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A Transcranial Magnetic Stimulation Study of the Effects of Cannabis Use on Motor Cortical Inhibition and Excitability

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Active compounds in cannabis such as tetrahydrocannabinol (THC) interact with the inhibitory neurotransmitter δ-aminobutyric acid (GABA) but little is known about the functional effects of cannabis on human cortical brain processes. Therefore, the aim of the study was to investigate whether patients with chronic cannabis use demonstrate abnormalities in cortical inhibition or excitability. In all, 42 chronic cannabis using subjects (divided into heavy and light using subjects) and 19 controls were included in the study. Single and paired pulse transcranial magnetic stimulation were used to assess a number of parameters of cortical inhibition and cortical excitability. In addition, psychomotor function and THC plasma levels were measured. Both cannabis using groups (heavy and light use) demonstrated a reduction in short interval cortical inhibition compared with healthy controls, but there was no difference in other measures of cortical inhibition or cortical excitability. There was also no difference between the two groups on measures of psychomotor performance. Chronic cannabis use is associated with a reduction in cortical inhibition potentially related to activity at the $GABA_A$ receptors. Further research is required to explore whether this results from chronic cannabis use or reflects an underlying predisposition to developing chronic substance use problems.

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INTRODUCTION

Cannabis is the third most widely used recreational drug in the world, being consumed by approximately 4% of the world adult population (UNODC, 2006). Over recent years, there has been a considerable escalation of research into the effects of cannabis, particularly at a basic neurochemical level (eg, see review in Fattore *et al*, 2008). However, less research has focused on the effects of cannabis at a functional neurophysiological level, especially in human subjects. The one area in which there is neurochemical evidence for the effect of cannabis on the human brain is in the interaction between the endogenous cannabinoid system and the functional inhibitory neuronal networks. For example, there is a complex interaction between cannabinoid and δ-aminobutyric acid (GABA) systems in brain areas such as the nucleus accumbens and hippocampus, potentially relevant to both the addictive and neurocognitive effects of cannabis (Hoffman and Lupica, 2000, 2001). The interaction between these systems at a neurochemical level is complex, however, with variations of the effects of cannabinoid stimulation on GABAergic neurons based on the GABA receptor subtype and brain region. To date, little research has investigated the functional relevance of the effects of cannabis use on the GABAergic system in human subjects.

One mechanism to explore cortical GABAergic function is transcranial magnetic stimulation (TMS). A number of TMS paradigms have been used to assess the activity of the $GABA_A$ and $GABA_B$ receptors in the motor cortex in human subjects (Chen, 2000; Fitzgerald *et al*, 2002a), and changes in this functioning in disease states such as schizophrenia and depression (Daskalakis *et al*, 2002, 2008; Fitzgerald *et al*, 2003; Wobrock *et al*, 2008). One of these paradigms involves suprathreshold stimulation of the motor cortex during the tonic contraction of a muscle in the contralateral hand. A period of suppression of ongoing tonic activity, referred to as the cortical silent period (CSP), is recorded and measured as an index of $GABA_B$ activity. A second paradigm uses a subthreshold conditioning stimulus and a suprathreshold test stimulus in a paired pulse experimental set up. Where there is a short inter-stimulus interval between these pulses (2–5 ms), inhibition of the motor activity induced by the second pulse is recorded and compared with the response from a single test pulse alone.

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This is referred to as short interval cortical inhibition (SICI) and is related to activity at $GABA_A$ receptors. An additional paired pulse paradigm, long interval cortical inhibition (LICI) may also be used to assess inhibitory activity using two suprathreshold stimuli at a long interstimulus interval (ISI) (often 100 ms). LICI is believed to assess aspects of $GABA_B$ activity (Sanger *et al*, 2001).

To date, no studies have used these methods to explore the effects of cannabis on the human brain. Therefore, the aim of this study was to investigate whether cannabis users demonstrate changes in TMS measures of motor cortical inhibitory activity. We studied three groups: a group of cannabis users that were either daily/heavy users, a group of irregular/light users, and a group of non-using healthy subjects. All subjects were assessed with three inhibitory TMS paradigms. We also assessed several excitatory TMS paradigms and performance on two tasks of psychomotor performance. Excitatory measures were assessed to allow us to investigate whether any abnormalities identified were specific to cortical inhibition.

