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Long-term effects of cannabis on oculomotor function in humans

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Abstract

Cannabis is known to affect human cognitive and visuomotor skills directly after consumption. Some studies even point to rather long-lasting effects, especially after chronic tetrahydrocannabinol (THC) abuse. However, it is still unknown whether long-term effects on basic visual and oculomotor processing may exist. In the present study, the performance of 20 healthy long-term cannabis users without acute THC intoxication and 20 control subjects were examined in four basic visuomotor paradigms to search for specific long-term impairments. Subjects were asked to perform: 1) reflexive saccades to visual targets (prosaccades), including gap and overlap conditions, 2) voluntary antisaccades, 3) memory-guided saccades and 4) double-step saccades. Spatial and temporal parameters of the saccades were subsequently analysed. THC subjects exhibited a significant increase of latency in the prosaccade and antisaccade tasks, as well as prolonged saccade amplitudes in the antisaccade and memory-guided task, compared with the control subjects. The results point to substantial and specific long-term deficits in basic temporal processing of saccades and impaired visuo-spatial working memory. We suggest that these impairments are a major contributor to degraded performance of chronic users in a vital everyday task like visual search, and they might potentially also affect spatial navigation and reading.

Key words

adverse effects; cannabis; eye movements; long-term effects; oculomotor control; saccades; THC

Introduction

Cannabis is known to be the most frequently used illegal drug. It interacts with an endogenous cannabinoid receptor system that is widely distributed in the central nervous system (Herkenham, *et al*., 1990; Glass, *et al*., 1997). CB-1 receptors show a high density in substantia nigra, cerebellum, hippocampus, cingulate cortex and dorsolateral prefrontal cortex. Acute effects of cannabis on perception, cognition and behaviour have been attributed to a change of activity in these areas because of the consumption of exogenous cannabinoids (see Solowij, 1998, for a review of acute cognitive effects). Opposed to acute effects, long-term effects are defined as persisting effects after at least one day of abstinence (Pope, *et al*., 1995). Research conducted over the last decades on long-term effects has led to rather heterogeneous results. One important reason for this was an inadequate methodology in many studies. These inadequacies comprise a lack of control for the abstinence length, the use of other drugs apart from tetrahydrocannabinol (THC) and/or general cognitive or psychiatric impairments (Gonzalez, *et al*., 2002).

Nonetheless, some studies with higher methodological standards have shown two major sources of cognitive impairment. One is a decrease of attentional functions (e.g., Fletcher, *et al*., 1996; Pope and Yurgelun-Todd, 1996; Croft, *et al*., 2001) and the other source is an impairment of memory functions (Fletcher, *et al*., 1996; Rodgers, 2000; Solowij, *et al*., 2002; Lamers, *et al*., 2006). For example, it was shown that THC lessens the action potentials of neurons in the hippocampus, consequently weakening the neural circuit required to create a memory (Sullivan, 2000). Although this finding rather refers to acute effects, similar mechanisms might also underlie rather long-lasting deficits.

However, none of these studies addressed the issue of oculomotor control. Given the scope of current debates on the impact of cannabis on society, including its therapeutic use, it appears essential to provide a clear answer to the question of whether there are relevant long-term adverse effects of chronic use on visual information processing and oculomotor control because this is a critical base for many important human skills and abilities like searching in a visual scene (Huestegge, *et al*., 2002), driving a vehicle (e.g., Warren, *et al*., 1981) or reading written text.

Previous research on effects of THC on basic oculomotor control focused on acute effects in non-regular cannabis users. Ploner, *et al*. (2002) analysed eye movements of 12 subjects in

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visually and memory-guided oculomotor paradigms 2 h after an oral dose of THC. As a result of this pre–post study, they found 12 ms increase of latencies in visually guided saccades and greater saccade amplitudes of memory-guided saccades compared with the baseline testing. However, the impairments were quite small, and it remained an open question whether these deficits might persist for longer periods of time, especially in chronic users.

In a previous study, we already obtained initial evidence for substantial long-term effects on visual processing (Ehrenreich, *et al*., 1999). Ninety-nine long-term users were tested with a neuropsychological test battery. Long-term cannabis users without acute intoxication exhibited prolonged response times in a visual scanning task, but not in other attention-related tests, including divided attention, short-term memory and alertness. The critical task required a serial visual search for a target in a two-dimensional array. Interestingly, the finding of slowed response times in this paradigm was only present in users who had started to use cannabis regularly before the age of 17. This is in harmony with results from animal studies that reported the crucial role of the age of onset for long-term consequences of cannabis consumption (Stiglick and Kalant, 1985; Soderstrom and Johnson, 2003).

In a follow-up study to Ehrenreich, *et al*. (1999), we replicated the finding of slowed visual search with a new group of THC subjects (Huestegge, *et al*., 2002). An analysis of eye movements in this task showed greater saccade amplitudes and a higher rate of reinspections of locations in the stimulus array that had already been fixated before. Also evident were differences in search strategy, with a more thorough scan of the THC group, that were explained in terms of a compensation for visuomotor deficits. Taken together, these results pointed towards deficits in basic oculomotor control and visuo-spatial working memory. However, because of the complexity of the task, it was not possible to exactly determine the causes of these deficits. Consequently, the goal of the present article is to obtain a comprehensive in-depth picture of long-term cannabis effects on visual processing and oculomotor control in chronic users.

