Neurophysiological and neuropsychological assessment of recent-onset schizophrenia
Nieman, D.H.

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Neuropsychological and clinical correlates of antisaccade task performance in schizophrenia

DH Nieman\textsuperscript{1,2}, LJ Bour\textsuperscript{1}, DH Linszen\textsuperscript{2}, J Goede\textsuperscript{1}, JHTM Koelman\textsuperscript{1}, BPR Gersons\textsuperscript{2}, BW Ongerboer de Visser\textsuperscript{1}

\textsuperscript{1}Department of Neurology, Clinical Neurophysiology Unit and \textsuperscript{2}Department of Psychiatry, Academic Medical Center, Amsterdam, The Netherlands

Abstract

Objectives: To elucidate pathophysiological mechanisms involved in abnormal antisaccade task performance in schizophrenia by investigating a possible relationship among antisaccade task performance, neuropsychological test results, and symptomatology in a group of young patients with recent-onset schizophrenia; to compare the effects of olanzapine and risperidone on antisaccades and reflexive saccades.

Background: Patients with schizophrenia consistently perform worse than controls on the antisaccade task in which the subject is required to inhibit a reflexive saccade to a suddenly appearing visual target and look in the opposite direction.

Methods: In 37 young (mean age 21 years), medicated patients with recent-onset schizophrenia we assessed antisaccades, reflexive saccades neuropsychological test performance and symptomatology. A subgroup of 18 patients was treated with olanzapine and 15 patients were treated with risperidone. Reflexive-saccade and antisaccade task results were compared with those obtained in 13 control subjects.

Results: The antisaccade error rate was significantly higher in the patients than in the controls. In the patients, poor working memory function was related to increased antisaccade error rate. Severity of disorganization symptoms at intake was related to prolonged mean latency of the correct anti-saccades. Patients on risperidone had a prolonged mean latency in the reflexive saccade task compared with patients using olanzapine.

Conclusions: Abnormal antisaccade task performance is already present in early schizophrenia and may reflect working memory dysfunction. In future studies, medication effects should be considered when interpreting eye movement test results of patients with schizophrenia.
Introduction

Eye movements are studied in schizophrenia because abnormalities may reflect CNS activities and circuitry that are relevant to the neurobiology of schizophrenia (Hutton and Kennard, 1998). Earlier studies demonstrated that reflexive saccades are normal in patients with schizophrenia (Iacona et al, 1981; Levin et al, 12982; Yee et al, 1987). They are elicited by a suddenly appearing visual target that captures attention and triggers a saccade to the target. In contrast, volitional saccades are abnormal. Unlike reflexive saccades, volitional saccades are cognitively demanding and must be elicited by behavioral paradigms. The antisaccade task, originally introduced by Hallet (1978), generates the most frequently observed volitional saccade abnormality in schizophrenia (Crawford et al, 1996; Fukushima et al, 1990). In the antisaccade task, subjects are asked not to look at a suddenly appearing visual target but to make a saccade in the opposite direction at an equal distance of the central fixation point. It has been suggested that the dorsolateral prefrontal cortex is involved in suppressing reflexive saccades, and that the frontal eye fields trigger the correct saccade to the opposite side (Muri et al, 1998). Most eye movement studies in schizophrenia merely have reported abnormalities rather than investigate any relationships between such abnormalities and particular clinical features (Hutton and Kennard, 1998).

Cognitive abnormalities reported in schizophrenia include dysfunctions in working memory, attention, semantic memory retrieval, goal-directed problem solving and motor speed (Grant and Adams, 1996). Working memory is fundamental to the human ability to reason and make judgments that rely on remembered contextual information and is believed to be mediated mainly by the dorsolateral prefrontal cortex (Beardsley, 1997). Attentional dysfunctions appear to be a “trait” marker for schizophrenia, because they are apparent in symptom-free patients (Neuchterlein et al, 1986) and in children at risk of schizophrenia (Neuchterlein 1983). Which cognitive function is mostly drawn on by subjects performing the antisaccade task is uncertain since correlations between this task and a comprehensive neuropsychological test battery are unexplored (Hutton and Kennard, 1998).

