J. Hyönä, D.P. Munoz, W. Heide and R. Radach (Eds.)
Progress in Brain Research, Vol. 140

CHAPTER 26

Visual search in long-term cannabis users with early age of onset

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Abstract: The present research tested the hypothesis that there is a specific deficit in visual scanning in chronic users of cannabis with early onset of their drug consumption (age 14 to 16). 17 users and 20 control participants were asked to search for targets on a 5 × 5 stimulus array while their eye movements were monitored. Cannabis users showed less effective search behavior, including longer response times and more fixations at about the same error level. Search patterns were more conservative and included more frequent reinspections of previously fixated areas. In sum, the results point to two loci of adverse effects: an impairment in visual short-term memory, and less effective visual processing at a more strategic, top down controlled level.

Introduction

Cannabis is the most widely used illicit drug today. Especially young people increasingly consume *Cannabis sativa* with its most important ingredient, Δ-9-tetrahydrocannabinol (THC). Smoked marijuana interacts with an endogenous cannabinoid receptor system in the human brain. The density of this frequent and widely distributed receptor type varies over different brain regions. Detailed distribution maps for mammal brains are provided, for instance, by Herkenham et al. (1991a,b); Herkenham (1992). Some of the regions with high cannabinoid receptor density are directly linked to motor areas, such as basal ganglia, hippocampus, and cerebellum. However, the specific functions of this receptor system still remain unclear.

McLaughlin and Abood (1993) demonstrated a down-regulation of THC-receptor density after chronic THC consumption in rats. Stiglick and Kalant (1985) reported data indicating that chronic exposure of immature rats to cannabinoids may result in irreversible changes of brain morphology as well as of behavior, an effect that did not appear using mature animals. These data suggest that a specific vulnerability for adverse effects of THC may exist during distinct phases of human development. This idea provided one of the major motivations for the present study. Our intention was to compare participants who had begun their chronic use of cannabis early in life, between age 14 and 16, with normal control subjects. Participants were asked to complete a visual search task that in prior research by Ehrenreich et al. (1999) has proven to be sensitive to impaired visual processing performance in early-onset users.

This chapter is divided into four parts. We will first provide more theoretical background and take a look at some of the rich literature on mental and behavioral effects of cannabis. The second part will discuss some relevant previous research on eye movements in visual search, and in the third part methodology and main results of the experiment will be reported.

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The concluding discussion will include suggestions for further research on cannabis effects on visual processing and eye movements.

Effects of cannabis on cognition and behavior

Short-term effects of cannabis

Effects of cannabis on human mental functions and behavior that are manifest until a few hours after the drug is ingested will be referred to as short-term effects. They range from emotional and perceptual to cognitive and motor skill changes (see Ashton, 2001, for a recent discussion). There is a rich literature on short-term effects of cannabis, especially with respect to basic neuropsychological processes. Impairments of mental and psychomotor functions due to acute consumption of cannabis have been demonstrated in studies examining body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, the digit–symbol substitution test as well as complex driving and flight simulations (Chait and Pierri, 1992). Although various adverse consequences of cannabis consumption are unquestioned, there is substantial disagreement on the weight of positive versus negative effects. For example, research on effects of cannabis on cognitive functions and motor skills in the context of driving has led to mixed results. Several studies clearly suggested negative effects on driving-relevant abilities, such as deficits in tracking and eye–hand coordination as well as attentional drop-outs (Moskowitz, 1973). On the other hand, there is evidence indicating that these deficits can to some extent be compensated (or even over-compensated) in terms of a reduction in driving velocity. Careful behavior of drivers under the influence of cannabis appears to be due to a subjective impression of impairment. This is in clear contradiction to the pattern of self-perception reported for subjects that were intoxicated with alcohol rather than THC (Robbe, 1994; Berghaus and Krueger, 1998).

Although the measurement of eye movements is a common methodology in drug research, there are only a few studies on short-term effects of cannabis on eye movements. As an example, Fant et al. (1998) looked for performance effects of smoking a single marijuana cigarette on ten volunteers who reported recent use of cannabis. Along with other physiological parameters, smooth-pursuit eye-tracking performance significantly decreased with a peak after 2 hours. However, all effects had completely disappeared after 24 hours, indicating that the residual effects of smoking a single marijuana cigarette are minimal.

Early research on long-term effects

Research efforts on long-term effects of cannabis have so far been of rather moderate extent. These persisting effects were not in the focus of interest, possibly because the pharmacology of THC interactions with brain metabolism and physiology had remained elusive. An excellent review of neuropsychological research up to the mid nineties has been provided by Pope et al. (1995). Following their line of discussion, a distinction can be made between experimental studies in which cannabis is administered to subjects in a controlled fashion, and quasi-experimental, naturalistic studies examining subjects with a specific drug history. An advantage of the experimental approach is that confounding variables like socio-demographic status, social history, or IQ differences can often be reasonably well controlled. However, most of these experiments included participants with a history of modest prior marijuana use, and in some cases the abstinence period before experimental intoxication was not controlled. Therefore, it remains unclear whether changes in behavior were exclusively a consequence of the administered dose of cannabis. Also, for ethical reasons this type of research allows to study drug effects only with respect to limited doses and times of intoxication. Nonetheless, using an experimental design, Leirer et al. (1991) observed significant performance deficits in a flight simulator task over a period of 48 hours.

The vast majority of early research on long-term effects consisted of quasi-experimental studies, in which heavy users without psychiatric disorders were tested on various neuropsychological measures (such as memory, concentration and attention tasks) after acute effects had dissipated. Interestingly, about half of these studies did not find any differences at all between users and non-users. Among those who reported evidence for adverse effects is a study by Varma et al. (1988), who examined subjects with an average period of 7 years of chronic cannabis use. In several perceptuomotor tasks they found increased response times after 12 hours of acute intoxication but no differences in memory and intelligence tests. Research by Block et al. (1990) and Block and Ghoneim (1993) indicated effects on response times and various measures of visuomotor and memory performance over periods longer than 12 hours and Mendhiratta et al. (1988) even claimed to have found deficits 10 years after the last intoxication. Millsaps et al. (1994) reported data pointing to a subtle memory impairment after an abstinence period of about 1 month. Finally, a study of Schwartz et al. (1989) suggested a 6-week effect on a visual retention task and on a Wechsler memory scale for prose passages in eight users vs. nine controls.

Taken together, the results gathered in this early phase of research are quite heterogeneous and methodological problems as well as the lack of an adequate theoretical foundation are apparent. Examples for typical methodological limitations are: missing control groups, confounding socio-economic status and intelligence differences, unknown or brief abstinence periods, an unclear history of other drugs, insufficient group matching and small sample sizes (see Pope et al., 1995, for a detailed discussion). The variables in question are most often not derived from a theoretical framework but rather seem to be randomly chosen. In sum, until the middle of the nineties there was an obvious lack of knowledge about potential persistent effects of cannabinoids on brain functions.

Recent research on long-term effects

In recent years, studies concerning neuropsychological long-term effects became more solid in their methodological foundation. An issue that has moved into the focus of attention is whether potential effects are due to a residue of the drug in the system or, alternatively, due to a long-lasting CNS alteration even after the drug has left the body. Especially in chronic users, the metabolite accumulation in fat stores may be slowly released back into the circulation, a process which can take days after cessation of intoxication (Pope et al., 2001). Therefore, a distinction between residual vs. irreversible effects has become common.

