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Chronic effects of cannabis on sensory gating

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Abstract

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Keywords

sensory, gating, cannabis, chronic, effects

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Abstract

Chronic cannabis use has been associated with neurocognitive deficits, alterations in brain structure and function, and with psychosis. This study investigated the effects of chronic cannabis use on P50 sensory-gating in regular users, and explored the association between sensory gating, cannabis use history and the development of psychotic-like symptoms. Twenty controls and 21 regular cannabis users completed a P50 paired-click (S1 and S2) paradigm with an inter-pair interval of 9 seconds. The groups were compared on P50 amplitude to S1 and S2, P50 ratio (S2/S1) and P50 difference score (S1-S2). While cannabis users overall did not differ from controls on P50 measures, prolonged duration of regular use was associated with greater impairment in sensory gating as indexed by both P50 ratio and difference scores (including after controlling for tobacco use). Long-term cannabis users were found to have worse sensory gating ratios and difference scores compared to short-term users and controls. P50 metrics did not correlate significantly with any measure of psychotic-like symptoms in cannabis users. These results suggest that prolonged exposure to cannabis results in impaired P50 sensory-gating in long-term cannabis users. While it is possible that these deficits may have pre-dated cannabis use and reflect a vulnerability to cannabis use, their association with increasing years of cannabis use suggests that this is not the case. Impaired P50 sensory-gating ratios have also been reported in patients with schizophrenia and may indicate a similar underlying pathology.

Key words: Cannabis, P50, sensory gating, schizophrenia, event-related potentials

1.0 Introduction

Cannabis sativa is the most commonly used illicit substance in the world. Regular and prolonged exposure to cannabis is associated with impaired cognition, particularly deficits in attention, learning and memory (Solowij and Michie, 2007; Solowij and Pesa, 2010), alterations in brain structure and function (Solowij et al., 2011; Yücel et al., 2008a; Yücel et al., 2008b), and deficits in electrophysiological indices of pre-attentive processes (e.g. P50: Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve, 2002; Patrick and Struve, 2000; Rentzsch et al., 2007; and mismatch negativity, MMN: Greenwood et al., in revision; Rentzsch et al., 2011; Roser et al., 2010) as well as selective attention (e.g. processing negativity and P300: Solowij et al., 1995). Chronic cannabis use has also been shown to increase the risk of developing psychotic symptoms in a dose-response fashion (Semple et al., 2005), and is considered by some to be a component cause of schizophrenia in vulnerable individuals (D'Souza et al., 2009; Murray et al., 2007). Δ^9 -Tetrahydrocannabinol (THC) is the primary psychoactive constituent of cannabis and is linked with altered cognition and the induction of psychotic-like symptoms (D'Souza et al., 2009). The subjective, behavioural and cognitive effects produced by THC are most likely due to the action of THC as a partial agonist at central cannabinoid (e.g. CB₁) receptor sites (Pertwee, 2008), altering the regulatory action of the endocannabinoid system on synaptic transmission and other neurotransmitter signalling, such as gamma-aminobutyric acid (GABA), glutamate and dopamine (Lopez-Moreno et al., 2008; Mathur and Lovinger, 2012). CB₁ receptors occur in high density throughout the brain, particularly in the hippocampus, anterior cingulate, basal ganglia and the cerebellum; regions which are involved in cognition and are particularly important for attention, learning and memory (Bhattacharyya et al., 2009; Bossong and Niesink, 2010; Iversen, 2004). Impaired cognition in chronic cannabis users is thought to be underpinned at least in part, by alterations to the regulatory role of the endocannabinoid system on synaptic plasticity following prolonged and regular exposure to exogenous cannabinoids such as THC (Hampson et al., 2011; Heifets and Castillo, 2009; Hoffman et al., 2007; Puighermanal et al., 2012). In light of deficits in cognition (e.g., selective attention, verbal learning and inhibition, Solowij and Michie, 2007), and alterations in brain function (e.g., prefrontal cortical, cingular, hippocampal and cerebellar activation in imaging studies, Solowij and Michie, 2007; Martin-Santos et al., 2010) and structure (e.g., reduced hippocampal volume, Yücel et al., 2008b) in long-term cannabis users being similar to those observed in patients with schizophrenia, further investigation of neurobiological markers of pre-attentive processes may inform mechanisms by which cannabis might result in schizophrenia-like conditions in the brain and induce psychosis in vulnerable individuals.

Sensory gating is the brain's ability to modulate its sensitivity to incoming stimuli (Braff & Geyer, 1990) and includes its ability to inhibit response to irrelevant sensory stimuli and thus 'gate-out' repetitive and redundant sensory stimulation of the brain (Boutros & Belger, 1999; Boutros et al., 1991; Brenner et al., 2009; Freedman et al., 1983; Gjini et al., 2010; Hu et al., 2012). In contrast, 'gating in' is conceptualised as the brain's preattentive ability to identify significant stimulus change or novel sensory input (Boutros & Belger, 1999; Gjini et al., 2010). The P50 component is a positive event-related potential (ERP) marker of sensory 'gating-out'¹ with a vertex maximum elicited approximately 50 milliseconds following an auditory stimulus. The

¹ In this study, we focus specifically on P50 as a measure of sensory 'gating-out' (as defined by Boutros & Belger, 1999; Gjini et al., 2010) and do not include a measure of 'gating-in' (e.g. mismatch negativity; see Gjini et al., 2010). While we henceforth refer to 'P50 sensory gating', we implicitly mean 'gating-out' rather than 'gating-in'.