For this purpose, four tasks were selected that are indicative of different levels of visuomotor control (Findlay and Walker, 1999). These include automatic saccade programming and execution (prosaccades), initiation of voluntary saccades (antisaccades), visuo-spatial memory processes (memory-guided saccades) and the ability to flexibly reprogram saccades based on new incoming visual information (double-step saccades). These paradigms reflect critical elements in the visuomotor control system supporting more complex perceptual and cognitive tasks. The corresponding saccadic eye movements are controlled by an extensive neural network, including the basal ganglia, the brainstem, the cerebellum and the parietal and frontal cortices. Any dysfunction in these regions leads to specific and distinct deviations in eye movement patterns from which the functional status of the neuronal substrates of the network can be inferred (Leigh and Kennard, 2004).

Methods and materials

Participants

The performance of 20 chronic THC users with a minimum abstinence period of 24 h and an age of onset below the age of 17 was compared with that of 20 control subjects without previous drug experience. THC users were recruited by advertisements in local newspapers in Aachen, Germany, and by word of mouth. A minimum requirement for chronic users was a twice per week consumption for at least 2 years. To avoid shortcomings of previous studies (see Gonzalez, *et al*., 2002), we selected students that were academically successful members of the university community without general cognitive impairments as indicated by a nonverbal intelligence screening (mean IQ = 118.1, SD = 9.9; Range: 107–137). Their mean age was 25 years, ranging from 19 to 45 years. A semi-structured interview was conducted to exclude subjects with past or present neurological or psychiatric diseases, head injury or experience with other drugs except nicotine, caffeine and a modest consumption of alcohol. During this interview, all subjects had to verbally confirm the requested 24 h of abstinence. Additionally, a personality screening (MMPI-S) was administered to exclude participants with considerable deviations from normal healthy personality profiles. The control group consisted of 20 healthy university students who participated voluntarily. They were matched in age (M = 24 years) and sex and of comparable educational and socio-demographic status (students at the local university), without any past or present drug history including cannabis. Alcohol consumption was limited to a modest amount of about 4 beers/week (or equivalent) in both groups. All subjects took part in standard optometric testing to exclude participants with degraded visual acuity. Informed consent was obtained from all participants.

Study protocol

All experiments were completed in one session immediately after a blood and urine screening. No cannabis or other drug consumption including alcohol was allowed 24 h before testing. The respective self-reports of all participants were confirmed by subsequent blood and urine analyses. Tests of blood samples included routine laboratory parameters and measured the concentration of delta-9-tetrahydrocannabinol and its metabolites THCOH and THCCOOH via gas chromatography/mass spectrometry (see Moeller, *et al*., 1992). THCCOOH is a long-lasting inactive metabolite, reflecting previous THC use even several days after modest drug exposure (Iversen, 2000). The urine screening was conducted to test for drugs of abuse (benzodiazepines, barbiturates, amphetamines, ephedrines, morphine and related opioids, methadone, cocaine and alcohol). The experimental session lasted for about 1 h, including breaks to avoid fatigue. During a second session later on the

same day, the interviews, as well as the neuropsychological and psychopathological testing (see above), were conducted.

Mean THC consumption duration in the THC group amounted to 9 years (SD = 7.4). Participants smoked on average 10.5 joints/week and had an accumulated life time doses of about 3500 joints (SD = 2200). The age of onset of chronic cannabis consumption was similar between participants, ranging from the age of 14 to 16. The drug screening that was applied to the 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, range: 0–7.6). This value is quite low and very similar to the mean value of 1.9 (SD = 3.7) reported in Ehrenreich, *et al*. (1999), emphasising the credibility of the self-report of at least 24 h of abstinence before testing.

Eye movement recording

Horizontal eye movements were recorded using a head-mounted infrared eye-tracking system (Eyelink, SR Research Ltd., Osgoode, Canada). The infrared reflection of the right pupil was monitored with a high-speed video camera, whereas a second camera tracked head movements for online compensation. The sampling frequency was 250 Hz with a relative spatial accuracy in the order of few minutes of arc. Subjects were seated comfortably in front of a 21-inch CRT monitor at a distance of 67 cm with the total display area subtending a visual angle of 34° horizontally and 25° vertically. A calibration procedure was executed before each block of trials within each experiment.

Paradigms

In the prosaccade paradigm (Figure 1A,B), subjects were instructed to fixate on the middle of a green cross as a central fixation point on a black screen. In the gap condition, this fixation point was switched off after 2000 ms. For 200 ms (gap period), no visual information was presented on the screen, before a green target square appeared at a pseudorandom position either at 6° to the left or right of the centre. After 1000 ms, the target disappeared and the central fixation point was switched on again. In the overlap condition, the central fixation point remained visible during the full duration of the trial. Subjects were instructed to look at the target as quickly and accurately as possible. Half of the trials consisted of gap trials, whereas the other half consisted of overlap trials, presented in random order within each block. The experiment consisted of four blocks with 30 trials each. Usually, the gap period leads to a reduction in saccadic response times (Fischer and Weber, 1997). This 'gap effect' is assumed to be based on two components: an unspecific warning signal component that can also be elicited by luminosity change of the central fixation point (Ross and Ross, 1980) and a specific oculomotor component that is based on a decrease in fixation cell activity in the brainstem (Dorris and Munoz, 1995).

