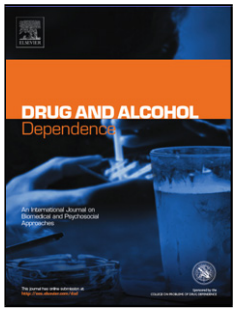

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History of cannabis use is associated with altered gait

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Highlights

- Cannabis users exhibit increased asymmetry at the hip during walking gait
- Cannabis users exhibit reduced shoulder flexion during walking gait
- Gait changes in cannabis users are not of a magnitude that is clinically detectable

Abstract

Background: Despite evidence that cannabinoid receptors are located in movement-related brain regions (e.g., basal ganglia, cerebral cortex, and cerebellum), and that chronic cannabis use is associated with structural and functional brain changes, little is known about the long-term effect of cannabis use on human movement. The aim of the current study was to investigate balance and walking gait in adults with a history of cannabis use. We hypothesised that cannabis use is associated with subtle changes in gait and balance that are insufficient in magnitude for detection in a clinical setting.

Methods: Cannabis users (n=22, 24±6 years) and non-drug using controls (n=22, 25±8 years) completed screening tests, a gait and balance test (with a motion capture system and in-built force platforms), and a clinical neurological examination of movement.

Results: Compared to controls, cannabis users exhibited significantly greater peak angular velocity of the knee (396±30 versus 426±50 degrees/second, P=0.039), greater peak elbow flexion (53±12 versus 57±7 degrees, P=0.038) and elbow range of motion (33±13 versus 36±10 degrees, P=0.044), and reduced shoulder flexion (41±19 versus 26±16 degrees, P=0.007) during walking gait. However, balance and neurological parameters did not significantly differ between the groups.

Conclusions: The results suggest that history of cannabis use is associated with long-lasting changes in open-chain elements of walking gait, but the magnitude of change is not clinically detectable. Further research is required to investigate if the subtle gait changes observed in

this population become more apparent with aging and increased cannabis use.

Keywords: cannabis; biomechanics; gait analysis; kinematics; kinetics

1. Introduction

Approximately 3.9% of the world's adult population have used cannabis, with the Oceania region having the highest prevalence of use (United Nations Office on Drugs and Crime, 2014). In Australia, 35% of individuals aged 14 years and over have tried cannabis at least once, with the estimated age of cannabis initiation at 16.7 years (Australian Institute of Health and Welfare, 2014).

The major psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (THC), binds to cannabinoid-type 1 (CB1) receptors that are widely distributed throughout the central nervous system (Hirvonen et al., 2012). High densities of CB1 receptors are found in the hippocampus, amygdala, and movement-related brain regions, including the basal ganglia, cerebellum, and cerebral cortex (Oliviero et al., 2012). CB1 receptors are primarily located on the presynaptic membrane (Hirvonen et al., 2012) and activation can inhibit neurotransmitter release (Schlicker and Kathmann, 2001).

Cannabis intoxication results in *acute* motor deficits, including changes in balance (Ramaekers et al., 2006). An acute concentration-dependent disturbance in balance has been observed, with increasing levels of THC resulting in increased body sway (Kiplinger et al., 1971; Zuurman et al., 2008), possibly due to activation of CB1 receptors in movement-related brain regions. However, it is not known if cannabis use is associated with *long-lasting* disturbances in functional movement tasks such as balance and walking gait.

There are several lines of evidence to suggest that cannabis use may have a long-lasting effect on both gait and balance. There is a high density of CB1 receptors in

movement-related brain regions (Takahashi and Linden, 2000) and within the dorsal and ventral horns of the spinal cord (Ong and Mackie, 1999). Animal studies suggest that cortical neurons exhibit a dose-dependent widening of the synaptic cleft and development of nuclear inclusion bodies in response to THC administration (Harper et al., 1977; Heath et al., 1980). Chronic cannabis use in humans is also associated with decreased white matter density in the left parietal lobe (Matochik et al., 2005) and long-term changes in cognitive functions (e.g., memory and executive functioning) (Solowij and Pesa, 2011). Therefore, it is conceivable that functional changes in the motor system may occur.

The aim of the current study was to investigate gait and balance in individuals with a history of cannabis use. We hypothesised that cannabis users would exhibit subtle features of ataxic gait and increased postural sway during quiet standing compared to non-drug users. The hypotheses were based on: (i) subjective observations of gait and balance abnormalities in individuals dependent on alcohol and either cannabis, stimulants, and/or opiates (Fein et al., 2012); and (ii) pathological and pathophysiological changes observed in the brains of cannabis users (Harper et al., 1977; Heath et al., 1980; Matochik et al., 2005). It was also hypothesised that disturbances in gait and balance observed in a laboratory setting would be too small to detect in a clinical setting. This hypothesis was based on the lack of reports of clinical movement dysfunction in cannabis users. The results of the current study advance knowledge of the long-lasting consequences of cannabis use in humans.