The effects of antipsychotic medication on reflexive saccades and antisaccades are still unclear. We treated patients with either olanzapine or risperidone. Because olanzapine has a different receptor binding profile than risperidone, differential effects of olanzapine and risperidone may lead to new hypotheses about the effect of blocking
certain receptors on saccades in schizophrenia.

The first aim of the present study was to elucidate pathophysiologic mechanisms involved in abnormal antisaccade task performance in schizophrenia, by investigating a possible relationship between antisaccade task performance and neuropsychological tests and symptomatology in a group of young patients with recent-onset schizophrenia. The second aim was to compare the effects of olanzapine and risperidone on antisaccades and reflexive saccades in young schizophrenic patients.

Methods

Subjects
Thirty-seven patients with schizophrenia performed the antisaccade task (6 women); their mean age was 21 years ± 3.1 (SD). All patients attended the adolescent psychiatric clinic of the Academic Medical Center, Amsterdam, the Netherlands, for inpatient and outpatient treatment and all satisfied the criteria in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) for the diagnosis of schizophrenia or schizoaffective disorder (n=5). The diagnosis at admission was made in a clinical consensus meeting of three experienced psychiatrists, a research psychologist and two residents with the use of all possible information (e.g., medical records, interviews with patients and parents). Clinical diagnosis was confirmed in all included patients at discharge and follow-up. Exclusion criteria were diagnosis of a primary alcohol- or drug related psychosis, vision disorders, endocrine disease and known neuropsychological impairment due to factors other than schizophrenia (e.g., closed head injury and mental retardation). Thirty-four of these patients were tested with a neuropsychological test battery (three patients refused). All 37 patients were assessed at intake and at the time of testing with the Positive and Negative Syndrome Scale (PANSS, Kay et al, 1987) for the evaluation of symptoms in schizophrenia. The scale is composed of 30 items, each of which is given a score of 1 through 7 according to defined criteria.

Patients were semirandomized for medication; if patients responded well to olanzapine or risperidone and before admission, then medication was continued. Otherwise, patients were randomly allocated to olanzapine or risperidone at admission. Eighteen patients were treated with olanzapine (mean dosage 15.8 ± 4.9 mg) and 15
patients with risperidone (mean dosage 3.9 ± 1.5 mg). One patient was receiving pimozide and one sertindole. Two patients were not compliant for their prescribed medication at the time of testing. Three patients with olanzapine and two with risperidone used an antidepressant (paroxetine) and one patient with olanzapine and two patients with risperidone used antiparkinsonian medication. Mean number of previous psychotic episodes was 0.2 ± 0.47. Mean duration for which the patients had been ill was 19.3 ± 15.1 months, including the prodromal phase. The study was approved by the research and ethics committee of the Academic Medical Center and all patients gave written informed consent. Thirteen healthy controls (6 women) with a mean age of 22.5 ± 4.2 years served as control group for antisaccade task performance. They were matched as a group on age and estimated intelligence.

Eye movement recording

In contrast to earlier studies, in the present study, antisaccades and reflexive saccades were recorded using the double magnetic induction method (Bour et al, 1984), with a high spatial and temporal resolution. The subject’s head was stabilized with a head tie and chin rest in a homogeneous alternating primary magnetic field with a constant amplitude. Horizontal as well as vertical eye positions of the right eye were derived from a secondary magnetic field picked up by a detection coil placed in front of the eye. A gold-plated lens was placed on the right eye after anesthesia with a few drops of oxybuprocaine. The lens generated the secondary magnetic field of which the strength was related to the position of the eye. The average resolution was 5-minute arcs. The visual target was a single, red, 0.5 degree diameter, circular laser-spot of 20 cd/m² luminance, that was projected on the rear of a white translucent screen by means of a mirror device. Before the antisaccade task, the subject was asked to make about 30 reflexive saccades to temporally unpredictable targets randomly located in the horizontal plane between -10 and +10 degrees. In the reflexive saccade task, subjects were instructed to look as quickly and precisely as possible at visual targets wherever they appeared. In the antisaccade task, subjects were told not to look at the appearing target but to look immediately in the opposite direction at an equal distance of the central fixation point. The laser-spot was first projected at gaze straight-ahead position (central fixation point). Then, after a random period between 600 and 1200 msec, the laser-spot was abruptly moved by the mirror, to an eccentric position, located 5 degrees randomly left or right of the fixation point. After two seconds the spot was
projected to the correct antisaccadic eye location (feedback signal). After 300 msec the spot was again projected to gaze straight-ahead position. After several practice trials, about 20 trials were presented to each subject.