The antisaccade paradigm (Figure 1A,B) was always conducted after the prosaccade experiment. In this study, the visual information on the screen was exactly the same, including gap and overlap conditions. Critically, subjects were instructed to look as quickly and accurately as possible in the opposite direction of the target with approximately the same saccade amplitude. Performance in this paradigm reflects the cognitive (voluntary) level of control, demanding the preparation and execution of a deliberate saccade despite a concurrent automatic response tendency (Hallett, 1978).

In the memory-guided saccade paradigm (Hikosaka and Wurtz, 1983), subjects first had to fixate a central fixation point (Figure 1C). After 2200 ms, a target appeared for 1000 ms at 3° or 6° eccentricity either to the left or right. During this time, participants were instructed to remain fixated at the central fixation point. After the target disappeared, they had to memorise its position for 1500 ms (memory delay). After this time interval, the central fixation point disappeared, which served as a signal to execute an eye movement to the previous target position as quickly and accurately as possible. After 1000 ms, they had to fixate the reappearing central fixation point. Memory-guided saccades differ from prosaccades because subjects are asked to perform a delayed response. A comparison of latency differences across both paradigms, therefore, allows a separation of early processes associated with saccade preparation from later processes of saccade execution. An analysis of spatial parameters can show the integrity of the saccade-related visuo-spatial working memory.

In the double-step paradigm (Figure 1D), each trial was started with the presentation of a central fixation point. After 2500 ms, a target appeared at 3° eccentricity either to the left or right for 40, 70 or 100 ms (interstimulus interval). In 50% of the trials, this target was replaced by a second target appearing at 6° eccentricity in the same direction as the first target. In their classic experiments, Becker and Jürgens (1979) referred to this stimulus pattern as the 'stair case' condition. After 1000 ms, this second target disappeared, and the central fixation point was presented again. In the other half of the trials, no second target appeared. Subjects were instructed to follow the targets with their eyes as quickly and accurately as possible. As in the previous paradigms, 120 trials, divided into four blocks, were presented in random order. The double-step paradigm allows examining the individual ability to reprogram saccades as a function of the sudden appearance of new visual information. More generally, it is assumed to be an excellent indicator for 'automated' saccade control on a level of routine visuomotor behaviour (Findlay and Walker, 1999). All paradigms were presented in the same order as described here.

Data analysis

In the prosaccade and antisaccade paradigm, data analysis focused on the first (primary) saccade after target onset. In the memory-guided saccade paradigm, initial saccades after the cueing signal (fixation point offset) were examined. In addition, erroneous saccades towards the target directly after its onset

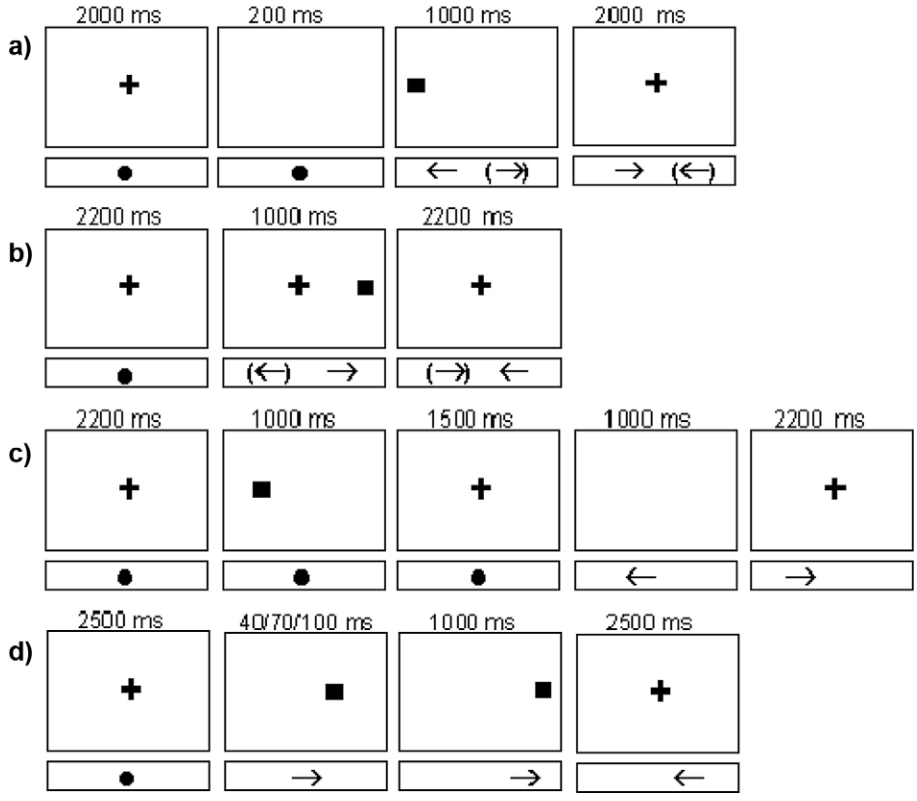

Figure 1 Oculomotor paradigms used in this study: Schematic screenshots of a single trial and instructed eye movements (*indicated below*). A) prosaccades and antisaccades (*in parentheses*), gap condition; B) prosaccades and antisaccades (*in parentheses*), overlap condition; C) memory-guided saccade paradigm; note that targets can appear at 3° or 6° eccentricity; D) double-step paradigm; note that in half of the trials the second target at 6° eccentricity is omitted.

were considered. For these three paradigms, we computed mean saccade latencies and amplitudes for each subject and condition. In the prosaccade paradigm, we additionally analysed the stability of the fixation by computing the fixation drift velocity. In the antisaccade and memory-guided paradigm, the frequency of erroneous saccades towards the appearing stimuli was also computed individually and compared between groups.

