Differential effects of cannabis use on event-related potential (ERP)-indexes of cortical inhibition in cannabis users and non-users

by

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Abstract

Differential effects of cannabis use on event-related potential (ERP)-indexes of cortical inhibition in cannabis users and non-users.

August 27th 2021

By Ashley Morgan Francis

Cannabis has psychoactive properties and is thought to be associated with potential structural and functional changes with early and heavy use. Previous research suggests cannabis users (CU) vs. non-users (NU) have deficits on EEG-derived event-related potentials elicited by paired click and visual Go/NoGo paradigms. We used these paradigms to examine inhibitory functioning in CUs (n = 14; 9 male) vs. NUs (n = 16, 4 male). Effect sizes suggest CUs had impaired N100 measures of sensory gating compared to NUs. Additionally, a trend level interaction and latency findings for the P200 suggested CUs had smaller amplitudes and quicker latencies to S_1 compared to NUs. Go/NoGo findings revealed enhanced P100 amplitudes in CUs (vs. NUs). No other between-group differences or sex differences were observed. This study provides further support for cannabis-induced deficits on early-attentional processing as indexed by the N100 and novel findings regarding enhanced P100 amplitudes to the Go/NoGo paradigm.

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Chapter 1: Introduction

1.1 Cannabis and the Endogenous Cannabinoid System

Cannabis is a term used to refer to any consumable product obtained from a species of the *Cannabaceae* family. This plant's primary psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), acts on the brain and central nervous system (CNS) through its interaction with the endocannabinoid system (Böcker et al., 2010). The endocannabinoid system is comprised of CB1 and CB2 receptors (CB1R and CB2R respectively), as well as the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol (2-AG; Devane et al., 1992). CB1 receptors are primarily found in the brain and central nervous system (Mechoulam & Parker, 2013). It was long believed that CB2 receptors were more commonly found in the peripheral nervous system (PNS; Munro, Thomas, & Abu-Shaar, 1993), with the exception of some being located throughout the brain in areas of the vagus nerve and brain stem (Sickle et al., 2005). A recent review of the current literature, however, suggests otherwise, providing evidence of CB2 receptors in the human brain (Jordan et al., 2018), specifically in areas of the hippocampus (Stempel et al., 2016) and cortical pyramidal neurons (Garcia-Gutierrez et al., 2018).

CB1 receptors, which are the primary site of action for the psychoactive effects of cannabis, are particularly dense in brain areas such as the prefrontal and cingulate cortices (Eggan & Lewis, 2007) as well as the hippocampus (Herkenham, 1991; Katona et al., 2006), basal ganglia (Herkenham, 1991), and white matter tracts (Crocker & Tibbo, 2015; Renard et al., 2014). These areas are especially important when considering the effects of cannabis on neural and cognitive functioning such as inhibitory control and working memory. The location of these CB1 receptors suggests that they play a role in

cognition and motivation. It has also been observed that the distribution and quantity of CB1 receptors varies across the lifespan, with high levels of CB1 receptors and endocannabinoids being present in children and adolescents only to decrease as individuals mature into adulthood (Crocker & Tiboo, 2015; Mechoulam & Parker, 2013). In addition to changes in receptor density relative to age, sex differences have also been observed (Van Laere et al., 2008), although findings are mixed. Specifically, some studies show that females have a significant increase in CB1 receptors as they age (Van Laere et al., 2008). Other more recent studies, show males have a higher volume of receptors across all brain regions (Laurikainen et al., 2019). Laurikainen et al. (2019) found that females using oral contraceptives tended to have decreased receptor volumes when compared to naturally cycling females, thus suggesting hormonal birth control may be an important factor to consider when conducting cannabis, brain-based research.

Structural changes have also been reported in heavy cannabis users, with the most common changes being reported in relation to hippocampal volume and grey matter density, such that with an increase in cannabis use there was a decrease in hippocampal volume and grey matter density (Ashtari et al.,2011; Battistella et al.,2014; Demirakca et al.,2011; Yücel et al.,2008, 2016). In addition, executive functioning, working memory, and attention were highlighted as areas that appear to be most heavily impacted by cannabis use (see Nader and Sanchez 2018 for full review). With the recent legalization of this potentially neurotoxic substance in our country, it is critical that we better understand the implications this drug can have on the human brain.

1.2 Cannabis Use Across North America

The legalization of cannabis is becoming more prominent worldwide, allowing the medical properties of the drug to become more well known. Legalization of the drug cannabis, however, can lead to a decrease in the perceived risk of using cannabis (Cuttler et al., 2016' Johnson et al.,2011). This is concerning given that relatively little is known about how the drug affects the developing human brain. Johnston et al. (2011) found that as the perceived risk of using cannabis decreased, the overall use of cannabis increased – particularly in adolescents between the ages of 13-18. Cannabis use risk is also related to outcome expectancies (beliefs about the effects of the drug). For example, one study asked students to self-generate expectancies of using cannabis; when students rated their expectancies as positive, they were more likely to be cannabis users by grade 7 compared to if they rated the expectancies as negative (Fulton et al., 2012).

In the United States of America (USA), cannabis use has significantly increased from 2018 – 2019 (U.S Department of Health and Human Services, 2019). Despite the increased usage, the age of substance use onset has remained relatively consistent with most individuals commencing in early-to-mid adolescence worldwide. Canada specifically reports an average age of initiation between 14.2 years (the 2016/17 Canadian Tobacco Alcohol and Drugs Survey [CTADS]) and 19.2 years (the 2019 Canadian Cannabis Survey [CCS]) (Červený et al., 2017; Chen et al.,2017; United Nations Office on Drugs and Crime 2018). However, the latter is potentially biased by the age of respondents and greater reliance on retrospective memory as it surveyed individuals 16 years of age and older; therefore, these two findings cannot be directly compared. Furthermore, substance use rates have been shown to peak at certain ages

(e.g., 16 and 18), specifically during the transition from adolescence to emerging adulthood, described as the period of time between ages 18-29 (Arnett, 2014; Chen et al., 2017; United Nations Office on Drugs and Crime 2018).

Canadian research findings, like those in the USA, show that 4.9 million Canadians aged 15+ (~16%) reported using cannabis within the past three months (Statistics Canada, 2019). Canadian data suggests a steady rate of use from the 3.1 million users in 2013, 3.6 million users in 2015, and 4.4 million users in 2017 while considering population growth during this five-year period (Government of Canada., 2017). Regional differences, however, suggest stronger trends towards increased usage, such that, Nova Scotia was found to be the highest using province in Canada (when sampling individuals over the age of 15; Statistics Canada, 2019), with 24.4% of Nova Scotians (vs. 16% of Canadians overall) reporting cannabis use in the past three months (Statistics Canada, 2019). Finally, usage rates proved to be on the rise with an increase in usage from 14% of Canadians to 18% between 2018 and 2019 (Statistics Canada, 2019). Furthermore, within the overall population of Canadian cannabis users, a quarter are between the ages of 15-24 years of age (Statistics Canada, 2019). Of the Canadian youth between the ages of 15-24, 24% were cannabis users, with 32% using daily, making this age category the most prevalent users (Government of Canada, 2017).

Within cannabis users, differences also appear between males and females. Males reported higher usage rates (Cookey et al., 2020; Cuttler et al., 2016; Horwood et al., 2010; Statistics Canada, 2019) and earlier usage when compared to females (Richmond-Rakerd, Slutske & Wood 2017). This was also noted in a sample of grade 12 students, where daily cannabis users were more likely to be male (17%) than female (12%;

Johnston et al., 2011). The national cannabis study in Canada showed similar findings, reporting males were almost twice as likely to be cannabis users compared to females, especially within the 15-24-year-old age range (Statistics Canada, 2019). Moreover, males were more likely to be daily or almost daily users and were found to use cannabis for primarily non-medical reasons (52%); this percentage of non-medical use was over four times the non-medical use reported by females (Statistics Canada, 2019). Females were found to have an overall lower risk of becoming a cannabis user in the future compared to males when a predictive survival analysis was completed, factoring in several risk factors that could lead to substance use (i.e., age, ethnicity, use by age 17, Chen et al., 2017). The National Cannabis Use study in Canada found females (4.5%) to be significantly less likely to be daily or almost daily users of cannabis when compared to males (7.6%; Statistics Canada, 2019). Furthermore, females were also less likely to be weekly (1.7%) and monthly (1.3%) users compared to their male counterparts (5.4% and 2.8% respectively; Statistics Canada, 2019). While there are sex differences in user profiles, it remains unclear if there are any differences in how cannabis affects the brains of males and females (see section 1.4 for full description of the known interactions to-date between cannabis use and biological sex).

1.3 Neurobiology of Cannabis Use

Due to the overwhelming research showing cannabis usage is increasing not only in Canada but also worldwide, it is important that we understand the potentially negative consequences involved with the consumption of this drug. The uncertainty regarding what cannabis may do to the human brain and the behavioural impacts it may have has

influenced research to focus on measuring not only behavioural but also neurological changes in cannabis users.

Past findings suggest cannabis users have decreased accuracy on tasks involving selective attention, behavioural inhibition, and decision making (Böcker et al., 2010; Crane et al., 2015; D'Souza et al., 2012; Galvez-Buccollini et al., 2012; Gruber & Yurgelun-Todd, 2005; Tibbo et al., 2018). The current state of the literature suggests there are mixed findings on how cannabis may impact executive functioning. While some studies report cannabis use is negatively associated with several neuropsychological impairments (i.e., attention, memory, and IQ scores) in those with cannabis use disorder (Camchong et al., 2017; Meier et al., 2012), other studies suggest cannabis users and non-users do not differ on various indexes of cognitive decline (as measured by IQ; Jackson et al., 2016; Meier et al., 2018). A recent review and meta-analysis suggest that frequent and dependent cannabis use (by age 18) is associated with a decline in IQ scores compared to baseline; this may be restricted to a decline in verbal IQ while other aspects of IQ appear to be spared (see Power et al., 2020 for full review). Another review of longitudinal data suggests a more nuanced result where only the heaviest users are impacted and, in some cases, third variables (e.g., education, sex, parental income) account for the observed deficits in neuropsychological outcomes (see Gonzalez et al., 2017 for full review). Taken together these findings suggest that heavy, consistent use at a younger age may be more detrimental to IQ and other neuropsychological outcomes, whereas those with more casual later life use may not be impacted. Similar to discrepancies found in the IQ literature, studies measuring cannabis initiation in adulthood compared to adolescence (before age 17) show mixed findings. Earlier studies found cannabis use onset at a young

age was associated with decreased cognitive performance and attentional deficits (Ehrenreich et al., 1999; Pope et al., 2003), while more recent findings suggest deficits are only found in verbal working memory (Auer et al., 2016). These findings suggest that more research is needed to fully understand the association between early and frequent/consistent cannabis use and neuropsychological outcomes (i.e., memory, attention, IQ, and inhibition).

Previous reports indicate that prolonged exposure to cannabis was associated with cognitive impairments compared to healthy controls or casual users (Pope & Yurgelun-Todd, 1996). These impairments have been shown to be related to structural (Rocchetti et al., 2013) and functional (Pillay et al., 2008) changes in the brain, specifically in areas of the hippocampus (Hirvonen et al., 2012). Primarily, relationships have been found between cannabis use and decreased working memory and executive functioning in adolescents between the ages of 13-18 (Harvey et al., 2007). Adolescence and emerging adulthood are the peroids of time spanning the ages of 10 to 25 during which the human brain is developing and changing, including changes in neural connections (Arnett, 2014; Beckman, 2004; Cannon et al., 2005; Chambers et al., 2003; Nelson, 2004; Slotkin, 2002; Spear, 2000; Steinberg, 2014). During adolescence and emerging adulthood, many neural pathways are pruned to ensure there are efficient pathways in comparison to an abundance of neural connections (Bossong & Niesink, 2010; Cohen-cory, 2002; Katz & Shatz, 1996; Luna, 2009; Tibbo et al., 2018; Whitford et al., 2007). These alterations are driven by changes in grey and white matter within the brain (Tibbo et al., 2018). Camchong et al. (2017) found there was a decrease in functional connectivity between the caudal anterior cingulate cortex and the prefrontal cortex in adolescents diagnosed

with a cannabis use disorder (CUD), suggesting that cannabis use is associated with this process.