2. Materials and Methods

2.1. Subjects and screening

Two groups of adults aged 18–49 years participated in the study: 22 subjects with no history of illicit drug use (‘control group’) and 22 subjects with a history of cannabis use (>5 occasions) but no history of illicit stimulant or opioid use (‘cannabis group’). All experimental procedures were approved by the Southern Adelaide Clinical Human Research

Ethics Committee and the University of South Australia Human Research Ethics Committee. The experimental procedures were conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from each subject prior to participation.

Each subject underwent a series of screening tests prior to participation. The full details of the screening procedure have been published previously (Pearson-Dennett et al., 2014). It included provision of a urine sample for drug screening (PSCupA-6MBAU, US Diagnostics Inc., Huntsville, Alabama, USA), a brief medical history questionnaire, an in-house drug history questionnaire, and a neuropsychological assessment of four cognitive domains. New learning was assessed with Logical Memory I and II (Wechsler, 1987), executive functioning was assessed with Verbal Trails (Grigsby and Kaye, 1995) and Verbal Fluency (Benton and Hamsher, 1983; Grigsby and Kaye, 1995), and attention and working memory were assessed with Digit Span forwards and backwards (Wechsler, 1981), respectively. Performance on each test was compared to published normative data matched for age and years of education. Recent symptoms of depression were also assessed with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996).

Exclusion criteria included history of neurological damage and/or neurological illness prior to first use of cannabis, current use of medications that affect movement (e.g., antipsychotics), self-reported history of major orthopaedic injury or surgery, and positive urine drug test for amphetamine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine or ‘ecstasy’), cocaine, benzodiazepines, and/or opioids. Subjects who tested positive for cannabis were allowed to participate if self-reported use was greater than 12 hours prior to experimentation. This exemption was due to THC remaining in body fat for up to 80 days after last use (Verstraete, 2004). Subjects were also excluded if poor performance was observed on more than two of the cognitive domains tested. Poor performance was defined as greater than two standard deviations below the mean of

published normative data for Logical Memory I and II (Mittenberg et al., 1992), Verbal Fluency (Tombaugh et al., 1999), Digit Span (Kear-Colwell and Heller, 1978), and performance greater than two standard deviations above the mean for Verbal Trails (Mrazik et al., 2010). Subjects then completed an experiment involving quantitative movement analysis. A subset of subjects were also examined by a neurologist on a different day.

2.2. Experimental Protocol

2.2.1. Quantitative Movement Analysis. Walking gait and balance during quiet stance were assessed using a 12-camera motion capture system (MX-F20, VICON, Oxford, UK) and four force platforms (two 9281B, Kistler Instruments, Switzerland; two AMTI BP400600, AMTI, MA, USA) for the measurement of kinematic (100 Hz) and ground reaction force (400 Hz) data. Sixty-three reflective markers (14 mm diameter) were attached to standardized anatomical landmarks on the head, trunk, pelvis, and upper and lower limbs (see Fig 1) (Cappozzo et al., 1995).

Subjects were instructed to walk naturally, at their preferred speed, along a 10 m walkway. A minimum of three successful trials were recorded. To assess balance, subjects were instructed to stand in a comfortable posture, arms by their side, and to look at a fixed point on the wall. The subjects' right and left feet were positioned on adjacent force platforms (inter-platform distance: 10 mm). Collection commenced once subjects adopted a stable posture (assessed by the fluctuation in the real time ground reaction force vector) and were instructed not to move their feet during the balance assessment. Data was then collected during four 60 s trials of quiet stance, two with the eyes-open and two with eyes-closed.

Kinematic data were reconstructed and identified with Vicon Nexus software (v.1.8.5, VICON, Oxford, UK). Data were then exported to Visual3D for further processing (v.5.0, C-Motion Inc., Maryland, USA). Kinematic data and ground reaction force were filtered using 4^{th} order recursive low-pass Butterworth filters (cut-off frequency of 6 Hz and 25 Hz,

respectively). For the walking gait data, ground reaction force data were used to identify gait events. Spatiotemporal gait metrics including walking speed and step length were computed. Time was normalized between gait events to 101 points. From the marker trajectories, a kinematic model was defined where each body segment was modelled in six degrees-of-freedom (Cappozzo et al., 1995). From this model, the joint angles and joint angular velocities of the ankle, knee, hip, shoulder and elbow were calculated according to the International Society of Biomechanics recommendations (Grood and Suntay, 1983; Wu et al., 2002; Wu et al., 2005). Joint angles were used to calculate symmetry between the left and right sides of the body (symmetry index; SI) (Nigg et al., 2013). From the joint angles, local maxima (peak flexion) and minima (peak extension), and range of motion (ROM) were calculated. From the joint angular velocities, peak angular velocity and the root mean square (RMS) velocity were extracted from each joint. The analysis addresses parameters in the sagittal plane.