Antisaccade task variables were mean error rate, latency of the correct and wrong antisaccades, antisaccade gain, and peak velocity. Reflexive saccade variables were mean latency, gain and peak velocity. All variables were calculated with an interactive computer program written in Matlab (The Math Works, Inc., USA). The antisaccade error rate is the percentage of wrong antisaccades. Only first responses and responses with a latency longer than 100 msec were included. The gain is always positive for the wrong antisaccades, that is, towards the visual target, and negative for the correct antisaccades, that is, away from the target. The peak velocities of reflexive saccades were plotted against the amplitudes for each subject. The velocity-amplitude relationship was expressed with an exponential curve (Smit et al., 1987), and the peak velocities for saccades of different amplitudes were computed from the best-fit logarithm curve. Correct antisaccade velocity-gain for each amplitude was calculated as the ratio of correct antisaccade peak velocity and reflexive saccade peak velocity, based on the exponential fit. A similar calculation was performed for wrong antisaccades.

Neuropsychological test battery
To estimate premorbid intelligence, a composite measure was constructed. In each subject, the level of education of the subjects’ parents was determined along with the subjects’ own level. As an estimate of current intelligence, the following four subtests of the Wechsler Adult Intelligence Scale (WAIS, Lezak, 1995) were administered: for the WAIS Vocabulary subtest the meaning of several words was asked. The WAIS Comprehension subtest consisted of several proverbs and questions about problematic situations. In the WAIS Picture Arrangement subtest several pictures with scenes had to be rearranged to make the most sensible story. Finally, the WAIS Block Design subtest comprises several red and white colored blocks that had to be placed according to an example pattern.

As an estimate of working memory the Subjective Ordering Task (SOT, Hijman et al., 1998) was administered. This test can be divided into SOT digit span, SOT missing item, SOT verbal and SOT visual subtests. For the SOT digit span test, digits had to be repeated that were read to the patient in strings of 4 to 12 digits. In the SOT
missing item test, random strings of digits (e.g., from 1 through 6) were read to the patient with one digit missing, which had to be named. In the SOT verbal test the patient was asked to verbally construct strings of digits, without naming three digits in ascending or descending order (e.g., 6, 7, 8) and without repeating digits. For the SOT visual test the digits had to be pointed to on printed paper. For the Spatial Working Memory Test (SWMT, Keefe et al., 1995), the patient was required to remember the location of a spot on the computer screen. The spot disappeared and after several minutes in which words had to be read aloud, the subject was asked to point to the location of the absent spot. The score consisted of the mean distance between the various locations of the displayed spot and each location that was pointed to after its disappearance. For the Continuous Performance Test (CPT) 3-7 (Lezak, 1995), a string of digits had to be monitored for a specific target (the digit 7 preceded by 3) and the patient had to respond by pressing the computer mouse. This test reflects attention but it includes also an important working memory component because one has to remember that the target is 7, only when preceded by 3. Semantic memory retrieval was assessed with Verbal Fluency (Lezak, 1995). The scores represented the number of words generated in the category of animals and occupations and the number of words generated beginning with the letters N, A and P. One minute was allowed for each letter and category.

The Stroop Test and Trail Making Test (TMT, Lezak, 1995) were administered to assess attentional dysfunctions. The Stroop Test consisted of two baseline tests and an incongruent test. In the first baseline test, congruent colored words were presented on a computer screen, such as red in the color red. The button with the same color had to be pressed. In the second baseline test, the subject was asked to press the button with the same color as a rectangular space on the screen. In the incongruent test, the color of the words did not correspond to their lexical meaning (e.g., the word red printed in blue, and the button with the color of the word had to be pressed and the lexical meaning had to be ignored. For the Stroop interference score, the reaction time estimated in the third test was subtracted from the reaction time in the second test. In TMT A, the digits from 1 through 26 had to be connected as quickly as possible with a pencil on a paper. In TMT B, the same had to be done for all letters from a through z. In TMT C, the subject was requested to connect alternating letters and digits (1-a-2-b, etc.). The Finger Tapping Test (Lezak, 1995) gives an indication of motor speed. With each hand as many finger taps as possible were made on a computer mouse key in five 10-second trials.
The score for each hand was the average for five trials.