Structural changes have been documented through the use of magnetic resonance imaging (MRI) whereby researchers have shown decreases in grey matter volume and whole-brain volume in cannabis-using adolescents compared to healthy controls. Additionally, positron emission tomography (PET) revealed that males whose cannabis use onset occurred prior to age 17 not only showed decreases in the brain and grey matter volume, but also higher cerebral blood flow (Renard et al., 2014). Contrary to these findings, Moreno- Alcàzar et al. (2018) used whole brain voxel-based morphometry and found cannabis users and non-users did not differ on cortical regional differences or grey matter volume, instead they found that cannabis users had a significant cluster of increased grey matter volume in the basal ganglia compared to non-users. While the current state of the literatre appears to be mixed on what structural changes occur with use, the current consensis appers to be that there are region specific volume changes associated with use.

Past studies argued that chronic exposure to THC was neurotoxic for hippocampal neurons (in terms of a decrease in the overall volume of neurons; Scallet et al., 1987) causing hippocampal neuron dealth when THC interacted with the CB1 receptors (Chan et al., 1998), however, more recent reports suggest that cannabis use may not impact the hippocampus as it was once believed (Koenders et al., 2017; Moreno-Alcàzar et al., 2018). These findings may allude to the fact that while THC alone (or in high quanities) may be neurotoxic, cannabis with a higher ratio of other cannabinoids (e.g., cannabidiol) may not impact neural functioning (i.e., hippocampal functioning) as much. Blest-Hopley

et al. (2019) examined if cannabis use impacted the metaboite markers of neurons and glia in the hippocampus and found altered myoinositol levels in cannabis users compared to non-users, however, the other metabolite concentrations (glutamate and *N*-acetyl aspartate) did not differ between groups. This suggests cannabis may only partially impact hippocampus. Further support for this can be found in Owens, Sweet and MacKillop (2019) where they found that only two regions of the hippocampus (head of the hippocampus and area CA1) were associated with recent cannabis use. Providing further clarity that while cannabis has been shown to impact the hippocampus, the effects cannabis has on the hippocampus may be restricted to certain areas and metabolites. While this suggests mixed findings on the potential risk of hippocampal damage due to cannabis use, this risk is potentially higher for individuals around the age of puberty who are using cannabis given the extent of the changes occuring in the brain during this time (O'Shea et al., 2004; Schneider & Koch, 2003, 2005). Cognitive functions such as focusing attention, inhibitory control, and filtering out irrelevant information have been shown to be negatively affected in heavy cannabis users compared to non-users and casual cannabis users (i.e., those using only once a month; Pope & Yurgelun-Todd, 1996; Solowij et al., 1991; Solowij & Michie, 2007). Research has investigated the neural pathways that are at work during attention and emotional processing tasks in cannabis users and non-users; during these tasks, cannabis users appeared to be drawing upon non-conventional neural networks to process this information (e.g., greater activation in the left middle and superior frontal gyrus), compared to the non-users (Colizzi et al., 2018). It was suggested that this reliance on alternative neural networks was to compensate for impairments in the standard brain networks and regions. This implies that while cannabis

may not impact entire neural structures (i.e., the hippocampus) it may impact one's ability to properly use these cognitive areas to process and act on incoming stimuli as a non-user would. At a broader level, this suggests that cannabis may partially affect the neural pathways and connections within the brain influencing both behavioural and cognitive outcomes with heavy cannabis-using youth being most at risk. Unfortunately, many of these studies only include males and do not consider the effects of cannabis on the female brain.

Furthermore, studies have shown that the dopamine system in the prefrontal cortex undergoes reorganization during adolescence (Bossong & Niesink, 2010; Spear, 2000). Given the changes occurring in this system happen around the same time as the onset of cannabis use, use at a young age may impact this critical neurodevelopmental process, which could then result in deficits in decision making, inhibition, and planning behaviours. Adolescence and emerging adulthood may be especially vulnerable periods as changes in the prefrontal cortex at this age that may arise from early cannabis use could possibly cause irreversible changes later in life (Bossong & Niesink, 2010). Moreover, previous cannabis use has been shown to impact inhibitory functioning even after short peroids of abstinence (Solowij et al., 2002; Aharonovich et al., 2008; Cunha et al., 2010). This implies that the sensory processing pathways in the brain may be impacted even after the acute administration of cannabis.

Cannabis use has been associated with several negative consequences, particularly as related to neuropsychiatric outcomes. Most notably is the potential relationship between early cannabis use and one's risk of developing psychosis or schizophrenia later in life (Arseneault et al., 2002; Fergusson et al., 2003; Henquet et al., 2005; Mauri et al.,

2006; Saito et al., 2013; Stefanis et al., 2004; Van Os et al., 2002; Weiser et al., 2002; Zammit et al., 2002). While genetic predispositions remain an important determinant in the development of psychosis/ schizophrenia, environmental factors are also at play (e.g., cannabis use or childhood trauma; Crocker & Tiboo, 2015; Renard et al., 2014; Tibbo et al., 2018). Multiple studies have found that age of cannabis use onset is negatively associated with psychosis, such that the age of first psychosis related hospitalization is earlier for those using cannabis (vs non-users) in individuals with no prior symptoms of psychosis (Arseneault et al., 2002; Galvez-Buccollini et al., 2012; Guloksuz et al., 2019; Henquet et al., 2005; Konings et al., 2008; Rubino & Parolaro, 2008; Stefanis et al., 2004; Zammit et al., 2002). Not only has cannabis use been shown to correlate with psychosis, but it has also been shown that cannabis usage increases one's risk of developing schizophrenia by 40% (Moore et al., 2007) or up to a 6-fold increase in heavy cannabis users (Saito et al., 2013). This relationship was shown to be impacted by the frequency of use, and potency of THC in the cannabis used with the more frequent users showing an increased risk of 5-200% (Smye, 2008) and higher potency of THC (>10%) showing more than 4x's an increased risk of psychosis (Di Forti et al., 2019). Furthermore, age of onset matters in this relationship: adolescents who used cannabis before the age of 15 increased their risk of being diagnosed with schizophrenia or related psychosis by 4.5 times, whereas those who used cannabis by the age of 18 were at only 1.6 times increased risk (Arseneault et al., 2002; Murray et al., 2008). These studies reflect the increasing need to better understand the consequences cannabis has on neural functioning when used at a young age.

1.4 Impact of Cannabis Use in Males vs. Females

MRI studies have been conducted to better understand brain development and potential sex differences in the changes that occur during development. There are robust findings showing that female neurodevelopment and mean cerebral volume peaks at around age 10.5 years while male development and cerebral volume do not peak until the age of 14.5 years (Lenroot et al., 2007). Additionally, longitudinal data have shown that subcortical structures and grey matter mature and change at different rates across adolescence depending on sex (Herting et al., 2019; Lenroot et al., 2007). Furthermore, studies mapping brain development trajectories suggest the prefrontal cortex may be the last brain region to mature during adolescent development (Gogtay et al., 2004; Lenroot and Giedd, 2006; Sowell et al., 2004). Given these brain development trajectories are not consistent across males and females, it is concerning that the age of critical neurodevelopment and the average age of onset of cannabis use intersect, this overlap may be particularly concerning for males given their later development (Herting et al., 2019; Lenroot et al., 2007). Additionally, the brain areas undergoing the greatest developmental changes during these age-related growth phases (i.e., prefrontal cortex) are densely packed with CB1 receptors (Eggan & Lewis, 2007; Giedd et al., 1999; Lin et al., 2009). The previously discussed differential rate of neurodevelopment in males vs. females also applies to the development of the frontal lobes (Lenroot et al., 2007). Furthermore, Lenroot et al. (2007) found that male brains showed a consistent and higher degree of change during childhood and adolescence than did female brains. A more recent meta-analysis (Ruigrok et al., 2014) suggests regional differences between sex such that males have larger volumes and higher tissue densities in a number of brain

regions (e.g., left amygdala, hippocampus, and putamen), this meta-analysis further suggests that males may have more left lateralized differences compared to females (see Ruigrok et al., 2014 for full review). Therefore, males may be more vulnerable to the neurotoxic effects of cannabis as the average age of initiation occurs earlier during prefrontal neurodevelopment in comparison to females. It is, therefore, not surprising that recent reports show increased cannabis use was related to poorer decision making, but only among males (Gonzalez et al., 2012). While Gonzalez et al. (2012) found worse decision making in males, other researchers (Gillies & McArthur, 2010) found female, but not male, cannabis users (vs. non-users) experience poorer performance on measures of episodic memory; it has been suggested that this sex difference could be due to cannabis affecting estrogen-related dendritic spine maturation in the hippocampus among females. Given these findings, it could be hypothesized that cannabis would differentially affect the brains of males and females, resulting in differing deficits depending on the cognitive processes under investigation. Overall, however, we would expect males to be more heavily impacted by cannabis use as they are stereotypically more frequent, heavy users and past reports suggest they are more impacted by cannabis than their female counterparts on a greater variety of tasks.

Most studies measuring sex differences in cannabis users measure the effects of cannabis on behavioural measures; however, these measures could be impacted by the psychomotor effects cannabis has on individuals (Crane, Schuster & Gonzalez, 2013; Felton et al., 2015; Herrman, Weerts and Vandrey, 2015). To truly understand the effects cannabis has on individuals and the sex differences that may be present, we must parse

apart the neural activity from the motor responses. To do so we can use tools like electroencephalography (EEG) and event-related potentials (ERPs).

1.5 Event-Related Potentials (ERPs)

EEG is a non-invasive procedure that measures the summation of the neural activity of large groups of neurons firing. ERPs are derived from EEG by assessing neuroelectric activity elicited in response to specific stimuli such as tones, visual stimuli, or internally generated processes such as decision making or inhibition. ERPs denote the average of the neural response following stimulus presentation. EEG raw data is averaged and small data sections, immediately following the event to be indexed, known as epochs, are isolated from the continuous EEG activity. These epochs are usually moments in time surrounding significant events such as stimulus onset or behavioural response. In order to obtain the ERP, multiple epochs are averaged to eliminate any concurrent electrical noise. Usually, ERPs are recorded during the performance of behavioural tasks, and the data collected from both behavioural measures and the EEG recording can be used to form the complete picture of the cognitive processes at work during particular situations or tasks. ERPs are well suited to index cognition due to their temporal sensitivity and can be used to help supplement and comprehend behavioural observations.

The ERP waveform is plotted with voltage measured in microvolts (μV) against time measured in milliseconds (ms). The waveform appears as a sequence of positive (P) and negative (N) peaks and deflections which are characterized and labeled in terms of the latency or succession in which they appear. Mid-latency auditory-evoked responses (MLAER: Lijffijt et al., 2009) are a series of ERPs commonly used to measure pre-early and late attentive phases of sensory gating-related information. Sensory gating is

conceptualized as the brain's ability to inhibit or 'gate-out' extraneous information from being processed by the brain (Broyd et al., 2013; Freedman et al., 1991), allowing the brain to focus and allocate attentional resources on relevant incoming information and thereby avoiding overload (Evans & Drobes, 2009). The MLAER is comprised of the P50, N100, and P200 ERPs. While the MLAERs rely on auditory stimuli to be measured, there are other ways to measure inhibition; specifically, this can be done by examining the Go/NoGo P300 described later.

1.5.1 Mid-Latency Auditory-Evoked Responses (MLAER)

While the pre-attentive P50 is the most studied marker of sensory gating, there has been a growing body of literature reporting that early and later attentive phases of sensory gating-related information processing can be captured by the N100 and P200 components of the MLAER, respectively (Boutros et al., 2004; Lijffijt et al., 2009; Shen et al., 2020; Zabelina et al., 2015). Recent studies show the N100 and P200 can be utilized as neurophysiological markers of sensory gating due to their superior reliability compared to the P50 (Anokhin et al., 2007; Boutros et al., 2019; Rentzsch et al., 2008; Shen et al., 2020; Thoma et al., 2020). While these three components are related, they appear to index different neural processes (Boutros et al., 2004; Sklar and Nixon 2014). The P50 appears to reflect pre-attentional inhibitory filter mechanisms and sensory gating, while N100 gating has been suggested to index filter mechanisms involved in attentional triggering (Wan et al., 2008), and P200 gating might index filter mechanisms involved in attentional allocation and early conscious awareness of a stimulus (Chien et al., 2019; Lijffijt et al., 2009; 2011).