Analysis of the balance data was performed on the second trial in each condition. Centre of pressure (COP) data from the two adjacent force platforms was combined mathematically (Gerber and Stuessi, 1987) to represent one larger force platform while retaining the fidelity of data at the individual limb level (Thewlis et al., 2014). The trials were truncated to 30 s by removing data from the first 20 s and the final 10 s of the task to ensure that the data were stable and to account for any anticipatory effects nearing the trial end. The anterior–posterior and medial–lateral components of COP were fitted to a 95% confidence ellipse. The magnitude of the major and minor hemi-axes and the axis angle were calculated in MATLAB (MathWorks Inc., USA) and used as a measure of postural sway (Thewlis et al., 2014).

2.2.2 Neurological Examination. A subset of subjects (n=19 per group) underwent a neurological examination performed by a neurologist who specializes in movement disorders

(RW). The neurologist was blinded to each subjects' drug history. The examination involved assessment of upper arm function during gait, limb rigidity, leg agility, posture, postural stability, and body bradykinesia. Each item was rated from 0 (normal) to 4 (severely abnormal), in-line with a well-validated clinical rating scale (Fahn and Elton, 1987). Subjects also underwent a timed 5 m walk, heel-toe walking, and assessment of impulsiveness. Family history of movement disorders and physical ailments that may alter movement were also noted.

2.3. Statistical Analysis

Group data are presented as mean±standard deviation in the text and mean±standard error of the mean in figures. Subject characteristics were analysed using either Independent Student's t-test or Mann-Whitney U test (IBM SPSS Statistics 22, Armonk NY, USA). Separate linear regression analyses were performed to investigate the main and interaction effects of group and lifetime alcohol use (estimated total drinks) on gait and neurology variables. Lifetime alcohol use was initially included in all models, but was found to only affect peak elbow flexion and elbow range of motion, and was therefore excluded from all other final models. Where a significant interaction between group and lifetime alcohol use was found, separate regression analyses were performed on each group to assess the main effect of alcohol. Probability plots were used to check that the model residuals approximated a normal distribution. Heteroskedacity and collinearity were assessed with Cameron and Trivedi's decomposition of IM-test and variance inflation factor, respectively. Final model selection was determined using the F statistic P value and the coefficient of determination (R^2). Balance data were analysed with a general linear model (GLM) for comparison of fixed effects of direction (within-subject factor: anterior-posterior, medial-lateral), condition (within-subject factor: eyes-open, eyes-closed), group (between-subject factor: control, cannabis), and lifetime alcohol use, and a random effect of participant ID (Stata 14,

StataCorp, College Station, TX, USA). Spearman Rank Order or Pearson Product Moment correlation was used to investigate the relationship between drug use parameters (e.g., lifetime estimated number of drinks, cigarettes, and occasions of cannabis use), and, a) gait parameters, b) balance parameters, and c) neurological parameters for each group separately (SigmaPlot 11.0, Systat Software Inc., Chicago, USA). Statistical significance was set at $P<0.05$.

3. Results

3.1 Subject Characteristics

The groups were matched for age and symptoms of depression (Table 1). Lifetime use of alcohol was significantly greater in the cannabis group than in controls ($P<0.001$). Lifetime use of tobacco was also tended to be greater in the cannabis group, but did not reach statistical significance.

Table 2 shows single-subject and group data for lifetime use of cannabis. Fifty per cent of the sample had used cannabis on >50 occasions and the average duration of abstinence from cannabis was 0.7±1.2 years (range: 1 day–4 years, median: 30 days).

Table 3 shows history of other illicit drug use in the cannabis group (at the first experimental session). Poly-drug use was uncommon in the cannabis group, with only 8 subjects (36%) reporting use of other illicit drugs (primarily ‘magic’ mushrooms and LSD).

3.2 Quantitative Movement Analysis

Five subjects returned a positive urine screen for cannabis, but none reported use of cannabis in the 12 hours prior to experimentation. A significant between-group difference in lower limb kinematics was observed. There was a main effect of group on peak knee angular velocity (P=0.039, Table 4). Peak angular velocity of the knee during the swing phase was significantly greater in the cannabis group than in the control group (Fig. 2A). Peak knee RMS angular velocity and symmetry of the knee and ankle did not differ between the groups, nor did peak angular velocity of the ankle.

