Neurophysiological and neuropsychological assessment of recent-onset schizophrenia

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Restricted visual scan patterns reflect deficient cognitive control of ocular movements in schizophrenia

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Summary

The aim of the present study was to gain insight into the nature of visual scan deficits in recent-onset schizophrenia by investigating relationships between visual scan patterns, neuropsychological dysfunctions and symptomatology in young schizophrenic patients. The relationship between scan patterns and interpretation was also investigated. Thirty-six patients with recent-onset schizophrenia (mean age 21 years) and 13 age-matched healthy control subjects were presented a drawing of Leonardo da Vinci, depicting a mother with child. Seven patients and five controls were also presented the ten Rorschach cards. During both scan tasks, eye movements were recorded with the double magnetic induction method. In addition, the patients were assessed with a comprehensive neuropsychological test battery and an interview to evaluate clinical features. Patients were stabilised on medication, psychotic symptoms were absent or in remission whereas negative symptoms were present in most patients. The patients with schizophrenia compared to the control subjects showed restricted scan patterns in both the da Vinci and Rorschach scanning task. A more restricted scan pattern in the da Vinci scanning task was related to poorer performance on a verbal working memory test in the patient group. Increased staring at the centre of the drawing related to reduced ability to interpret scenes on cards and rearrange them correctly (WAIS Picture Arrangement) as well as increased perseveration on the California Verbal Learning Test. Fixation duration prolonged with increased disorganisation symptomatology in the da Vinci scan task. Prolonged fixation duration in the Rorschach scan task was related to prolonged fixation duration in the da Vinci scan task. Finally, the patients showed a trend for increased rightward asymmetry in the Rorschach paradigm compared to control subjects. Our results suggest that restricted scan patterns are related to impaired functioning of the prefrontal cortex, i.e., the primary locus of working memory. This impairment may consist of a reduced ability to implement a strategy for visual scanning and it may influence interpretation of reality. Furthermore, disorganisation symptoms may interfere with information uptake during fixation.
Introduction

Schizophrenia is a complex and serious disorder with a characteristic onset in adolescence. Its heterogeneous course and outcome is skewed heavily in the direction of chronicity and life-long disability (McGlashan, 1999). The pathophysiology and etiology of schizophrenia remain an enigma. However, it has become apparent in the previous decades that neurobiological dysfunctions underlie the disturbances in thought and experience that characterise schizophrenic pathology. Neurobiological dysfunctions in schizophrenia also underlie abnormalities in eye movement control (Hutton and Kennard, 1998a; Crawford et al., 1995, 1996). Reduced eye movement performance has been reported frequently in patients with schizophrenia and their non-affected first degree relatives (Blackwood et al., 1991; Matsue et al., 1994; Crawford et al., 1998; Hutton et al., 1998a,b; O'Driscoll et al., 1999). Eye movements are studied in schizophrenic patients because abnormalities may reflect CNS activities and circuitry that are relevant to the neurobiology of schizophrenia (Hutton and Kennard, 1998a; Tien et al., 1996).

Patients with schizophrenia, compared to healthy control subjects, especially show reduced performance on eye movement tasks that require cognitive control like the antisaccade task (Hutton et al., 1998b; Matsue et al., 1994; Allen et al., 1996; Crawford et al., 1995, 1996; Ross et al., 1998; Nieman et al., 2000). 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. In contrast, reflexive saccades are normal in patients with schizophrenia (Levin et al., 1982; Yee et al., 1987). Reflexive saccades are elicited by a suddenly appearing visual target that captures attention and triggers a saccade to the target. Visual scanning is an eye movement task that contains both cognitive and reflexive components. If subjects are requested to scan a picture freely, the eyes are initially drawn reflexively to points of interest, indicating the allocation of attention to the object (Noto and Stark, 1971). Subsequently, subjects may cognitively implement a scanning strategy to gather additional information about the scene.