METHODS

Subjects

Sixty-one adults participated. Twenty-five were heavy cannabis users (20 males; 5 females; mean age: 28.6 years), 17 were light users (11 males; 6 females; mean age: 25.1 years), and 19 were non-using healthy subjects (13 males; 6 females; mean age: 28.9 years). Exclusion criteria included a history of any neurological condition, intellectual disability, personal or family history of mental illness, use of psychotropic medication or other contraindication to TMS. Participants were also excluded if they were using any other psychoactive illicit drug or consumed more than two standard drinks of alcohol per day. All subjects were required to have a negative urine drug screen (except for cannabis in the cannabis using groups) at the time of participation. This study was approved by the Monash University Standing Committee on Ethics in Research Involving Humans as well as the Alfred Hospital Ethics Committee.

Cannabis Users

The cannabis using groups were defined in terms of their frequency of use in accordance to the criterion outlined by Block and Ghoneim (Block and Ghoneim, 1993). These authors defined heavy users as those smokers who use cannabis seven or more times per week. All heavy users had consumed cannabis within 48 h before testing.

Light users (Block and Ghoneim, 1993) were those who used cannabis between 1 and 4 times per week. Light users were required to have consumed cannabis within the last 7 days but not the 24 h before testing.

Although it was anticipated that the differences in periods of abstinence between the groups would confound our capacity to make judgments about differences between the two using groups, we chose these time intervals to (1) allow us to study a group of subjects who were likely to have high plasma levels of cannabis at the time of testing and (2) to have a group in contrast with substantially lower levels. The groups were chosen to allow us to explore the effects of current cannabis level as the primary comparison rather than differences based on clinical use subtypes.

Cannabis Use Questionnaire

All participants completed a 10-item self-report questionnaire (Cannabis Amount Used and Symptom Evaluation) that was developed to quantify and assess an individual's pattern of cannabis use. It contained questions relating to the most common type and method of cannabis use, use frequency, quantity and duration, and last time of use. Additionally, a number of questions regarding problems associated with an individual's current pattern of use were included.

TMS and EMG Equipment

Single pulse TMS was administered with a Magstim-200 stimulator whereas paired pulse was administered using two Magstim-200 stimulators linked with a BiStim device (Magstim Company Ltd, UK) using a 70 mm figure-of-eight coil. The stimulators were triggered through pCLAMP software and Digidata 1320A Data Acquisition board (Axon Technologies, Melbourne Australia). EMG data were recorded with electrode placed over the APB muscle bulk and another on the dorsal aspect of the interphalangeal joint of the thumb. An earth electrode was placed on the mid forearm. All EMG signals were amplified and filtered (bandpass 10 Hz–2.4 kHz) and sampled at 10 kHz. When the subject was required to make a sustained contraction, feedback was provided on a simple analog force transducer read on a dial. When recordings were made at rest, background EMG activity was monitored. Offline averaging and data analysis were performed with the Clampfit 8.0 software package (Axon Technologies, Melbourne, Australia).

Procedure

Participants were recruited through advertizing on various University and Hospital notice boards and word of mouth. After informed consent was obtained, demographic and substance use information was collected. Current psychiatric illness was excluded using the Mini Neuropsychiatric Interview (Sheehan *et al*, 1998). When the study was initially designed, the aim was to match the three comparison groups on the level of education attained. However, early in data collection it became apparent that it was difficult to match the groups on this variable as most individuals who used cannabis had less education than non-users. Thus, a measure of pre-morbid IQ, namely the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), was administered to ensure that groups were matched on a measure of intelligence. Consequently, some participants at the beginning of the study were not administered the WTAR. Subjects provided a urine sample and then participated in the TMS experiment, which was undertaken in the late morning. The urine sample was initially tested with an immunoassay (level of detection for cannabinoids of $>50\,\mu g/ml$) confirmed on gas chromatography-mass spectroscopy (detection level of $>19\,\mu g/ml$). In addition,

a blood sample was gathered from the cannabis using participants to measure plasma levels of tetrahydrocannabinol (THC). The blood samples were stored and later transferred to the toxicology unit at the Institute of Forensic Medicine, in Melbourne Australia, for analysis using ion mass spectrometry with capillary gas chromatography (SIM) (Hok Chi Chu and Drummer, 2002). This method of analysis allowed plasma THC levels >2 ng to be detected. All storage and transfer procedures recommended to ensure adequate stability of the samples were followed.