Pope and Yurgelun-Todd (1996) demonstrated an adverse effect on word list memory and mental flexibility after one day of abstinence among 65 heavy-smoking participants in comparison to infrequent smokers. Fletcher et al. (1996) found deficits in word list memory even after three days as well as impairments in selective and divided attention among older, but not younger users. In contrast, Lyketsos et al. (1999) found no differences in the degree of 'cognitive decline' between heavy, light, and non-users during a 12-year longitudinal study. In an impressive recent study Pope et al. (2001) examined 108 subjects (current and former users vs. controls) over an 28-day observation period and found deficits exclusively in current users with respect to visual retention (only at begin of the study), word list memory (only up to 7 days) and card sorting (up to 24 days). Former users did not show any such deficits at all. Pope et al. interpret their results in terms of reversible residual effects rather than long-lasting neurotoxic damage.

Of particular interest for the present research are studies pointing to EEG abnormalities after cannabis intoxication (Struve et al., 1999; Patrick and Struve, 2000). They reported deviating patterns of results in various EEG measures one day after intoxication that were related to the duration of long-term consumption duration. Solowij (1998) conducted an experiment where subjects had to discriminate complex auditory patterns while event-related potentials (ERP) were recorded. She examined P300 delays and processing negativity, a measure reflecting attention processes, in this task after more than 12 hours of drug abstinence. The main result was that users were not only less successful in solving the discrimination task but also showed a larger processing negativity to complex irrelevant stimuli. Surprisingly, in a subsequent experiment where the abstinence period was at a mean of two years, subjects still showed poorer performance as well as higher processing negativity for irrelevant items, with effects that were still about a half of those reported before. This finding suggests a rather long-lasting neurotoxic effect.

Pope et al. (2001) discuss the results obtained by Solowij (1998), and note that "the possibility remains that more sophisticated neurocognitive assessment measures, such as electroencephalographic or functional magnetic resonance imaging measures, might reveal deficits in long-term cannabis users below the threshold detectable with our neuropsychological test battery" (Pope et al., 2001, p. 915). It is exactly at this point where the measurement and analysis of eye movements can come into play. It provides a methodology that can go beyond the scope of classic neuropsychological testing and may reveal subtle abnormalities in basic oculomotor behavior, visual information processing, visual working memory and/or higher cognitive abilities (visual strategies) that are all relevant for success in solving complex visual tasks.

Long-term effects on visual processing and early age of onset

As noted above, the present study is based on the idea that performance in visual tasks may be impaired in long-term cannabis users who have started their consumption of the drug during their adolescence. Evidence in favor of this hypothesis was provided in a prior study conducted while the third author of this chapter was at the University of Göttingen. Ehrenreich et al. (1999) used a computer-assisted battery of neuropsychological tests to examine performance in 99 exclusive cannabis users in comparison to 50 control subjects. The last cannabis use was at a mean of about 30 hours prior to testing. The groups were matched with respect to age, sex, educational and socio-demographic status, and intelligence level. Individuals with psychiatric diseases, head injury or previous or present use of drugs other than cannabis were excluded.

The test battery addressed a broad spectrum of cognitive and attentional functions and consisted of the following tasks (Zimmermann and Fimm, 1993): alertness (response times with or without an acoustic warning signal), divided attention (a dual detection task for visual and acoustic input), flexibility (a task where subjects respond either to a specific letter or digit), working memory (consecutively presented digits to be compared with the one previously presented), and a visual scanning task. In visual scanning, the subject was asked to indicate via key press the presence or absence of a fixed critical item in a 5×5 matrix of squares with one open side (see Fig. 4).

Results indicated that there were virtually no performance differences in all tasks except for visual scanning. Subjects with relatively late onset of cannabis consumption (age 17 or older, $n = 51$) were as successful as normal controls in the visual scanning task. However, subjects with early onset (age 16 or younger, $n = 48$) were significantly slower in response to both target present and target absent trials. Ehrenreich et al. discussed the possibility that these effects were due to residual intoxication rather than a persistent effect related to the early onset of drug abuse. To counter this objection, they showed that in stepwise regression analyses over the whole sample of 99 users, age of onset was a very good predictor of performance, whereas indicators of acute intoxication and cumulative toxicity were not. In supplementary analyses of variance, sex, age (which was lower in the early onset group), blood level of THC and estimated life dose were entered as covariates; nevertheless the group differences persisted. The response time measures reported by Ehrenreich et al. (1999) triggered our interest in asking a number of more detailed questions about characteristics of visual processing and eye movement control in cannabis users solving the visual scanning task. Before reporting the experiment, a brief look at some relevant evidence on eye movements in visual search will be taken.

Eye movements in visual search

The fundamental finding that eye fixations are not equally distributed over a picture represents one of the landmarks of early oculomotor research (Buswell, 1935; Yarbus, 1967). Fixation locations clearly depend on the informativeness of specific regions, an effect that emerges already during the first few seconds of scanning (Mackworth and Morandi, 1967). Even in tasks with a rather homogeneous target area, fixations are neither evenly distributed nor randomly spread. According to Ford et al. (1959), they tend to be underrepresented in the center as well as in the periphery of the search screen. The systematicity of visual search in the scanning of faces under degraded conditions was examined by Noton and Stark (1971), indicating that subjects used stereotypical scan paths in this task. A more theoretical and quantitative approach to this phenomenon was developed by Groner et al. (1984) and Groner and Menz (1985). They introduced a distinction between a local scan path guided by bottom-up processing and a global scan path that appeared to be guided by strategic planning and top down processing. This approach allowed to generate quantitative hypotheses about scanning behavior in naturalistic scenes or pictures, but it appears rather difficult to transfer the idea to scanning tasks that consisted of rather homogenous search arrays or backgrounds.

Gordon (1969) first demonstrated in a letter search task that there is a systematic relation between task difficulty and saccade amplitudes, with more difficult tasks leading to smaller saccades. Jacobs (1986) proposed a model where an increasing amount of visual information to be processed could either lead to a reduction of saccade amplitude, an increase in fixation duration, or both. Hooge and Erkelens (1996) conducted an experiment where expected low discriminability of targets caused strategically prolonged fixation durations. Furthermore, a reinspection analysis for targets in this study revealed that results of foveal target analysis were not used in the preparation of the subsequent saccade. This suggests a pre-programmed control of fixation duration, using estimations of the foveal analysis time of previous fixated stimulus elements (see also Hooge and Erkelens, 1998).