Compared to antisaccades and reflexive saccades, scan patterns in schizophrenia have not been investigated extensively. Luria (1977) was one of the first scientists to explore scan patterns in healthy control subjects. Visual scanning of a picture depicting five people in a room shows a different pattern if the subject is asked to estimate the
age of the people in the room, to remember their clothing or to interpret the scene. The differentiation of scan patterns with different instructions illustrates the effect of implementing a cognitively driven scan strategy. Deviant visual scan patterns may thus be associated with cognitive deficits.

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 decisions that rely on remembered contextual information and is believed to be mediated mainly by the dorsolateral prefrontal cortex (Beardsley, 1997). Furthermore, working memory plays an important role in the inhibition of unwanted reflexive responses (Muri et al., 1998). Attentional dysfunctions appear to be a "trait" marker for schizophrenia, because they are apparent in symptom-free patients (Nuechterlein et al., 1986) and in children at risk of schizophrenia (Nuechterlein, 1983). Which cognitive function is mostly drawn on by subjects performing a scanning task is uncertain because correlations between this task and a comprehensive neuropsychological test battery are yet unexplored. It is also unclear whether abnormal scan patterns are related to abnormal interpretations of situations. Patients with schizophrenia often have a deviant interpretation of reality. The Picture Arrangement subtest of the Wechsler Adult Intelligence Scale (WAIS) assesses partly accuracy of interpretation. In this subtest, the patient is requested to look at scenes depicted on cards. Subsequently, the cards have to be rearranged in the correct order by the patient so that the scenes convey a logical sequence of events (e.g., a bird making a nest and laying eggs). Relating scan patterns to neuropsychological test results, especially the WAIS Picture Arrangement subtest, in a group of schizophrenic patients, may provide more insight into the relationship between scan patterns and interpretation.

The symptomatology of schizophrenia is heterogeneous. In psychotic episodes, patients have delusions and sometimes hallucinations. Psychotic episodes are frequently followed by enduring negative symptoms including apathy, avolition, social withdrawal, blunted affect and anhedonia. Disorganisation symptoms are also enduring and entail symptoms like difficulty in abstract thought and conceptual disorganisation (Marengo and Harrow, 1997; Nieman et al., in press). Previous studies have found a relationship of abnormal scan patterns in schizophrenic patients with psychotic (Phillips and David, 1998) and negative symptomatology (Streit et al., 1997). Patients with negative symptomatology tend to show restricted scan patterns (Streit
et al., 1997; Gaebel et al., 1987) whereas patients with psychotic, positive symptoms tend to have extensive scan patterns (Phillips and David, 1998). These studies were performed in chronic patients with schizophrenia. In young patients, compared with older patients, disorganisation symptomatology may affect oculomotor (Nieman et al., 2000) and neuropsychological (Van der Does et al., 1996) performance more than positive or negative symptomatology. We investigated the relationship between scan patterns and symptomatology in young patients with recent-onset schizophrenia.

A visual scan pattern of a picture is partly dependent on the contents of the picture. To gain more insight into the nature of visual scanning deficits in patients with schizophrenia, we presented several kinds of pictures. On the one hand we assessed scan patterns of a picture with an obvious content; a drawing of Leonardo da Vinci depicting a mother with a child. On the other hand, we presented pictures with no predetermined meaning: ten Rorschach cards. Rorschach (1962) based his test on the premise that amorphous shapes, e.g., clouds, can be perceived as objects or scenes. The Rorschach test consists of ten inkblots, some with colour, others just black. Subjects are asked what the inkblot depicts (Kopfler and Davidson, 1962). The concept of the Rorschach test is that the answers of the subject can reveal psychopathological and personality characteristics. In the present study, the Rorschach inkblots were merely used as amorphous shapes and not as possible means of discovering certain psychopathological or personality features.