P50 component is typically investigated using an auditory paired-click paradigm in which pairs of brief (approximately 1 millisecond) clicks are presented 500 milliseconds apart. In this paradigm, the amplitude of the P50 component elicited to the second click is attenuated relative to the first click in healthy individuals. The relative reduction in P50 amplitude to the second click within the pair (i.e. the ratio P50 to the second click / P50 to the first click) is the most commonly used marker of sensory gating in this context (Clementz et al., 1997). Although the neural generators of the auditory P50 evoked potential have been localised to Heschl's gyrus (Knott et al., 2009; Korzyukov et al., 2007; Weisser et al., 2001), the neurobiological underpinnings associated with the phenomenon of sensory gating are less clear (Korzyukov et al., 2007). While it is possible that the populations of neurons in the auditory cortex activated to the first click undergo a refractory period and therefore cease to be active to the second click, there is increasing evidence to suggest that additional inhibitory inputs attenuate the brain's response to repetitive stimuli and specifically the P50 response to the second click (see, Korzyukov et al., 2007). Evidence from animal work suggests these inhibitory inputs may arise in the CA3 region of the hippocampus and are involved in sensory gating (Freedman et al., 1996). In humans however, intracranial recordings have revealed that hippocampal engagement occurs approximately 200 milliseconds post-stimulus and therefore, although not directly related to P50 generation (Grunwald et al., 2003), instead may suppress P50 generators activated by the second click (Korzyukov et al., 2007). Also implicated in sensory gating are generators in the frontal lobe (Korzyukov et al., 2007; Weisser et al., 2001), superior temporal gyrus (Thoma et al., 2005), prefrontal cortex (Grunwald et al., 2003), and cingulate and parietal lobe regions (Boutros et al., 2013), along with multiple neurotransmitter systems including GABAergic, cholinergic, dopaminergic, serotonergic and glutamatergic systems (Adler et al., 1998). Relevant to the current study and as noted earlier, THC is thought to disrupt the regulatory action of the endocannabinoid system on these neurotransmitter systems (Lopez-Moreno et al., 2008; Mathur and Lovinger, 2012).

Impaired P50 suppression has been reported extensively in patients with schizophrenia (Bramon et al., 2004), and is a candidate endophenotype for the disorder (Braff and Light, 2005) with P50 deficits observed at an intermediate level in unaffected family members of patients with schizophrenia (e.g., Clementz et al., 1998b) and associated with schizotypy in a non-clinical population (Croft et al., 2001). Meta-analyses suggest P50 ratios in patients with schizophrenia are 1.28 to 1.56 standard deviations larger than those of healthy controls, although there is large variability in P50 ratios between studies (Bramon et al., 2004; de Wilde et al., 2007). Despite the relatively robust finding of altered sensory gating, the association between symptomatology and P50 suppression in patients with schizophrenia is less clear. Croft et al., (2004) argue this may be a function of medication status or lifestyle factors such as smoking history. Pharmacological work has highlighted the involvement of the α -7 nicotinic receptor in P50 sensory gating (Hajos and Rogers, 2010), compatible with improved P50 suppression in cigarette smokers (Crawford et al., 2002) and underlining the potential for tobacco use to confound P50 measurement in patient studies given the increased rates of smoking in this group (Croft et al., 2004). There is also large variability in P50 measures across studies, including the measurement of P50 amplitude (peak to peak vs. baseline to peak), the number of trials contributing to an average, time on task and the time between click pairs (inter-pair interval, Dalecki et al., 2011).

A small body of research has examined P50 sensory gating in cannabis users. This work has reported reduced P50 suppression in chronic cannabis users compared to non-user controls (Edwards et al.,

2009; Patrick et al., 1999; Patrick and Struve, 2002; Patrick and Struve, 2000; Rentzsch et al., 2007), and interestingly in comparison to patients with schizophrenia with and without concurrent cannabis use (Rentzsch et al., 2007). Some of these studies found that poor sensory gating in cannabis users is associated with prolonged durations of exposure (Rentzsch et al., 2007) and dose (the number of joints smoked in the previous six months, Edwards et al., 2009). The association between P50 sensory gating and propensity to develop psychotic-like symptoms associated with prolonged exposure to cannabis has not been addressed in prior work. Nor have the above studies attempted to control for patterns of tobacco use, which may affect these data given the high rates of tobacco use by cannabis users. The current study attempted to explore both of these issues and to clarify the association between prolonged exposure to cannabis and sensory gating more precisely. Further, consistent with prior work demonstrating impairments in verbal learning in cannabis users and patients with schizophrenia (Solowij and Michie, 2007), we explored a potential association between a measure of verbal learning and P50 sensory gating. Finally, prior research in cannabis users focused predominately on a ratio measure of sensory gating (Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve, 2002; Patrick and Struve, 2000; Rentzsch et al., 2007), while more recent research also investigated the difference metric (P50 amplitude to S1 – P50 amplitude to S2) with mixed results (Edwards et al., 2009; Rentzsch et al., 2007). In accordance with this recent work and research which suggests that the P50 difference score may be a more reliable index of sensory gating (Smith et al., 1994), the current study compared cannabis users with controls on both P50 ratio and difference measures (see also Chang et al., 2011 for a meta-analysis of S1, S2 and P50 ratio differences in patients with schizophrenia and controls). First, we set out to replicate the findings of reduced P50 suppression in chronic cannabis users by comparing P50 metrics in regular cannabis users and age- and gender-matched healthy non-user controls. Consistent with prior work, we predicted that in comparison to non-user controls, chronic cannabis users would exhibit significantly larger P50 ratios, and smaller P50 difference scores, indicative of impaired sensory gating. Second, we explored the association between the degree and duration of cannabis exposure, and of psychotic-like symptoms, verbal learning and P50 sensory gating.