Performance in visual search should depend on visual acuity and discrimination in the periphery (Bloomfield, 1975). The area within which a certain degree of visual detail can be discriminated has been termed conspicuity area, functional visual field, useful field of view or visual lobe (see Findlay and Gilchrist, 1998, for a discussion). On a very general level, the purpose of eye movements is to bring regions or objects of interest outside the functional field of view close to foveal vision. It directly follows that individual effectiveness of extrafoveal processing should co-determine visual search performance. This prediction was tested by Nies et al. (1999), who studied eye movements of novice and expert subjects while searching for very small targets within a homogeneous background. They mapped the spatial extent of the useful field of view (UFV) for trials with target present. This was accomplished by discriminating between fixations around the target that immediately led to detection and those that were not successful. Fitting ellipses corresponding to 70% detection performance led to estimated individual UFVs differing substantially in size as well as horizontal and vertical extent. The validity of this technique was subsequently confirmed in a psychophysical detection experiment. Most importantly, within the sample of 15 subjects examined by Nies et al., the estimated size of the UFV showed a correlation of $r = 0.73$ with search performance. Hence, extrafoveal visual discrimination can be seen as a good predictor of effective search.

On the other hand, the amount of information that can be extracted from the periphery may also be a function of fixation duration. However, in an experiment by Hooge and Erkelens (1999), subjects were not able to strategically vary fixation durations in response to a task variation that required intensive peripheral information processing. This corresponds to a recent analysis of eye movements in reading by Radach and Heller (2000). They found no evidence in support of the hypothesis that a longer fixation duration, possibly allowing for more parafoveal processing, should lead to a longer subsequent saccade amplitude.

There is substantial evidence suggesting that features of the task determine scanning behavior. In addition to basic effects, such as the influence of distractor heterogeneity and target–distractor similarity (Duncan and Humphreys, 1989), recent experiments demonstrated a specific influence of search type ('serial' vs. 'parallel') on eye movement behavior. Gilchrist et al. (1999) found that in serial search subjects showed a greater stereotypical scanning behavior than in a search task where targets 'popped out'. In a series of experiments including both parallel vs. serial search, Zelinsky and Sheinberg (1997) found a substantial correlation between saccade number and response time, but only a weak correlation between average fixation duration and response time. This suggests that fixation durations more likely depend on stimulus factors than on differences in search type (serial vs. parallel) or task difficulty. Today, the distinction between serial and parallel processing as a strict dichotomy is generally seen as a useful, but fictitious heuristic (Wolfe, 1996).

In the current literature on visual search there is a lively debate about the role of memory processes. In response to a provocative study by Horowitz and Wolfe (1998), claiming that 'visual search has no memory', Gilchrist and Harvey (2000) measured eye movements while subjects had to scan an array of letters for a specific item. A reinspection [1] analysis showed that subjects relatively often returned to previously fixated items and that this pattern did not fit in a model of chance. Similarly, Peterson et al. (2001), who were also monitoring eye movements during a visual search task, showed that some items were reinspected during search and that the pattern of reinspections was incompatible with a memory-less search model. A large proportion of reinspections were directed to the target, indicating that subjects memorized which items were not adequately identified. In a dual task paradigm, Woodman et al. (2001) found that independent of the visual working memory load (2 vs. 4 items) visual search remains efficient.

An experimental manifestation of low-level short-term memory for locations already fixated has been termed the 'inhibition of saccade return' effect (Hooge and Frens, 2000), based on the concept of inhibition of return for spatial attention (Posner and Cohen, 1984; see Klein, 2000, for a recent discussion). In the critical experiment, subjects had to fixate a number of dots in accordance to a pre-specified scanning pattern. In this paradigm, reinspection saccades are part of the normal scan path. Interestingly, the duration of the preceding fixations were increased by up to 40%, a result that Hooge and Frens take as evidence for the proposed inhibition. This is in contradiction to eye movement patterns in reading, where the duration of fixations before regressive saccades back to positions to the left of the current fixation is short in comparison to fixations followed by progressions (Radach and Heller, 2000).

Methodology

The present experiment was carried out as part of a series of experimental tasks including a number of oculomotor standard paradigms whose results are not reported in this chapter. It used the visual scanning task developed by Zimmermann and Fimm (1993). As in the prior research discussed above (Ehrenreich et al., 1999), a group of cannabis users and a group of healthy controls were compared. However, there are two major differences between these two studies. First, in the present research, the cannabis group exclusively consisted of users with early onset of chronic drug consumption, in fact many of these users started already at the age of 14. Second, during the present experiment eye movements were recorded while participants were solving the task. Based on the evidence discussed in the previous sections, oculomotor irregularities in cannabis users can be expected in various respects. The neural control of eye movements is organized in terms of a hierarchy of control levels, from elementary, purely automatic control, to 'automated' control in terms of overlearned scanning routines (as found in reading), and to more top-down-based, strategic control (see Findlay and Walker, 1999, for a comprehensive review). The visual scanning task has the advantage that all of these levels are involved in generating appropriate oculomotor behavior such that analyses of eye movement parameters may generate evidence pointing to possible loci of adverse drug effects.

Participants

17 healthy pure cannabis users (14 male, 3 female) were recruited by advertisements in a local newspaper and by word of mouth. Mean age of participants in this group was 24.9 years (SD = 7.8) with a minimum of 19 years and a maximum of 45 years. The minimum requirement for long-term regular use of cannabis was a 4-year consumption period of about one joint per 1 or 2 days. Mean consumption duration amounted to 9.3 years (SD = 7.4; min. = 4, max. = 28). Participants smoked on average 10.5 joints per week (SD = 9.0; min. = 2, max. = 28) and had accumulated a mean life dose of 3526 joints (SD = 2210.8; min. = 728, max. = 7280). Most importantly, their age of onset of chronic cannabis consumption was low and quite homogeneous, ranging between age 14 and 16 (mean = 15.4; SD = 0.7). Users were free from any drug consumption between 16 and 40 hours before testing (mean = 30.9 hours; SD = 7.9 hours).

[1] In research on eye movements in visual search such as Gilchrist and Harvey (2000) a return to a previously fixated item is often called a 'refixation'. In basic oculomotor research the same term is used to describe the generation of a single, goal directed saccade (e.g. see Deubel et al., 2002, this volume) and in reading research it commonly refers to successive fixations on the same word (Inhoff and Radach, 1998). To avoid confusion, we decided to use the neutral term 'reinspection' instead.

Samples were taken from each user for (a) blood analysis of routine laboratory parameters, (b) urine screening using immunological routine methods for drugs (benzodiazepines, barbiturates, amphetamines, alcohol, cocaine and opiates), (c) determination of blood concentrations of Δ9THC and its major metabolites, THCOH and THCCOOH, by gas chromatography/mass spectrometry, and (d) measurement of total THC metabolites in urine by flúorescent polarization immunoassay (FPIA) (Moeller et al., 1992). Moreover, subjects underwent a semistructured psychiatric interview and a psychopathometric test (MMPI) to exclude individuals with depression or other psychopathological conditions potentially affecting test results. Cannabis users were also IQ-tested (mean = 118.1, SD = 9.9; min. = 107, max. = 137). The control group consisted of 20 healthy participants, matched in age and sex and without any past or present drug history including cannabis. Both groups consisted mainly of university students, all were socially integrated, successful individuals with comparable educational and socio-demographic status. Alcohol consumption was limited to a modest amount of about four beers per week (or equivalent) in both groups. All subjects took part in standard optometric testing to exclude participants with degraded visual acuity.