The inkblots of all ten Rorschach cards are symmetrical shapes. Therefore, asymmetry of scan patterns can be investigated. Differences in scanning asymmetry between schizophrenic patients and controls of more or less symmetrical shapes (faces) have been reported previously (Phillips and David, 1997). Patients with schizophrenia showed an initial right-sided gaze bias for simple facial stimuli. Several studies have found a right hemisphere bias in the perception of chimeric facial stimuli in healthy control subjects (Kim et al., 1990; Levy et al., 1983a,b), whereas others have found a left hemisphere bias (Mertens et al., 1993). We investigated scanning asymmetry in schizophrenic patients and controls of non-facial symmetrical shapes.

The aim of the present study was to gain insight into the nature of visual scan deficits in recent-onset schizophrenia by investigating relationships among visual scan patterns, neuropsychological dysfunctions and symptomatology in young schizophrenic patients. The relationship between scan patterns and interpretation was also investigated.
Chapter 3

Methods

Subjects
Thirty-six patients (six women) with schizophrenia were presented the Leonardo da Vinci drawing, depicting a mother with child. Their mean age was 21 years ± 3.1 (SD). Seven of these 36 patients, were also presented the ten Rorschach cards. Thirteen healthy controls (six women) with a mean age of 22.5 ± 4.2 years served as control group for visual scan performance. Five controls were presented the Rorschach cards. They were matched as a group on age and estimated intelligence.

All patients attended the adolescent psychiatric clinic of the Academic Medical Centre, 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 = 4). 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 such as 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).

All 36 patients were assessed at intake 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. The negative symptom dimension was composed of the PANSS items for blunted affect, emotional withdrawal, lack of spontaneity, passive/apathetic withdrawal and stereotyped thinking. The disorganisation symptom dimension comprised conceptual disorganisation, difficulty in abstract thinking, disorientation and lack of attention. The positive symptom dimension was composed of delusions, grandiosity, suspiciousness and unusual thought content. Thirty-four patients were tested with the neuropsychological test battery (two patients refused to cooperate).

Seventeen patients were treated with olanzapine (mean dosage 15.8 mg ± 4.9) 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 given olanzapine and two given risperidone used an antidepressant (paroxetine) and one patient given olanzapine and two patients given risperidone used antiparkinsonian medication. Mean number of previous psychotic episodes was 0.2 ± 0.5. Mean illness duration was 19.3 ± 15.1 months, including the prodromal phase. The study was approved by the Ethical Committee of the Academic Medical Centre, and all included subjects gave written informed consent according to the declaration of Helsinki.

Eye movement recording
In the present study scan patterns were recorded using the double magnetic induction (DMI) method (Bour et al., 1984) with a high spatial and temporal resolution. The subject's head was stabilised 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-metallic lens was placed on the right eye after anaesthesia 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. Within the range of -15 to +15 degrees raw eye signals did not deviate more than five percent from linearity. The average resolution was 5-minute arcs. Horizontal and vertical position signals were low-pass filtered (-3 dB at 150 Hz), digitised with a sample frequency of 250 Hz and stored in the computer.

A visual scan pattern consists of fixations and saccades. Fixations were defined as focusing of the eye on the same position for 100 ms or more. Saccades are fast eye movements that move the eyes from one fixation point to another. The first visual target was a drawing of Leonardo da Vinci (Fig. 3.1).

Fig. 3.1: A drawing of Leonardo da Vinci depicting a mother with a child, used in the first scanning task.
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For calibration, the subject was asked first to look at the corners of the drawing, indicated by markers, that was placed on a screen 1.14 m in front of the subject. The subject was subsequently requested to freely scan the drawing for 20 seconds. Thereafter, a random subgroup of the 36 patients was presented the ten Rorschach cards one by one. For calibration, the subject was requested first to look at the four corners of the card, indicated by markers. Subsequently, each card was presented to the subject for 20 seconds and the subject was asked what the inkblot represented. An example of a Rorschach card (card no. 4) with perceptions of all subjects is shown in Fig. 3.2.

Schizophrenic Patients
Giant animal with tail
Hells angel on a Harley
Gondola
Two penguins with big boots
Animal
Man looking down on you
Road with trees and water on the side

Control Subjects
Tiger skin
Animal
Not much
Dead animal
Giant with big feet

Fig. 3.2: An example of a Rorschach card (card no. 4) with the highly variable perceptions of the inkblot.

