</td>
<td>0.81</td>
<td>2–5</td>
</tr>
<tr>
<td>Phenothiazine medication (dose equivalents)</td>
<td>1095</td>
<td>564</td>
<td>200–2550</td>
</tr>
</tbody>
</table>
All patients were interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS: Endicott and Spitzer, 1978) by two trained raters simultaneously, with the raters generating independent diagnoses that were then presented to a senior clinician for a consensus determination. The reliability of the diagnostic agreement between the raters, based on 179 cases, was good (kappa = 0.89).

2.2. Testing and assessment procedures

2.2.1. Brief Psychiatric Rating Scale

Positive and negative symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) on the day of testing by two raters from a pool of trained assessors. The average reliability of the ratings conducted by this pool on the basis of 1000 overlapping ratings was high (kappa > 0.90). A negative symptom score was formed using the sum of BPRS items measuring emotional withdrawal, blunted affect, and motor retardation. The sum of the ratings of hallucinatory behavior, unusual thought content, and conceptual disorganization formed the positive symptom score. These BPRS scores were formed based on previous groupings of BPRS symptoms (Nicholson et al., 1995; Harvey et al., 1996a,b; Overall, 1974; Nuechterlein et al., 1986).

2.2.2. Wechsler Adult Intelligence Scale-Revised (WAIS-R), Vocabulary subtest

This test was used as an estimate of general verbal intellectual abilities. It was chosen in this study to determine the relationship of CPT and eye tracking performance with levels of general intelligence. The age-corrected scaled score was used to measure performance.

2.3. Continuous Performance Test

The 3–7 version of the Continuous Performance Test (CPT) was performed on all subjects. The 3–7 version, which is a variant of the A–X CPT, has been used extensively in investigations of attentional impairment in schizophrenic patients (Orzack and Kornetsky, 1971; Wohlberg and Kornetsky, 1973; Epstein et al., 1996; Harvey et al., 1996a,b) and has been shown to be psychologically reliable (Cornblatt and Keilp, 1994). Other versions of the CPT, such as the Degraded Stimulus CPT (Nuechterlein, 1983) which produces a higher perceptual processing load and the Identical Pairs version (CPT-IP) (Cornblatt and Erlenmeyer-Kimling, 1985; Erlenmeyer-Kimling and Cornblatt, 1992) which produces an increased cognitive processing load, were not used in this study because they were designed to detect more subtle deficits in subjects who were not yet clinically affected.

A series of 500 white digits in the center of a gray background were presented in a quasi-random sequence on a Compaq portable computer with a Taxan monochrome video monitor. The entire task contained 50 target sequences (a ‘7’ immediately followed by a ‘3’), 50 non-target ‘7’s and 50 ‘3’s followed by a number other than ‘7’. Each number was presented for a duration of 50 ms, with an interstimulus interval of 1.0 s. Subjects pressed a response key whenever they believed a 3–7 sequence had occurred. To ensure that the subject fully understood the nature of the task, a brief training trial was administered and feedback was given to the patient during and immediately following the practice trial when necessary. Performance was measured using the standard performance measures of omission errors and commission errors and signal detection indices, d-prime ($d'$) and beta ($\beta$) (Nuechterlein, 1983). $d'$ is a measure of the subject’s ability to discriminate a signal from background noise, whereas $\beta$ is a measure of response bias: the individual’s tendency to either over- or under-respond on the CPT. $d'$ is typically considered a measure of attentional capacity, while $\beta$ appears more directly related to motivational state (Cornblatt and Keilp, 1994). Furthermore, previous studies of attention suggest that $d'$ is more reliable than $\beta$ (Cornblatt et al., 1989).

2.4. Eye tracking

Eye tracking dysfunction was assessed using an infrared eye tracking system (Gulf and Western Eye Track Model 200 Spectra-Sensors Part No. 719-2000) used in previous work from our
laboratory (Siever et al., 1994; Keefe et al., 1997). An infrared light source affixed to a set of eyeglass frames was securely attached to the subject’s head to minimize head movement artifact and was positioned several millimeters from the surface of one eye, just below its center. Head position was fixed with a chin and head support. The eye tracking trials were run on a Compaq portable computer with a microprocessor that samples up to three channels at 250 Hz.