The groups also significantly differed in some parameters of upper limb kinematics. There was a significant main effect of group (P=0.038) and alcohol (P<0.0001) on peak elbow flexion (Table 4), but not peak elbow extension. Peak elbow flexion was significantly greater in the cannabis group than in the control group (Fig. 3A). There was also a significant group-by-alcohol interaction on peak elbow flexion (P<0.001, Table 4). Peak elbow flexion increased with increasing alcohol use (P=0.001) within the control group but no such association was observed within the cannabis group (P=0.463). The changes observed in the control group due to lifetime alcohol use were very small, and are therefore unlikely to be of practical significance. There was also a significant main effect of group (P=0.044) and alcohol (P<0.001), and a group-by-alcohol interaction (P<0.001), on elbow range of motion (Table 4). Elbow range of motion was significantly greater in the cannabis group than in the control group (Fig 3C). Within the control group, elbow range of motion increased with increasing alcohol use (P<0.001) but, there was no effect of alcohol on elbow range of motion within the cannabis group (P=0.754). Again the changes observed in the control group due to lifetime alcohol use were very small. At the shoulder, there was a main effect of group on peak shoulder flexion (P=0.007, Table 4). Peak shoulder flexion was significantly

smaller (less flexed) in the cannabis group than in the control group (Fig. 3D). Peak shoulder extension and shoulder range of motion did not differ between groups.

No other gait parameters significantly differed between the groups and there were no significant correlations between drug use (cannabis, alcohol, or tobacco) parameters and gait parameters in either group.

One subject (cannabis group) was excluded from the balance analysis, as they did not remain stationary for the 60 s trial. There was a significant main effect of direction on postural sway ($P<0.001$). As expected, subjects swayed significantly more in the anterior-posterior direction (hemi-axis: 14.2±13.6 mm) than in the medial-lateral direction (hemi-axis: 5.2±2.7 mm, $P<0.001$). Sway was also slightly larger in the eyes-closed condition than the eyes-open condition (hemi-axis: 9.1±6.3 mm and 8.5±5.8 mm, respectively), but the difference did not reach statistical significance. Postural sway did not differ between the groups and there were no significant interactions.

In the cannabis group, there were significant correlations between a) duration of cannabis use and the magnitude of anterior-posterior sway in the eyes-closed condition ($r=0.454$, $P=0.030$), b) lifetime alcohol use and the magnitude of anterior-posterior sway in the eyes-closed condition ($r=0.478$, $P=0.028$), and c) lifetime tobacco use and medial-lateral sway in the eyes-open condition ($r=-0.376$, $P=0.019$). In the control group, there were no significant correlations between drug use parameters (alcohol, tobacco) and balance parameters.

3.3 Neurological Examination

Four subjects in the cannabis group returned a positive urine screen for cannabis, but none reported use in the 12 hours prior to the examination. The average time between experimental sessions was 40±63 days (median: 18 days). Neurological parameters did not significantly differ between the groups and there were no significant interactions. No significant correlations between drug use and neurological parameters were observed for either group.

4 Discussion

The aim of the study was to investigate the long-lasting effect of cannabis use on gait and balance in healthy adults. The results of the study suggest that individuals with a history of cannabis use exhibit subtle changes in gait, primarily in open-chain components of walking gait, but not balance.

Individuals with a history of cannabis use exhibited abnormalities in the lower limb during gait. The velocity of the knee during the swing phase of gait was significantly greater (7%) in cannabis users than in non-drug users. A faster knee velocity is indicative of increased cadence, however, no difference in walking speed was observed between the groups.

Individuals with a history of cannabis use also exhibited subtle abnormalities in the upper limb during walking gait but not in the expected domains. Peak shoulder flexion was significantly smaller (36% less flexed) in cannabis users than in non-drug users. In addition, peak elbow flexion (9% more flexed) and elbow range of motion (9% greater range of motion) were significantly greater in cannabis users. However, peak elbow extension was unchanged. This suggests that movement of the upper limb in response to contralateral leg movement is preserved, but the trajectory of the upper arm exhibits less shoulder flexion and greater elbow flexion in cannabis users.

The gait changes observed in the cannabis group were evident during open-chain components of movement and were more pronounced in the upper limb where there is only centripetal force due to arm swing. In the lower limb, the groups tended to differ when there was no force feedback from contact with the floor. As expected, the gait changes observed in the laboratory were not of a magnitude that was clinically detectable, supporting our initial hypothesis. Although small in magnitude, the subtle changes may be long lasting in nature given that subjects in the cannabis group had not used cannabis for an average of 0.7±1.1 years (median: 30 days).