In the double-step paradigm, the first two saccades after the presentation of the two subsequent targets in the 'stair case' condition were selected for analysis. Critically, saccade amplitudes and the mean probability of a single saccade response were computed as a function of reprogramming time, defined as the interval between the appearance of the second target and the onset of the initial saccade response (Becker and Jürgens, 1979). Typically, if this interval is short, there is no time for cancellation and/or modification of the impeding saccadic response. Therefore, participants execute a two-step response, including an initial saccade towards the first target followed by a secondary saccade towards the final target. If reprogramming time is long, the second target triggers the reprogramming of the saccade amplitude, and in the following single-step response, the eyes attain the position of the second target. Interestingly, if the available reprogramming time ranges between about 70 and 140 ms, a linear relationship of time and saccade amplitude can be observed (amplitude transition function). This dependency can be used to assess the individual ability to rapidly take into account new visual information for saccade preparation (Becker, 1989).

Because of data loss, one subject of the THC group had to be excluded from analysis of memory-guided saccades. In the prosaccade and antisaccade task, we were also interested in any differences regarding the gap effect, requiring the test of interactions. We, therefore, carried out multi-factor ANOVAs in these tasks. In the memory-guided task, we were not interested in interactions and therefore chose to test the directional hypotheses about the effect of the group factor with more powerful Bonferroni-adjusted one-tailed a priori contrasts. In the double-step paradigm, ANOVAs were used for the comparison of several intervals of the reprogramming time across groups. The critical α-level was 5%. Saccade amplitudes in prosaccades and antisaccades were pooled for overlap and gap conditions because previous research has never suggested gap effects on spatial saccade parameters.

Results

In the prosaccade paradigm, mean latencies of initial saccades were significantly reduced in the gap compared with the overlap trials ($F(1,38) = 260$; $P < 0.01$). In the THC group, the mean latency amounted to 135 ms (SD = 17) in the gap condition and 197 ms (SD = 36) in the overlap condition. In the control group, the latency in the gap condition amounted to 126 ms (SD = 16) compared with 175 ms (SD = 26) in the overlap condition. Latencies were significantly prolonged in the THC group compared with the controls ($F(1,38) = 4.25$; $P > 0.05$; see Figure 2). The two-way interaction between the factors group and condition (gap versus overlap) was not statistically significant ($F(1,38) = 3.60$; $P = 0.064$) although the difference between users and controls tended to be nominally greater in the overlap compared with the gap condition. The initial saccade amplitude had a length of 5.81° (SD = 0.18) in the THC group and 5.73° (SD = 0.22) in the control group. It did not differ significantly between groups ($F(1,38) = 1.35$; $P > 0.05$; see Figure 3). An additional analysis of fixation drift velocity in this task as a measure for fixation stability yielded no significant differences between the THC (0.341°/s) and the control group (0.367°/s) ($F(1,38) = 0.72$; $P > 0.05$).

In the antisaccade paradigm, saccade latencies were also significantly reduced in the gap compared with the overlap trials ($F(1,38) = 205$; $P < 0.01$). In the THC group, the mean latency amounted to 224 ms (SD = 40) in the gap condition and 299 ms (SD = 62) in the overlap condition. In the control group, the mean latency in the gap condition amounted to 196 ms (SD = 38) compared with 265 ms (SD = 39) in the overlap condition. Latencies were significantly prolonged in the THC group compared with the controls ($F(1,38) = 5.01$; $P < 0.05$; see Figure 2). The two-way interaction between the factors group and condition was not statistically significant ($F(1,38) = 0.42$; $P > 0.05$), indicating that the gap effect did not differ between groups. The mean amplitude of the initial saccade had a length of 5.50° (SD = 0.66) in the THC group and 4.99° (SD = 0.65) in the control group. It was significantly larger in the THC group compared with the controls ($F(1,38) = 6.20$; $P < 0.01$; see Figure 3).

In the gap condition, the percentage of erroneous saccades amounted to 24% (SD = 12) in the THC group and 25% (SD = 14) in the control group compared with 9% (SD = 6) and 12% (SD = 14) in the overlap condition. Overall, the number of erroneous prosaccades towards the target did not differ between groups ($F(1,38) = 0.36$; $P > 0.05$).

In the memory-guided paradigm, mean saccade latencies did not differ between groups with virtually identical mean values of 268 ms at 6° eccentricity (SD = 48 for the THC group and SD = 45 for controls). At 3° eccentricity, the mean latencies amounted to 286 ms (SD = 48) for the THC group and 271 ms (SD = 34) for the control group ($F(1,37) = 1.28$; $P > 0.05$). Mean saccade amplitudes for targets at 3° eccentricity had a length of 2.88° (SD = 0.45) for the THC group and 2.63° (SD = 0.25) for controls ($F(1,37) = 4.49$; $P < 0.05$). Saccade amplitudes for targets at 6° eccentricity amounted to 5.22° (SD = 0.57) for the THC group and 5.06° (SD = 0.54) for controls ($F(1,37) = 0.86$; $P > 0.05$). Mean amplitudes tended to be greater for the THC group in both eccentricity conditions, but group differences only reached statistical significance in the 3° condition (see Figure 3).