2.0 Materials and Method

2.1 Participants

Twenty-one regular cannabis users and twenty-one non-user controls took part in the study. Participants were recruited via an advertisement in a local newspaper and were first screened over the telephone to ensure they met inclusion criteria. Regular cannabis use was defined as minimum fortnightly use for at least two years. Control participants were required not to have used cannabis more than 20 times in their life and not at all in the previous year. Exclusion criteria included regular polysubstance use within the previous two years, or use of an illicit substance within the past month (other than cannabis for the cannabis group), a current psychiatric diagnosis, and a neurological or medical disease that would interfere with EEG testing. Participants were asked to abstain from using cannabis, alcohol or any illicit substance for a minimum of 12 hours prior to testing, and self-reported cannabis use and abstinence from other drugs was corroborated by urinalysis. Participants also abstained from cigarettes and caffeinated drinks during testing: EEG protocols were completed 1.5 hours into the testing schedule. To screen for the presence of a psychiatric condition the

Kessler Psychological Distress Scale (K10, Andrews and Slade, 2001) was administered over the phone to all participants. Participants were also asked detailed questions about whether they had ever been diagnosed with any psychological/psychiatric disorders as part of a structured interview administered during the testing session. One control participant was excluded after they admitted to currently taking an anti-epileptic medication. Two participants in the cannabis user group reported that they had used ecstasy on a single occasion between 2 and 4 weeks prior to testing. No amphetamine derivatives were detected in their urines and therefore data from these participants were included in the analysis. No polysubstance use was reported in the non-user control group, and was minimal in the cannabis user group: 2 participants reported regular cocaine use over 15 years ago, and two other participants reported a period of regular (approximately 6 months) amphetamine use over 2 years ago. The study was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee.

2.2 Procedure

All participants were familiarised with the study procedure before written informed consent was obtained. Demographic and detailed substance use information was then obtained through a structured interview, and alcohol consumption was assessed using the Alcohol Use Disorder Identification Test (AUDIT, Saunders et al., 1993). Full scale IQ was estimated using the vocabulary and matrices subscales of the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). All participants were asked to complete the Community Assessment of Psychic Experiences (CAPE, Stefanis et al., 2002) and Schizotypal Personality Questionnaire (SPQ, Raine, 1991) as measures of psychotic-like symptoms, and cannabis users also completed the Cannabis Experiences Questionnaire (CEQ, Barkus et al., 2006) as a measure of symptoms experienced while intoxicated, the Marijuana Withdrawal Checklist (MWC, Budney et al., 2004) and the Severity of Dependence Scale (SDS, Gossop et al., 2002). The Rey Auditory Verbal Learning Task (RAVLT) was also administered to all participants. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971) and all participants underwent audiometric testing to screen for hearing impairments; all were found to have hearing within the normal range (i.e. ≤ 25 dB) at 1000Hz and 1500Hz. EEG electrodes were then fitted, and participants first completed an eye-movement calibration task (Croft and Barry, 2000) and multi-feature mismatch negativity paradigm (Greenwood et al., in revision; Todd et al., 2008) before completing the P50 paired-click paradigm. All participants were reimbursed AUD\$50 for their participation.

2.3 Experimental paradigm

The P50 task comprised one 10-minute block of 100 pairs of click stimuli. To control attention, participants were instructed to silently count each of the pairs of clicks and respond with a button press after every 25th click pair. Prior research suggests there are no differences between 'active' paradigms which control attention by counting or button pressing, and passive paired click paradigms on P50 metrics (Jerger et al., 1992; Kho et al., 2003; White & Yee, 1997). Participants were asked to minimise movement and to keep their eyes open, resting their gaze on the computer monitor in front of them. The stimuli were auditory clicks of 1 ms duration and presented binaurally using headphones (Sennheiser HD215) at 90 dB SPL. The first and second clicks within a pair were separated by a fixed inter-stimulus interval of 500 ms. The inter-pair interval (IPI) was the duration between the second click within a click pair and the first click of the next pair. There

were two different IPI conditions, a long IPI condition in which click pairs were presented with an average of 9 seconds apart (in order to give the appearance of randomness, 3 different IPIs were chosen for each condition, the mean of which was the target IPI: e.g. 8930, 8990 or 9080ms) and a short IPI condition in which click pairs were presented an average of 3 seconds apart. The current study will focus on data from the 9 second IPI condition as this condition is most comparable to paired-click paradigms employed in previous research (e.g., Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve, 2002; Patrick and Struve, 2000; Rentzsch et al., 2007). Data for the 3 second IPI condition were collected as part of another study and will not be discussed further here. Fifty pairs of each of the short and long IPI conditions were presented in a random fashion.