N100 and P200 gating may reflect protective neural mechanisms that shield cognitive function through interactions with working memory processes to enhance target discrimination (Lijffijt et al., 2009). A series of replication studies have shown P50 suppression to be reduced in chronic cannabis users who were medically and psychiatrically healthy and did not abuse any illicit substances other than cannabis, with the greatest reduction in P50 suppression observed in those with the greatest cannabis exposure (Broyd et al., 2013; Edwards et al., 2009; Patrick et al., 1999; Patrick & Struve 2000; Rentzsch et al., 2007). To date, only one study has measured the effects of cannabis on N100- and P200-indexed sensory gating (Francis et al., 2021). This study from our lab found that gating was inhibited in cannabis users compared to non-users (Francis et al., 2021). Of interest, this study found no deficit in P50 amplitudes in cannabis users relative to non-cannabis-using controls.

This inhibitory process can be shown through the MLAER in response to paired tones (Freedman et al., 1991). In a paired click paradigm, commonly used to measure the MLAERs, a pair of tones are presented to participants; the first tone (S_1), considered to be the conditioning tone, is presented with an identical second tone (S_2) being presented 500 ms after (Boutros & Belger, 1999; Broyd et al., 2013). The MLAERs typically display a reduction in amplitude when a second click (S_2) is presented approximately 500ms following the preliminary click (S_1; Turetsky et al., 2007). It has been shown that with healthy individuals there is a decrease of approximately 80% in the second P50 wave in comparison to the first; it is believed that this is due to the brain's activation of the inhibitory network following the conditioning stimuli (Braff & Light, 2004; Broyd et al., 2013). Due to the presence of MLAERs in response to both the S_1 and S_2 (Braff & Light,

2004), researchers have used this to quantify the brain's sensory gating ability, in the form of a *ratio* (i.e., the amplitude of the response to S_2 divided by the amplitude of the response to S_1 (S_2/S_1; Smith, Boutros, & Schwarzfopf, 1994)). Though less often used, sensory gating can also be quantified as the *difference* between the P50 amplitude elicited by S_1 and S_2 (i.e., S_1-S_2; Smith et al., 1994). This latter measure has been suggested to be more reliable than the ratio (Smith et al.,1994; Turetsky et al.,2009). Lower ratios or larger differences represent a better ability to inhibit extraneous information for all three MLAERs (Boutros & Belger, 1999).

The neural circuitry responsible for this process of inhibition has been reported to involve the hippocampus and hippocampal structures (Waldo et al., 1994), specifically arising from the inhibitory interneurons located in the hippocampus (Freedman et al., 1991). Of particular interest is the fact that these hippocampal brain areas also have a significant distribution of CB1 receptors – specifically in the dentate gyrus which projects to CA3 (Herkenham et al., 1990; Li et al., 1994). Furthermore, the hippocampus appears to be particularly vulnerable to the long-term effects of cannabis use. One study measuring the CB1 receptor density in cannabis users found that all brain areas showing downregulation of CB1 receptor density returned to normal after an abstinence period of approximately one month with the exception of the hippocampus (Hirvonen et al., 2012). Due to the neural generators of the P50 being located in the hippocampus (Freedman et al., 1991; Waldo et al., 1994), this suggests chronic cannabis users would be expected to have reduced P50-indexed sensory gating. Such results have been shown in chronic cannabis users, who showed significantly higher sensory gating ratios (i.e., worse gating) compared to non-using controls (Broyd et al., 2013; Patrick et al., 1999). Further research

looked at how sensory gating was affected by cannabis use in adolescence; the same pattern of high gating ratios were present in adolescent cannabis users (vs. non-users), where increased THC use was associated with a decreased ability to inhibit sensory information (Patrick & Struve, 2000). Furthermore, the degree to which sensory gating is impacted is relative to the individual's daily consumption rate or the number of joints smoked, indicating the more cannabis one uses the more one's sensory gating is impacted (Edwards et al., 2009; Patrick et al., 1999; Rentzsch et al., 2007). Of concern is that these studies did not consider biological sex when measuring these impacts. This gap in the literature is concerning given previously discussed sex-based differences in neurodevelopment relative to the average age of first cannabis use and the predominance of male cannabis users.

While all three ERP components are said to measure sensory gating (i.e., P50, N100, P200), they are not all generated by the same brain structures. This suggests that one component could be impacted while the others are spared, as was shown in the first published study measuring all three MLAER components in individuals with schizophrenia (Freedman et al., 1983). The N100 is a negative-going waveform occurring roughly 100ms post stimulus presentation. The N100 is generated for auditory stimuli suggesting its link with the auditory cortex (Ren et al., 2021). Prior research has shown that individuals with schizophrenia present with reductions in N100 amplitude (Connolly et al., 1985; Iwanami et al., 1994; O'Donnell et al., 1994; Shelley et al., 1999). This has since been linked to a deficit in bottom-up auditory sensory-perceptual processing (Ren et al., 2021). In addition, it has been suggested that attentional factors play a role in the later components (N100/P200) suggesting active attention could impact the expression of

these components (Boutros et al., 1999). Other work has since verified this by indicating that selective attention can increase N100 amplitudes (Hackley et al., 1990; Hillyard et al., 1973; Näätänen et al., 1981; Woldorff, Hackley and Hillyard 1991). It has, therefore, been suggested that the N100 is a reliable measure of sensory filtering when the ratio of S2/S1 is used (Fuerst et al., 2017; Rentzsch et al., 2008) while P200 is a measure of early attentional processing (Näätänen et al.,1992).

1.5.2 Visual Evoked Potentials (VEP)

The P100 is a measure of primary visual cortex activity that is elicited by any visual stimulus to which an individual attends. It has a peak amplitude at roughly 100-130 ms post-stimulus presentation (Luck, 2014). The P100 has been suggested to be an index of early attentional processing occurring in the primary visual cortex (Mangun 1995; Mangun & Hillyard 1990). It has been shown to present differently in males and females, with females showing increased amplitudes compared to males (Sharma et al., 2015). To date, only one study has examined the P100 in cannabis users; this study examined the effects of the administration of oral THC in two groups of cannabis users: occasional and heavy users (Theunissen et al., 2012). They found that there was a decrease in P100 amplitude for occasional users when THC was administered relative to a placebo control condition; however, the opposite was true of heavy users where an increase in P100 amplitude was shown (relative to placebo control; Theunissen et al., 2012). However, the decrease in occasional users was significantly different from their placebo control whereas the increase in heavy users' P100 amplitude was not, suggesting the P100 was impacted by THC administration more in occasional users than heavy users (Theunissen et al., 2012).

Another more commonly studied VEP is the visual P300 ERP. The P300 is an index of CNS activity that reflects one's ability to process incoming information and incorporate it into a memory trace of the given stimuli or the context for which the stimuli are presented (Polich & Herbst, 2000). Additionally, P300 latency is known to represent the processing time required by an individual before being able to generate a response, therefore classifying P300 as a measure of neural activity that underlies attentional resources and immediate memory (Polich & Herbst, 2000). Due to the nature of P300, it has been found that any brain disorder that alters the primary cognitive operations of attention allocation and immediate memory will show an effect in P300 amplitude or latency – or both (Polich & Herbst, 2000). Changes in P300 amplitude (i.e., decreased amplitude, maximal amplitude shifts more posteriorly for participants with schizophrenia who are unmedicated) have been shown in individuals diagnosed with depression and schizophrenia (Boutros et al., 1997; Bruder et al., 1995; McCarley, Faux, Shenton, Nestor, & Adams, 1991). The P300 waveform is characterized as a large positive-going waveform that occurs approximately 300 ms post-stimulus presentation (Gray et al., 2004). This ERP arises when higher-order cognitive processes are at work, specifically those involved with attentional resources (Donchin & Coles, 1988). It has been found that the amplitude of the P300 ERP is proportional to the degree of attentional resources dedicated to processing said stimuli; therefore, the more resources that are used, the higher the P300 amplitude (Duncan-Johnson & Donchin, 1977). Notably, the term P300 refers to a series of related but different positive-going waveforms, including the NoGo P300 that has been shown to represent behavioural inhibition on particular tasks (Falkenstein et al., 1999; Polich, 2007; Salisbury et al., 2004).

The Go/NoGo paradigm has been used to address response inhibition. This paradigm measures one's ability to inhibit a response during a sequence of stimuli. The Go/NoGo task has two responses required by participants: perform a behavioural response (e.g., click a mouse) if the trial is a 'Go' trial or inhibit this response if the trial is a 'NoGo' trial. The majority of trials are Go trials, which makes it more difficult for participants to inhibit responses. Conversly, NoGo trials require participants to inhibit a prepared response, indexed through the P300 ERP (Salisbury et al., 2004). The NoGo P300 has been reported to be reflective of the activation of frontal networks with little activation of the parietal cortex; conversely, the Go P300 reflects increased activation of the parietal cortex compared to the frontal networks (Laurens et al., 2005; Salisbury et al., 2004). The NoGo stimuli activate frontal areas of the brain that coincide with the distribution of the inhibitory network, also located in the frontal cortex (Nash, Schiller, Gianotti, Baumgartner, & Knoch, 2013; Salisbury et al., 2004). This is measured as a positive waveform occurring approximately 300 ms following the NoGo stimulus, with a fronto-central maximum.

Similar to the sex differences observed with the MLAERs, the NoGo P300 also exhibits sex differences (Melynyte et al., 2017). It was found that females took longer to respond and displayed larger P300 amplitudes on NoGo trials relative to males (Melynyte et al., 2017). Additionally behavioural differences between sexes have been shown, suggesting males are more accurate in responding to Go trials than females however, the same was not true for the NoGo trials whereby groups did not differ (Melynyte et al., 2017). This finding suggests that females allocate more resources to inhibiting the response to the NoGo trials (Melynyte et al., 2017). Additionally, other studies have

reported P300 amplitudes correlated with parietal lobe grey matter volume independent of body and brain size (Sowell et al., 2007). These observed differences in parietal lobe grey matter are in accordance with the recent findings of sex differences in NoGo P300 latency and amplitude (Melynyte et al., 2017) given females have been found to have thicker temporal and parietal cortices compared to males (Sowell et al., 2007). Moreover, hormone levels influence latency times for females on the NoGo task. For example, it was found that progesterone levels negatively correlated with NoGo responses (i.e., higher progesterone levels were correlated with shorter latencies on the NoGo task; Galvez-Buccollini et al., 2012). This finding is consistent with reports that progesterone has neuroactive metabolites that modulate the transmission of GABA, which in turn activates the dopamine system (Barth et al., 2015). Seeing as the NoGo response is dependent on dopamine and serotonin, it is not surprising that a change in progesterone would affect these responses (Galvez-Buccollini et al., 2012).

In addition to the observed sex differences on the NoGo P300, different recreational substances such as cannabis can affect this ERP as well. This is not surprising, considering the distribution of CB1 receptors in the frontal networks and the frontal neural networks involved in the generation of the NoGo P300 ERP. It was found that administration of small levels of THC (3.45%) decreased the NoGo P300 amplitude (Ilan et al., 2005). This suggests that even low dosages of THC in cannabis can exert acute negative impacts on inhibitory systems and therefore, the NoGo P300.