In the double-step paradigm, half of the trials consisted of single target steps. Mean saccade amplitudes to these targets with 3° eccentricity had a length of 3.1° (SD = 0.18) in both groups. Mean saccadic latencies amounted to 170 ms (SD = 26.1) in the THC group compared with 167 ms

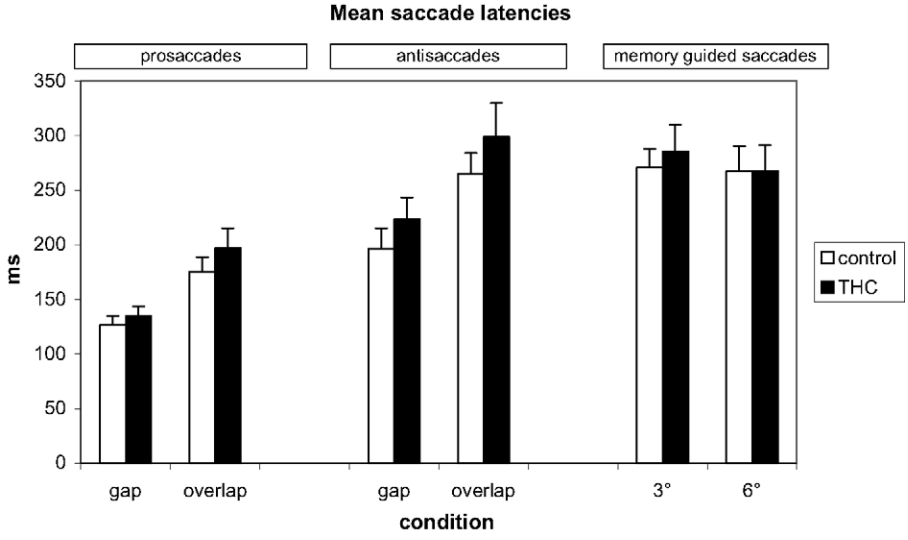

Figure 2 Latencies of initial saccades (ms) for the control and THC group. Prosaccades and antisaccades are depicted with gap and overlap conditions. Memory-guided saccade latencies are shown separately for targets at 3° and 6° eccentricity.

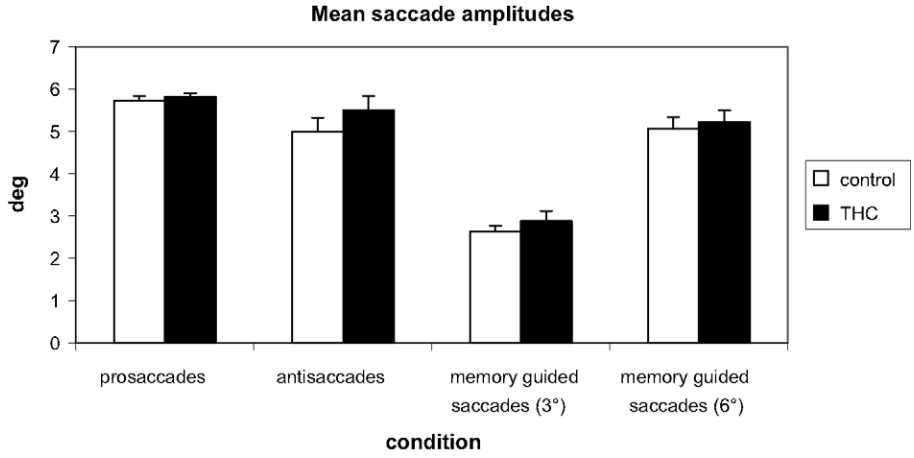

Figure 3 Amplitudes of initial saccades (°) for the control and THC group. For prosaccades and antisaccades, mean values are calculated across gap and overlap conditions. For memory-guided saccades, amplitudes are reported separately for 3° and 6° target eccentricity.

(SD = 17.4) for controls. Although these means did not differ significantly between groups, a Levene test showed significant differences in interindividual variation between groups ($F(1,38) = 7.59$; $P < 0.01$). In double-step trials, saccades were analysed as a function of reprogramming time, which is defined as the time interval between the onset of the second target and the execution of the initial saccade. In the interest of group comparisons, reprogramming time was divided into 30-ms intervals ranging from <50 ms to >140 ms. Consequently, mean saccade amplitudes could be computed for the five separate intervals of reprogramming time. There was a significant main effect of reprogramming time on saccade amplitude ($F(4,31) = 1141$; $P < 0.01$), but no group differences ($F(1,34) = 0.001$; $P > 0.05$) were found. This pattern also held with respect to the likelihood of executing a single saccade response, with a significant main effect of reprogramming time ($F(4,31) = 247$; $P < 0.01$), but no significant group differences were found ($F(1,34) = 0.89$ $P > 0.05$). Table 1 depicts the means of both parameters for the five categories.

Discussion

As one key result of the present research, we found consistent evidence for deficits in temporal aspects of saccade control. In the prosaccade and antisaccade tasks, where subjects were asked to immediately respond to the appearance of a peripheral target, saccadic latencies were substantially larger in the THC group compared with control subjects. On the contrary, we did not find significant latency differences in the memory-guided saccade task, where subjects were asked to execute a delayed response. We, therefore, conclude that the observed deficit is associated with the initial phase of saccade programming rather than being due to the process of response initiation or response execution at the motor level. The observation that in the prosaccades, the group difference was nominally less pronounced in the gap compared with the overlap condition might be due to a floor effect in the gap condition, where oculomotor response times are generally on a very low level.