Both a sinusoidal and a constant-velocity target were presented on a Taxan 720 monitor. For the three sinusoidal target trials, the target traversed 24 degrees of visual angle on a horizontal plane at a velocity of 0.4 Hz. Two of these trials consisted of the following stimulus presentation: a pendulum motion target, which was the letter X moving horizontally across the subject’s visual field (referred to as nonmonitor, pendulum motion target). The first of these trials was used as a practice trial to ensure that subjects understood the task and that adjustment to the task was not mistaken for legitimate eye tracking deficits. The third sinusoidal target trial involved the presentation of a pendulum motion target that changed from X to O in a random, irregular sequence, during which the subject was asked to count the number of target changes (monitor, pendulum motion target). This monitor target was used to motivate the subject’s attentional focus on the eye tracking task. For the fourth trial, the constant-velocity target trial, the target (X only) was presented moving at a constant velocity.

The degree of eye tracking impairment was assessed by two experienced raters who were blind to diagnosis. Raters used global qualitative ratings from 1 (best) to 5 (worst) following exemplars produced by Shagass et al. (1974). Inter-rater reliability was high (ICC = 0.85, df = 1.79, p < 0.0001). In cases of disagreement that were less than 0.5 qualitative rating points, the mean of the two ratings was computed as a consensus score for data analysis. When disagreement was greater than 0.5 qualitative rating points, the ratings were discussed with a third rater and a rating was unanimously agreed upon. A subset of these consensus scores was assessed for reliability with an outside expert (Dr Philip Holzman), which was very high (ICC = 0.96, df = 1.28, p < 0.001).

3. Results

Subjects’ age, level of education and caffeine consumption on the day of testing were not significantly correlated (pearson correlation) with symptom scores and neurocognitive test performance (all rs < 0.18, ps > .05). WAIS-R Vocabulary subtest scores were not significantly correlated with performance on CPT (r = 0.04, ns) or eye tracking (r = 0.1, ns). Number of hospitalizations and age of onset were not significantly related to neurocognitive test performance (all rs < 0.24, ps > 0.1). To test for the possible effects of anti-cholinergic medication on test performance, t-tests were done comparing subjects taking neuroleptic medication plus anti-cholinergic medication (n = 20) with those taking only neuroleptic medication (n = 10). There were no significant differences on any of the reported measures. All demographic data are presented in Table 1.

Table 2 presents the correlations between CPT and eye tracking and clinical symptom measures. CPT errors of omission, errors of commission, and d’, and poor eye tracking, measured by the average of qualitative scores on the constant-velocity trial and two sinusoidal target trials, all correlated significantly with negative symptoms. In contrast, none of these measures were significantly correlated with positive symptoms. Furthermore, none of the CPT or eye tracking measures were significantly related to total BPRS scores. CPT β was not significantly related to either symptom dimension or total BPRS score.

Since there was a significant correlation between eye tracking performance and CPT errors of omission (r = 0.39, p < 0.01) the independent contributions of attentional and eye tracking deficits to negative symptoms were examined using stepwise multiple regression analyses. Results of the regression analyses indicated that only CPT errors of omission contributed unique variance to the prediction of negative symptoms (r² = 0.52, F(2,26) = 15.03, p = 0.0001), while eye
Table 2
Means, standard deviations and correlations of Continuous Performance Testing performance and eye tracking performance with positive, negative and total BPRS symptoms (n=30)

<table>
<thead>
<tr>
<th>CPT variables</th>
<th>Mean (SD)</th>
<th>Positive symptoms (r)</th>
<th>Negative symptoms (r)</th>
<th>Total BPRS symptoms (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors of omission</td>
<td>6.30 (7.19)</td>
<td>0.07</td>
<td>0.67*</td>
<td>0.22</td>
</tr>
<tr>
<td>Errors of commission</td>
<td>3.07 (5.22)</td>
<td>0.02</td>
<td>0.36*</td>
<td>0.05</td>
</tr>
<tr>
<td>d’</td>
<td>3.33 (1.24)</td>
<td>−0.10</td>
<td>0.63*</td>
<td>−0.23</td>
</tr>
<tr>
<td>β</td>
<td>0.33 (0.62)</td>
<td>0.25</td>
<td>0.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Average eye tracking qualitative ratings</td>
<td>2.96 (0.68)</td>
<td>−0.07</td>
<td>0.43*</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*p < 0.001; *p < 0.01; *p < 0.05.

tracking contributed only an additional 4% ($r^2 = 0.56$).