With an off-line data analysis program, the scan patterns were aligned with the drawing using the fixations of the eye movements to the calibration markers.

The da Vinci drawing was divided into four different areas, i.e., the face of the mother, the face of the child, the arm of the child and the rest of the drawing. The relative contribution of each area to the total area was 17.9, 11.3, 12.9 and 57.9 percent, respectively. These percentages also represent the expected percentage of time a subject should spend examining each area if his scanning behaviour was merely based on chance. Variables in the scan task of the da Vinci drawing were: percentage of time spent looking at the four areas of the drawing, mean fixation duration and median fixation duration.

Variables in the scan task of the Rorschach cards during 20 sec scan time were: mean distance of fixation areas leftward from the midline, mean distance of fixation areas rightward from the midline, mean distance of fixation areas to the midline, total number of fixations in 20 seconds scan time, total scan path, mean fixation duration and median fixation duration, left/right asymmetry (0 = no asymmetry, -1 = is complete asymmetry leftward, 1 = complete asymmetry rightward). The left/right asymmetry
was calculated with the following formula: \((\text{mean distance of fixation areas leftward from the midline} - \text{mean distance of fixation areas rightward from the midline}) / (\text{mean distance of fixation areas leftward from the midline} + \text{mean distance of fixation areas rightward from the midline})\). All variables were calculated with an interactive computer program written in Matlab (The Math Works, Inc., USA).

Neuropsychological test battery
To estimate premorbid intelligence, a composite measure was constructed. In each subject, level of education of the subject's parents was determined along with the subject's 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, scenes on cards had to be interpreted and subsequently rearranged to make the most sensible story. Finally, the WAIS Block Design subtest comprises several red and white coloured 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, Keele 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. As a measure of sustained attention, the Continuous Performance Test (CPT) 3-7 (Lezak, 1995) was administered. 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. 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.

Visuo-spatial memory was assessed with the Complex Figure of Rey (Lezak, 1995). The subject was requested to copy a complex figure, subsequently to reproduce the figure immediately after it was removed and again 20 minutes after removal. Verbal learning and memory was assessed with the Dutch version of the California Verbal Learning Test (Lezak, 1995). A list of words was presented and the recollection of these words was tested in five trials. One of the variables in this test is perseveration (i.e., repeating words that the subjects has already said). 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 coloured words were presented on a computer screen, such as red in the colour red. The button with the same colour had to be pressed. In the second baseline test, the subject was asked to press the button with the same colour as a rectangular space on the screen. In the incongruent test, the colour of the words did not correspond to their lexical meaning (e.g., the word red printed in blue) and the button with the colour 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 within two weeks after eye movement recording.

Statistical analysis
Percentages of time looked at the four different areas of the da Vinci drawing during the 20 second scan period in the patient group were compared with the percentages
in the control group using two-tailed $t$-tests. Correlations between scan patterns of the drawing and the neuropsychological test battery were examined with Pearson correlation coefficients. Using a Bonferroni correction for these correlation coefficients, only two-tailed $P$ values smaller than 0.02 were considered significant. Distribution of fixation duration is often skewed. For this reason median fixation duration appears to be a more reliable variable than mean fixation duration. Therefore, we only report relationships with median fixation duration. Median duration in the da Vinci scanning task was compared with median fixation in the Rorschach task for the patient and control group with Pearson correlation coefficients. Scanning asymmetry in the Rorschach task was investigated in the patient and control group with one sample $t$-tests with a test value of 0 (= no asymmetry). Variables in the Rorschach task in the patient group were compared with those in the control group using the nonparametric Mann-Whitney U Test. The data were analysed with a statistical computer program (SPSS 9.0 for Windows, Chicago, IL).