These results are consistent with recent research on acute cannabis intoxication using a pre–post design (Ploner, *et al.*, 2002). In their study, subjects without explicit previous drug history exhibited a 12-ms prolongation of saccadic response times in visually guided saccades 2 h after drug intake. In the present study, subjects had a minimum self-reported abstinence period of 24 h before testing. This could be confirmed by the laboratory parameters, which were similar to those found in previous studies of long-term effects (e.g., Ehrenreich, *et al.*, 1999). Therefore, all measured adverse effects qualify as long-term effects of cannabis consumption although a small degree of uncertainty regarding the abstinence period cannot

Table 1 Mean saccade amplitudes (°) and probabilities of a single saccade response (%) as a function of reprogramming time intervals (ms) for the control and THC group

	Control group (SD)	THC group (SD)
Saccade amplitude (°)		
<50 ms	2.93 (0.25)	2.96 (0.41)
50–80 ms	3.20 (0.25)	3.23 (0.24)
80–110 ms	3.95 (0.36)	3.83 (0.43)
110–140 ms	5.23 (0.49)	5.28 (0.75)
>140 ms	5.78 (0.33)	5.78 (0.37)
Probability of a single saccade response (%)		
<50 ms	0.0 (0.0)	3.0 (1.1)
50–80 ms	0.2 (1.0)	1.2 (3.0)
80–110 ms	5.0 (6.0)	6.0 (9.0)
110–140 ms	50 (30)	52 (30)
>140 ms	90 (20)	92 (13)

completely be ruled out on the basis of the present data and would ideally request supervised abstinence periods. Additionally, the levels of THC and its metabolites at the time of testing were considerably lower than that of the subjects in Ploner, *et al*. (2002) during testing. Nevertheless, the size of the effect is comparable. This makes it unlikely that the effects in the present study represent only residual acute deficits. However, although a rather long-lasting impairment is likely, on the basis of the present results, it cannot be decided whether these adverse effects are irreversible (see Pope, *et al*., 1995, for a critical discussion on irreversible effects). Further evidence for rather long-lasting effects would be a null correlation between the plasma levels of THC and its metabolites and the latencies in the THC group, but the current sample of users seems too small for meaningful correlations, especially for the demonstration of a null effect. However, in a previous study of Ehrenreich, *et al*. (1999), which included a substantially larger sample of chronic users ($N = 99$), neither the estimated life-time dose nor THC plasma levels significantly correlated with response times in a visual scanning task that demanded eye movements as the central behavioural element. This can be interpreted as indirect evidence for rather long-lasting impairments of the oculomotor system in chronic users.

We did not find prolonged mean latencies in single-step trials in the double-step paradigm as one might expect on the basis of the results regarding the prosaccades. We attribute this result to the need for a flexible adjustment to a stimulus–response pattern varying from trial to trial in the double-step paradigm, so that the primary saccade latency is determined by much more complex processing operations compared with prosaccade blocks. Note, however, that the interindividual variability of the mean saccade latency in the double-step paradigm was significantly higher in the THC group, suggesting a group difference in the ability to adjust to the more complex task.

We would like to emphasise that the apparent specific impairment in basic temporal saccade control is most likely the core reason for the longer mean fixation durations that we observed earlier using a sequential visual search task (Huestegge, *et al*., 2002). This shows that the basic deficits found in the present study carry over to more complex, natural behavioural patterns. Although the size of the present effects might appear small, with latency prolongations of 21 ms in overlap conditions, these effects might be crucial in tasks like driving a vehicle, where a prolongation of each fixation on control instruments might yield crucial implications for road safety.

As an alternative explanation for the latency difference, it could be argued that subjects who are regularly consuming cannabis generally tend to react more slowly as a result of a more relaxed attitude towards life. However, it is widely assumed that single prosaccades are executed in an automatic or quasi-reflexive mode of control without voluntary influences (Findlay and Walker, 1999). A voluntary initiation of a single goal-directed saccade should necessarily be associated with latency increases way beyond the differences observed in our experiments. Moreover, if a 'general slowing' account was adequate, one would expect significantly prolonged latencies also in the memory-guided saccade paradigm, which we did not find. Additionally, this makes it unlikely that the observed effects represent a general withdrawal symptom (e.g., Vandrey, *et al*., 2008), which should also affect latencies in all paradigms. However, a more specific withdrawal pattern that is selectively represented only in some of the parameters cannot finally be ruled out on the basis of the present data.

Furthermore, it might be possible that the THC group had deficits in staying motivated throughout the time of testing, subsequently leading to the observed effects. However, on the basis of the present data, this is not a likely option because response times in the memory-guided and the double-step paradigms, which were always conducted at the end of the experimental series, remained unaffected.

Finally, it is also unlikely that the observed effects are based on different smoking habits between groups because tobacco is rather known to affect smooth pursuit performance (Sibony, *et al*., 1988) and antisaccade errors (Powell, *et al*., 2004).