Similar deficits in NoGo P300 amplitude have been found in those with cannabis use disorder (CUD) suggesting inhibitory functioning is not only impacted by acute use but also by heavy consistent use. Individuals with CUD had significantly reduced NoGo

P300 amplitudes compared to non-using controls (Maij et al., 2017). Furthermore, CUD individuals took longer to respond to Go trials, although amplitudes were unaffected; this was theorized to be due to a speed-accuracy tradeoff whereby cannabis users try to to be correct in their response and therefore, must decrease the speed at which they can respond to allow for adequate processing time (Maij et al., 2017). Spronk, De Bruijn, van Wel, Ramaekers, and Verkes (2016) found similar results on the NoGo task where cannabis users showed decreased amplitude on the NoGo P300 ERP, with prolonged latencies shown as well compared to non-users. In addition, cannabis users had impaired behavioural response inhibition and increased errors during the NoGo task (Spronk et al., 2016). Exploratory analysis showed that the frequency of cannabis use was positively associated with the slowing of responses (Spronk et al., 2016). These findings need be interpreted with caution however, given that these participants were polydrug users using not only cannabis but also cocaine on a yearly basis (i.e., cocaine use more than 5 times in the past year; Spronk et al., 2016) indicating it may be the combination of drug use that impacts behavioural inhibition. While the frequency of cannabis use has been shown to impact inhibition and response times, other studies have measured THC quantity in the cannabis strain and how the acute effects of cannabis may be dose-dependent. Hunault et al. (2009) found that as the concentration of THC increased, participants' response time slowed down, motor control worsened, and the number of errors made increased, along with a concurrent decline in short-term memory and sustained attention. These results suggest that these effects are not uniform across cannabis strains, but are dependent on the dosage of THC consumed. Moreover, the effects on cannabis users may vary depending on biological sex. These factors, however, are rarely taken into consideration

when discussing cannabis use. In fact, females are typically not included in cannabis research and, if included, differences between biological sex are often not tested or discussed. Moreover, no study to date has measured the interaction of sex and cannabis use on the NoGo P300.

1.6 The Current Study

The current study was originally designed to address gaps in the literature by assessing the potential differences in cannabis-related deficits in neural functioning between males and females. Unfortunately, due to an insufficient sample size, this moderation analysis was not possible. A secondary goal of this study was to better understand the main effects of : 1) cannabis use (users vs. non-users), and 2) biological sex (males vs. females), on ERP measures of sensory gating and inhibitory processing.

Hypothesis 1: With prior work showing cannabis users have decreased amplitudes to inhibitory stimuli (Broyd et al., 2013; Edwards et al., 2009; Francis et al., 2021; Ilan et al., 2005; Maij et al., 2017; Patrick et al., 1999; Patrick & Struve 2000; Rentzsch et al., 2007; Spronk et al., 2016), we hypothesized that cannabis users would show reduced amplitudes in all ERP indexed measures of cortical inhibition (MLAERs and NoGo P300 amplitudes) compared to the non-using controls.

Hypothesis 2: While there has been limited research done regarding sex differences within the chosen paradigms the research that does exist suggets females have larger NoGo P300 amplitudes and longer latencies relative to males (Melynyte et al., 2017). For this reason we hypothesized that there would be larger NoGo P300 amplitudes and longer latencies (NoGo P300) in females compared to males. Given the limited research surrounding sex differences in the MLAER, this latter analysis was exploratory.

Hypothesis 3: Based on the ehanced visual cortex processing in cannabis users shown by Theunissen et al. (2012), it was hypothesized that we would see increased P100 amplutudes in CUs compared to NUs. The analyses of biological sex (males vs. females) effects on P100 amplitude were exploratory.

Hypothesis 4: Finally, while age of first use has been not found to correlate with sensory gating, sensory gating deficits have been shown to correlate with the number of years with consistent consumption (Rentzsch et al., 2007). With these findings in mind, we anticipated that cannabis users with more years of consistent use would show deficits on indexes of sensory gating. We also anticipated that number of years of daily (or almost daily) cannabis use would correlate with the Go/NoGo behavioural inhibition measures such that higher years of consistent cannabis consumption would be associated with deficits on behavioural measures.

Chapter 2: Paired Click Paradigm

2.1 Participants

Individuals (N = 30) between the ages of 18-30 years were recruited from the local community, including 14 regular cannabis users (CU; 9 males, 5 females) and 16 cannabis non-using controls (NU; 4 males, 12 females). CUs were defined as individuals who used cannabis 3 or more times a week at the time of study entry, with this rate of usage maintained for at least six months prior to participation (James et al., 2011). NUs were those who had used cannabis less than 10 times in their lifetime, with no use in the past year (James et al., 2011). Thirty years old was chosen as the upper limit due to changes in circulating estrogen levels that initiate at approximately age 30 in females that may confound our data (Musey et al., 1987). Additionally, this age captures the emerging adult age range (18-29 years) allowing us to focus in on specific cognitive changes that may take place in this critical developmental phase (Arnett, 2014).

Demographic and health information was disclosed through a series of questions posed during a screening session to establish eligibility to participate. Participants ranged in age from 19-26 years (M = 21.6; SD = 2.21; see Table 1 for full demographic information). All female participants had a regular length menstrual cycle (i.e., approximately 28 days, Wilcox, Dunson & Baird 2000) and were not using any medications that could alter sex hormones (e.g., oral contraceptives) at the time of the study. All female participants were required to be nulliparous and not currently pregnant to minimize the influence of the hormonal changes caused by prior and current pregnancy (Cost et al., 2014; Walia, Aggarwal & Wadhwa 2013). All participants were required to be right-handed, as determined by a handedness inventory to ensure source localization

during analysis (Oldfield, 1971). Participants were required to have normal or corrected-to-normal vision and normal hearing, as determined by self-report, to ensure these were not confounds to the study. To measure sex as a biological variable, participants were asked to self-disclose their sex; sex was defined to our participants as their biological sex at birth, which is generally divided into two categories: male and female. Finally, it was mandatory that participants could read and understand both spoken and written English for the purposes of the informed consent procedures and self-report measures.

Written informed consent was obtained prior to testing during the in-lab session. This study was approved by the Research Ethics Boards of the Nova Scotia Health Authority ROMEO file #1024305, Saint Mary's University Research Ethics Board #21-007, and Mount Saint Vincent University Research Ethics Board #2018-190.

2.1.1 Exclusion Criteria

Participants were excluded if they met any of the following criteria: diagnosis of a DSM-5 disorder, apart from cannabis use disorder (CU group only); a history of head injury with diagnosed concussion or loss of consciousness within the past six months; diagnosis of epilepsy or any other form of neurological disorder; current or regular use of psychoactive medication (other than cannabis); or diagnosis of a learning disorder. All exclusion criteria were assessed during a screening call where participants were asked to self-report this information.

2.2 Study Procedure

To determine eligibility, participants completed a screening procedure over the phone. Following this, eligible volunteers were each invited to attend an in-person

laboratory session where they participated in a battery of neurophysiological tests. All testing sessions took place between 8 am and 11 am to control for circadian fluctuations in alertness and EEG patterns throughout the day (Hines, 2004). All participants were required to abstain from drug use (including cannabis, tobacco, and alcohol, any medication that can alter neurological functioning, and caffeine) beginning at midnight the night before EEG recording.

2.3 Questionnaires

To better understand participants' overall substance use patterns, several validated questionnaires were administered. The Alcohol Use Disorders Identification Test (AUDIT; Bohn et al., 1995; Saunders et al., 1993) was administered by a trained researcher to every participant to quantify risky alcohol consumption, as well as risk factors correlated with alcohol use and dependency. The AUDIT uses a mix of three and four-point scales to classify individuals into one of four categories (abstinence, low-risk consumption, hazardous/harmful level, high risk for dependence) based on how risky their drinking behaviours are. Questions one through eight on the AUDIT are scored on a five-point scale (0-4) while questions nine and ten are scored on a three-point scale (0, 2, 4) ($\alpha = 0.82$). Scoring protocols were obtained from Saunders via the following link https://auditscreen.org/about/scoring-audit/. Scores range from 0-40 where 0 represents abstinence and no issues with alcohol use. A score ranging from 1-7 indicates low risk consumption, while scores ranging from 8-14 suggest hazardous levels of alcohol consumption. Finally, scores exceeding 15 indicate likelihood of alcohol dependence. All scoring was completed by a trained research assistant with higher scores indicating more hazardous drinking behaviour. Additional information on alcohol use, as well as

information regarding nicotine and cannabis use, was gathered through the administration of the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST, WHO ASSIST Working Group, 2010). The ASSIST is a validated measure used to identify substance misuse and related issues. The ASSIST is used in research to gather information on a wide range of commonly used substances and was used in this study to help identify any potential confounds between cannabis use groups. The ASSIST is an eight-item measure where participants were asked to indicate with the selection of yes or no which substances they have used in their lifetime (e.g., Cannabis, alcohol, inhalants, opioids). The remaining seven questions were follow-up questions to gather more information on substance use. Participants were asked to indicate how many times over the past three months they had used the substances for which they indicated previous use, as well as questions regarding how the substances affected their health and social life, and how their substance use may have impacted their productivity. Questions two through eight were answered on a four-point scale; higher numbers indicate a need for intervention level (i.e., indexing problematic use).

Participants who disclosed regular cannabis use (i.e., all CU's), were given the Reasons for Substance Use Scale (ReSUS; Gregg et al., 2009) to assess their motivations behind using cannabis. This is a 38-item measure using a four-point scale (0 = never; 3 = almost always) that assesses three common reasons for use: 1. Coping with distressing emotions and symptoms (18 items; Cronbach's α= 0.91; e.g., "when I am feeling depressed", "when I am feeling stressed" and "when I hear sounds or voices other people can't hear"); 2. Individual enhancement (11 items; Cronbach's α = 0.81; e.g., "when I want to chill out or relax", "when I want to feel drunk, stoned or high" and "when I want

to fit in with other people"); and 3. Social enhancement and intoxication (9 items; Cronbach's $\alpha = 0.82$, e.g., "when I want to feel more self-aware", "when I need motivation to do things" and "When I want to feel normal"). Scores on each question are totaled to generate subscale totals; higher scores indicate more likely use for the indicated reason; these were reported in descriptive statistics as well as used for the correlational analysis.

To assess differences in cannabis strains, any participant that identified as a cannabis user was asked to answer self-report questions on an author-generated measure regarding the THC:CBD content of their preferred strain to the research team, along with information concerning the frequency of use and the duration of consistent cannabis use (in years).

2.4 EEG Recording and Computation

Electrical activity was recorded from a BrainVision 64-channel electrode cap with Ag^+ /Ag^+Cl^- ring electrodes (Brain Products GmbH, Gilching, DE). Electrodes were placed on all 64 scalp sites using the 10-20 system of electrode placement, including three midline sites (frontal [F_z], central [C_z], parietal [P_z]), three left hemisphere sites (frontal [F_3], central [C_3], parietal [P_3]), and three right hemisphere sites (frontal [F_4], central [C_4], parietal [P_3]). Electrodes were also placed on the nose to serve as reference channels, while left and right mastoid were built into the cap at site TP9 (left) and TP10 (right) and were used to serve as the offline reference channels. Electro-oculogram activity was recorded from external canthi sites via bipolar channels; additional supra-orbital electro-oculogram activity was captured by site FP1 (left eye) and FP2 (right eye). All electrode impedances were kept below 5 kΩ and all electrical activity was recorded using

BrainVision Recorder software and a BrainVision ActiCHamp amplifier (Brain Products GmbH, Gilching, DE) with an amplifier bandpass of 0.1 and 30Hz digitized at 500 Hz. Data was stored on a hard drive for offline analysis using the BrainVision Analyzer software. All data was re-referenced offline to the mastoid channels (TP09, TP10) before being digitally filtered, and segmented based on the paradigm (i.e., Paired click paradigm, and Go/NoGo).

2.5 Test battery

The paired click paradigm used a series of sixty-four paired clicks (S_1-S_2) presented to participants at a sound level of 80 dB while they fixated on a silent movie (i.e., Disney's Fantasia) presented in front of them. Clicks were separated with an inter-click interval of 500 ms and an intrapair interval of 8 seconds. Tones were presented binaurally through Etymotic 3C in-ear headphones (Etymotic Research, Inc., Elk Grove Village IL). This paradigm follows well-established procedures (Boutros & Belger, 1999; Knott et al., 2009; Rentzsch et al., 2007; Zouridakis & Boutros, 1992) to elicit three components of the MLAER: the P50, N100, and P200, all of which have a maximal amplitude at scalp site C_z.