This paper intended to characterize the subtle gait changes in individuals with a history of cannabis use. It then leads one to speculate on what mechanisms may underlie these changes. Factors such as age, symptoms of depression, and changes in memory and cognition are unlikely to have contributed to the results because age and symptoms of depression did not differ between groups, and all subjects exhibited normal performance on the neuropsychological tests. Lifetime use of alcohol was significantly greater in the cannabis group than the non-drug control group. However, the effect of alcohol on the results is likely to be minimal because i) there was no main effect of alcohol within the cannabis group, ii) there was no correlation between alcohol and gait parameters, and iii) only two subjects in the cannabis group would be considered heavy alcohol drinkers (defined as five or more drinks, on the same occasion, for at least five days in the past month) (National Institute on Alcohol Abuse and Alcoholism, 2016).

It is likely that use of cannabis contributed to the between-group difference in gait parameters and there are several physiological mechanisms that support this assumption. For example, endocannabinoids are involved in setting the baseline activity level of the spinal locomotor circuitry, with CB1 receptor activation and antagonism resulting in an increase and decrease in locomotor frequency, respectively (El Manira et al., 2008). Thus, consumption of

cannabis may result in changes to the normal rhythmic neural activity of locomotor circuitry. Cannabinoids can also depress motoneurone activity by modulating glycinergic (El Manira et al., 2008) and glutamatergic (García-Morales et al., 2015) signaling via CB1 receptor activation. CB1 receptor activation could also affect descending activity from the motor cortex, via modulation of neurotransmitter release from neurons in the basal ganglia and motor cortex (Oliviero et al., 2012; Romero et al., 2002).

It was hypothesised that history of cannabis use would be associated with impaired balance evidenced by increased postural sway. However, this was not observed and none of the balance parameters differed between groups. The expected pattern of greater sway in the anterior-posterior direction was evident across groups but still no between-group difference or interactions were observed. An acute effect of cannabis use on balance has been previously noted (Zuurman et al., 2008), but the results of the current study suggest that disturbed balance may not be long lasting.

The main limitation of the current study was a relatively small sample size. A larger sample would allow greater confidence in the detection of smaller changes and may reveal more pronounced changes in gait. Inclusion of a group with a longer duration of abstinence may also help to determine if recovery over time is evident. Another limitation was inclusion of five subjects that returned a positive urine screen for cannabis, and thus reliance on self-reported duration of abstinence for these individuals. Inclusion of only subjects with a negative screen would enable stronger interpretation of the data. Poly-drug use (e.g., history of cannabis and hallucinogens) and uncertainty about the dose and potency of cannabis is also a limitation that affects all studies on human cannabis users.

The results of the current study suggest that individuals with a history of cannabis use exhibit subtle movement abnormalities during walking gait. Further research is required to investigate if the gait disturbances diminish with increasing duration of abstinence and if age-

related changes in gait are augmented in this population. The results of the study expand knowledge of the long-lasting consequences of cannabis use and inform on the proposed therapeutic uses of cannabis, in for example, epilepsy (Koppel et al., 2014).

Author Disclosures

Role of Funding Source

Nothing declared

Contributors

GT, JMW, DT, RAW, and APV contributed to study concept and design. VPD, DT, GT, and RAW were involved in acquisition of the data. VPD, GT, JMW, DT, RAW, and APV were involved in analysis and interpretation of the data. VPD, DT, and GT were involved in drafting of the manuscript. VPD, GT, JMW, DT, RAW, and APV contributed to critical revision of the manuscript for important intellectual content and approved the final manuscript before submission.