Task and procedure

The visual scanning task was developed by Zimmermann and Fimm (1993) as part of a computer-assisted neuropsychological test battery. Participants are asked to respond to the presence vs. absence of a prespecified fixed target appearing in a random position within a 5 × 5 matrix of squares. The squares all have an opening towards one side, thus there are four different possible stimuli in one matrix. During trials, the target stimulus is permanently presented in the left upper corner of the screen (see Fig. 4). There were 50 trials with and 50 trials without target, presented in fixed random order. Following the original instruction suggested by Zimmermann and Fimm (1993) and also used by Ehrenreich et al. (1999), subjects were explicitly asked to scan each matrix in a reading-like fashion line-by-line until they would either find a target or reach the end of the matrix.

Apparatus

Eye movements were recorded using an SR Research Ltd. EyeLink infrared eye tracking system at a sampling rate of 250 Hz (4 ms temporal resolution). The relative accuracy of the system is in the order of a few minutes of arc. Absolute accuracy in terms of short-term repeatability of fixation position mapping (McConkie, 1981) was estimated in independent test sessions to be better than 0.5° for a two-dimensional stimulus field. The on-line saccade detector of the eye tracker was set to detect saccades using an acceleration threshold of $9500°/s^2$ and a velocity threshold of 30°/s. Stimuli were displayed on a 21 inch EyeQ monitor subtending a visual angle of 34° horizontally and 25° vertically at a viewing distance of 67 cm. Each stimulus square was 16.5 mm wide and the effective visual angle amounted to 1.4 × 1.4° for each stimulus square and 9.6 × 9.6° for the whole 5 × 5 search array. The display was generated using a 'Matrox Millennium' video card running at a refresh rate of 100 Hz.

Results

General results

The drug screening applied to urine samples taken before the experiment indicated that none of the participants in the cannabis group had consumed any drugs in addition to cannabis. Their blood level of THC + THCOH was 1.7 ng/ml plasma (SD = 1.7, min. = 0, max. = 7.6). This value is quite low and very similar to the mean value of 1.9 (SD = 3.7) reported in Ehrenreich et al. (1999). In the analyses of response times and mean number of fixations, outliers of three or more standard deviations from the group mean were excluded, leading to the elimination of one control participant.[2] Subjects in the group of cannabis users with early age of onset were significantly slower in their responses in comparison to normal controls (see Fig. 1). This difference amounted to 316 ms ($F(1,34) = 6.24$,

[2] This altered the mean values for the control group in these two measures but did not change significance levels in the statistical tests.

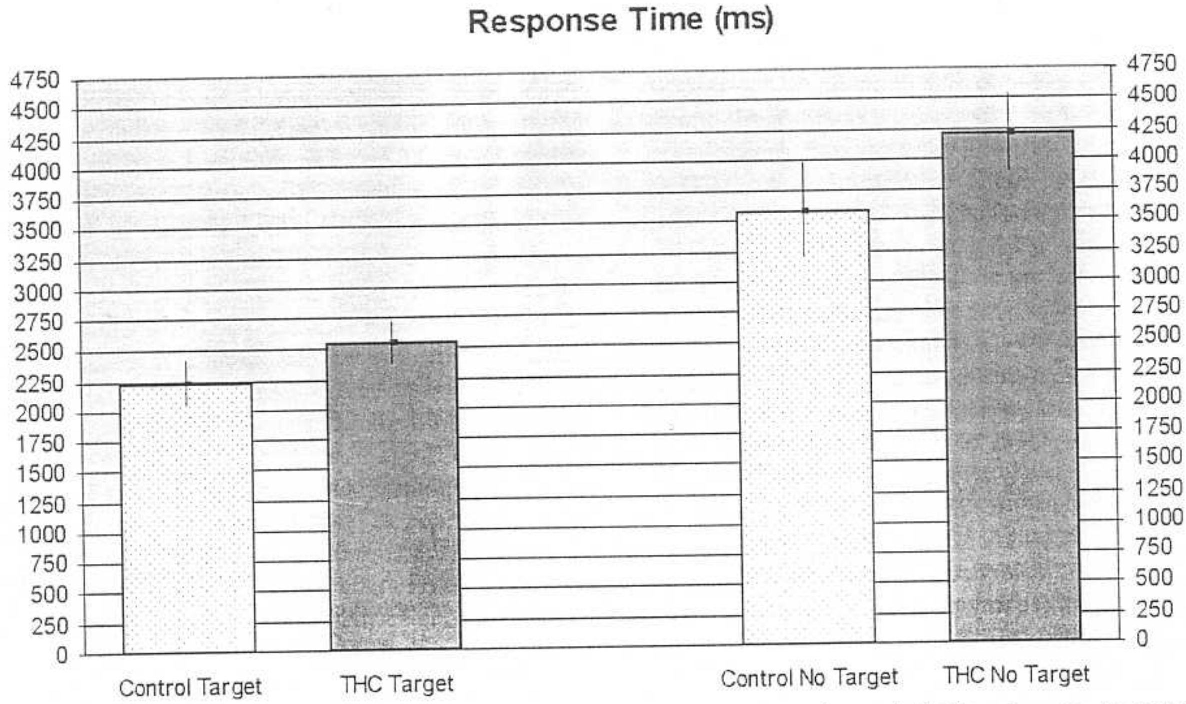

Fig. 1. Mean response times of cannabis users (dark columns) in comparison to normal controls (bright columns) in trials with target present (left columns) and trials with target absent (right columns). Vertical bars represent the standard error of the means.

TABLE 1

General results for participants in the control group vs. THC group

		RT, target (ms)	RT, no target (ms)	Fixation duration (ms)	Saccade amplitude (°)	Fixations per item (N)	Correct answers (N)
Control	mean	2225	3584	224	3.37	12.86	90.25
	SD	394	793	29	0.43	2.58	0.07
THC	mean	2541	4209	221	3.81	14.67	90.51
	SD	361	647	29	0.72	1.91	0.04

Group means are computed on the basis of subject means. SDs indicate the standard deviation of the subject means.

$p < 0.05$) in the target present condition and 625 ms ($F(1,34) = 6.62$, $p < 0.05$) in the target absent condition. There was no difference in the proportion of correct answers between the two groups (THC 91% vs. controls 90%; $F(1,35) = 0.02$). Mean fixation durations did not differ (THC 221 ms; controls 224 ms; $F(1,35) = 0.09$), but saccade amplitudes were significantly larger in the THC group (3.81° vs. 3.37°; $F(1,35) = 5.17$, $p < 0.05$). A significant difference was also present in the mean number of fixations per item. On average, cannabis users made 14.7 fixations on a 5×5 square stimulus page as opposed to 12.9 fixations in controls ($F(1,34) = 5.66$, $p < 0.05$). Table 1 gives an overview of these general performance and eye movement parameters.