On the basis of what is known about the neurophysiology of temporal saccade programming, it is possible to derive hypotheses on brain dysfunctions that underlie the observed pattern of results. Temporal saccade programming is supported by a neural network including the frontal eye fields (FEF) for voluntary saccades, the intraparietal sulcus (IPS) for reflexive saccades, as well as the basal ganglia and prefrontal and parietal association cortices (Leigh and Kennard, 2004). Impairments of the FEF or IPS should lead to increased latencies and hypometria in the memory-guided saccade paradigm (Pierrot-Deseilligny, *et al*., 1991; Gaymard, *et al*., 1999), which we did not observe. Additionally, in our earlier work on long-term THC effects in visual search, the variability of saccade amplitudes was large enough for meaningful comparisons of the relation of saccade amplitude and peak velocity between groups. However, we could rule out any group differences (Huestegge, *et al*., 2002). Taken together, our results suggest that – instead of premotor areas – deficits of the associative cortex or subcortical structures are likely to be responsible for the observed temporal control deficits. This is also in line with the observation that CB-1 receptor density is high in both association cortices and basal ganglia (Herkenham, *et al*., 1990; Glass, *et al*., 1997).

We also obtained important results with respect to spatial aspects of saccade control. In the two experiments where saccades were not visually guided, that is, in the antisaccade and memory-guided saccade tasks, we found significantly greater saccade amplitudes in the THC group compared with controls. One might argue that, expressed in terms of saccadic gain, THC subjects actually showed better performance than controls with saccadic landing positions that were located closer to the targets. However, given that the saccadic undershoot observed in the control group has been found in many studies conducted with healthy subjects, it seems safe to interpret this difference in terms of a deficit in the THC group. Common to both, antisaccades and memory-guided saccades, is that spatial parameters need to be stored in visuo-spatial working memory (see Roberts, *et al*., 1994; Walker, *et al*., 1998), which is unnec-

essary in the execution of prosaccades and double-step saccades. Therefore, it is likely that an impaired visuo-spatial working memory represents the source of the observed deficit. This is in harmony with research suggesting that memory deficits are the most robust cognitive phenomena found as a result of acute cannabis intake (Solowij, 1998; Sullivan, 2000) although memory functions in previous studies do not directly address the saccade-related visuo-spatial working memory. Additionally, it is consistent with our previous results on THC effects in visual search, where THC subjects exhibited a significantly higher rate of reinspections of items that were already previously fixated than did controls (Huestegge, *et al*., 2002).

Greater saccade amplitudes in memory-guided saccades were also found earlier in research on acute THC effects (Ploner, *et al*., 2002). However, on the contrary to this work, we did not find evidence for an impaired suppression of erroneous prosaccades in the antisaccade task. This leads to the conclusion that alterations in voluntary inhibition processes are typical only for acute effects of cannabis, whereas the systematic spatial inaccuracy can persist in long-term users after an abstinence period of more than 24 h. Again, this different pattern of results between the present study and the study of acute effects suggests that the observed effects not merely represent residual acute effects but rather long-lasting deficits.

Known neurophysiological substrates for visuo-spatial working memory in memory-guided saccades are the dorsolateral prefrontal cortex (DLPFC) and the basal ganglia (Leigh and Kennard, 2004). Previous research showed that a stimulation of the subthalamic nucleus (STN) in patients results in greater memory-guided saccade amplitudes, presumably by a modulation of activity in the substantia nigra pars reticulata (SNPR) (Rivaud-Pechoux, *et al*., 2000). Additionally, this area shows a very high density of CB-1 receptors compared with other areas of the basal ganglia.

The absence of any group differences in the double-step trials of the double-step paradigm suggests that long-term cannabis consumption has no persistent effect on processes of rapid reprogramming of saccades, and the underlying neural network consisting of the FEF and the posterior frontal cortex for the triggering and supplementary motor areas for the timing of saccadic sequences seems intact.

Taken together, we found a consistent pattern of specific deficits that can be summarised as impairments of temporal saccade programming, but not saccade execution, and visuo-spatial working memory. These deficits proved to be stable and selective across paradigms, with changes of temporal parameters in prosaccades and antisaccades, but not in memory guided saccades, and changes of spatial parameters in antisaccades and memory-guided saccades but not in visually guided prosaccades and double-step saccades. We would like to emphasise the striking similarities of our results with the recent work by Ploner, *et al*. (2002) on acute cannabis effects in a pre–post design. They also found a significant increase of latencies of immediate visually guided saccades and greater saccade amplitudes of memory-guided saccades 2 h after drug intake compared with baseline testing. Our results indicate that, given chronic use, this pattern of deficits persists also in the absence of acute intoxication. Nevertheless, further studies are needed with longer abstinence periods to directly determine the persistence of the impact of cannabis smoking on ocular functioning. Because we only tested subjects with early age of onset, it remains an open question whether the results also generalise to a later age of onset.

The data pattern is fully consistent with our previous results in a visual search task (Huestegge, *et al*., 2002). We would, therefore, like to suggest that the specific impairments reported in this study may potentially lead to severe degraded performance of chronic cannabis users in all tasks involving visuomotor control, including spatial navigation (e.g., driving), scene perception and reading.

References

Becker, W (1989) The neurobiology of saccadic eye movements. Metr Rev Oculomot Res *3*: 13–67.

Becker, W, Jürgens, R (1979) An analysis of the saccadic system by means of double step stimuli. Vision Res *19*: 967–983.

Croft, RJ, Mackay, AJ, Mills, ATD, Gruzelier, JGH (2001) The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology *153*: 373–379.

Dorris, MC, Munoz, DP (1995) A neuronal correlate for the gap effect on saccadic reaction times in the monkey. J Neurophysiol *73*: 2558–2562.

Ehrenreich, H, Rinn, T, Kunert, HJ, Moeller, MR, Poser, W, Schilling, L, *et al*. (1999) Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology *142*: 295–301.