Magnetic Stimulation

Subjects were seated in a reclining chair with a headrest for stabilization of the head. The coil was held tangential to the scalp with the handle pointing back and away from the midline at 45 degrees. The current flow in the junction of the figure-of-eight coil was anterior—posterior producing induced posterior—anterior flow in the cortex perpendicular to the line of the central sulcus. EMG data were analyzed by an investigator who was blind to the status (control or cannabis group) of the subjects.

Measurement of Resting and Active Motor Threshold

The resting motor threshold (RMT) was determined as the minimum stimulator intensity that evoked a peak-to-peak motor evoked potential (MEP) of $>50\,\mu$V in at least 5 out of 10 consecutive trials. The active motor threshold (AMT) was determined as the lowest intensity producing at least 1 MEP of $100\,\mu$V size in five trials during sustained low intensity contraction (5–10% of maximal).

Measurement of MEP Size and CSP

Mean resting MEP size was measured as the average response generated during 10 stimulations applied at each of 115 and 130% above the RMT. The 10 trials were averaged off-line and the measurements of the peak-to-peak MEP size was calculated (shown in Figure 1).

Measurement of the CSP occurred with a sustained contraction of 5% of maximum. Stimulation was provided at 20 and 40% of the RMT with 10 trials collected at each intensity level. The 10 trial data blocks were averaged off-line and CSP duration measured on averaged (non-rectified) recordings. The CSP was calculated as the time of offset of the period of EMG activity suppression minus the time of onset.

Cortical Inhibition and Facilitation

SICI and cortical facilitation (CF) were assessed using standard procedures (Kujirai *et al*, 1993; Ziemann *et al*, 1996). The conditioning stimulus was set 5% below the AMT. The test stimulus was of a consistent intensity that would produce a MEP response of 0.5–1.0 mV. The ISI was varied through the procedure in a pseudo-random allocation. Ten trials of data were recorded for four conditions; a control single stimulus and at 2, 3 (inhibition), and 15 ms (facilitation) intervals. Paired stimuli were provided at 5 s intervals throughout. For each sweep, the peak and anti-peak of the MEP were measured and an average peak-to-peak MEP size calculated for each ISI and the control condition. SICI and CF were then calculated as percentages of the mean control condition. Unlike sensory gating paired