2.6 ERP analysis

To analyze each component, data was segmented separately into the 1st (S1) and 2nd (S2) clicks. Both S1 and S2 were segmented from -40-110 ms relative to the onset of the click. For the P50 analysis, electrical epochs were then digitally filtered using low and high filters of 10-50 Hz respectively, to increase the signal-to-noise ratio. The N100 and P200 were analyzed within epochs of 400 ms duration (including 50 ms pre-stimulus) using a frequency filter ranging from 0.1-30 Hz. All epochs were then ocular corrected

for eye movement (residual movement and blinks) using the Gratton and Coles algorithm (Gratton, Coles & Donchin, 1983) and baseline corrected (relative to the 0 ms pre-stimulus segment). Epochs containing voltages above 50 μV were excluded from the analysis and the remaining data was used for the final ERP averaging.

Taken from the Cz scalp site, the site of maximal amplitude, P50 amplitudes were measured as the amplitude of the most positive peak from 40-80 ms relative to click onset. Peak picking was done using the averaged waveforms for each participant using a semi-automatic process with each peak verified by the first author AMF. To ensure accurate detection of the P50, additional constraints were applied to the analysis protocol (Nagamoto et al., 1991; Zouridakis & Boutros, 1992): the P50 had to be observed in at least one of the other central electrode sites (C_3 and C_4), and S_2 P50 activity must peak within 10 ms of the peak observed from the P50 of S_1. The N100 was defined as the largest negative deflection between 80 – 180 ms while the P200 was defined as the largest positive deflection between 100 and 250 ms (Gooding et al., 2013). Latency (time to reach peak P50 amplitude from stimulus onset) was derived for S_1 and S_2 of each component (P50, N100, P200). Latency scores were generated during the semi-automatic peak picking processes and were taken from the averaged waveform for each participant at the site of maximal amplitude (i.e., Cz).

For each component, we calculated sensory gating in two ways following Broyd et al. (2013): to facilitate comparisons between past cannabis research (Edwards et al., 2009; Patrick et al., 1999; Rentzsch et al., 2007), gating ratios (S_2/S_1) for each component (i.e., rP50, rN100, rP200: S_2/S_1) were generated. Difference measures (S_1 – S_2) of sensory gating have been used more recently (Broyd et al., 2013; Edwards et al.,

2009; Rentzsch et al., 2007; Smith et al., 1994; Turetsky et al., 2009) to provide a more reliable index of sensory gating. Accordingly, we also calculated difference scores for each component (i.e., dP50, dN100, dP200).

2.7 Behavioural analysis

There is no behavioural data for the paired-click task as it is a passive listening task.

2.8 Statistical analysis

Two mixed analyses of variances (ANOVA) were conducted for P50 amplitudes using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY), the first with one between-groups factor (2 levels: CU and NU) and one within-groups factor (2 levels: Stimulus one (S_1) and Stimulus two (S_2)). The second mixed ANOVA included one between-groups factor (2 levels: Male and Female) and one within groups factor (2 levels: Stimulus one (S_1) and Stimulus two (S_2)); this analysis also included weekly cannabis consumption as a covariate to account for any confound sex differences in cannabis use may bring to the analysis. For the sex-based analysis, estimated marginal means and standard errors were reported to account for the impact of our covariate in the analysis.

In addition, the amplitude values for each stimulus were used to calculate both gating ratio (rP50: $S_2/S_1 \times 100$) and difference (dP50: $S_1 - S_2$) indices. Two separate univariate ANOVAs were performed with gating ratio (rP50) and gating difference (dP50) scores as dependent measures. The first included cannabis use (CU and NU) as a fixed factor, while the second used sex (Male and Female) as a fixed factor. For the

analysis of sex on gating ratio and difference scores, weekly cannabis use was added as a covariate in the analysis as was done for P50 amplitudes.

These same processes were carried out for the other components of the MLAER (i.e., N100, P200) with the exception of the ratio and difference scores which were only carried out for the N100 consistent with prior research conducted in our lab (Francis et al., 2021). Non-significant F-test parameters are reported in Tables 3-6. These values are only reported in text when significant (i.e., $p < .05$) or at the non-significant trend level (i.e., p =.07 - .05).

Latency was calculated as the time to reach peak amplitude from stimulus onset; latencies were generated for S_1 and S_2 separately for each of the three ERPs of interest. Additional mixed ANOVAs were computed to assess influences on latency for each of the three ERPs of interest with one between-groups factor, cannabis use (2 levels: CU, NU) and one-within groups factor, stimuli (2 levels: Stimulus 1 Latency (S_1), Stimulus 2 Latency (S_2)). An additional mixed ANOVA was run to address the potential impact of sex; this ANOVA had one between-groups factor, sex (2 levels: Males and Females) and one-within groups factor, stimuli (2 levels: Stimulus 1 Latency (S_1), Stimulus 2 Latency (S_2)) with a covariate of weekly cannabis use.

Latency was used to assess differences between cannabis use groups and between male and female participants. Latency was defined at the time to reach peak amplitude for each of the three MLAER components of interest for both S_1 and S_2 trials. As with amplitudes, non-significant F-test parameters are reported in Tables 3-6. These values were only reported in text when significant (i.e., $p < .05$) or at the non-significant trend level (i.e., p =.07 - .05).

A priori planned comparisons involving cannabis use and sex were examined for neurophysiological outcomes (i.e., amplitudes and latencies) in regions of maximal amplitude. All marginal interactions were probed as it takes more power to detect an interaction effect, than a main effect. All analyses were accompanied by effect size calculations due to our small sample size. We used Hedges' g (a corrected version of Cohen's *d*) to calculate effect sizes due to our uneven sample sizes (Lakens, 2013). Effect sizes were interpreted the same as Cohen's *d*: $g = .2$ represents a small effect, $g = .5$ represents a medium effect, and $g = .8$ represents a large effect (Lakens, 2013).

Finally, a bivariate correlational analysis was conducted using a two-tailed significance level to analyze correlations between demographic variables, questionnaires (AUDIT, ASSIST), and ERP data (amplitude and latency).

Power analyses were conducted separately for each component (P50, N100 and P200) to determine observed power (post-hoc analysis; see section 2.9 for outcome of the power analysis), the statistical test used was an independent samples t-test as this would allow sufficient power to detect differences between groups (i.e., cannabis conditions and sex). Two tailed tests with the following effect sizes (P50: small $d = .42$), N100- small ($d = .13$); and P200- small ($d = .43$)) were used along with the appropriate group size (i.e., CU vs. NU analysis: n = 14, n = 16; Sex based analysis: n = 13, n = 17). *A priori* analyses were also conducted using the independent samples t-test as the statistical test, all while maintaining 80% power. Effect sizes for the P50 power analysis were based off (Rentzsch et al., 2007, 2017), while the N100 effect sizes were based off prior work in our lab (Francis et al., 2021). Due to the novelty surrounding the P200 ERP we were unable to conduct an *a priori* power analysis.

2.9 Paired click paradigm power analysis

The observed power for between groups (CU vs NU) differences for the paired click P50 amplitude was 20% power, suggesting we would need a sample size of 84 participants per group to observe differences at an 80% power threshold. Power analysis was also computed for the N100 and suggested we had an observed power of 6% with a sample size of 144 per group necessary to observe differences at 80% power. We had an observed power of 20% for the P200; no *a priori* power analyses were able to be completed with the novelty in this area and no effect sizes could be generated from prior papers. Given these are larger than normal sample sizes for ERP studies, this suggests there are no differences between groups.

2.10 Results

All 30 participants (CU = 14; NU = 16) were included in the analysis of the paired click paradigm. The CU condition contained more males (n= 9) than females (n = 5) while the NU condition contained more females (n = 12) than males (n = 4). A chi-square test for independence was performed to examine differences between cannabis use groups on sex distribution; the relationship between these variables was significant, X^2 (1, N = 30) = 4.69, p = .03. Cannabis use groups did not differ on measures of age, education, or weekly alcohol consumption (see Table 1). There were significant differences between groups on total AUDIT score. While both groups were below the clinical cut off (i.e., 8) for risky drinking behaviours CUs (M = 6.92, SD = 4.78) were closer to this cut off than NUs (M = 2.30, SD = 2.02; p = .001). There were also significant differences between cannabis groups on four of the drug subscales measured: tobacco (M_{CU} = 6.00, SD_{CU} = 6.61; M_{NU} = 0.31, SD_{NU} = 0.87; p = .002), alcohol (M_{CU} = 12.14, SD_{CU} = 8.26; M_{NU} =

6.31, $SD_{NU} = 4.06$, $p = .018$), cannabis ($M_{CU} = 17.71$, $SD_{CU} = 8.98$; $M_{NU} = .75$, $SD_{NU} = 1.34$; $p < .001$) and cocaine ($M_{CU} = 3.64$, $SD_{CU} = 6.03$; $M_{NU} = .19$, $SD_{NU} = .75$; $p = .031$). CUs were above the clinical cut off for levels of use needing intervention on the tobacco, alcohol, and cannabis subscales. Non-users reported no use of amphetamines and hallucinogens; therefore, groups were not compared (see Table 1). Participants were not consistent in the manner in which they reported their THC:CBD content (e.g., while some provided exact ratios, other suggested they bought the highest THC content available at the time); this variability in reporting it made it impossible to determine the actual ratio of THC:CBD present in the cannabis used by our participants. Thus, this data proved to be inconsistent and at times unquantifiable; therefore, it was not used for analysis.

Cannabis users were using, on average, almost 5 days a week ($M = 4.7$, $SD = 2.7$) for a consistent period of about 4 years, on average ($M = 3.7$, $SD = 3.03$, range = 1-10 years). Based on the age of our sample, this suggests that the average cannabis user in our sample began use around the age of 18 years.

The ReSUS was administered to all cannabis users in our sample to help gain a better understanding of the reasons why our participants' consumed cannabis. Participants total scores on the ReSUS were divided into the three subscales of the ReSUS (i.e., coping with distressing emotions and symptoms, social enhancement and intoxication, and individual enhancement; Gregg et al., 2009) with high scores on each subscale representing a higher risk of consumption for those reasons. A full analysis of all 38-items was done to determine the frequency in which each motivation is reported, the most reported reason for cannabis use in our sample was for social enhancement and intoxication where "when I want to chill or relax" was the most reported reason for use

(57%). Other common reasons for use were "when I want to feel good, have a laugh or be happier", and "when I am with friends, and we want to have a good time", each of which was reported in 50% of our cannabis using sample (for a full breakdown of reasons see Table 2).

2.10.1 Cannabis Users Versus Non-Users' Analysis.

Due to insufficient sex-specific sample sizes within our CU and NU conditions, a fully factorial analysis between cannabis use and sex on our ERP measures was not able to be completed as proposed. Please see COVID-19 limitations in appendix D for further explanation as to why this analysis was not possible at this time.

2.10.1.1 Amplitude

Repeated measures ANOVA revealed a main effect of stimulus type identified for P50 amplitude, $F\ (1,28) = 22.23$, $p < .001$, such that S_1 amplitude was larger than S_2 for both CUs ($M_{S1} = 1.75$ µV, $SD_{S1} = 1.14$; $M_{S2} = .55$ µV, $SD_{S2} = .58$, $p = .006$) and NUs ($M_{S1} = 1.54$ µV, $SD_{S1} = 1.75$; $M_{S2} = .64$ µV, $SD_{S2} = .76$; $p = .004$, *CI* [**S1**: CU: 1.09 – 2.42; NU: .90 – 2.18; **S2**: CU = .21 – .89; NU: .24 – 1.04]; Table 3). There was neither a main effect of group (Figure 1) or a group by stimulus type interaction (Table 4). Effect sizes and confidence intervals (*CI* [-1.09 - .67]; *CI* [-.43 - .60], S1 and S2 respectively) corroborated the between-groups findings with inconsequential effects, suggesting no differences between CUs and NUs as measured by Hedges' *g* ($g_{S1} = .18$, $g_{S2} = .12$, respectively).