Saccade peak velocities

The velocity of saccadic eye movements in relation to their amplitude is often seen as a key indicator to "access the overall neurologic integrity of the saccadic eye movement system" (Ciuffreda and Tannen,

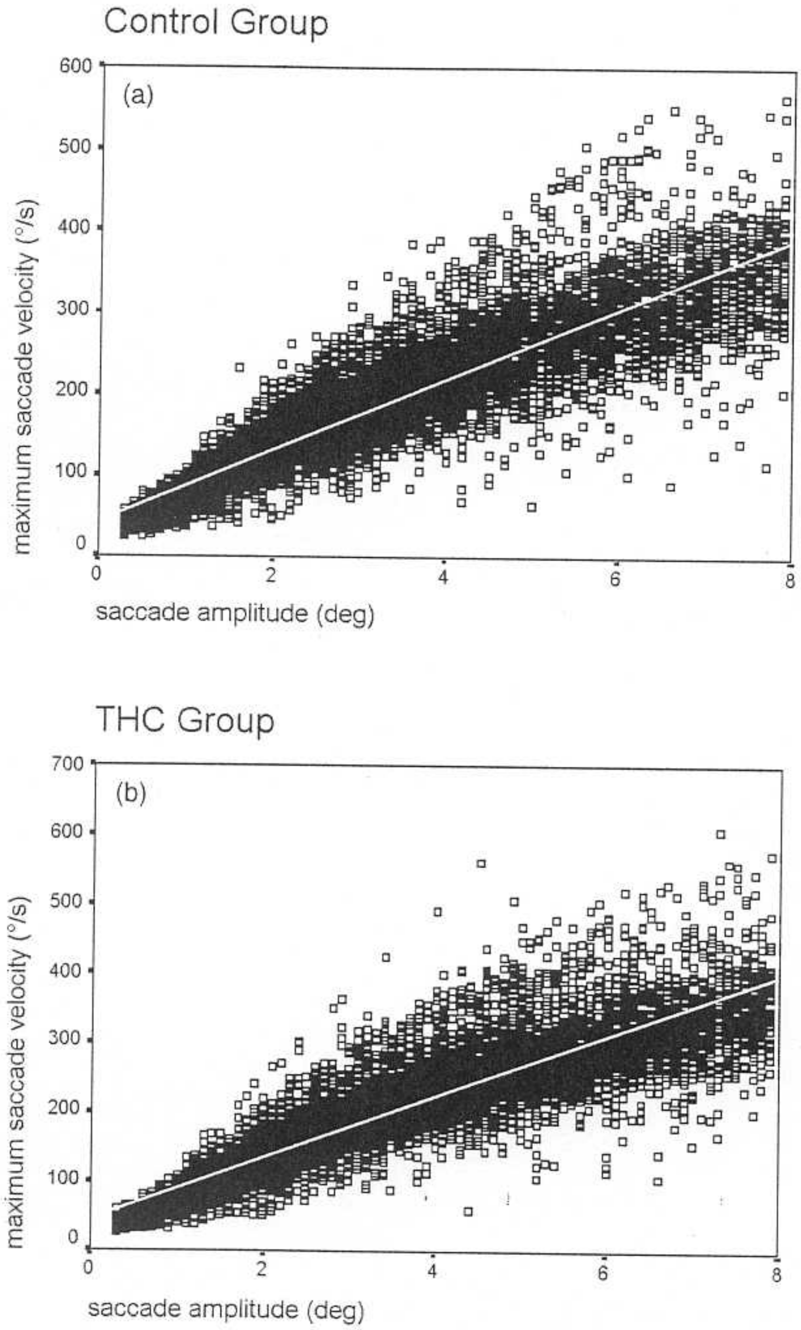

Fig. 2. Scatterplots of main sequence relations between saccade amplitude (°) and maximum velocity for participants in the control group (upper panel) and cannabis users (lower panel).

1994). This relation has been called the "main sequence" (Bahill et al., 1975) and reflects the pulse component of the pulse–step controller signal for saccade generation. Among the possible causes for decreased saccade peak velocities are drugs that reduce alertness (alcohol, barbiturates and diazepam), with most studies examining effects of acute alcohol intoxication (e.g. Heller and Lücke, 1987; see Moser et al., 1998 and Holdstock and de Witt, 1999, for recent discussions).

Fig. 2 presents scatterplots for both groups of the relation between saccade amplitude and peak velocity for saccades made in any direction within the search array (up to 8°). It is apparent from the figure that this relation is linear both for control participants (upper panel) and cannabis users (lower panel). The slopes of the linear regression curves are 43.27 for controls and 43.58 for users ($F(1,35) = 0.004$, $p > 0.05$), and the respective intercepts are 45.02 and 46.42 ($F(1,35) = 0.156$, $p > 0.05$). The mean correlation between saccade amplitude and maximum velocity is $r = 0.91$ in both groups. From these data it is evident that the main sequence relation is virtually identical for cannabis users and control participants. Separate analyses for horizontal, vertical and oblique saccades led to the same results. This can be taken as evidence that the neurophysiological machinery generating the pulse signal for saccades (see Sprenger et al., 2002; Munoz et al., 2002) is intact in chronic cannabis users with early onset.

Relations between saccade amplitudes and fixation durations

In a detailed analysis of a large corpus of reading data, Radach and Heller (2000) examined relations between spatial and temporal eye movement parameters. They found that fixations durations generally do not predict the extent of subsequent saccades. On the other hand, there was a significant relation between the amplitude of incoming saccades and the following fixation duration. This result is in harmony with prior observations in sentence reading tasks (Heller and Müller, 1983; Pollatsek et al., 1986) and was recently replicated in another study on a large corpus of reading data (Vitu et al., 2001). The interpretation suggested by Radach and Heller for this phenomenon is straightforward: the further away from its target an eye movement has been launched, the less opportunity for extrafoveal processing of the target object can be assumed. In the context of the present study this allows for an indirect assessment of extrafoveal processing. If cannabis users have a deficit in peripheral processing (target–non-target discrimination), this should be manifest in longer fixations as a function of incoming saccade

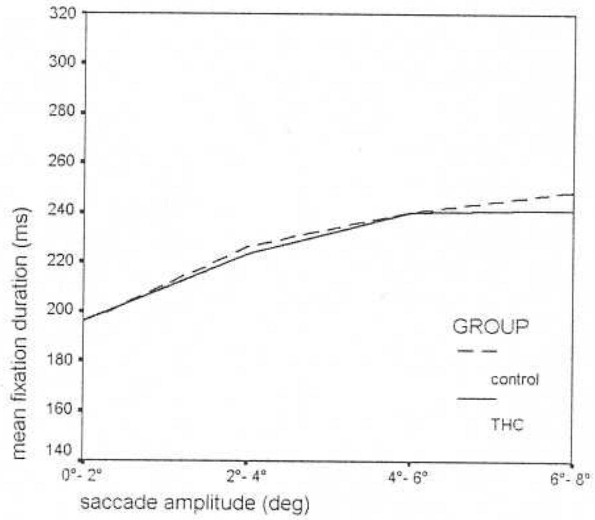

Fig. 3. Relation between saccade amplitude and subsequent fixation duration for control subjects vs. cannabis users. Group means are computed on the basis of subject means. One data point represents at least 5000 observations and each subject contributed at least 50 observations to the group means.

amplitude. Fig. 3 shows this relation for saccade amplitude ranges of up to 2°, 2–4°, 4–6° and 6–8°, including a total of more than 40,000 observations. As the figure indicates, fixation durations are longer following larger incoming saccades, replicating the results found by Radach and Heller (2000) in reading ($F(3, 105) = 106.82$, $p < 0.01$). Most importantly, the two groups do not differ significantly ($F(1,35) = 0.148$, $p > 0.05$).