**Results**

**Da Vinci drawing scan task**

The percentage of time spent looking at the four different areas of the da Vinci drawing in the patient and control group is listed in Table 3.1. The patients looked significantly more at the face of the mother and significantly less at the rest of the drawing compared

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic patients $(n = 36)$</th>
<th>Control subjects $(n=13)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face mother, %</td>
<td>37.4 (22.8)*</td>
<td>24.9 (10.8)</td>
</tr>
<tr>
<td>Face child, %</td>
<td>30.5 (14.7)</td>
<td>24.8 (9.7)</td>
</tr>
<tr>
<td>Arm child, %</td>
<td>14.4 (11.3)</td>
<td>13.2 (11.3)</td>
</tr>
<tr>
<td>Rest drawing, %</td>
<td>19.4 (16.8)#</td>
<td>37.1 (14.5)</td>
</tr>
<tr>
<td>Median fixation duration, msec</td>
<td>278.1 (63.4)</td>
<td>282.5 (47.3)</td>
</tr>
<tr>
<td>Mean fixation duration, msec</td>
<td>298.4 (60.7)</td>
<td>312.1 (47.0)</td>
</tr>
</tbody>
</table>

* $P < 0.015$ (t-test with pooled variances), # $P < 0.002$
to the control subjects. A representative example of a scan pattern of a patient and control subject is depicted in Fig. 3.3.

There was no significant correlation of dose of antipsychotic medication and any scan variable. Furthermore, no significant differences in visual scanning were found between the patient group that received olanzapine and the group that received risperidone. Men and women did not display significantly differential scan patterns.

Increased visual attention to the rest of the da Vinci drawing related to better scores on the digit span and missing item subtests of the Subjective Ordering Task in the patient group ($r = 0.45$, $P < 0.02$). This relationship showed a trend for three pooled subtests of the Subjective Ordering Task ($r = 0.38$, $P < 0.05$) and for the four pooled subtests ($r = 0.34$, $P < 0.08$). Thus, patients with better scores on a verbal working memory test showed increased attention to the rest of the drawing. A better performance on the Picture Arrangement subtest of the WAIS was related to more visual attention to
the face of the child \( (r = 0.45, P = 0.02) \) and less visual attention to the arm of the child \( (r = -0.48, P = 0.01) \). The arm of the child constitutes the centre of the drawing. Thus, those patients who stared a large proportion of time at the centre of the drawing performed poorly on the WAIS Picture Arrangement. Furthermore, increased perseveration in the California Verbal Learning Test was related to increased fixation on the centre of the drawing (arm of the child \( r = 0.60, P = 0.001 \)). Increased time to complete copying the complex figure in the Complex Figure of Rey test was related to prolonged median fixation duration \( (r = 0.50, P < 0.01) \).

Increased disorganisation symptomatology assessed at the time of the scanning task was related to prolonged median fixation duration \( (r = 0.51, P < 0.004) \). The patient group did not show prolonged fixation duration compared to control subjects because in the patient group, a larger range of fixation durations was present than in the control group. Thus, only a subgroup of patients with increased disorganisation symptomatology showed prolonged fixation duration. In this subgroup, median fixation duration was prolonged compared to the patient group with few disorganisation symptoms \( (327 \text{ and } 263 \text{ msec, respectively; } t(34) = -3.34, P = 0.002) \). Increased score on the blunted affect item of the PANSS was related to prolonged median fixation duration \( (r = 0.55, P < 0.003) \). We did not find a relationship with the other PANSS items.

Rorschach card scan tasks

Mean and standard deviation (SD) of the variables in the Rorschach scan task in the patient and control group are listed in Table 3.2.