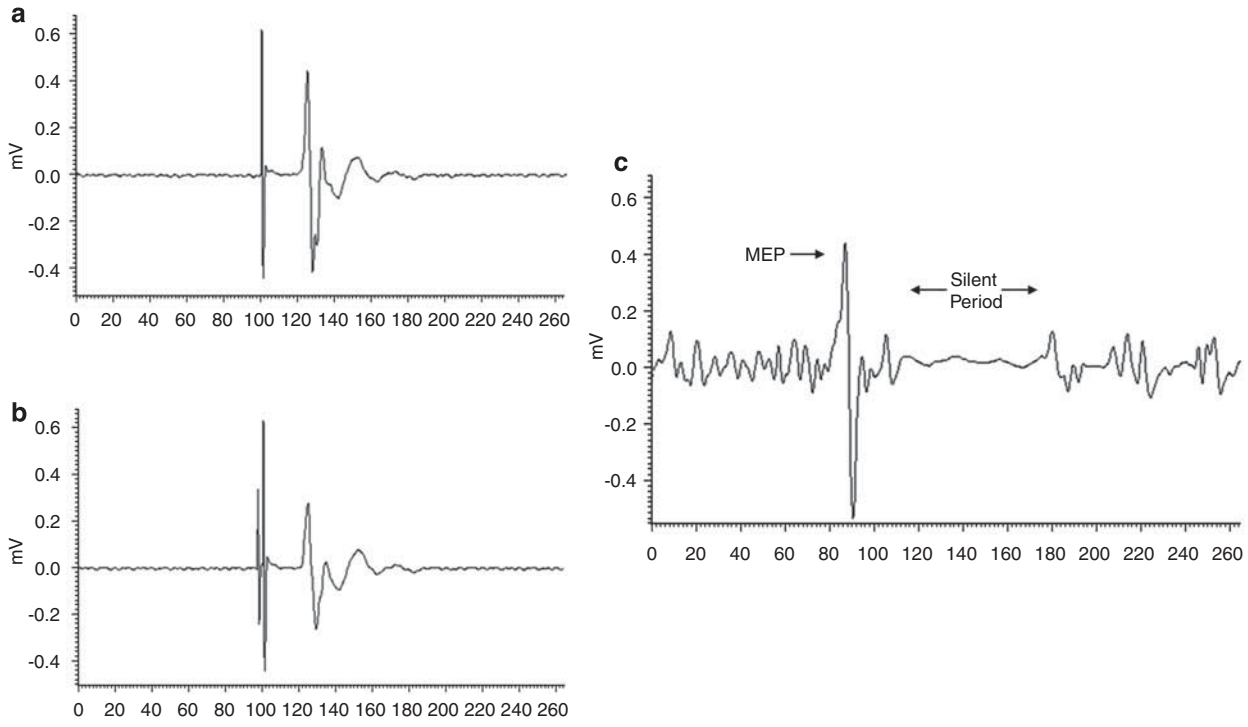

Figure 1 A sample trace demonstrating short interval cortical inhibition. (a) A standard motor evoked potential (MEP) response to a suprathreshold single TMS pulse is shown. (b) The smaller response to a paired pulse with a subthreshold conditioning and suprathreshold test stimulus is displayed. (c) A single trace during active tonic contraction demonstrating an induced motor evoked potential (MEP) and the cortical silent period (CSP) is shown.

pulse paradigms, a single test pulse is used as the control condition rather than response to the first pulse as the condition stimulus is sub rather than suprathreshold.

LICI was assessed with an ISI of 100 ms. Both the test and conditioning pulses were set at 120% of the RMT. Ten single test and 10 paired pulses were measured and LICI calculated as a percentage of the mean control condition.

Psychomotor Performance

Two standard tasks were used to assess psychomotor performance.

(1) The finger-tapping test is one of the most widely used tests of manual dexterity and measures the motor speed of the index finger of each hand (Reitan and Wolfson, 1993). Subjects were required to tap a key as rapidly as possible, using the index finger of the preferred and non-preferred hand. Five 10 s trials were assessed on each hand and averaged.
(2) The Grooved Pegboard test is a measure of manual dexterity and visual-motor coordination. The test consists of a small board with a 5×5 set of slotted holes that are angled in different directions. The task is to insert pegs into the board matching a groove on the peg with a groove on the board as quickly as possible.

Statistical Analysis

One-way analysis of variance (ANOVA) and χ^2 tests were used to investigate differences between the three groups on demographic variables (ie, age, gender, education level, and intelligence). The primary analysis was performed to look at differences between the three groups on the measures of RMT, AMT, CSP, MEP size, cortical inhibition, CF, finger-tapping test, and grooved peg board performance. The two measures of SICI (2 and 3 ms) were entered into a multivariate ANOVA and the other variables analyzed using ANOVA models (with *post hoc t*-test with the Bonferroni correction for multiple comparisons). Education was included in secondary analyses if a significant group difference was seen in the primary analysis. MEP and CF data were square root transformed and grooved pegboard data were log transformed for analysis to meet conditions of normality. The relationship between THC plasma levels and TMS measures in the heavy cannabis using group was examined using Pearson product-moment correlation coefficient.

RESULTS

Sample and Substance Use

Forty-nine cannabis users were initially tested and of these seven participants were excluded. There were two main reasons for exclusion: positive urine drug screen for substances other than cannabis ($N=4$) and time of last cannabis use exceeded a 1-week period ($N=3$). The characteristics of the final sample are presented in Table 1. There were no group differences in age, sex, or WTAR scores but the controls did have a higher number of years of education. The mean education level for heavy users was significantly lower than that for the control group ($p<0.05$). The light users did not significantly differ on education level from heavy ($p>0.05$) users or controls ($p>0.05$).

All heavy users and 6 of 17 (35.3%) of light users had a positive urine test for cannabis use. On self-report, 40% of the heavy users were smoking 3–7 g per week whereas 28% were smoking >7 g. In all, 52.9% of the light users were using less than a gram per week and 47.1% were using 1–3 g a week. The duration of cannabis use was similar across the groups; 64% of the heavy users and 58.8% of the light users reported smoking cannabis for >5 years. In all, 32% of the heavy users reported use on the actual day of testing.