Conflict of Interest

No conflict declared

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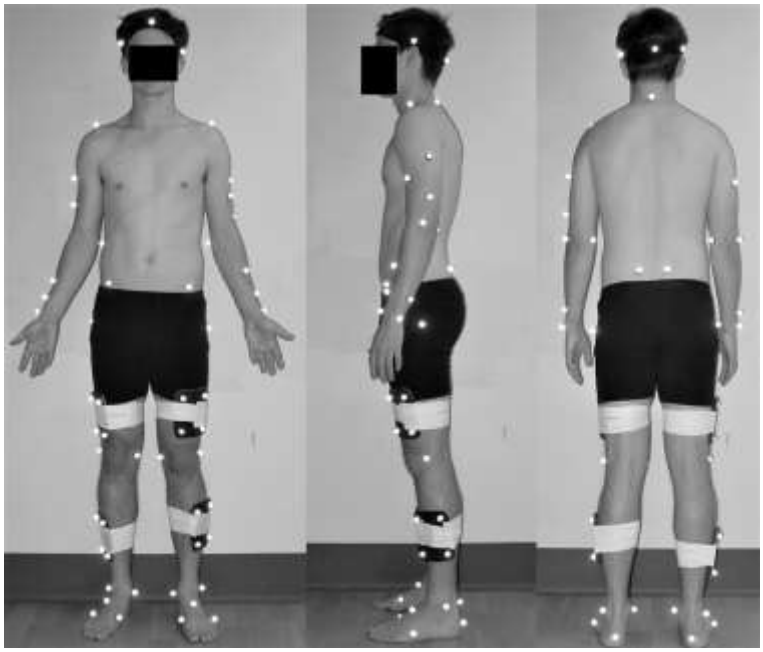
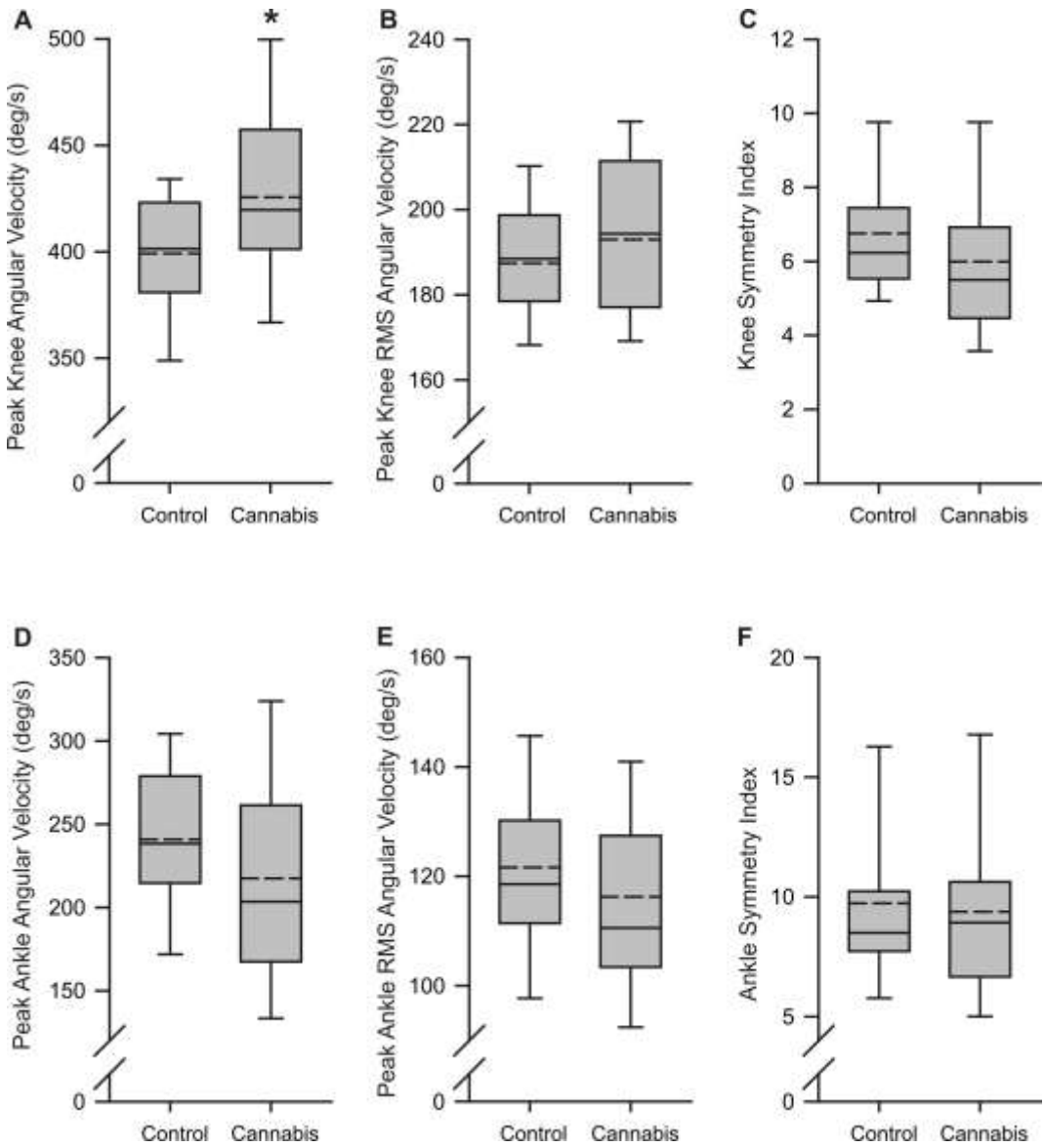
Figure Legends

Figure 1. Positions of the reflective markers for assessment of gait and balance. Markers were placed bilaterally on the head of the first and fifth metatarsal bones, dorsal aspect of the second metatarsal, posterior aspect of the calcaneous, medial and lateral malleoli, medial and lateral femoral epicondyles, greater trochanter, anterior inferior iliac spine, posterior inferior iliac spine, acromion process, spinous process of the 7^{th} cervical vertebra, medial and lateral humeral epicondyles, and ulna and radial styloids. Non-collinear clusters of markers were placed on the forearm and upper arm (n=3 per cluster) and the lower leg and thigh (n=4 per cluster).