Table 3.2 Mean (SD) of variables in the Rorschach task in the patient and control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Schizophrenic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation leftward, degrees</td>
<td>1.89 (0.78)*</td>
<td>1.15 (0.37)</td>
</tr>
<tr>
<td>Fixation rightward, degrees</td>
<td>2.01 (0.92)</td>
<td>1.72 (0.82)</td>
</tr>
<tr>
<td>Fixation midline, degrees</td>
<td>1.96 (0.75)‡</td>
<td>1.43 (0.53)</td>
</tr>
<tr>
<td>Asymmetry (-1 to 1)</td>
<td>0.024 (0.19) #</td>
<td>0.18 (0.18)</td>
</tr>
<tr>
<td>Scan path, degrees</td>
<td>150.3 (32.7)</td>
<td>144.0 (42.4)</td>
</tr>
<tr>
<td>Number of fixations</td>
<td>54.5 (6.3)</td>
<td>52.0 (8.8)</td>
</tr>
<tr>
<td>Median fixation duration, msec</td>
<td>221.7 (37.6)</td>
<td>232.5 (46.5)</td>
</tr>
<tr>
<td>Mean fixation duration, msec</td>
<td>252.3 (40.0)</td>
<td>260.6 (47.3)</td>
</tr>
</tbody>
</table>

* \( P < 0.009 \), ‡ \( P < 0.06 \), # \( P < 0.07 \)
In the Rorschach scan task, mean distance of fixation areas left from the midline was significantly reduced in the patient group compared to the control group ($z = -2.60$, $P = 0.009$) for all cards pooled. Reduction of mean distance of fixation areas to the midline in the patient group compared to the control group showed a trend for all cards pooled ($z = -1.85$, $p = 0.06$; Fig. 3.4A).

Fig. 3.4A: Iso-contour plot of average fixation distribution for the control and patient group. Horizontal and vertical axes are depicted in degrees. Rorschach card no. 5 clearly demonstrates restricted scan patterns in patients (not looking at the 'wings').
Thus, the patients stayed more closely to the midline of the card when scanning left of the midline. Furthermore, we found a trend for more asymmetry to the right in the patient group compared to the control group ($z = -1.73$, $P < 0.08$). An example of significant rightward asymmetry is shown in Fig. 4B (card no. 9).

Rorschach card 9

Fig 3.4B: Iso-contour plot of average fixation distribution for the control and patient group. Horizontal and vertical axes are depicted in degrees. In Rorschach card no. 9 the patients show a strong rightward asymmetry whereas the control subjects scan equally left and right of the midline.
One sample t-tests showed significant rightward asymmetry in the patient group \(t(9) = 3.20, P = 0.01\) and not in the control group \(t(9) = 0.41, P < 0.7\). No significant difference in handedness was present between the patient and control group. The ten individual Rorschach cards showed variation in asymmetry and restricted scan patterns. The patients compared to the control subjects demonstrated considerable asymmetry and restricted scan patterns in a subset of four cards whereas the patients demonstrated less asymmetry and restricted scan patterns when scanning the other cards.

Median fixation duration in the Rorschach scan task was related to median fixation duration in the da Vinci scan task \(r = 0.70, P = 0.05\). For most Rorschach cards, the main point of fixation for both patients and control subjects was the area of the inkblot that resembles most the ‘head’ of the shape. We did not investigate relationships of the Rorschach scan patterns with symptomatology and the neuropsychological tests because of the small sample size in the Rorschach scanning task.

**Discussion**

Patients with schizophrenia compared to control subjects showed restricted scan patterns in both the da Vinci and Rorschach scanning task. A more restricted scan pattern in the da Vinci scanning task was related to a poorer performance on a verbal working memory test in the patient group. Increased staring at the centre of the drawing was related to reduced ability to interpret pictures on cards and put them in the right order (WAIS Picture Arrangement) as well as increased perseveration on the California Verbal Learning Test. Prolonged fixation duration was related to increased disorganisation symptomatology and blunted affect in the da Vinci scan task. Prolonged fixation duration in the Rorschach scan task was related to prolonged fixation duration in the da Vinci scan task. Finally, the patients showed a trend for increased rightward asymmetry in the Rorschach paradigm.