2.4 Electrophysiological data acquisition

Electroencephalographic (EEG) data were recorded continuously from 19 Ag/AgCl electrodes positioned on an Electrocap according to the international 10-20 system (FP1, FP2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, T3, T4, T5, T6, O1 and O2), and two electrodes positioned over the left and right mastoid. EEG data were grounded to an electrode placed midway between FPz and Fz, and referenced online to an electrode positioned on the tip of the nose. Four monopolar electrodes were placed above and below the left eye and 1 cm from outer canthi of the left and right eye and used to calculate vertical, horizontal and radial electrooculogram (EOG) data required for the EOG correction procedure of Croft and Barry (2000). Data were sampled at 500 Hz, with a bandpass filter of 0.1 to 100 Hz. All electrode impedances were below 10 k Ω at the start of recording.

2.5 Electrophysiological data analysis

EEG data were analysed offline using Neuroscan software (Scan 4.4). Data were re-referenced offline to the average of the mastoids and corrected for ocular artifacts according to Croft and Barry (2000). Data were bandpass filtered from 10 to 45 Hz (down 12 dB/octave roll off), epoched from 100 ms pre-stimulus to 300 ms post-stimulus, and baseline corrected using the 100 ms pre-stimulus interval. Epochs were rejected if signals at any EEG channel exceeded $\pm 50 \mu\text{V}$. EEG epochs were then averaged to the first (S1) and second (S2) click.

P50 peaks were identified as the largest positive peak ± 15 ms around the peak of the average P50 peak latency in the grand mean (i.e. 62 ms $\pm$ 15 ms) following the Na peak (i.e. 48 $\pm$ 15 ms) and were required to have a frontocentral topography (Rentzsch et al., 2007). No minimum peak amplitude was required for a peak to be classified as such. An automatic peak detection algorithm was applied first and the data were then verified visually by an experienced researcher, although not blind to group status. If no peak was present within the specified latency range and/or did not have a frontocentral topography, the P50 amplitude was scored as '0' (see also Dalecki et al., 2011). P50 data were measured at Cz only, in accordance with Clementz et al., (1998a), relative to the peak of the preceding peak (Na). The following P50 measures were computed: P50 peak to peak amplitude to the first (S1) and second (S2) click; P50 ratio, defined as the ratio of P50 peak amplitudes (i.e. S2/S1, where smaller P50 ratios are indicative of better sensory gating); and P50 difference, defined as the difference between P50 peak amplitude to the first and second click (i.e. S1- S2, where larger difference scores are indicative of better sensory gating).

2.6 Statistical analysis

The groups were compared on demographic variables and measures of psychotic-like symptoms using independent samples t-tests (or Mann-Whitney U tests where data were not normally distributed). P50 measures were not consistently normally distributed in the chronic cannabis user group, so all data were transformed using a square root transformation to approximate normality. Univariate ANOVAs were then used to examine the effect of Group (cannabis, control) on each transformed P50 variable (P50 amplitude to the first (S1) and second (S2) click stimuli, P50 ratio and P50 difference). Pearson's correlations were used to examine the association between transformed P50 measures and cannabis use measures (also transformed using a natural log transformation, and including duration of regular (weekly and daily) cannabis use, frequency and quantity of use, age at which participants first tried cannabis, age of onset of regular use, number of hours since participants last smoked cannabis, and urinary cannabinoid metabolite levels (THC-COOH, creatinine normalised)). Given the previously reported association between P50 gating, nicotine exposure and α -7 nicotinic receptor activity, we re-ran the aforementioned correlations using Pearson's partial correlations controlling for tobacco use defined as the number of cigarettes smoked per day. To further examine the effect of prolonged exposure to cannabis on P50, the cannabis group was divided into short- and long-term users using a median split procedure. Univariate ANOVAs compared P50 amplitude to S1 and S2, P50 ratio and P50 difference scores in short- and long-term users with non-user controls and with each other. Finally, a natural log transformation was applied to the following variables: CAPE total frequency score, CAPE total distress score, SPQ total score, CEQ Euphoric experiences score, CEQ Paranoid Dsyphoric score, CEQ Amotivational score, CEQ After effects score and CEQ psychotic like experiences score. With the exception of MWC score, RAVLT total score and SPQ total score, all other variables were successfully transformed. Pearson's correlations were used to explore the association between P50 ratio and difference score and CAPE total frequency and distress scores as well as each CEQ subscale. Spearman's correlations were used to examine the association between the untransformed MWC score, RAVLT total score and SPQ total score and P50 measures. P50 data (transformed) were examined for outliers (± 1.5 times the inter-quartile range) and analyses were repeated with and without identified outliers excluded. Where the pattern of effects remained unchanged the data were retained in their original form and the analyses with all cases included are reported. Where the pattern of results changed following the exclusion of outliers, the data are reported with and without outliers included.

3.0 Results

3.1 Demographic, substance use and psychotic-like symptoms

Demographic, substance use and psychotic-like symptom measures for cannabis users and controls are provided in Table 1. Cannabis users did not differ significantly from controls in terms of age or gender. All participants were right-handed. Cannabis users had used cannabis regularly for a median 9.4 years (range 2.6 to 36.0 years), at a rate of approximately 4 joints per day on a median of 27 days per month (range 15 to 30 days/month). Cannabis users had significantly fewer years of education, lower IQ scores and recalled significantly fewer words than controls on the RAVLT. Cannabis users consumed a greater quantity of alcohol

and tended to drink more frequently than controls. However none of these variables were found to correlate with P50 (S1 or S2 amplitudes, P50 ratio or P50 difference score; all p values $> .10$ for the control group, and $p > .29$ for the cannabis group) and were therefore not appropriate for inclusion as covariates in subsequent analyses. Cannabis users also smoked more cigarettes per day than controls, and although P50 metrics were not associated with cigarettes per day in the cannabis group (p values $> .80$), given the aforementioned association with P50 gating in the literature and an association between duration of cannabis use and cigarettes smoked per day ($r(21) = .59, p = .02$) in the current dataset, we controlled for the possible effects of tobacco use on P50 when testing for associations with cannabis use, using partial correlations. Finally, although cannabis users tended to have higher CAPE total frequency scores compared to controls, the groups did not differ in terms of total CAPE distress or SPQ scores.