In most patients, the neuropsychological test sessions were divided over two days and in a few patients over three days. Patients were tested when they had been on the same medication for six weeks, when they were no longer in an acute, positive phase of the disease and within two weeks after the eye movement test.

**Statistical analysis**

Reflexive- and antisaccade variables in the patient and control group were compared using two-tailed t-tests. For the antisaccade error rate, a t-test with pooled variance was used because SD was significantly unequal between the two groups. Correlations between the antisaccade task and the neuropsychological test battery were examined with Pearson correlation coefficients. Using a Bonferroni correction, only two-tailed p-values below 0.02 were considered significant for correlation coefficients. Both antisaccade error rate and neuropsychological test results are known to be influenced by intelligence. Therefore, correlations between error rate and neuropsychological tests were examined with partial correlation coefficients controlling for premorbid and current intelligence. Mean latency of the correct and wrong antisaccades were compared with mean latency of the reflexive saccades using the nonparametric Wilcoxon matched-pairs signed-ranks test. An one-sample t-test with a test value of 1.00 was used for antisaccade velocity-gain analysis. The data were analyzed with a statistical computer program (SPSS 8.0 for Windows, Chicago, Il).

For ethical reasons, the antisaccade task and neuropsychological test battery were performed when positive and disorganization symptoms were reduced. To examine relationships between antisaccade task performance and positive and disorganization symptoms, PANSS scores at intake were related to antisaccade task results in a more stable phase of the disease.

**Results**

Representative examples of antisaccades in a control subject and a patient are shown in the figure.

Antisaccade error rate and latencies and gains (i.e., metrics) of the antisaccades and reflexive saccades are listed in table 2.1.
Antisaccade task performance in schizophrenia

Figure: Antisaccade task performance in a control subject and a patient. The bold lines represent the laser-target (fixation, appearance, feedback) and the thin lines represent the eye movements. The patient looks in each trial directly at the visual target, whereas the control inhibits this reflexive response.

Four patients had none of the antisaccades correct (error rate 100%). Four controls had all of the antisaccades correct (error rate, 0%). None of the controls had an error rate of 100% and none of the patients had an error rate of 0%.

In the patient group, antisaccade error rate was higher than seen in the control group ($t^{5b} = 4.83, p < 0.001$). Furthermore, in the patient group, reflexive saccade gain was reduced in comparison with the control group ($t^{5b} = -2.00, p < 0.05$). Latencies of correct and wrong antisaccades were longer than latencies of reflexive

Table 2.1: Mean (SD) antisaccade error rate and mean (SD) of the antisaccade and reflexive saccade metrics in the schizophrenic patients and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic Patients</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 37</td>
<td>n = 13</td>
<td></td>
</tr>
<tr>
<td>Error rate, %</td>
<td>51 (30)*</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Latency correct antisaccades, msec</td>
<td>366.7 (75.1)</td>
<td>328.3 (61.0)</td>
</tr>
<tr>
<td>Latency wrong antisaccades, msec</td>
<td>215.3 (66.4)</td>
<td>215.8 (40.7)</td>
</tr>
<tr>
<td>Latency reflexive saccades, msec</td>
<td>172.2 (24.5)</td>
<td>173.4 (24.4)</td>
</tr>
<tr>
<td>Gain correct antisaccades</td>
<td>-.80 (.26)</td>
<td>-1.05 (.48)</td>
</tr>
<tr>
<td>Gain wrong antisaccades</td>
<td>.73 (.14)</td>
<td>.68 (.08)</td>
</tr>
<tr>
<td>Gain reflexive saccades</td>
<td>.83 (.09)‡</td>
<td>.88 (.06)</td>
</tr>
</tbody>
</table>

* p < 0.001; ‡ p = 0.05
saccades in both the patients \((z = -5.01, p < .001)\) and \(z = -4.62, p < 0.001)\) and in the controls \((z = -3.06, p = 0.002)\) and \(z = -2.66, p = 0.008)\).