Ratio and difference scores showed no main effects of cannabis use (Table 5) suggesting no differences between CUs and NUs on gating measures. Effect sizes and

confidence intervals were generated for rP50 (*g*= .40) and dP50 (*g* = .24; *CI* [ratio scores: -.37 – 1.18; difference scores: -1.22 - .61], indicating there was only a small effect of cannabis group for both ratio and difference scores.

There were no main effects or interaction effects for the N100 amplitude for the paired click paradigm (Table 4), and effect sizes and confidence intervals were inconsequential and small (respectively) suggesting no difference between groups (*g* = .02; *CI* [-1.64 – 1.51]) and no interaction between groups and stimuli S_1 (*g* = .30) or S_2 (*g* = .38, *CI* [S1: CU = [-3.43 – (-.28)], NU = [-4.27 – (-1.32)]; S2: CU = [-3.76 – (-1.43)], NU = [-2.87 – (-.70)] Figure 2). Ratio and difference scores showed no statistically significant differences between groups (Table 5); however, effect sizes and confidence intervals helped better understand these potential differences. Effect sizes were medium-to-large, suggesting the possibility of a between-groups effect, such that, CUs have larger ratios (*M* = 1.20, *SD* = .38) relative to NUs (*M* =.36, *SD* = .34; *p* = .11, *g* = .80; *CI* [-1.88 - .21]). Effect sizes for difference scores suggest CUs have smaller difference scores relative to NUs (M_{CU} = .73, SD_{CU} = 2.98; M_{NU} = -1.01, SD_{NU} = 2.63; *p* = .098, *g* = .63; *CI* [-3.85 - .35], Figure 3). Confidence intervals for both ratio and difference scores suggest these findings should be interpreted with caution and further research is needed. These findings suggest the possibility of worse sensory gating as indexed by the N100 in the CU group relative to the NU group, however, indicate more research is needed to fully understand this relationship.

There was no main effect of stimulus type for P200 (Table 4, Figure 2); and no stimulus-by-group interaction, *F* (1, 28) = 4.14, *p* = .052, Figure 4. Planned pairwise comparisons revealed CUs (*M* = .01 μV, *SD* = 3.32) had smaller amplitudes to S_1 than

NUs (M = 2.93 µV, SD = 3.45; p = .03, g = .86; CI [.37 – 5.46]). Pairwise comparisons revealed the between-group differences for P200 amplitudes to S_2 were non-significant, small effect sizes and wide confidence interval ranges suggesting no difference between cannabis use groups on P200 amplitudes to S_2 (M_{CU} = 1.25, SD_{CU} = 2.87; M_{NU} = 1.19, SD_{NU} = 2.23; p = .95, g = .02; CI [-1.85 – 1.97]).

2.10.1.2 Latency

There were no main effects of stimulus type or cannabis group on P50 latency and no interaction effect (Table 4). Effect sizes and confidence intervals were generated for between groups effects. Broad confidence intervals and small effect sizes for S_1 between groups suggests no differences between CUs and NUs on S_1 latency (M_{CU} = 108.85 ms, SD_{CU} = 7.47; M_{NU} = 105.88 ms, SD_{NU} = 5.44; p = .22, g = .46; CI [-7.83 – 1.86]). Medium effect sizes were found for S_2 suggesting CUs may have longer latencies to S_2 than NUs (M_{CU} = 108.00 ms, SD_{CU} = 8.81; M_{NU} = 104.63 ms, SD_{NU} = 4.11; p = .18, g = .50; CI [-1.66 – 8.41]) confidence intervals suggest more research is needed to fully understand this finding.

A main effect of stimulus type was found, F (1,28) = 91.09, p < .001, for the N100 latency such that latencies were shorter for S1 (M = 121.67 ms, SD = 31.78) than S2 (M = 179.86 ms, SD = 23.39, g = 2.09). Pairwise comparisons revealed that this was consistent across groups ([S1]: M_{CU} = 112.42 ms, SD_{CU} = 28.07; M_{NU} = 129.75 ms, SD_{NU} = 33.47, p < .001; [S2]: M_{CU} = 177.57 ms, SD_{CU} = 27.65; M_{NU} = 181.87 ms, SD_{NU} = 19.65; p < .001). There was a medium effect-size for the simple main effect of group (g = .55) however, confidence intervals suggest this finding needs further exploration (CI [-5.98 – 40.62]). The effect sizes and broad confidence intervals for the S_2 group simple

main effect suggest, there may be no differences between groups (*g* = .18; *CI* [-13.46 – 22.07]), despite significance test findings.

A main effect of stimulus type was found for P200 latency F (1,28) = 39.56, $p <$ .001, such that S_1 (*M*= 167.87 ms, *SD* = 58.67) had shorter latencies than S_2 (*M* = 231.47 ms, *SD* = 38.63; *CI* [43.81 - 86.13]). There were no significant main effects of group, F (1,28) = 3.96, p = .057. While large effect sizes appear to suggest CUs (*M* = 184.93 ms, *SD* = 10.15) have shorter latencies than NUs (*M* = 212.56 ms, *SD* = 9.49, *g* = 2.8; *CI* [-.83 – 56.10]), confidence intervals suggest caution is needed when interpreting this finding. While there was no stimulus type by group interaction revealed, F (1,28) = 3.98, p = .056; pairwise comparisons indicate latencies were quicker for S_1 in CUs (*M* = 109.38 ms, *SD* = 57.38) relative to NUs (*M* = 142.14 ms, *SD* = 50.44, p = .022, *g* = .61; *CI* [7.55 – 88.91]; Figure 4). Pairwise comparisons suggest no differences between CUs (*M* = 227.71 ms, *SD* = 45.36) and NUs (*M* = 234.75 ms, *SD* = 32.81; p = .63, *g* = .17; *CI* [-22.31 – 36.38]) on S_2 latencies (see Figure 5).

2.10.1.3 Correlations

Spearman's rho bivariate correlations were performed to measure the relationships of the MLAER components with the demographic and psychological variables. The N100 (S_2) amplitude was negatively correlation with alcohol use (r = -.45, p = .01) as measured by the ASSIST, such that as alcohol use increases, N100 amplitude to S_2 decreased (i.e., became larger). Risky alcohol use as measured by the AUDIT was found to correlate with P200 amplitude (S_1) such that as risky drinking behaviours increased, P200 amplitude decreased (r = -.39, p = .04).

Significant correlations were found for cannabis users' scores on the ReSUS individual enhancement scale and the P50 measures of inhibition, specifically P50 S_1 (r = -.58, p = .03), rP50 (r = .54, p = .05) and dP50 (r = -.57, p = .03). This pattern suggests that increased use for individual enhancement is associated with decreased P50 amplitude for S_1 and worse overall gating as indexed by decreases in dP50 and increases in rP50. There was also a correlation with N100 amplitude and the ReSUS subscales, specifically N100 S_1 amplitude negatively correlated with the ReSUS coping with distressing emotions and symptoms subscale (r = -.56, p = .04) and the ReSUS social enhancement and intoxication subscale (r = -.63, p = .02). These correlations point to the fact that increased use of cannabis for coping or social reasons would decrease N100 amplitude (making it more negative).

dN100 and N100 S_1 latency also correlated with the ReSUS coping with distressing emotions and symptoms subscale (r = -.57, p = .032; r = .55, p = .004 respectively) suggesting that as cannabis use for coping reasons increases, sensory gating as indexed by the N100 gets worse, and N100 S_1 latency gets longer.

2.10.1.4 Summary

Overall, these analyses are underpowered (see section 2.10); while we found no statistically significant differences between groups and confidence intervals suggest no differences our effect sizes suggest possible differences between groups may exist. Specifically, it appears that P50-indexed gating is not impaired in cannabis users, while the later, early attentive phase (as indexed by the N100) may be more impacted by cannabis use. Latency findings suggest that P50 latencies were longer for cannabis users while the later processing appears to be quicker (i.e., N100 and P200) as indexed by

shorter latencies in CUs (vs. NUs) to S_1 and S_2 stimuli. All findings need to be interpreted with caution as our confidence intervals suggest more research is needed to fully understand these relationships.

Correlational findings suggest decreases (i.e., more negative) in S_2 N100 and S_1 P200 amplitudes may be related to increased alcohol use. While decreased N100 amplitudes goes against prior findings with alcohol users (Miyazato & Ogura 1993; Kaseda et al., 1994; Sklar & Nixon, 2014) very little research has been done examining this component with this sample (alcohol users). Prior work suggests larger N100 amplitudes may be related to situations inducing high levels of cerebral cortex activation such as states of anxiety or stress (Ermutlu et al., 2005; Golimbet et al., 2013; Rosbuurg et al., 2008; Schofield et al., 2009). With the known relationship between alcohol use and anxiety disorders, it may be that the correlation between N100 amplitudes and alcohol use are impacted by anxiety. Unfortunately, anxiety was not measured in this study and thus we cannot further explore this relationship. While Sklar and Nixon's (2014) found increased N100 amplitudes in alcohol users, thus going against what we found, our findings do perfectly align with their P200 findings such that they found reduced amplitudes to S_1 for those that received moderate doses of alcohol (BrAC = .0065%), suggesting that alcohol use impacts the P200 (S_1) amplitude.

Additionally, correlations revealed that an increased use for individual enhancement was associated with decreased S_1 P50 amplitude and decreased dP50 suggesting those who used for individual enhancement have worse gating ability and worse gating-in (as indexed by smaller S_1 amplitudes) compared to cannabis users who primarily use for other reasons. Another correlation was found between reasons for use

and the MLAERs such that use for coping or social reasons correlated with decreases in N100 amplitudes increases in N100 latencies. This suggests that the reasons behind why someone uses cannabis are an important factor to consider when examining how sensory gating may be impacted as they may represent trait-level differences independent of drug use.

2.10.2 Male Versus Female Analysis Covarying for Weekly Cannabis Use.

2.10.2.1 Amplitude

There was a main effect of stimulus type identified for P50 amplitude, F (1,27) = 7.0, p = .013, such that while accounting for weekly cannabis use and sex, S_1 (M = 1.64 μV, SE = .23) amplitudes were larger than S_2 (M = .60 μV, SE = .13, g = 1.11). No stimulus by sex interaction was identified (p = .114, Figure 6). While accounting for weekly cannabis use, the effect size for sex was small for S_1 (g = .41) and inconsequential for S_2 (g = .10), confidence intervals substantiate this finding *CI* S1(female [1.33 – 2.53], male [.58 – 1.96]); S2 (female [.19 - .91], male [.26 – 1.08], suggesting no difference between sexes for either stimulus type (Table 6). Ratio and difference scores were examined, no main effects of sex were found (Table 7). Effect sizes, and confidence intervals were generated for rP50 and dP50 separately. These were inconsequential and small, again suggesting that there are no differences between sexes on rP50 (g = .18; *CI* [.23 - .48) and dP50 (g = .45, *CI* [.59 – 1.49) measures of sensory gating.

There were no main or interaction effects observed for N100 amplitude to the paired click paradigm (Table 6). Inconsequential to small effect sizes of sex supported this suggesting no effect of sex on S_1 (g = .10; *CI* [.28 – 1.53]) or S_2 (g = .20; *CI* [.54 – 1.87]) amplitudes (Figure 7). N100 ratio and difference scores indicated no main effect of

sex while accounting for weekly cannabis consumption (Table 7). In agreement with this, effect sizes were small and inconsequential, and confidence intervals had wide ranges, thus, suggesting no difference between males and females on gating ratios (*g* = .47; *CI* [-.23 – 1.57]) or difference scores (*g* = .01; *CI* [-1.32 – 3.30]).

Finally, the analysis of P200 amplitude showed no main or interaction effects while controlling for the impact of weekly cannabis use (Table 6). Effect sizes supported this conclusion with inconsequential between-sex effects on P200 amplitude for both S_1 (*g* = .17; *CI* [-5.15 - .11]) and S_2 (*g* = .19, *CI* [-1.28 – 2.54]; Figure 7).