3.2 Sensory gating in cannabis users and non-user controls

Grand mean ERP waveforms to the first (S1) and second (S2) click at Cz are presented for cannabis users and controls in Figure 1 and mean (SD) P50 amplitude to S1 and S2, P50 ratio and difference score are presented in Table 2. Cannabis users were not found to differ from controls in terms of P50 amplitude to S1 ($F(1,39) = 0.99, p = .33$), P50 amplitude to S2 ($F(1,39) = 0.45, p = .51$) or P50 difference score ($F(1,39) = 2.57, p = .12$). A main effect of group reached trend level for P50 ratio ($F(1,39) = 3.44, p = .07$) indicating larger P50 ratios in cannabis users relative to controls. However, two outliers were identified in the control group and when the analysis was repeated without these cases included, the effect of group was non-significant ($F(1,37) = 1.15, p = .22$). P50 ratio and difference scores were found to be significantly associated with the overall duration of regular use (P50 ratio: $r(21) = .44, p = .05$, P50 difference: $r(18) = -.49, p = .04$; see Figure 2) and P50 ratio tended to be associated with the duration of daily cannabis use ($r(18) = .46, p = .054$) indicating larger P50 ratio and smaller P50 difference scores (worse sensory gating) with prolonged exposure to cannabis. After controlling for cigarette use in partial correlations, the association between P50 ratio and duration of cannabis use was reduced to trend level ($r(13) = .48, p = .07$), while the association with P50 difference score remained significant ($r(13) = -.69, p = .01$). Further, the association between P50 ratio and duration of daily use was no longer significant after controlling for cigarette use ($r(11) = .46, p = .12$). No association was identified for P50 ratio or difference score and any other measure of cannabis use (all p values $> .10$; including after controlling for cigarette use). Finally, no associations between P50 ratio nor P50 difference score and time since last use (p values $> .80$), urinary cannabinoid metabolite levels (p values $> .10$) or score on the MWC (p values $> .10$) were identified.

3.3 Sensory gating in long- versus short-term cannabis users

Grand mean ERP waveforms to the first (S1) and second (S2) click at Cz are presented for short- and long-term cannabis users and controls in Figure 3 and mean (SD) P50 amplitude to S1 and S2, P50 ratio and difference score are presented in Table 2. In terms of group characteristics, long-term cannabis users had used cannabis regularly for a median of 23.2 years, and were currently using approximately 2 joints per day for a median of 26 days per month. Short-term users had used cannabis regularly for a median duration of 6.1 years and used approximately 4 joints per day, on a median 29 days per month. Long-term users were older than short-term users, had used cannabis regularly for longer and reported fewer withdrawal symptoms, but did not differ in any other cannabis use parameters. Compared to controls, short-term users had

significantly higher CAPE frequency scores and recalled significantly fewer words on the RAVLT. Age was not found to be associated with any P50 measure for controls (p values $> .10$), short-term (p values $> .10$) or long-term cannabis use groups (p values $> .19$). Since age and duration of cannabis use were highly correlated ($\rho = 0.734$, $p = .002$), and age did not correlate significantly with any P50 measure for any group, age was not considered appropriate for inclusion as a covariate.

Short-term cannabis users did not differ from controls in terms of any P50 measure (P50 S1: $F(1,28) = 0.06$, $p = .80$; P50 S2: $F(1,28) = .02$, $p = .90$; P50 ratio: $F(1,28) = 0.37$, $p = .55$; P50 difference score: $F(1,28) = 0.21$, $p = .65$). For the comparison of long-term users and controls, no effect of group was observed for P50 amplitude to S1 ($F(1,29) = 1.45$, $p = .24$) or S2 ($F(1,29) = 0.75$, $p = .39$), however a significant effect of group was observed for P50 ratio ($F(1,29) = 5.64$, $p = .02$) and P50 difference score ($F(1,29) = 4.35$, $p = .05$), such that P50 ratios were increased and P50 difference scores decreased in long-term cannabis users.

Finally, for the comparison of long- and short-term users, no effect of group was identified for P50 to S1 or S2, P50 ratio or difference score (P50 S1: $F(1,19) = 1.50$, $p = .24$; P50 S2: $F(1,19) = 0.65$, $p = .43$; P50 ratio: $F(1,19) = 2.53$, $p = .13$; P50 difference: $F(1,19) = 2.21$, $p = .15$). However for P50 amplitude to S1, one outlier in the long-term group was identified, and for P50 ratio and difference score, 1 outlier was identified in the short-term group. When the analysis was repeated with these outliers excluded, long-term users were found to have significantly reduced P50 S1 amplitude, significantly larger P50 ratios and significantly smaller difference scores than short-term users (P50 S1: $F(1,18) = 5.64$, $p = .03$; P50 ratio: $F(1,18) = 4.47$, $p = .05$; P50 difference: $F(1,18) = 5.06$, $p = .04$). Furthermore, no association between P50 ratio or difference score, and recency of cannabis use (time since last used and urinary cannabinoid metabolite levels) or withdrawal measures (MWC score), was observed in either the long- or short-term user groups (all p values $> .08$).