Findlay, JM, Walker, R (1999) A model of saccade generation based on parallel processing and competitive inhibition. Behav Brain Sci *22*: 661–674.

Fischer, B, Weber, H (1997) Effects of stimulus conditions on the performance of antisaccades in man. Exp Brain Res *116*: 191–200.

Fletcher, JM, Page, JB, Francis, DJ, Copeland, K, Naus, MJ, Davis, CM, *et al*. (1996) Cognitive correlates of long-term cannabis use in Costa Rican men. Arch Gen Psychiatry *53*: 1051–1057.

Gaymard, B, Ploner, CJ, Rivaud-Pechoux, S, Pierrot-Deseilligny, C (1999) The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. Exp Brain Res *129*: 288–301.

Glass, M, Dragunow, M, Faull, RLM (1997) Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in fetal neonatal and adult human brain. Neuroscience *27*: 299–318.

Gonzalez, R, Carey, C, Grant, I (2002) Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review. J Clin Pharmacol *42*: 48–57.

Hallett, PE (1978) Primary and secondary saccades to goals defined by instructions. Vision Res *18*: 1279–1296.

Herkenham, M, Lynn, AB, Little, MD, Johnson, MR, Melvin, LS, de Costa, BR, *et al*. (1990) Cannabinoid receptor localization in the brain. Proc Natl Acad Sci U S A *87*: 1932–1936.

Hikosaka, O, Wurtz, RH (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulata: III. Memory-contingent visual and saccade responses. J Neurophysiol *49*: 1268–1284.

Huestegge, L, Radach, R, Kunert, HJ, Heller, D (2002) Visual search in long-term cannabis users with early age of onset. Prog Brain Res *140*: 377–394.

Iversen, LL (2000) The Science of Marijuana. Oxford: Oxford University Press.

Lamers, CT, Bechara, A, Rizzo, M, Ramaekers, JG (2006) Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. J Psychopharmacol *20*: 302–311.

Leigh, RJ, Kennard, C (2004) Using saccades as a research tool in the clinical neurosciences. Brain *127*: 460–477.

Moeller, MR, Doerr, G, Warth, S (1992) Simultaneous quantitation of delta-9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) in serum by GC/MS using deuterated internal standards and its application to a smoking study and forensic cases. J Forensic Sci *37*: 969–983.

Pierrot-Deseilligny, C, Rivaud, S, Gaymard, B, Agid, Y (1991) Cortical control of reflexive visually guided saccades. Brain *114*: 1473–1485.

Ploner, CJ, Tschirch, A, Ostendorf, F, Dick, S, Gaymard, BM, Rivaud-Pechoux, S, *et al*. (2002) Oculomotor effects of delta-9-tetrahydrocannabinol in humans: implications for the functional neuroanatomy of the brain cannabinoid system. Cereb Cortex *12*: 1016–1023.

Pope, HG, Gruber, AJ, Yurgelun-Todd, D (1995) The residual neuropsychological effects of cannabis. Drug Alcohol Depend *38*: 25–34.

Pope, HG, Yurgelun-Todd, D (1996) The residual cognitive effects of heavy marijuana use in college students. JAMA *275*: 521–527.

Powell, JH, Pickering, AD, Dawkins, L, West, R, Powell, JF (2004) Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation. Addict Behav *29*: 1407–1426.

Rivaud-Pechoux, S, Vermersch, AI, Gaymard, B, Ploner, CJ, Bejjani, BP, Damier, P, *et al*. (2000) Improvement of memory-guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry *68*: 381–384.

Roberts, RJ, Hager, LD, Heron, C (1994) Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. J Exp Psychol Gen *123*: 374–393.

Rodgers, J (2000) Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology *151*: 19–24.

Ross, LE, Ross, SM (1980) Saccade latency and warning signals: stimulus onset, offset and change as warning events. Percept Psychophys *27*: 251–257.

Sibony, PA, Evinger, C, Manning, KA (1988) The effects of tobacco smoking on smooth pursuit eye movements. Ann Neurol *23*: 238–241.

Soderstrom, K, Johnson, F (2003) Cannabinoid exposure alters learning of zebra finch vocal patterns. Brain Res Dev Brain Res *142*: 215–217.

Solowij, N (1998) Cannabis and Cognitive Functioning. Cambridge: Cambridge University Press.

Solowij, N, Stephens, RS, Roffman, RA, Babor, T, Kadden, R, Miller, M, *et al*. (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. J Am Med Assoc *287*: 1123–1131.

Stiglick, A, Kalant, H (1985) Residual effects of chronic cannabis treatment on behaviour in mature rats. Psychopharmacology *88*: 346–349.

Sullivan, JM (2000) Cellular and molecular mechanisms underlying learning and memory impairments produced by canabinoids. Learn Mem *7*: 132–139.

Vandrey, RG, Budney, AJ, Hughes, JR, Liguori, A (2008) A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. Drug Alcohol Depend *92*: 48–54.

Walker, R, Husain, M, Hodgson, TL, Harrison, J, Kennard, C (1998) Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. Neuropsychologia *36*: 1141–1159.

Warren, RA, Simpson, HM, Hilchie, J, Cimbura, G, Lucas, DM, Bennett, RC (1981) Characteristics of fatally injured drivers testing positive for drugs other than alcohol. In: Goldberg, L (ed), Alcohol, Drugs, and Traffic Safety, *vol. 1*. Stockholm: Almqvist and Wiksell, pp. 203–217.