**Neuropsychology**

The relation between restricted scan patterns and reduced verbal working memory may imply that patients with a disturbed function of working memory repeatedly return to previous fixation points. Working memory dysfunctions may be related to difficulty in redirecting the initial focus of attention (Phillips and David, 1997). Most
patients spent a large proportion of the 20 seconds, scanning a few parts of the drawing and therefore paid less attention to the whole scene than control subjects. In contrast, control subjects with normal working memory processed the most important information in the drawing in a few fixations and subsequently experienced no difficulty with redirecting attention to the remaining parts of the drawing for additional information.

From several studies in which neuropsychological findings were correlated with functional MRIs in healthy subjects, it has been postulated that cognitive tests of working memory are mainly associated with the dorsolateral prefrontal cortical region, i.e., Brodmann area 46 (Kammer et al., 1997; Callicott et al., 1999). Fig. 3.5 represents a model that outlines the relationship between the reflexive and cognitive components in visual scanning.

Fig. 3.5: A model of visual scanning. The dotted line encompasses working memory. In generating a saccade, two projections are competing; a direct route (depicted by the arrow from the visual input box to the saccade box) and an indirect route via the prefrontal cortex (working memory). Long-term memory input provides information about similar previous situations. The supervisory attention system plays a role in willful actions and directs the central executive part of working memory. In addition, this system can inhibit the direct reflexive pathway (bold arrow).

Visual input can trigger a saccade without higher cognitive prefrontal control; a bottom-up projection. However, working memory can intervene and inhibit the reflexive saccade (Fig. 3.5, bold arrow) and can also instigate a saccade; a top-down projection. In patients with schizophrenia, reflexive processes are not affected (bottom-up), however, cognitive control is lacking (top-down) (Walker et al., 2000; Theeuwes et
Prefrontal lobe dysfunction in schizophrenia may lead to reduced ability to inhibit reflexive motor processes, e.g., saccades, and possibly also to reduced ability to inhibit reflexive thought processes. A psychotic thought, e.g., I am the victim of a conspiracy, could be considered as a reflexive thought without higher cognitive inhibition. Healthy people may have the same reflexive thought for a moment but inhibition of the thought usually induces a more realistic view of the situation.

The relationship between the decreased WAIS Picture Arrangement score and prolonged staring at the centre of the da Vinci drawing suggests that scan patterns of a picture are related to interpretation of that picture. In the Picture Arrangement test, each card has to be scanned for information about the scene on the card. If patients mainly stare at the centre of the picture and do not scan the whole scene for additional information, the scene may be misinterpreted. Furthermore, staring at the centre of the da Vinci drawing was related to perseveration on the California Verbal Learning Test. Perseveration is also a symptom of prefrontal lobe impairment (Rogers et al., 1998; Sandson and Albert, 1987) and may reflect both the increased returning to previous fixation points and the lack of scanning strategy. Our results are in concordance with those reported by Pantelis et al. (1997) in which patients with schizophrenia were severely impaired on strategy when performing frontal, executive neuropsychological tests. It is noteworthy that other cognitive functions, such as attention, motor speed and semantic memory retrieval, demonstrated no relationship with visual scanning characteristics in our study.

The increased attention of the patients to the mother could be explained by difficulty in interpreting the facial expression of the mother. With respect to this hypothesis, earlier studies (Morrison et al., 1988; Borod et al., 1993; Whittaker et al., 1994) have demonstrated that the interpretation of facial expressions is disturbed in schizophrenia, especially in those patients who suffer from blunted affect. In our study, increased severity of blunted affect was related to prolonged median fixation duration. However, our patients also showed restricted scan patterns in the Rorschach scan task, that did not include faces. Our results thus converge into the direction of a generalised lack of scanning strategy.

Symptomatology
The patients in the present study were stabilised clinically, i.e., experienced no or few psychotic symptoms and only residual negative symptoms. Our result of restricted
scan patterns in patients with no or few psychotic symptoms and residual negative symptoms is in concordance with previous findings (Streit et al., 1997; Gaebel et al., 1987).