On plasma assay, 16 heavy using subjects (no light users) obtained a quantifiable THC plasma level (of 2 ng/ml or more).

In regards to DSM-IV diagnosis, 19 of the heavy and one of the light users met dependence criteria, 4 of the heavy and 11 of the light users met abuse criteria, and 2 of the heavy and 5 of the light users met neither ($\chi^2=19.9$, $p<0.001$).

TMS Results

Table 2 presents the data for each of the TMS variables as a function of group.

Inhibitory Measures: CSP, SICI, and LICI

There was no significant difference between cannabis users and controls in the size of the CSP at 120% ($F(2, 58)=0.517$, $p=0.599$) or 140% ($F(2, 58)=0.095$, $p=0.909$).

Figure 2 presents SICI data for cannabis users *vs* controls. In the multivariate model, there was a significant overall effect of group ($F(4, 116)=5.3$, $p=0.001$). This remained significant controlling for education level as a covariate.

Table 1 Demographic Details for Total Sample

Demographics	Heavy users		Light users		Controls		*p*
	Mean	SD	Mean	SD	Mean	SD	
Age	28.56	9.45	25.12	6.94	28.89	9.05	0.356
Gender (M/F)	20/5	—	11/6	—	13/6	—	0.518
Education (Years)	13.08	2.90	14.85	2.32	15.55	3.30	0.018
WTAR (raw scores)	40.88 ($N=16$)	5.71	40.18 ($N=11$)	4.02	41.31 ($N=16$)	6.91	0.886

Table 2 Means and Standard Deviation Results for all TMS Variables by Group

Group	Heavy		Light		Control		*p*
	Mean	SD	Mean	SD	Mean	SD	
RMT (%)	49	9.37	45	8.77	45	8.28	0.256
AMT (%)	37	6.67	33	4.89	33	5.76	0.092
MEP size (mV)							
115% above RMT	490	468.51	496	437.87	392	243.34	0.767
130% above RMT	1034	737.12	857	647.78	830	418.48	0.670
CSP (ms)							
120% above AMT	120	32.47	109	30	114	35.49	0.599
140% above AMT	158	36.25	153	42.33	158	39.07	0.909
SICI (%)							
2 ms	29	34.42	41	22.43	69	16.21	0.000
3 ms	42	34.75	43	39.48	63	16.89	0.063
CF (%)							
15 ms	142	64.58	127	48.37	110	20.49	0.120
LICI (%)							
100 ms	86	21.04	84	21.23	77	49.63	0.570

AMT, active motor threshold; CF, cortical facilitation; CSP, cortical silent period; LICI, long interval cortical inhibition; MEP, motor evoked potential; RMT, resting motor threshold; SICI, short interval cortical inhibition.

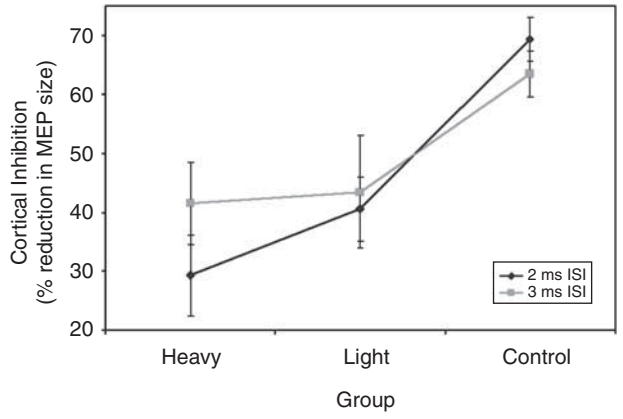

Figure 2 Mean SICI (±SD) for cannabis users *vs* controls.

Analyzed by ISI, there was a significant difference between groups at the 2 ms ISI ($F(2, 58) = 12.522$, $p < 0.05$) and a trend toward a difference between cannabis users and controls at the 3 ms ISI, ($F(2, 58) = 2.899$, $p = 0.063$). *Post hoc* comparisons for the two ISI measures revealed no significant difference in SICI between heavy and light users ($p = 0.566$), but SICI was significantly less in heavy users ($p < 0.001$) compared with controls and the light users ($p = 0.006$) compared with controls.