The mean peak velocity of 10-degree reflexive saccades, based on the exponential fit curve, was \(312 \pm 39\) deg/s in the patient group and \(315 \pm 23\) deg/s in the control group. Mean velocity gain of the correct antisaccades was \(0.90 \pm 0.14\) and of the wrong antisaccades \(1.00 \pm 0.11\) in the patient group. In the control group, mean correct antisaccade velocity gain was \(0.92 \pm 0.08\) and wrong antisaccade velocity gain was \(1.00 \pm 0.06\). None of the velocity variables showed a significant difference between the patient and control group. Correct antisaccade velocity gain was smaller than the test value of \(1.00\) in both the patients \((t_{12} = -3.82, p < 0.001)\) and controls \((t_{12} = -3.77, p = 0.003)\). Wrong antisaccade velocity gain did not differ significantly from the test value of \(1.00\).

The antisaccade error rate increased with decreased estimated premorbid \((r = -0.51, p = 0.007)\) and current intelligence \((r = -0.40, p = 0.02)\). The following correlations between the performances on the antisaccade task and the neuropsychological test battery did not have intelligence as an underlying explaining factor: a high percentage of wrong antisaccades (high error rate) was related with poor working-memory function (SOT digit span: \(r = -0.56, p = 0.001\)), whereas this relationship showed a trend in two other working-memory subtests (SOT verbal: \(r = -0.34, p = 0.05;\) SOT missing item: \(r = -0.30, p = 0.09\)). Poorer performance on the pooled SOT subtests was related to increased error rate \((r = -0.46, p = 0.006)\). Furthermore, there was a correlation between high error rate and poor spatial working memory (SWMT: \(r = 0.48, p = 0.006\)) and decreased attention that includes a working-memory component (CPT: \(r = -0.42, p = 0.01\)).

No correlation of antisaccade error rate with the Stroop interference score was found in the risperidone group \((r = 0.13, p = 0.70)\), whereas in the olanzapine group there was a trend \((r = 0.51, p = 0.036)\). TMT A \((r = 0.64, p = 0.006)\), B \((r = 0.60, p = 0.01)\) and C \((r = 0.62, p = 0.007)\) correlated strongly with antisaccade error rate in the olanzapine group and and not in the risperidone group. There was no significant difference between patients treated with olanzapine or risperidone in the CPT, SOT digit span test or SWMT.

Our results showed several correlations between the metrics of the antisaccade task and PANSS scores at intake. Increased latency of the correct antisaccades correlated with increased severity of conceptual disorganization \((r = 0.47, p = 0.005)\),
difficulty with abstract thought ($r = 0.44$, $p = 0.01$), disorientation ($r = 0.34$, $p = 0.05$), and poor rapport ($r = 0.46$, $p = 0.006$). These PANSS items correlated highly with each other, and the first three items especially are considered generally to belong to the disorganization symptom dimension. The total score of these four PANSS items at intake correlated with the total score of the four items at the time of testing ($r = 0.46$, $p < 0.004$). Thus, the patients with disorganization symptoms at intake had disorganization symptoms at time of testing, but the severity of disorganization symptoms was reduced.

Table 2.2 depicts differential effects of olanzapine and risperidone on the metrics of anti- and reflexive saccades.

Mean latency of the reflexive saccades was prolonged in the risperidone group compared with the olanzapine group ($t^\alpha = -2.02$, $p < 0.05$). Peak velocity of saccades smaller than 20 degrees showed no significant difference between the two medication groups.