Figure 2. Group data for lower limb kinematics during the swing phase of gait. A) Peak angular velocity of the knee. B) Peak RMS velocity of the knee. C) Symmetry index of the knee. D) Peak angular velocity of the ankle. E) Peak RMS angular velocity of the ankle. F) Symmetry index of the ankle. The boundary of each box indicates the 25^{th} and 75^{th} percentile and the whiskers indicate the 10^{th} and 90^{th} percentiles. The solid and dashed lines within each box indicate the median and mean values, respectively. * Significantly different from control group (P=0.039).

Figure 3. Group data for upper limb kinematics during the swing phase of gait. A) Peak elbow flexion. B) Peak elbow extension. C) Elbow range of motion. D) Peak shoulder flexion. E) Peak shoulder extension. F) Shoulder range of motion. The boundary of each box indicates the 25th and 75th percentile and the whiskers indicate the 10th and 90th percentiles. The solid and dashed lines within each box indicate the median and mean values, respectively. * Significantly different from control group ($P \leq 0.044$).





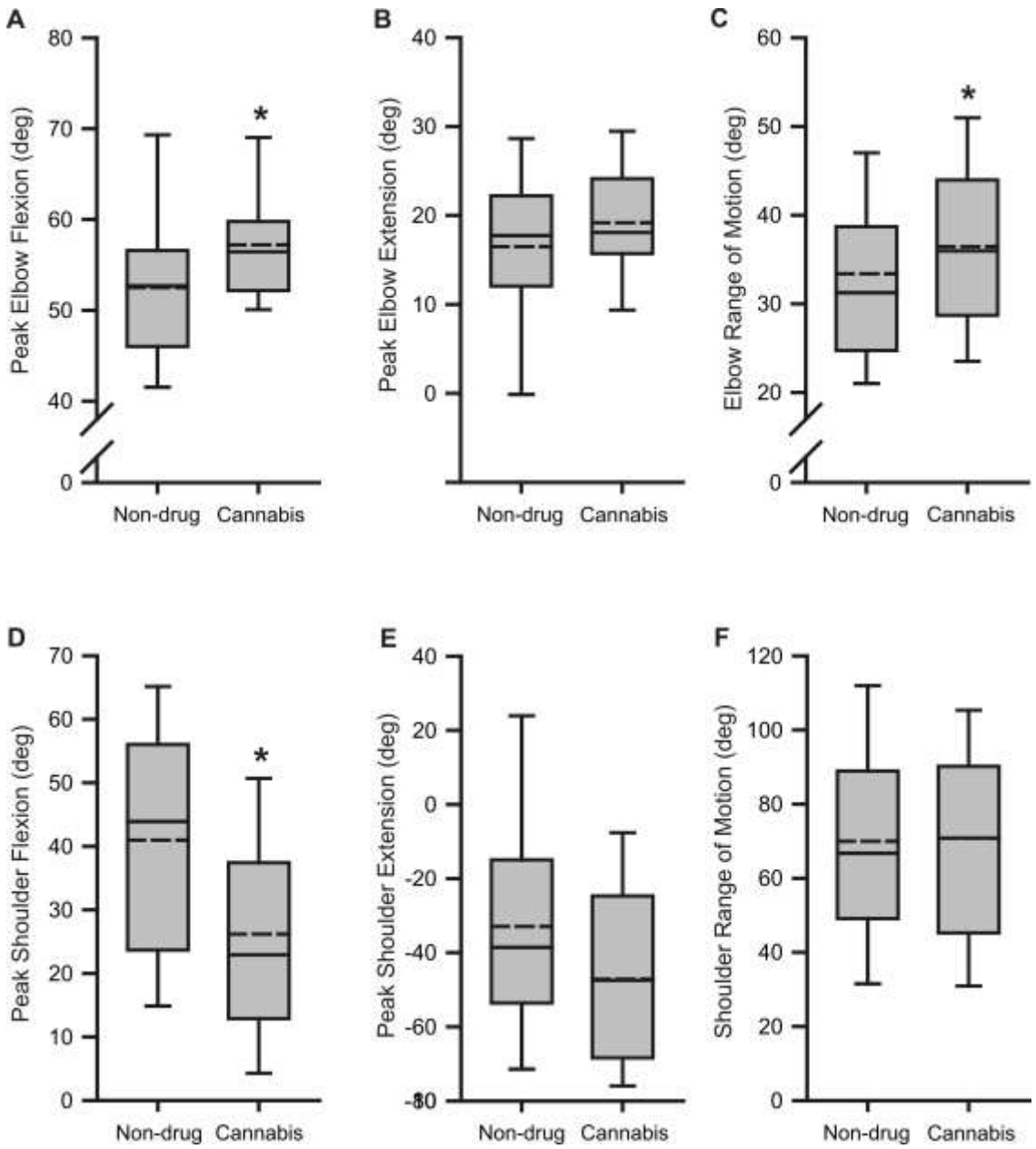


Table 1. Subject characteristics in the control and cannabis groups.