3.4 Associations between P50 metrics, verbal learning and psychotic-like symptoms in cannabis users

No association between our measure of verbal learning or any measure of psychotic-like symptoms and P50 ratio or difference score was observed in the total sample of cannabis users, or in the short- or long-term user groups (all p values $> .10$).

4.0 Discussion

In this study we report an association between prolonged durations of exposure to cannabis and larger impairment in sensory gating as indexed by P50 ratio and difference scores. Consistent with prior work, long-term cannabis users were found to exhibit larger P50 ratios relative to controls, and we also found evidence for reduced P50 difference scores. Previous studies of cannabis users that included P50 difference scores reported mixed results: Edwards et al., (2009) found that only P50 ratio but not P50 difference scores differentiated cannabis users from controls, while Rentzsch et al., (2007) reported significantly larger P50 ratios and P50 difference scores in cannabis users. The latter study, however, focused all subsequent analyses on P50 ratio only and did not explore P50 difference scores further. Although the group difference for P50 ratio in our overall sample of cannabis users and controls reached trend level only, we observed an

association between duration of cannabis use and P50 metrics suggesting protracted exposure to cannabis was associated with impaired sensory gating even after controlling for tobacco use. Rentzsch and colleagues (2007) also reported an association between P50 gating and daily cannabis consumption, while Edwards et al. (2009) found an association between gating and the quantity of cannabis used in the previous six months. Neither study accounted for the possible effect of cigarette smoking on these measures. The current study represents the first attempt to account for tobacco use when examining P50 metrics in cannabis users.

To explore the nature of the effect of duration of cannabis use on P50 further, we used a median split to divide the sample of users into long- and short-term user groups, finding significantly larger P50 ratios and reduced P50 difference scores (indicative of a gating deficit) in long-term users compared to non-user controls and short-term users. Interestingly however, the short-term user group had a history of exposure to cannabis that was more similar to the duration of use of the samples of cannabis users in the studies of Edwards et al. (2009) and Rentzsch et al. (2007), with significantly fewer years of cannabis use than the median 23 years of our long-term users. Nevertheless, the current pattern of findings highlights the importance of the duration of exposure on sensory gating, and suggests the P50 difference score may be particularly sensitive to deficits in long-term cannabis users. P50 difference scores are arguably a more psychometrically reliable method than P50 ratio (Smith et al., 1994), however it is also possible that P50 ratio and difference scores may reflect slightly different neurobiological processes (Smith et al., 1994) and this may in part account for the difference in the pattern of results we report here as a function of cannabis use and prior research (e.g., Edwards et al., 2009). Long-term users were also observed to have significantly smaller P50 amplitude to the first click, a finding consistent with the patient literature (e.g. Clementz and Blumenfeld, 2001; Smith et al., 2010) and suggests long-term exposure to cannabis may adversely affect encoding as well as well as gating (Smith et al., 2010).

Consistent with prior work, cannabis users exhibited impaired verbal learning memory compared to controls (Solowij and Michie, 2007), although no association with P50 measures was observed. We also set out to explore a possible association between the presence of psychotic-like symptoms in cannabis users and P50 sensory gating deficits as a potential marker of vulnerability to psychosis. Although prior work has found an association between P50 ratio and schizotypy in non-clinical populations (Croft et al., 2004; Croft et al., 2001), the current study did not observe any association between P50 metrics and psychotic-like symptoms in long-or short-term cannabis users, including a retrospective measure of psychotic-like symptoms during intoxication. This lack of association bears some similarity with the inconsistent relationship between symptomatology and P50 deficits reported in patients with schizophrenia (Potter et al., 2006). Further, it should be noted that only the short-term users in our sample differed significantly from controls in terms of one measure of psychotic-like symptomatology (CAPE frequency scores), and this suggests that perhaps the current sample of cannabis users were not particularly psychosis-prone (consistent with no clear differences between controls and cannabis users on our two measures of psychotic-like experiences). Our study exclusion criteria were strict with regard to psychiatric history, and it is plausible that our sample of cannabis users were less susceptible to developing psychosis, particularly given that despite their prolonged histories of exposure to cannabis, none had developed psychosis. It is also interesting however, that short-term users reported a greater number of paranoid dysphoric and psychotic-like experiences during intoxication compared to long-term users. One possibility is that given their younger age, short-term users may have been exposed

to more potent (high THC content) forms of cannabis during a neurodevelopmentally critical period associated with these increased psychotic-like experiences, although we did not observe a significant effect on P50 gating. This group difference should also be considered alongside demographic differences between short- and long-term groups including a greater proportion of males, younger age and lower IQ scores in the short-term group which may also have influenced sensory gating effects and associations between P50 metrics and psychotic-like experiences. Nevertheless, in light of increasing evidence of an association between cannabis and psychosis, and the fact that P50 deficits are extensively reported in patients with schizophrenia, and those at risk of developing the disorder (Bramon et al., 2004), our findings provide some support for the notion that chronic cannabis use may result in an underlying pathology similar to schizophrenia (Solowij and Michie, 2007).