Scan path analyses

In the present visual scanning task, participants were asked to scan a 5×5 array of potential targets sequentially in a reading-like fashion. A straightforward indicator for the degree to which viewing behavior corresponded to this instruction is the correlation between the ordinal number of each fixation with the 'line' in the stimulus array that is currently fixated.[3] Interestingly, this correlation is

[3] This is similar to a suggestion in the original test documentation by Zimmermann and Fimm (1993). They propose for all items in the target present condition to compute a correlation between response time and the ordinal number of the line in which the target occurred.

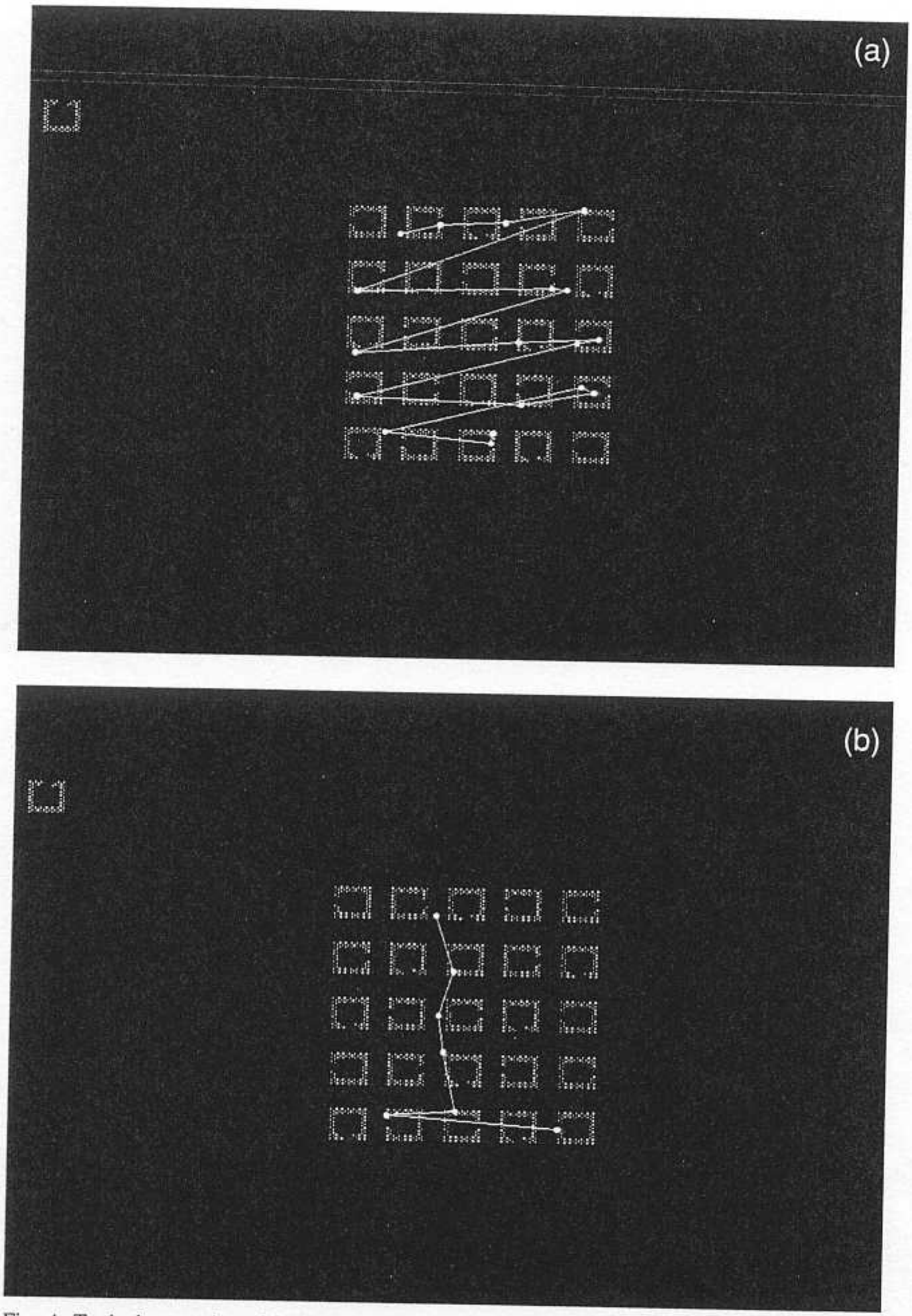

Fig. 4. Typical examples of individual scan paths on a search array; item without critical target. The upper panel shows a sequential, reading-like scanning pattern and the lower panel depicts a more holistic and 'parallel' pattern.

substantially larger for the group of cannabis users ($r = 0.52$; $p < 0.01$) than for the controls ($r = 0.44$; $p < 0.01$). This appears to indicate, somewhat surprisingly, that scan paths in cannabis users were more 'systematic' or 'regular', and in better agreement with the instruction. Independent visual inspection of all scan paths produced in this study by two experts (the first two authors of this chapter) suggested that most participants adopted a coherent scanning pattern throughout the experiment. These individual scanning patterns can be grouped into two classes, a sequential line by line pattern and a more holistic (or 'parallel') pattern with only one or two fixations on each line. In the second class of scanning patterns there were several, intraindividually stable types of scan paths, for example moving from the center of the first line to the center of the last line or moving around the search array in one u-shaped scan path. Two typical examples are given in Fig. 4.

In the control group, both patterns were almost evenly represented, with 9 subjects scanning rather sequentially and 8 in a more holistic way, while 3 participants appeared to have no clear strategy. However, in the group of chronic cannabis users 14 of 17 subjects were classified 'sequential scanners', and 3 showed more unsystematic patterns. These observations, together with the finding that control subjects made significantly less fixations per item, suggest that, contrary to the correlation analysis reported above, their scanning behavior was not necessarily more unsystematic or irregular. Instead, many of the control subjects appeared to have developed their own, more effective way to solve the task. A comparison of subjects in the control group classified as 'sequential' vs. 'holistic' scanners indicted that the latter were markedly more efficient. On average, they responded to items with target absent 1297 ms faster (3012 ms vs. 4309 ms for 'sequential' scanners; $F(2,15) = 11.22$, $p < 0.01$) and to items with target present 653 ms faster (1918 ms vs. 2571 ms for 'sequential' scanners; $F(2,15) = 14.86$, $p < 0.01$) than subjects scanning in a more sequential way. Remarkably, this better search performance was achieved at almost the same error level (89% as opposed to 92.1% in serial scanners; $F(1,15) = 1.09$, $p > 0.05$).

In an attempt to assess scan systematicity and to quantify group differences we used a method proposed by Ponsoda et al. (1995). In a first step of analysis, a probability vector was computed that represents the relative number of saccades targeted towards each of eight direction categories (north, northeast, east and so forth). In a second step, for each fixation incoming and outgoing saccades are set into relation to create a transition matrix representing conditional direction vectors. Every entry in this matrix displays the proportion of outgoing saccades to a specific direction relative to a certain incoming saccade direction. This technique is relatively simple but provides an effective tool to determine quantitatively how systematic the scanning behavior is in a given subject. For example, if scanning is systematic in terms of a reading-like sequential pattern, most of the saccades coming from the west should be succeeded by saccades directed to the east, or, in the case of 'returns sweeps' to the beginning of the text line, saccades to the west or southwest. If a subject scans the search array in a u-like fashion starting in the left upper corner, saccades coming from the north should regularly be followed by saccade going to the south or the east, etc. As opposed to the regular patterns described above, unsystematic scanning would produce a random distribution of saccades over the different direction vectors and conditional vectors.