4. Discussion

Correlational analyses revealed a differential relationship of CPT and eye tracking with positive and negative symptoms. Results of this study suggest that poor performances on eye tracking and CPT are related to the severity of negative symptoms in medicated schizophrenic patients, as evidenced by significant correlations in all of the evaluated relationships with the BPRS negative symptoms of emotional withdrawal, blunted affect, and motor retardation. In contrast, eye tracking and CPT performance were not significantly related to the severity of the positive symptoms of hallucinations, delusions, and conceptual disorganization or to total BPRS symptom ratings.

These results support the hypothesis of a relationship between attentional deficits and negative symptoms and are consistent with previous reports suggesting that negative but not positive symptoms are related to cognitive impairment in schizophrenic patients (Johnstone et al., 1978; Green and Walker, 1984; Iacono et al., 1992). The lack of a correlation between WAIS-R Vocabulary subtest scores and CPT and eye tracking performance suggests that poor performance on these attentional tasks is not the result of the generalized deficit often seen in schizophrenic patients (Chapman and Chapman, 1973). Furthermore, the absence of a significant correlation between the WAIS-R Vocabulary subtest and negative and positive symptoms supports the specificity of the relationship reported.

Our results indicate that there is only a modest relationship between performance on the CPT and eye tracking tasks, and that eye tracking performance does not uniquely contribute to the variance in negative symptoms seen in this sample. While it is clear from this and other studies (e.g., Keefe et al., 1997) that CPT and eye tracking measure somewhat different aspects of cognitive dysfunction, the modest correlation of these two measures may result from an aspect of attentional functioning that is a common determinant of both measures. It seems possible that visual attention is required for both tasks and that a deficit in visual attention is associated with negative symptoms. A general attentional impairment may be present prior to the onset of psychosis, and interact with a biological liability to schizophrenia, causing difficulties in processing complex social information (Nuechterlein and Dawson, 1984; Cornblatt and Keilp, 1994). This could lead to more severe negative symptoms, such as emotional withdrawal, in response to difficulties they have processing social information.

There are several limitations to this study. All subjects were drawn from a VA population of chronic schizophrenic patients, which may limit its generalizability to other samples. It is known that more severe negative symptoms may be associated with a more chronic course of illness (Keefe et al., 1987; McGlashan, 1986). Therefore, the same results may not be found in a group of patients with remitting schizophrenia.

In addition, because the qualitative ratings used
as a measure of eye tracking performance in this study are a global assessment of eye tracking, it is unclear what the specific nature of the abnormality is (Friedman et al., 1995). As suggested above, it is possible that the qualitative ratings are measuring a performance deficit which overlaps only partially with that measured by CPT performance. The use of global quantitative measures such as pursuit gain, along with more specific measures of compensatory and intrusive saccades, may provide more information about what aspects of the task are related to the presence of negative symptoms in schizophrenic patients. These same qualitative ratings were not significantly correlated with positive or negative schizotypal symptoms in relatives of schizophrenic patients, but these ratings were shown to have superior discriminating power relative to CPT performance in distinguishing between relatives of schizophrenic patients and control subjects (Keefe et al., 1997). This raises the possibility that qualitative ratings may be detecting a deficit that has a genetic component but is independent of symptomatology.

The results of this study and previous studies looking at eye tracking and CPT deficits in schizophrenia-spectrum disorders suggest that eye tracking deficits, although characteristic of the schizophrenia spectrum, may be relatively independent from symptom expression. Whereas attentional impairment, as measured by CPT performance, appears to be consistently related to negative symptoms. It is possible that both CPT performance and negative symptoms are mediated by a yet undetermined third variable which accounts for the correlation found between the two.

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