The mechanisms by which exogenous cannabinoids such as THC might affect P50 gating are largely unknown, however consistent with rat models of sensory gating (Boutros et al., 1997; Boutros and Kwan, 1998; Dissanayake et al., 2013), as well as intracranial recordings in humans which have implicated hippocampal involvement (e.g., Grunwald et al., 2003), disrupted sensory gating in cannabis users might be due to the partial agonist effects of THC at CB1 receptors in the hippocampus in terms of reducing GABAergic inhibition of excitatory glutamatergic neurons (Dissanayake et al., 2013). This could lead to deficits in inhibitory processing, including reduced inhibitory inputs to P50 generators in auditory and frontal cortices. Consistent with this notion, when CB1 agonists were administered to rats, sensory gating was disrupted as measured by local field potentials in the CA3 region of the hippocampus (Dissanayake et al., 2008; Hajos et al., 2008) as well as the medial prefrontal cortex (Dissanayake et al., 2008). Further work, however, is required to elucidate the interaction between cannabis, the endogenous cannabinoid and other neurotransmitter systems such as prefrontal dopamine circuits which have also been implicated in sensory gating (for a review see, Gallinat et al., 2012). A related methodological issue is the use of an active paradigm in order to control attention and the possibility of differential effects of attention as a function of group status on sensory gating. To date, research examining the effects of cannabis on P50 has used both active attention paradigms (e.g. Edwards et al., 2009) and passive tasks (e.g. Patrick et al., 1999; Rentzsch et al., 2007). Gjini et al. (2011) found attention to S2 increased the S1 response in both healthy controls and patients with schizophrenia, while only S2 amplitudes increased as a function of attention in healthy participants. This resulted in improved sensory gating ratios in patients, and a reduced group difference (Gjini et al., 2011). Future studies might consider using both passive and active paired click paradigms in order to ascertain whether attention might have a differential effect on sensory gating in cannabis users.

There are a number of limitations in the current study that may be addressed in future work. First, future research could extend these findings to a larger sample of cannabis users. Second, further consideration of study inclusion/exclusion criteria regarding personal and familial psychiatric history to include potentially more psychosis-prone individuals might address the efficacy of P50 deficits in cannabis users as a possible marker of vulnerability to psychosis. For example, longitudinal work investigating P50 deficits and the development of psychotic symptoms would serve to clarify the role of chronic cannabis exposure and vulnerability to psychosis, and genetic moderation of effects might be examined. Third, it is possible that the P50 deficits we observed in long-term users may have pre-existed cannabis use, although the association with duration of use and impaired sensory gating ratios suggests this is unlikely. Nevertheless, longitudinal

work would facilitate our understanding of premorbid functioning in cannabis users and help clarify the role of prolonged exposure to cannabis on these measures. Fourth, although the current findings are most likely the result of chronic cannabis use, there are alternative explanations including possible residual effects of THC associated with recent use (Pope et al., 2001) or effects associated with withdrawal (Budney et al., 2004). However these explanations are unlikely as we found no association between P50 measures and either recency of cannabis use (time since last use or urinary cannabinoid metabolite levels) or withdrawal measures. Participants in the current study were asked to abstain from using cannabis (alcohol or any other illicit substance) for at least 12 hours prior to the experiment (median time since last use was 15 hours), so they were not acutely intoxicated and withdrawal effects were minimal. Future work however could examine the acute effects of cannabis on P50 metrics in regular and non-naïve non-users to address these issues. Finally, while we found age to not be correlated with P50 measures in any group in our sample (although see Patterson et al. (2008) for a review of age effects on P50 gating in patients with schizophrenia), it is difficult to disentangle the effects of age and duration of use (long-term cannabis users were older than short-term users) on sensory gating. Future work should attempt to better match long- and short-term cannabis use groups on demographic variables such as age to more fully understand and interpret these effects. Future work might also examine the contribution of altered neural oscillations to sensory gating deficits in chronic cannabis users (see also Edwards et al., 2009) as well as applying wider filter settings to examine the potential role of lower frequency oscillations in P50 sensory gating (see Jansen et al., 2004).

In summary the findings from the current study suggest that regular, long-term exposure to cannabis may be associated with impairments in auditory sensory gating as indexed by P50 metrics. P50 deficits are also extensively reported in patients with schizophrenia and arguably represent a candidate endophenotype for the disorder. In combination, mounting evidence of cognitive, electrophysiological, structural and functional brain abnormalities observed in chronic cannabis users and patients with schizophrenia, along with the current data suggest chronic cannabis use may result in schizophrenia-like conditions in the brain with common underlying pathology (Solowij and Michie, 2007). Impairments in sensory gating processes as a result of chronic exposure to cannabis may be related to disruption of the regulatory role of the endocannabinoid system on synaptic neurotransmission, and particularly the disruption of CB1 receptor activity in hippocampal and anterior cortical regions.

5.0 References

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Table 1. Demographic data, substance use measures and symptoms in cannabis user and healthy nonuser control groups. Median (range) are displayed.