2.10.2.2 Latency

There were no main or interaction effects for P50 latency while accounting for weekly cannabis consumption (Table 6). Confidence interval ranges and inconsequential effect sizes suggested there were no between sex effects for S_1 or S_2 amplitude (*g* = .036, *CI* [-10.50 - 10.61], *g* = .14, *CI* [-12.26 – 11.83] respectively). A main effect of stimulus type was discovered for the N100 latency analysis, F (1,27) = 38.06, $p < .001$. Pairwise comparisons revealed that this was due to smaller latencies to S_1 (*M* = 122.93 ms, *SE* = 5.82) than S_2 (*M* = 180.06 ms, *SE* = 4.47, *g* =2.08). The results suggested no main or interaction effects of sex on N100 latency while accounting for weekly cannabis use. Effect sizes and confidence intervals support this conclusion with inconsequential to small effects, and broad ranges between sexes for N100 latency for both S_1 (*g* = .38; *CI* [-20.42 – 51.59]) and S_2 (*g* = .14; *CI* [-31.52 – 43.78]).

A main effect of stimulus type was found for the P200 latencies, F (1,27) = 11.11, $p = .002$; pairwise comparisons indicated this was due to shorter latencies at S_1 (*M* = 170.67 ms, *SE* = 10.42) when compared to S_2 (*M* = 232.17 ms, *SE* = 7.33, *g* = 1.28).

There was no interaction effect found between sex and stimulus type for P200 latency ($p = .20$). In addition, effect sizes for sex for each stimulus type were small and confidence interval ranges were very large, suggesting no impact of sex on P200 latency for either S_1 ($g = .41$; *CI* [-30.79 – 91.78]) or S_2 ($g = .23$; *CI* [-70.01 – 55.71]).

2.10.2.3 Summary

We found a main effect of stimulus type for the P50 amplitude in addition to main effects of stimulus type for latency for the N100 and P200 ERPs; however, there were no main or interactive effects of sex. Overall, these findings are underpowered (see section 2.9); however, our analysis in conjunction with effect sizes and confidence intervals suggest no evidence of sex-based differences in amplitude of the MLAERS or latency of these components.

Chapter 3: Go/NoGo Paradigm

Participant information, study procedure, questionnaires, and EEG recording and computation, were all identical to that previously described; please see chapter 2 section 2.1 -2.4 for full information.

3.1 Test Battery

The Go/NoGo paradigm is a well-established visual task (Maij et al., 2017; Salisbury et al., 2004) that required participants to withhold a behavioural response when presented with an infrequent 'NoGo' stimulus (P=0.25) randomly embedded among frequent 'Go' stimuli (P=0.75). Stimuli were white numbers between 1-9 presented on a black computer screen; participants were instructed to press the mouse key (i.e., 'go') for every non-repeated number, but to withhold their response (i.e., 'no go') when repeated numbers were shown (see Figure 8). Stimuli were presented in four blocks of 150 trials each (i.e., 600 total trials) in a pseudo-randomized order, such that no number was presented more than two times in a row (Maij et al., 2017). Each number was presented for 700 ms, with an interstimulus interval of 300 ms.

3.2 ERP analysis

The Go/NoGo paradigm allowed us to measure several components of interest (i.e., the P100 and P300 for both the Go and NoGo stimuli), specifically the inhibitory NoGo P300. To be consistent with previous research (Spronk et al., 2016), we applied filters from 0.10-30 Hz and a notch filter at 60 Hz. Data was then segmented into Go and NoGo trials separately including 100ms before and 700ms after each stimulus. Electrical epochs (800 ms period, commencing 100 ms pre-stimulus) were corrected for eye

movement (residual movement and blinks) using the Gratton and Coles algorithm (Gratton, Coles, & Donchin, 1983). The data was then baseline corrected between -100 – 0 ms and put through an artifact rejection process whereby data with a 20μV/ms or greater voltage step or containing electrical activity exceeding ±75 μV were excluded from the analysis. The remaining epochs were then averaged, with the resulting waveform used to identify the peaks.

Peak identification took place at the respective sties of maximal amplitude of each ERP of interest. The site of maximal amplitude varied for each component, with the Go components having a more posterior distribution (i.e., Go P300 – Pz) whereas the NoGo components have a more centro-parietal topography (i.e., P300 – Cz; Salisbury et al., 2004). P100 amplitudes were also of interest with a site of maximal amplitude occurring at Oz for both the Go and NoGo conditions. Peak amplitudes were quantified as the most positive or negative deflection within the identified peak detection windows. Peak detection windows were determined based on grand averaged waveforms: (P100 for both Go and NoGo: (80 – 150 ms); Go P300: (375 – 500 ms); NoGo P300: (200 – 350 ms)). Participant data was averaged in preparation for peak identification; a semi-automatic process involving verification by the first author (AMF) was used to identify peak amplitude separately for each participant. Latency (time to reach peak amplitude from stimulus onset) was derived for each component from the averaged waveform of the Go and No/Go trials separately for each participant.

3.3 Behavioural analysis

The average number of misses (i.e., missing a response to a Go trial), and false alarms (i.e., incorrect response during a NoGo trial) for the Go/NoGo task were

determined by generating averages across all four blocks of the task. Proportional averages for reaction time across all four blocks were also generated for false alarms and correct responses. In addition, proportional percent correct and false alarms was created . Two one-way ANOVAs were used to determine group (CU and NU) and sex (Male and Female) differences on behavioural performance measures (i.e., percent correct, false alarms, proportional reaction time, misses).

3.4 Statistical analysis

A mixed ANOVA was conducted using SPSS 24 (SPSS Inc., Chicago, IL) separately for each ERP of interest within this paradigm. Each analysis is fully described below.

Go analyses included the analysis of the P100 and P300 waveforms. All ERPs were analyzed using separate mixed ANOVAs that included the following variables: one between groups measure (2 levels: CU and NU) and two within groups measures: Region (2 levels: parietal and occipital) and Scalp site (3 levels: left, midline, and right). A separate set of mixed ANOVA analyses was conducted for each ERP component of interest using sex as the between-groups measure and adding in the covariate of weekly cannabis use. Non-significant F-test parameters are reported in Table 9. These values are only reported in text when significant (i.e., $p < .05$) or at the non-significant trend level (i.e., $p = .07 - .05$).

NoGo analysis included a similar approach for the P100 and P300 ERP components with separate mixed ANOVAs being performed for each. For the P100 the variables of interest were one between groups measure (2 levels: CU and NU) and two within groups measures: Region (2 levels: parietal and occipital); and Scalp site (3 levels:

left, midline, right). The P300 has a site of maximal amplitude at Cz; therefore, the analysis for the P300 focused on more central electrodes using the same between groups measure (2 levels: CU and NU) and modifying the within-groups measure of region to include frontal and central regions (2 levels: frontal and central). Site remained the same with three levels (left, midline, right). As was done with the Go analysis, a separate mixed ANOVA was performed for each ERP with sex as the between-groups factor and adding the covariate of weekly cannabis use, with non-significant F-test parameters reported in Table 9. These values are only reported in text when significant (i.e., $p < .05$) or at the non-significant trend level (i.e., $p = .07 - .05$). Amplitudes for the NoGo stimuli are the focus of our results, as they assess inhibitory processing.

Latency was calculated as the time to reach peak Go/NoGo amplitude from stimulus onset. Latencies were calculated for each of the Go and NoGo ERPs of interest separately. Univariate ANOVAs were computed separately for the latency corresponding to each of the ERPs of interest, with a dependent factor of latency and fixed factor of cannabis use (CU and NU). In addition to this, separate univariate ANOVAs were performed for the latency of each ERP of interest to measure sex as a fixed factor with latency as the dependent variable and weekly cannabis use as a covariate. As with amplitudes, non-significant F-test parameters are reported in Table 9. These values are only reported in text when significant (i.e., $p < .05$) or at the non-significant trend level (i.e., $p = .07 - .05$).

Bivariate correlational analyses were conducted in a similar manner to what was previously described (see Chapter 2, section 2.8 for full details). As was done with the MLAERs, *a priori* planned comparisons were performed for any cannabis use, sex and

neurophysiological outcomes (i.e., amplitude and latency). Additionally, the same process was followed as to what is described in Chapter 2 regarding the probing of interactions and the calculation of effect sizes (please see Chapter 2, section 2.8 for full details).

3.5 Go/NoGo Power Analysis

Power analyses were conducted separately for each component (P100 and P300) to determine observed power (post-hoc analysis; see section 3.5 for outcome of the power analysis), the statistical test used was an independent samples t-test as this would allow sufficient power to detect differences between groups (i.e., cannabis conditions and sex). Two tailed tests with the following effect sizes (P300: Go - small (d = .07), NoGo- small (d = .25) P100: Go – medium (d = .68), NoGo – small (d = .18) were used along with the appropriate group size (i.e., CU vs. NU analysis: n = 14, n = 16; Sex based analysis: n = 13, n = 17). *A priori* analyses were also conducted using the independent samples t-test as the statistical test, all while maintaining 80% power. Effect sizes for the P300 were based off (Salisbury et al., 2004). Due to the novelty surrounding the P100 ERP in our sample (cannabis users) we were unable to conduct an *a priori* power analysis.

The observed power for between-group (CU vs NU) differences (ANOVA) for the P300 in the Go and NoGo condition were 10% and 5% respectively. This suggested we would need an unrealistic sample size of 478 to expect to see between-group differences for the P300 Go and 12,562 to see between-group differences for the P300 NoGo. Given these are substantially larger than normal sample sizes for ERP studies this suggests there are truly no differences between cannabis groups in P300. With the

novelty in the area of the P100 in this sample (cannabis users) no *a priori* power analyses were able to be obtained for this ERP.

3.6 Results

Participants were the same as those described in Chapter 2, thus demographic information for this sample can be found in Chapter 2, section 2.10.

3.6.1 Cannabis users vs non-users' analysis.

Due to insufficient sex-specific sample sizes within our CU and NU conditions, a fully factorial analysis between cannabis use and sex was not able to be completed as proposed for the ERP components. Please see COVID-19 limitations in the discussion for further explanation as to why this analysis was not possible at this time.

One CU male participant had to be excluded from this analysis due to missing data (e.g., no trigger information or behavioural data was captured during this task). The final sample size for the Go/NoGo paradigm was thus n = 29.

3.6.1.1 Amplitude Go

There was a main effect of region, of moderate effect size, for P100 amplitude in the Go condition, F (1,27) = 14.05, p = .001, with larger amplitudes in the occipital (M = 3.47 μV, SD = 2.90) compared to parietal (M = 1.95 μV, SD = 2.91, g = .52; CI [.71 – 2.41]) region. The ANOVA revealed there were no region by group (p = .30) or region by site by group interactions (p = .61). Effect sizes arising from for *a priori* between-group comparisons at the region of maximal amplitude (occipital). This suggested medium sized differences between cannabis groups such that CUs (M = 4.32 μV, SD = 3.40) had larger P100 amplitudes than NUs (M = 2.78 μV, SD = 2.28, p = .14, g = .50, CI [-2.54 –

1.20], Figure 9). Finally, the P300 Go amplitude was assessed for group differences. There were no main effects or interaction effects. Effect sizes indicated medium effects at the region of maximal amplitude (parietal) suggesting CUs (M = 4.82 µV, SD = 2.29) had larger P300 Go amplitudes than NUs (M = 3.55 µV, SD = 2.70; p = .16, g = .50) however, confidence intervals suggest more research is needed to understand this relationship (CI [-3.08 - .54]).

3.6.1.2 Amplitude NoGo

A main effect of region was found for the P100 NoGo amplitude F (1,27) = 21.14, $p < .001$, due to larger amplitudes in the occipital (M = 3.86 µV, SD = 2.85) compared to parietal (M = 2.11 µV, SD = 2.97, g = .60; CI[.99 – 2.59]) regions. There was no other main or interaction effects. While this suggested no impact of group on the P100 NoGo amplitude, effect sizes suggested otherwise and indicated that at the region of maximal amplitude (occipital) there was a medium effect size of group, with CUs (M = 4.66 µV, SD = 2.97) having larger amplitudes than NUs (M = 3.21 µV, SD = 2.66, p = .15, g = .52, CI[-3.45 - .54], Figure 10), although confidence intervals corroborate findings of no differences between groups.