The frequency distribution of saccade directions, as expressed in angular saccade vectors, is presented in Fig. 5. Both show a relatively systematic scanning behavior, with most of the saccades being directed to the east (controls 35.4%; THC 36.9%). In the figure, this large peak somewhat obscures significant group differences in westward and northwestward saccades. Subjects in the cannabis group made significantly more saccades directed to the west (25% vs. 22.4% for controls; $F(1,35) = 5.62$, $p < 0.05$), and significantly less saccades directed to the northwest (6.4% vs. 7.6% for controls; $F(1,35) = 6.45$, $p < 0.05$), corresponding to a more reading-like type of scanning.

In a second step of analysis, conditional transition vectors of saccade direction were computed, expressing the relative frequency of a specific direction pairing relative to all pairs beginning with a specific direction. Of the 64 pairs that could be analyzed in the respective transition matrix, we focused on the horizontal directions, as they were most frequent and also promised to provide some additional information regarding the differences in westward saccade frequencies mentioned above. Looking at saccade pairs starting with an eastward saccade (reading direction), it turned out that many of them were followed by a saccade in the opposite direction (Table 2). This effect was substantially stronger in the cannabis group (THC 45%; controls 38%; $F(1,35) = 4.58$, $p < 0.05$). This means that after an eastward saccade, THC subjects were more likely to continue with a saccade in the opposite direction. A subsequent eastward saccade was slightly less likely (38% for both groups; $F(1,35) = 0.01$, $p > 0.05$). A second significant group difference was present

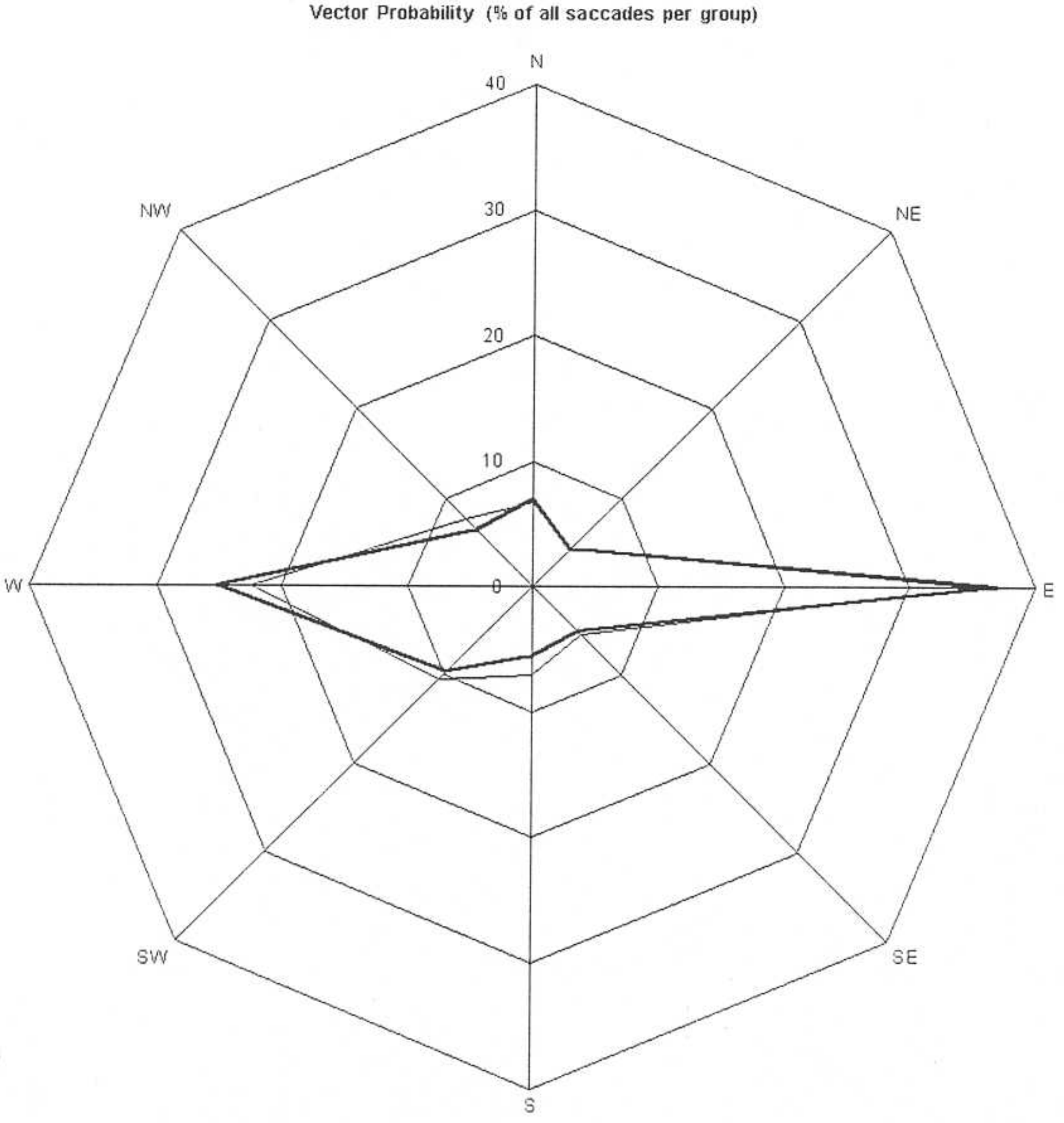

Fig. 5. Spatial distribution of relative vector probability of saccade direction. The thick line represents the THC group, and the thin line represents the control group.

in south-going subsequent saccades (THC 8%; controls 14%; $F(1,35) = 4.71$, $p < 0.05$). Saccades to the north did not differ between the groups. In pairs starting with a westward saccade about half were followed by a saccade to the east, which was significantly more frequent in the THC group (63% vs. 54% for controls; $F(1,35) = 4.67$, $p < 0.05$). On the other hand, control subjects significantly more often continued with a saccade to the north (16% vs. 11% for THC; $F(1,35) = 4.80$, $p < 0.05$). Subsequent saccades to the west did not differ between the groups, and saccades to the south were slightly more frequent in the control group (13% vs. 10% for THC; $F(1,35) = 1.99$, $p > 0.05$), without producing a significant difference.