	Control (C) <i>n</i> = 20	Cannabis (ALL) <i>n</i> = 21	Short-term (S-T) <i>n</i> = 10	Long-term (L-T) <i>n</i> = 11	<i>All v C</i> <i>p</i>	<i>S-T v C</i> <i>p</i>	<i>L-T v C</i> <i>p</i>	<i>S-T v L-T</i> <i>p</i>
Age (years)	24.7 (18.1-52.6)	26.4 (18.5-52.0)	20.5 (18.5-26.4)	39.61 (21.4-52.0)	.696	.214	.072	.000
Gender (M/F)	8/12	14/7	8/2	6/5	.121	.058	.477	.361
IQ ^a	112.5 (89-125)	104 (86-135)	94 (86-116)	109 (94-135)	.040	.000	.910	.005
Education (years) ^a	14.3 (11.5-18.0)	12.0 (10.0-17.0)	12.1 (11.0-14.0)	12.0 (10.0-17.0)	.001	.000	.020	.666
RAVLT (Total 1 to 5)	56.5 (29.0-71.0)	45.0 (28.0-62.0)	42.5 (28.0-52.0)	49.0 (29.0-62.0)	.002	.000	.095	.223
Cigarettes per day	0 (0-11)	4 (0-20)	2.5 (0.0-12.5)	7.0 (0.0-20.0)	.000	.017	.000	.099
Alcohol frequency (days/month)	2.1 (0.0-4.0)	30.0 (0.0-30.0)	2.5 (0.0-10.0)	3.0 (0.0-30.0)	.099	.397	.079	.349
Alcohol quantity (drinks /month)	6.4 (0.0-70.0)	20.0 (0.0-180.0)	14.9 (0.0-96.0)	21.0 (0.0-180.0)	.049	.131	.095	.863
Psychotic-like symptoms								
CAPE Frequency total	57 (45-89)	64 (50-90)	65 (52-92)	64 (42-84)	.099	.040	.471	.314
CAPE Distress total	17 (4-50)	32 (13-79)	36 (13-79)	27 (0-53)	.196	.069	.735	.223
SPQ total	12 (0-39)	27 (0-42)	33 (1-42)	21 (0-34)	.220	.157	.576	.128
CEQ Euphoric experiences	-	49 (29-72)	44 (35-56)	37 (29-72)	-	-	-	.105
CEQ Paranoid Dysphoric	-	44 (25-76)	48 (33-76)	33 (25-56)	-	-	-	.024
CEQ After effects	-	22 (0-50)	23 (0-50)	19 (11-28)	-	-	-	.274
CEQ Amotivational	-	14 (0-34)	14 (0-34)	15 (7-21)	-	-	-	.621
CEQ Psychosis-like experiences	-	6 (0-16)	10 (0-16)	5 (4-9)	-	-	-	.025
Cannabis Use								
Hours since last use	-	15 (13-168)	14 (13-48)	18 (13-168)	-	-	-	.083
Frequency (days/month)	-	27 (15-30)	29 (20-30)	26 (15-30)	-	-	-	.433
Quantity (cones/month)	-	338 (34-3150)	372 (138-3150)	195 (34-1080)	-	-	-	.523
Age of first use (years)	-	14.5 (10-19)	14.8 (10-16)	13.5 (11-19)	-	-	-	.859
Age started regular use (years)	-	16 (10-21)	15.5 (10-19)	16 (13.5-21.0)	-	-	-	.391
Duration of regular use (years)	-	9.4 (2.6-36.0)	6.1 (2.6-8.4)	23.2 (9.4-36.0)	-	-	-	.000
Duration of daily use (months)	-	60 (0.25-204.0)	30 (0.25-88.3)	72.0 (12.0-204.0)	-	-	-	.062
MWC (withdrawal) score	-	6.50 (1-33)	12.5 (2-33)	4.5 (1-11)	-	-	-	.008
Urinary cannabinoid metabolite (THC- COOH) (ng/ml)	-	745 (108-9351)	828 (239-3658)	393 (108-9351)	-	-	-	.130

Notes: ^aParametric tests performed (independent samples t-test). Significant *p* < .05 are noted by italics

Table 2.Mean (SD) P50 metrics for healthy nonuser controls, cannabis users (all), short-term and long-term user groups.

P50 metric	Control (n = 20)	Cannabis (All; n = 21)	Short-term users (n=10)	Long-term users (n=11)
P50 S1 amplitude (μ V)	4.55 (3.03)	3.51 (1.81)	3.87 (1.22)	3.18 (2.22)
P50 S2 amplitude (μ V)	1.39 (1.10)	1.50 (1.04)	1.25 (0.70)	1.71 (1.28)
P50 ratio (S2/S1)	0.32 (0.24)	0.50 (0.40)	0.37 (0.29)	0.63 (0.45)
P50 difference score (S1-S2)	3.17 (2.41)	2.02 (1.73)	2.62 (1.43)	1.47 (1.85)

Figure captions

Figure 1: ERP waveforms to the first (S1; left) and second (S2; right) click at Cz. Cannabis users are shown in grey and control participants in black. Amplitude is shown in μV on the y-axis and time in milliseconds along the x-axis.

Figure 2: Scatter plots showing association between P50 metrics (after square root transformation) and duration of regular cannabis use in years (after natural log transformation) in cannabis users. P50 ratio (transformed) shown on left and P50 difference score (transformed) shown on right.

Figure 3: ERP waveforms to the first (S1; left) and second (S2; right) click at Cz. Short- and long-term cannabis users are shown in the solid grey thin and thick lines respectively and control participants in black. Amplitude is shown in μV on the y-axis and time in milliseconds along the x-axis.

Figure 1

Figure 2

Figure 3