Ishizuka et al. (1998) found eye fixation time to be correlated with degree of thought disorder. We also found that prolonged fixation time was related to more severe disorganisation symptomatology. Disorganisation symptoms may interfere with information uptake during fixation. Furthermore, prolonged fixation duration was related to increased time to complete copying the Complex Figure of Rey. In the process of copying, the eyes are repeatedly focused on the complex figure to obtain information. When a subject looks longer at the complex figure, the time to complete the copy increases. The prolonged fixation duration implies that the information about the complex figure is not taken in and not processed at a normal pace. Positive symptoms fade in most young patients over a period of weeks and negative symptoms are usually not as pervasive as in older and more chronic patients. Disorganisation symptoms in young schizophrenic patients with concomitant difficulties in information uptake and processing may lead to the most severe problems compared to positive and negative symptoms with returning to study, job and daily life in general.

Increased fixation duration in the Rorschach scan task was related to increased fixation duration in the da Vinci scan task. This relationship suggests that fixation duration is partly idiosyncratic and may be related to symptomatology in schizophrenia, especially disorganisation symptoms.

Scanning asymmetry

Patients with schizophrenia showed in the Rorschach task restricted scan patterns predominantly on the left side of the midline. Furthermore, they showed a trend for increased rightward asymmetry. Patients with unilateral right hemispheric neglect show a similar scan pattern. Chédru et al. (1973) recorded the eye movements of patients with left-sided spatial neglect and demonstrated that they had a failure to explore the left side of visual space. Making a voluntary eye movements leftward or rightward, requires activation of the contralateral hemisphere (Oliveri et al., 2000). According to the model of Kinsbourne (1970), in the horizontal or transversal plane, each hemisphere is responsible for directing attention toward the opposite side of visual space. In a study of Husain et al. (2000), neglect patients with lesions to the right frontal lobe were slow to execute reaches to left targets, regardless of movement...
direction. Right visual distractors slowed visual reaction times to left targets more than vice versa in frontal neglect patients. Our result that schizophrenic patients show restricted leftward scan patterns may be related to right hemisphere dysfunction and a subsequent inability to activate the gaze systems that mediate leftward movement. Right hemisphere lesions are also associated with reductions in overview of the scene (Lezak, 1995). In addition, right sided frontal lesions have been reported to produce deficits of strategic ability (Pantelis et al., 1997; Miotto et al., 1996).

Several training models have been described for visual scan deficits in spatial unilateral neglect patients. The basic principles can be traced back to ideas of Diller and Weinberg (1977), who suggested that these patients are confronted with deficits in visual scanning ability that can be dissected into several specific basic abilities. These basic abilities like systematic scanning and remembering where attention has already been focused can be trained in a modular way. The neglect patients receive training until a compensation mechanism is formed that is executed relatively automatic. Such abilities are not formed spontaneously in daily life and should therefore be taught explicitly (Robertson, 1993). Good results are described by Pizzamiglio et al. (1992). Considering the results in the present study, the visual scan training technique for neglect patients could perhaps also be useful for patients with schizophrenia. In a natural situation, scan patterns are unconscious and automatic. The information, taken in during fixations, is the basis on which the cognitive process of inference and interpretation draw. Making scan patterns more conscious and controlled may have an effect on inferences and interpretations. Phillips et al. (2000) also suggest on the basis of their study on visual scan paths in schizophrenic patients with persecutory delusions, that the employment of scan strategies may be useful for reduction in severity and extent of persecutory delusions in schizophrenic patients.

In conclusion, the nature of visual scan deficits in recent-onset schizophrenia may consist of a reduced ability to implement a strategy for visual scanning. The resultant reflexive scan patterns may influence interpretation of reality. Therefore, enhancing cognitive control on ocular movements may be beneficial for patients with schizophrenia. Finally, several variables in the Rorschach scan task such as complexity of the inkblot, colour and ambiguity may have influenced the scan patterns of the different cards. The effect of these variables on scan patterns should be investigated in a prospective study by manipulating these variables in a controlled manner.
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