Table 3 Correlations between Plasma THC Levels and TMS Variables

TMS variable	Pearson correlation (*r*)	*p*
RMT	−0.29	0.28
AMT	−0.22	0.40
Resting MEP size (115%)	0.111	0.682
Resting MEP size (130%)	−0.079	0.770
Active MEP size (120%)	0.234	0.383
Active MEP size (140%)	0.196	0.468
CSP (120%)	0.147	0.588
CSP (140%)	0.222	0.408
ppTMS—2 ms ISI	−0.501	0.048
ppTMS—3 ms ISI	−0.407	0.118
ppTMS—15 ms ISI	−0.321	0.226
LICI	0.11	0.68

ppTMS, paired pulse TMS.

There was no significant difference between cannabis users and controls on LICI ($F(2, 55) = 0.568$, $p = 0.570$).

Excitability Measures: Motor Thresholds, MEP Size, CF

There were no significant differences between the groups in resting ($F(2, 58) = 1.40$, $p = 0.256$) or active ($F(2, 58) = 2.49$, $p = 0.092$) motor thresholds. No significant group difference in resting MEP size was observed with stimulation at either intensity (115%: $F(2, 58) = 0.266$, $p = 0.767$, 130%: $F(2, 58) = 0.403$, $p = 0.670$). There was also no significant difference in CF between cannabis users and controls ($F(2, 58) = 2.202$, $p = 0.120$).

Correlation Analysis

There was a significant, negative correlation between SICI at the 2 ms ISI and THC plasma levels ($r = -0.50$, $p < 0.05$). No other correlations between THC plasma levels and TMS measures were observed (Table 3).

Psychomotor Performance

Means and SDs of participants' performance on the finger-tapping task and grooved pegboard were calculated and are shown in Table 4. For the finger-tapping task, there was no significant difference between the cannabis using groups and controls with either the dominant ($F(2, 58) = 0.717$, $p = 0.493$) or non-dominant ($F(2, 58) = 0.045$, $p = 0.956$) hand. There was also no significant difference between the groups on the grooved pegboard for dominant hand completion time ($F(2, 58) = 0.273$, $p = 0.762$) or total score ($F(2, 58) = 0.299$, $p = 0.743$), or for non-dominant hand completion time ($F(2, 58) = 0.140$, $p = 0.870$) or total score ($F(2, 58) = 0.101$, $p = 0.904$).

DISCUSSION

The main finding of this study was that of reduced SICI in cannabis users with no differences seen in CSP or LICI measures. The SICI finding was significant at the 2 ms

Table 4 Performance for Measures of Psychomotor Performance

Group	N	Dominant hand				Non-dominant hand			
		Mean FT		SD		Mean FT		SD	
FTT									
Heavy	25	339.76		22.15		315.80		27.05	
Light	17	340.59		34.11		313.00		26.84	
Control	19	330.42		32.85		314.37		35.80	
		Mean completion time	**SD**	**Mean total score**	**SD**	**Mean completion time**	**SD**	**Mean total score**	**SD**
GP									
Heavy	25	62.00	6.71	87.28	6.82	69.20	8.04	94.36	8.12
Light	17	64.06	8.36	89.41	8.39	69.71	8.62	94.94	8.50
Control	19	63.89	12.82	88.46	9.33	70.74	12.0	95.68	12.2

FTT, finger-tapping test; GP, Grooved Pegboard.

interval, with a trend for a similar result at 3 ms. Interestingly, there was also a significant correlation between SICI at the 2 ms ISI and THC plasma levels among heavy cannabis users. On measures of cortical excitability, this study found no differences in the MEP size, RMTs or AMTs or CF of cannabis users and non-users. There were no differences between the groups in psychomotor performance. Of note, although we recruited groups with deliberately divergent plasma levels of cannabis, reduced SICI was seen in both groups.