<table>
<thead>
<tr>
<th></th>
<th>Reflexive saccades</th>
<th>Antisaccades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency</td>
<td>Latency</td>
</tr>
<tr>
<td>Olanzapine (n=18)</td>
<td>163.8 (18.0)*</td>
<td>343.7 (55.4)</td>
</tr>
<tr>
<td>Risperidone (n=15)</td>
<td>178.0 (22.4)</td>
<td>376.4 (85.2)</td>
</tr>
<tr>
<td></td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>.84 (.06)</td>
<td>-.82 (.29)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>.81 (.10)</td>
<td>-.78 (.27)</td>
</tr>
</tbody>
</table>

* $p < 0.05$

**Discussion**

We confirmed that the antisaccade error rate in a homogeneous group of young patients with schizophrenia was significantly higher than in a control group. The percentage of errors in the antisaccade task increased with decreased working memory function.
(measured by the SOT and SWMT) and attention that includes a working-memory component (by the CPT). In the olanzapine group but not in the risperidone group an increased percentage of errors in the antisaccade task was related to reduced performance on attentional tests (Stroop Test, TMT). In contrast to positive and negative symptoms, increased disorganization symptoms at intake were related to increased latency of correct antisaccades. Finally, in the risperidone patient group, latencies of reflexive saccades were longer than in the olanzapine group.

Young schizophrenic patients performed worse on the antisaccade task than age- and intelligence matched controls, which suggests that antisaccade task performance is already reduced in the early phase of schizophrenia. This suggestion is in accordance with two studies that reported increased error rate in small groups of relatively young schizophrenic patients without previous antipsychotic medication (Crawford et al, 1995; Hutton et al, 1998). In our young group of patients, severity of disorganization symptoms at intake was related to increased antisaccade latencies. Van der Does et al (1993) reported in a similar-aged schizophrenic group that severity of disorganization symptoms was related to decreased neuropsychological test performance, whereas severity of positive or negative symptoms showed no relation. These data suggest that in young recent-onset schizophrenic patients, disorganization symptoms may affect test performance more than positive or negative symptoms.

Our study has demonstrated that working memory is the cognitive function that possibly mediates the suppression of unwanted reflexive saccades in young patients with recent-onset schizophrenia. Other cognitive functions, such as semantic memory retrieval and motor speed, were not related to reflexive saccade suppression. From several neuropsychological studies using functional MRI, performed in healthy subjects, it has been postulated that cognitive tests of working memory are associated with the dorsolateral prefrontal cortex (Kammer et al, 1997; Callicott et al, 1999). In addition, a study of patients with cerebral lesions has indicated that only lesions restricted to the dorsolateral prefrontal cortex resulted in increased error rate whereas lesions to other prefrontal areas did not affect error rate (Pierrot-Deseilligny et al, 1991). These data and our findings may therefore indicate that a high antisaccade error rate in recent-onset schizophrenia may result, at least in part, from dorsolateral prefrontal cortex dysfunction.

Peak velocity of correct antisaccades was slower than peak velocity of reflexive saccades with the same amplitude in both patients and controls; peak velocity of
wrong antisaccades was similar to reflexive saccade peak velocity. Smit et al (1987) also found correct antisaccade peak velocity to be slower than reflexive saccade peak velocity in healthy controls.

In the olanzapine patient group, and not in the risperidone group, an increased percentage of errors in the antisaccade task was related to reduced performance on attentional tests (Stroop, TMT). This finding may be the result of an increased dispersion of scores on the Stroop and TMT in the olanzapine group compared with the risperidone group.

In the present study, patients taking risperidone showed longer reflexive saccade latencies than patients taking olanzapine. Sweeney et al (1997) reported that in schizophrenic patients, risperidone was associated with longer latencies and smaller gains of saccadic eye movements, while haloperidol was not. The authors assumed that these effects might caused by a powerful serotonergic (5-HT$_{2A}$) antagonistic action of risperidone, which may interfere with mechanisms in brainstem regions controlling saccadic eye movements. However, another study showed that olanzapine has a similar 5-HT$_{2A}$ receptor occupancy as risperidone (Kapur et al, 1998), and therefore it is unlikely that this assumption is correct. Risperidone binds to the alpha$_2$ adrenergic receptor, whereas olanzapine and haloperidol as well bind weakly or not at all to this receptor (Schultz et al, 1999). Because risperidone is associated with latency prolongation and olanzapine and haloperidol are not, the alpha$_2$ adrenergic receptor may be implied in latency prolongation of saccadic eye movements.

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Chapter 2


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