In general, this analysis provides a quantitative base for the group differences reported above. First, it shows that control subjects are significantly more

TABLE 2

Relative frequencies of conditional saccade direction pairs (see text for further explanations)

		First saccade eastward				First saccade westward			
Second saccade (percent):		north	east	south	west	north	east	south	west
Control	mean	10	38	14	38	16	54	13	17
	SD	8.5	14.4	11.1	7.3	8.5	15.2	9.1	7.0
THC	mean	9	38	8	45	11	63	10	16
	SD	5.9	12.9	5.9	12.2	4.7	11.0	6.2	5.9

likely to continue an incoming horizontal saccade with a vertical saccade. Second, it indicates that cannabis users, following an incoming horizontal saccade more frequently continue to make a saccade into the opposite direction. It needs to be noted that this last figure includes both reinspection saccades going back to locations on the current and 'return sweeps' going to the beginning of the scan path on the next line in the search array. In an attempt to address the question of reinspections in a more direct way, we computed the probability with which the same stimulus element was returned to after the eyes had scanned another element. Due to the nature of the task (fairly easy discrimination of only four possible stimuli), usually more than one element was processed during one fixation and the total number of reinspections is relatively small. In the control group this frequency was 4.5% (SD = 2.3) and in the cannabis group it amounted to 6.4% (SD = 2.3). Despite these small probabilities of reinspection, the group difference was significant ($F(1,35) = 6.35$, $p < 0.05$).

Discussion

The present chapter started with reviewing some of the literature on long-term effects of cannabis on human cognition and behavior. This discussion indicated that much of the earlier literature suffered from various methodological and theoretical problems, but that recent research is more solid in its methodology and theoretical base. However, the results of this literature review are also not conclusive in that many of the studies show no differences between cannabis users and controls, while others appear to demonstrate massive performance deficits in various tasks. In some cases such deficits may be caused by residual intoxication, but there are also a few observations that point to the possibility of permanent damage to the nervous system.

One of the studies supporting the idea of long-term impairments due to cannabis was the research by Ehrenreich et al. (1999). They developed the novel hypothesis that there may be a specific vulnerability for cannabis in terms of interactions between THC and other cannabis metabolites and the human brain's cannabinoid receptor system at a peripubertal age. The empirical part of this chapter again tested their suggestion that visual search performance is degraded in cannabis users with early onset of their drug consumption. This hypothesis was confirmed in showing that cannabis users needed substantially more time than controls to complete a visual scanning task at about the same error level.

In our analyses of eye movements while participants were solving the task, several aspects were considered. First, we examined the 'main sequence relation' of saccade velocity as a function of saccade amplitude and found in both groups a linear relation with virtually identical slopes and intercepts. This indicates that the step component of the pulse–step signal in the saccade generation is not affected by chronic use of cannabis. This finding may be generalized to the claim that the basic brainstem machinery of saccade generation (see Sprenger et al., 2002; Munoz et al., 2002) is intact. This corresponds to results of recent experiments in our laboratory involving the same groups of subjects but using the standard gap and overlap paradigms. Here saccade velocity was also identical for the two groups, but latencies were significantly slower in cannabis users.

In a second stage of analysis we considered the relation between saccade amplitude and the duration of the subsequent fixation. Consistent with earlier findings on eye movements in reading (Radach and Heller, 2000), fixation duration increased substantially following saccades that came from more distant locations. This effect has recently been replicated by Vitu et al. (2001) who termed it the 'saccade distance effect'. These observations are in harmony also with supplementary unpublished analyses of a data set by Nies et al. (1999) on visual search of small targets over an unstructured (in half of the cases empty) stimulus field, where we found the same relation. In the current experiment, there were no group differences between control subjects and cannabis users with respect to the saccade distance effect. Following the logic suggested in the section on visual search and eye movements, this can be taken to suggest that chronic cannabis consumption does not result in an impairment of extrafoveal discrimination. A more modest interpretation would be that the use of extrafoveal information is not degraded to the degree that this information is used to determine the subsequent fixation duration. This includes the possibility that it is not the immediate use of processing results from extrafoveally acquired information that determines the duration of the following fixation. Instead, it is possible that information about the saccade amplitude or launch distance is utilized to pre-determine a fixation duration that is likely to allow for successful search (Hooge and Erkelens, 1998).

Our analysis of scan paths started with the observation that the correlation between ordinal number of fixation and the number of the line in the stimulus array that is being fixated is larger in cannabis users. This suggested that these participants scanned the search array in a more regular way and in better correspondence with the instruction. However, visual inspection of scan paths appeared to indicate that many of the control subjects used a more holistic strategy including more parallel processing of adjacent elements. Several aspects of these observations were subsequently confirmed in a quantitative analysis of conditional transition vectors of saccade direction. Most importantly, this analysis suggests that cannabis users may have made more reinspection saccades to regions in the stimulus array that had been previously processed. This hypothesis was tested in a more direct way by computing the frequency of returns to single elements, with the result that indeed cannabis users made more such reinspections.

In many search tasks, participants have to deal with two concurrent sources of memory load. One is to memorize the relevant target and one is to keep track of the regions or objects that have already been processed. The first kind of memory load can be considered minimal in the present experiment since the critical element that participants are asked to find never changed. In fact, subjects in both groups almost never fixated the comparison target. However, the second source of visual short-term memory load is present in this task, and the data indicate that participants in the cannabis group have greater difficulties to deal with it. The suggestion that cannabis users may have a deficit in visual short-term memory nicely corresponds to results of a recent experiment examining the same subjects in a memory guided saccade paradigm. We asked participants to delay a response to a target that disappeared after a short presentation duration. In the group of cannabis users, saccades towards the former target locations were substantially hypermetric relative to controls. Similarly, saccades were also hypermetric in the standard antisaccade task that requires a spatial re-mapping of stimulus coordinates.

Taken together, the results of the present study indicate that long-term cannabis users with early age of onset are substantially less efficient in visual scanning. In line with Ehrenreich et al. (1999), we assume that early and massive use of cannabis starting at peripubertal age (up to age 16) is causing specific impairments in visual processing and that these deficits are due to permanent neurotoxic damage as opposed to residual effects of recent drug use. This interpretation is also backed by the fact that there was no suggestion of any alteration in the saccade amplitude–velocity relation for the cannabis group which could have been diagnostic for behaviorally relevant residual effects. Two possible loci of adverse effects have been identified in this study. One is at the level of visual short-term memory, and one at a more strategic, top down controlled level of individual search patterns.

It is not easy to conclude on the basis of our data whether the observed differences in search patterns are of clinical importance. One may claim that although cannabis users were significantly less efficient, their visual search behavior was not nearly as dramatically disrupted as seen in patients with damage to specific brain areas in the visual and oculomotor systems (e.g. see the research on consequences of visual neglect after parietal lesions by Husain et al., 2001, or Sprenger et al., 2002). However, the observed conservatism of cannabis users in visual scanning strategies takes on a different aspect when seen in the context of the classic "a-motivational syndrome hypothesis" (McGlothlin and West, 1968). This hypothesis states that regular use of marijuana in young people may contribute to the development of passive, inward-turning, a-motivational personality characteristics.[4] An alternative or complementary idea is that conservative scanning may have developed *in response* to a self-perceived, neurotoxically caused reduction in visual processing efficiency. This argument could be based on the observations made in the present experiment pointing to problems with visual short-term memory and on results recently obtained in our laboratory using the memory-guided saccade paradigm (s.a.). These hypotheses will need to be addressed in future research.

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[4] In the laboratory, participants in the group of cannabis users portrayed themselves not as suffering from an addiction but rather as people pursuing a certain way of life. They appeared extremely motivated, asserting that they were eager to show that people who take cannabis are 'not stupid'. It is possible that in our study this extra motivation has acted to counterbalance deficits that may well make a larger difference in real life.

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