In regards to our finding of reduced SICI, evidence has been progressively accumulating that SICI is a reflection of cortical activity and activity at the $GABA_A$ synapse. For example, $GABA_A$ involvement in SICI is supported by the time course of its effect. Stimulation of the neocortex produces disynaptic fast and slow inhibitory postsynaptic potentials (IPSPs) with a distinctly different time course (Davies *et al*, 1990). Fast IPSPs are mediated by $GABA_A$ receptors and are coupled to chloride channels, lasting approximately 20 ms, whereas slow IPSPs are mediated by $GABA_B$ receptors that activate potassium channels and peak around 150–200 ms. This difference in time course roughly corresponds to the different ISIs of SICI (1–6 ms) and LICI (50–150 ms) (Sanger *et al*, 2001). Further support has come from pharmacological studies that have found that stimulation of $GABA_A$ receptors with benzodiazepines (eg Lorazepam) enhances SICI (Di Lazzaro *et al*, 2008).

This study is the first demonstration of the direct effects of cannabis in the human cortex. Given the dependence of SICI on GABAergic activity, it is possible that this effect directly relates to GABAergic modulation by cannabis, especially as a sizeable proportion of subjects had measurable plasma THC levels. This finding is at least in part consistent with a number of studies that support an interaction between cannabis and the GABAergic neurotransmission. These motor cortical findings could arise from effects at a cortical level or potentially in other areas of the pyramidal and extrapyramidal systems. For example, some studies have suggested that activation of the cannabinoid CB1 receptor exerts a presynaptic modulatory increase of GABA transmission at the level of the output nuclei of the basal ganglia (Pertwee and Greentree, 1988; Pertwee *et al*, 1988). Other studies have suggested an inhibitory rather than a stimulatory effect of GABA neurons by cannabinoids in the basal ganglia (Chan *et al*, 1998) and striatum (Szabo *et al*, 1998). It is notable that despite the clear SICI finding, there were no differences in either paradigm assessing $GABA_B$ activity (CSP and LICI) or in any measure of cortical excitability. Some studies at a pharmacological level have demonstrated specific effects of cannabinoids on $GABA_A$. For example, whole-cell voltage clamp recordings of hippocampal CA1 pyramidal neurons in rat brain slices revealed that the activation of cannabinoid receptors reduced $GABA_A$ but not $GABA_B$ receptor mediated synaptic inhibition (Hoffman and Lupica, 2000). However, effects of cannabinoids on GABA have also been shown at $GABA_B$ receptors, for example in behavior studies in rats (Romero *et al*, 1996). Given the apparent complexity of the interaction between cannabinoids and GABA, it is quite possible that the $GABA_A$ but not $GABA_B$ effects in the study could be explained by variation in cannabis effects across brain regions.

Another, and perhaps more likely possibility, is that the reduced SICI relates not directly to the effect of cannabis on $GABA_A$ receptors but is more related to neurobiological changes in patients who use cannabis regularly. Strong support for this conclusion is found in the observation that reduced SICI was found in patients who were both heavy and light cannabis users with the latter group predominantly having quite low or non-detectable plasma levels of cannabis. The main distinguishing factors between heavy and light cannabis users was the former group's frequency and quantity of use, the fact that the majority of the heavy users met DSM-IV criteria for cannabis dependence, and the time period from recent use to TMS testing. Despite these differences, reduced SICI was seen in both groups and to a similar degree. However, the observation that reduced SICI could be independent of current use is somewhat contradicted by the correlation between SICI and plasma THC in the heavy use group.

If we do presume that reduced SICI is a characteristic of cannabis users rather than an effect directly of the drug itself, it is possible that this results from long-term cannabis use. That is, long-term cannabis use results in a down regulation of activity within cortical inhibitory circuitry. The users in the two groups did not differ substantially in the duration of their lifetime cannabis use, although they differed substantially in the degree of current use. This finding is in line with some of the cannabis and cognition research, which suggests that the duration of cannabis use is a more prominent contributor to the development of cognitive impairment than frequency or quantity of use (Solowij *et al*, 2002). Interestingly, cannabis users in this study demonstrated normal motor performance; motor deficits have been reported earlier when cannabis users are drug free (eg (Bolla *et al*, 2002)). Speculatively, this suggests that chronic cannabis may result in brain changes such that performance is substantially impaired, as supported by much research, but partially maintained during the presence of the drug itself. A study of information processing speed in cannabis users also found normal performance in an acute use state with impaired performance in a non-acute state although this could be confounded by withdrawal effects (Kelleher *et al*, 2004).