Demographic characteristics	**Control**	**Cannabis**
Age (years)	25±8	24±6
Sex	13M, 9F	14M, 8F
Education (years)	15±2	17±3 *
BDI-II score	6±8	5±5
Depression diagnosis	0	2
Drug overdose	0	1 (alcohol)
Lifetime alcohol (~drinks)	753±2,594	2,776±4,150 *
Lifetime tobacco (~cigarettes)	7±11	326±696

Subject characteristic data are reported as mean±SD. * Significantly different from control group ($P \leq 0.029$).

Table 2. Single-subject and group data for lifetime cannabis use in the cannabis group.

Subject	Age of onset (yrs)	Duration of use (yrs)	Estimated dose per session	Total occasions of use
1	15	26	2 joints	8425
2	17	9	1 bowl	1355
3	15	8	1 joint	348
4	15	5	1.5 joints	327
5	15	7	1 joint	244
6	15	8	1 spliff	190
7	16	4	1 joint	115
8	14	2	1.5 cones	104
9	12	25	1 pipe	87
10	18	4	2 cones	56
11	18	3	1 joint	51
12	22	3	1 joint	39
13	17	3	1 joint	38
14	19	2	3 cones	25
15	17	6	2.5 joints	15
16	18	3	1 joint	11
17	16	7	1 joint	10
18	18	5	1 joint	10
19	23	1	1 joint	8
20	16	2	2.5 joints	7
21	18	3	1.5 joints	6
22	19	2	1 joint	6

Mean (SD)	17 (2.5)	6 (7)	–	522 (1789)

Table 3. Lifetime history of other illicit drug use in the control and cannabis groups.

Drug Class	**Control**	**Cannabis**
Cannabis	0%	100% (522±1,789)
Hallucinogens	0%	32% (3±3)
Inhalants	0%	5% (2)
Sedatives	0%	0%
Opioids	0%	0%
Stimulants	0%	0%

Drug class data were compiled from the first experimental session and are reported as the percentage of subjects that have consumed that class of illicit drug in their lifetime and mean±SD for number of occasions of use (in brackets). The term ‘hallucinogen’ describes LSD (lysergic acid diethylamide), ‘magic’ mushrooms, LSA (d-lysergic acid amide), 2C-B (2,5-dimethoxy-4-bromophenethylamine), 2C-I (2,5-dimethoxy-4-iodophenethylamine), salvia divinorum, datura, ketamine, and/or DOI (2,5-dimethoxy-4-iodoamphetamine). The term ‘inhalant’ describes amyl nitrate, nitrous oxide, chloroform, and/or chloroethane.

Table 4. Results of the linear regression models showing the main effects of, and interactions between, group and lifetime alcohol use (estimated total drinks) for peak knee angular velocity, peak elbow flexion, elbow range of motion, and peak shoulder flexion.

	Unadjusted model			**Adjusted model**		
	β	**95% CI**	**Sig**	**β**	**95% CI**	**Sig**
Peak knee velocity						
Intercept	399.2	381.5, 416.9	<0.001	397.7	378.9, 416.5	<0.001
Group	26.4	1.44, 51.4	0.039	29.1	0.314, 57.9	0.048
Alcohol				0.002	-0.005, 0.009	0.567
Group x alcohol				-0.003	-0.011, 0.006	0.552
Peak elbow flexion						
Intercept	52.5	-1.11, 10.5	<0.001	50.45	46.8, 54.1	<0.001
Group	4.71	48.4, 65.6	0.110	5.98	0.36, 11.6	0.038
Alcohol				0.003	0.002, 0.004	0.003
Group x alcohol				-0.0027	-0.004, -0.001	<0.001
Elbow range of motion						
Intercept	33.4	28.4, 38.4	<0.001	30.50	26.4, 34.6	<0.001
Group	3.06	-3.9, 10.1	0.385	6.429	0.19, 12.6	0.044
Alcohol				0.0042	0.002, 0.006	<0.001
Group x alcohol				-0.0044	-0.006, -0.003	<0.001
Peak shoulder flexion						
Intercept	40.9	33.5, 48.5	<0.001	40.4	32.4, 48.4	<0.001
Group	-14.8	-25.4, -4.17	0.007	-14.3	-26.5, -2.00	0.024
Alcohol				0.008	-0.002, 0.004	0.602
Group x alcohol				-0.008	-0.004, 0.003	0.658