Another alternative is that individuals who are vulnerable to becoming long-term users of illicit substances such as cannabis may have underlying pre-existing deficits in SICI. In contrast, lighter, irregular users may also exhibit this decrease in SICI but have a number of protective factors that lead to a less chronic pattern of use. It is possible that this physiological deficit may result in reduced behavioral inhibition affecting an individual's capacity not respond to drug cues. Deficits of inhibition have been found in other substance-dependent populations (Fillmore and Rush, 2002), there is evidence of impairment of other frontal executive functions in cannabis users (Pope and Yurgelun-Todd, 1996), and cannabis users have been shown to use different brain networks during inhibitory tasks (Gruber and Yurgelun-Todd, 2005). Several studies have also shown abnormalities in cortical excitability in cocaine users that are not related directly to current cocaine consumption (Boutros *et al*, 2001, 2005; Sundaresan *et al*, 2007). These studies have demonstrated changes in motor thresholds with no change in CSP or LICI. Unfortunately to date, SICI has not been investigated in cocaine users. It is possible that changes in cortical excitability and inhibition represent a more general vulnerability to becoming substance dependent.

There were several methodological issues in this study that must be considered. For instance, we assessed cannabis users in association with their ongoing use (rather than following controlled exposure) and did not test at a uniform time point. An alternative may have been to test cannabis users following a similar period of abstinence. We deliberately recruited the subjects to allow us to explore the relationship of TMS measures to the likely presence in the brain of high and low (or absent) levels of cannabis metabolites, rather than the groups as equal clinical entities studied under identical conditions. The resultant undetectable cannabis levels in most of the light users allowed us to make this comparison but due to the sensitivity of the assay also prevented us from conducting correlations with plasma level across the entire sample. The undetectable levels in the light users most likely reflected a combination of their lighter overall use and the greater duration from most recent use compared with the heavy group. Because of the undetectable cannabis levels in most of the light users, we were not able to confirm the nature of the use in these subjects other than by self-report. However, there is no reason to assume they would have systematically under or over estimated their use in a manner that would have influenced our capacity to interpret the results of the study. A complementary approach would involve a placebo—active THC drug challenge in light users with SICI measured pre and post drug. In addition, despite efforts to match participants, there was a significant difference in education level between heavy users and controls, highlighting some degree of heterogeneity within the sample. We did match the sample on WTAR levels although a slightly higher proportion of subjects received this measure in the control group. The incomplete data on the WTAR should not have biased the overall results as the missing data were related to the time of recruitment in the study, not a systematic variable likely to influence cortical inhibition. However, although this study attempted to control for a number of possible confounding variables, we did not match the groups based on the actual amount of current or past consumption of licit drugs including alcohol.

Of some note is that our finding of reduced cortical inhibition, reflecting abnormalities of $GABA_A$ neurotransmission, is similar to that seen in several TMS studies of schizophrenia (for example Daskalakis *et al*, 2002; Fitzgerald *et al*, 2002b; Wobrock *et al*, 2008). A range of other studies have also implicated deficits of $GABA_A$ in schizophrenia (Lewis and Hashimoto, 2007). This is particularly relevant as cannabis can precipitate a psychotic episode in individuals who are predisposed to develop schizophrenia (Andreasson *et al*, 1987; Hambrecht and Hafner, 2000). Additionally, there are also extremely high rates of cannabis abuse among patients with schizophrenia, and this abuse often worsens outcomes (Hall and Degenhardt, 2000; Bersani *et al*, 2002; Rehman and Farooq, 2007). It is possible to speculate that if chronic cannabis use results in a down regulation of GABAergic function, this could have a role in the development of schizophrenia.

In conclusion, subjects with a history of persistent cannabis use, independent of the level of current use, demonstrate a reduction in cortical SICI likely consistent with altered activity at $GABA_A$ receptors. They demonstrated no abnormalities in inhibitory paradigms assessing $GABA_B$ activity or in assessments of overall cortical excitability. Further research, in particular using longitudinal designs, is required to further explore whether reduced SICI predisposes to, or is the result of, sustained cannabis use.

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DISCLOSURE/CONFLICT OF INTEREST

PF and ZD have received support for participation in a research study from Neuronetics Ltd and have no relevant conflicts of interest. SW has nothing to disclose.

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