Finally, the NoGo P300 was assessed, and a main effect of region was found, F (1,27) = 38.98, $p < .001$. Pairwise comparisons revealed these differences were due to significantly larger P300 amplitudes at the central (M = 7.79 µV, SD = 4.34) compared to frontal (M = 4.92 µV, SD = 3.36, g = .74; CI [2.02 – 3.10]) region. There were no other main or interaction effects, suggesting no differences between CUs and NUs. Effect sizes and confidence intervals substantiate this finding as the effect between CUs (M = 7.81

μV, *SD* = 2.69) and NUs (*M* = 7.78 μV, *SD* = 5.26, *p* = .98; *CI* [-3.19 – 3.11]) at the central region was inconsequential (*g* = .01).

3.6.1.3 Latency

A one-way ANOVA was conducted to measure the latency of each ERP of interest at the site of maximal amplitude. We found no between-group differences on measures of latency for any of our ERPs of interest. In addition, all between-group effect sizes were inconsequential and small suggesting no impact of group on latencies (Table 9).

3.6.1.4 Correlations

Spearman's Rho bivariate correlations were performed to assess our behavioural measures of Go/NoGo performance on our demographic variables. We found that tobacco use as measured by the WHO ASSIST was negatively correlated with correct reaction time ($r = -.37$, $p = .046$) indicating that as self-reported tobacco use scores increased, response time for correct responses decreased. We also found correlations with total number of false alarms and total AUDIT scores ($r = -.55$, $p = .002$) such that as AUDIT scores increased, number of false alarms decreased. In addition, false alarms were found to correlate negatively with self-disclosed weekly alcohol consumption ($r = -.43$, $p = .019$) indicating as weekly drinking increased false alarms decreased.

Behavioural measures were found to correlate with our ERPs of interest in the following ways. Overall, P300 Go latency correlated negatively with total false alarms ($r = -.62$, $p < .001$) indicating more false alarms were made when P300 latency was shorter. With regard to the NoGo correlational findings, NoGo P300 amplitude was found to

correlate with several behavioural factors, specifically, the percentage of correct responses made by participants (r = .48, p = .009), the total false alarms made (r = -.41, p = .029), reaction time for the false alarms (r = -.43, p = .019), and the number of misses made by participants (r = -.48, p =.009). This suggests that the larger the amplitude, the more correct responses were being made while the false alarms (reaction time and behavioural response) and misses made decreased as amplitude increased (or vise-versa).

To better understand the nature of these correlations, the sample was divided between CUs and NUs to determine if one group was driving these correlations. The correlation between false alarm reaction time and the P300 NoGo amplitude was only present in the CUs (r = -.52, p = .039). In addition, a new correlation was found for the CUs between total number of false alarms made and P300 Go amplitude (r = -.62, p = .011) suggesting that P300 amplitude for both conditions of the Go/NoGo task is decreased when false alarms are increased in quantity or reaction time. Interestingly, there were no correlations with false alarms (reaction time or quantity) within the NUs. The correlations between percent of correct responses (r = .56, p = .048) and number of misses made (r = -.56, p = .048) with NoGo P300 amplitude appear to be driven by NUs. This suggests P300 amplitude in CUs is not associated with the number of correct responses made; however, it is associated with the number of false alarms made. There were no other significant correlations to report.

3.6.1.5 Behavioural

Analysis of behavioural data revealed that cannabis users and non-users did not differ on any of the behavioural measures (i.e., percentage of correct responses, reaction

time for correct responses, false alarms, reaction time on false alarms, and misses; see Table 8).

3.6.1.6 Summary

Overall, these findings are underpowered (see section 3.5); while our statistical findings and confidence intervals suggest no differences between groups, our supplemental effect size analysis suggests differences between groups may exist. Specifically, while confidence intervals suggested no real differences exist, effect sizes suggested CUs may have enhanced P100 and P300 Go amplitudes compared to NUs. Overall, this signifies that more research needs to be done to clarify these potential differences.

3.6.2 Male versus Female Analysis Covarying for Weekly Cannabis Use.

3.6.2.1 Amplitude Go

Repeated measures ANOVAs were run to measure sex differences on our ERPs of interest while controlling for the impact of weekly cannabis use. For the Go P100, a main effect of region was found, F (1, 26) = 16.59, $p < .001$. Pairwise comparisons revealed this was due to larger amplitudes in the occipital (M= 3.62 μV, SE = .51) compared to parietal (M = 1.95 μV, SE = .45; CI[.84 – 2.50]) region. No interaction effect was found between region and sex, F (1,26) = 4.10, p = .053. Pairwise comparisons were done and revealed males had significantly larger P100 amplitudes in the occipital (M = 4.51 μV, SE = .81) region when compared to the parietal region (M = 1.97 μV, SE = .72, p = .001). The amplitudes in females were not significantly different across region (p = .16). Further pairwise comparisons revealed that there were no differences between male and

female P100 amplitudes at either region ([parietal] $p = .98$; [occipital] $p = .12$).-Effect sizes were generated to determine the effect between groups at the site of maximal amplitude (Oz): a medium/large effect was found in support of our main finding indicating that males have larger amplitudes than females ($g = .74$; *CI*[-4.04 - .47], Figure 11). There were no other main effects or interaction effects found for the P100 Go.

A main effect of region was also found for the P300 Go ERP, $F(1, 27) = 33.08$, $p < .001$, reflecting larger P300 Go amplitudes in the parietal ($M = 4.18$ µV, $SE = .44$) compared to occipital region ($M = 1.32$ µV, $SE = .47$; *CI*[-1.0 - .78]). There were no other main or interaction effects found. Effect sizes were calculated between groups, at the site of maximal amplitude (Pz); these also suggested an inconsequential effect of sex on P300 Go amplitude ($g = .019$).

3.6.2.2 Amplitude NoGo

Similar to the P100 Go, a main effect of region was found for the P100 NoGo, $F(1,26) = 19.80$, $p < .001$, reflecting larger amplitudes in the occipital ($M = 3.90$ µV, $SE = .51$) compared to parietal regions ($M = 2.05$ µV, $SE = .47$; *CI*[1.85 – 3.82]). There were no other significant main, or interaction effects found. Effect sizes at the site of maximal amplitude (Oz) were generated to determine if there were any effects between groups. This analysis revealed only a small effect of sex: $M = 4.02$ µV, $SE = .70$ [males] vs. $M = 3.77$ µV, $SE = .58$ [females]; $g = .21$; *CI* [-2.76 – 3.17]. A main effect of region was also found for the P300 NoGo, $F(1,26) = 22.53$, $p < .001$, such that amplitudes in the central ($M = 7.71$ µV, $SE = .79$) region were larger than amplitudes in the frontal ($M = 4.87$ µV, $SE = .63$, *CI* [1.85 – 3.82]) region. No other main or interaction effects were found. Effect sizes of sex for the site of maximal amplitude (Cz) suggest only a small effect of sex: $M =$

8.66 μV, *SE* = 1.57 [males] vs. *M* = 10.19 μV, *SE* = 1.30 [females]; *g* = .23, *CI* [-2.79 – 5.87].

3.6.2.3 Latency

There was no main effect of biological sex found suggesting no difference between groups on P100 or P300 latency for the Go stimuli while controlling for weekly cannabis use (*p* = .27, *p* = .71, respectively). Effect sizes for sex on the latency of each were calculated and suggest only inconsequential to small magnitude differences between males and females on the latency of P100 (*g* = .38) and P300 (*g* = .15).

There was no main effect of sex on latency measures for the NoGo P100 or P300 (*p* = .43, *p* = .38, respectively). Effect sizes suggest an inconsequential difference between males and females for the P100 (*g* = .004); however, the effect size for the P300 latency suggests a medium effect such that females (*M* = 393.45 ms, *SE* = 14.06) have shorter latencies than males (*M* = 425.45 ms, *SE* = 16.95, *g* = .53; *CI* [-78.88 – 14.87]).

3.6.2.4 Behavioural

The data was divided by sex and behavioural measures were assessed for group differences. No sex differences were found on any of the behavioural measures of interest.

3.6.2.5 Summary

We found main effects of region were shown for all ERPs of interest such that there were larger amplitudes in the occipital (vs. parietal region) for the P100 Go and NoGo stimuli. Additionally, the Go P300 had a main effect of region with largest amplitudes in the parietal (vs. occipital) region while NoGo P300 showed maximal

amplitudes at central sites (vs. frontal). Overall, our findings suggest no differences between males and females Go/NoGo measures of P300 or NoGo P100 processing.

Chapter 4: Discussion

4.1 Primary outcomes

4.1.1 Amplitude and Latency

The goal of the study was measuring the separate and combined effects of cannabis use and biological sex on inhibitory functioning and sensory gating as measured by the MLAER (i.e., P50, N100, P200) and VEP (i.e., P100, P300) components. Based on prior research we anticipated that cannabis users would have reductions in amplitude to all components and that females would present with larger P300 amplitudes than males. No sex-specific hypotheses were generated for the MLAER and P100 – VEP components due to the novelty of this area. This study originally intended on measuring the interactive effect of biological sex and cannabis use; however, due to unforeseen circumstances (i.e., pandemic-related interruption), the sample size to accurately measure this question was not obtained. [Please see appendix D for a description of the limitations of this study due to the COVID-19 pandemic].

A stimulus main effect, consistent with prior literature for the P50 (Turetsky et al., 2007), was found suggesting reductions in S_2 amplitudes (vs. S_1). Contrary to our first hypothesis, we found that there were no difference between CUs and NUs on P50, N100 and P200 amplitudes. In addition to this, we found no significant differences between the three MLAER components between sexes suggesting no difference between males and females for P50 or N100 in our study.

The lack of P50-indexed differences between CUs and NUs on measures of sensory gating deviates from prior work done on cannabis users (Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve 2000; Rentzsch et al., 2007); however, it is in line

with recent work found by our lab (Francis et al., 2021). The difference between past work (Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve 2000; Rentzsch et al., 2007) may come down to the amount of cannabis consumed by our sample. While these prior studies report on average 9 years of heavy consistent cannabis use (beginning around age 15 and daily or more (upwards of 23 joints per week; Patrick & Struve, 2000), our sample had only been using cannabis consistently for roughly 3 years, with most using only 4 times a week. These discrepancies in our findings may, therefore, be more representative of a moderate using group with a relatively recent onset of use as opposed to a group of chronic and heavy cannabis users. This interpretation is supported by the finding that when cannabis-using participants were stratified into long and short-term users, sensory gating deficits were only reported only in long-term users but not short-term users (Broyd et al., 2013). Furthermore, it has been shown that cognitive changes are only present with high levels of circulating THC (Hunault et al., 2009) which often can be reversed with periods of abstinence (Rabin et al., 2017; Schuster et al., 2018). While our sample was not abstinent for longer than 24 hours, it is possible that with their lower overall cannabis use (relative to prior samples), their cognitive functioning was not impacted as is seen with heavy users. These findings are consistent with recent reviews looking at longitudinal data and neuropsychological outcomes in cannabis users, where it was found that only heavy consistent cannabis users presented with neurological deficits (Gonzalez et al., 2017; Power et al., 2020).

This literature helps quantify and understand our lack of significant findings within the Go/NoGo paradigm as well. Consistent with prior research (Salisbury et al., 2004) we found main effects of amplitude for both Go and NoGo stimuli such that the

intended site of maximal amplitude (i.e., P300 (Go: Pz, NoGo: Cz); P100 (Go and NoGo: Oz)) had significantly larger amplitudes compared to all other sites measured for each stimuli (i.e., Go and NoGo). No main effects of cannabis group were found. Several other studies (Ilan et al., 2005; Theunissen et al., 2012) have reported deficits in Go and NoGo processing with acute use in heavy and occasional cannabis users. In addition, deficits have been shown in those with chronic use and a diagnosis of CUD (Maij et al., 2017) however, our study found no evidence of between group differences. Consistent across these studies, however, is the fact that cannabis use was higher in years of use and joints per week/month than our CU condition where users were using approximately 4-5 times per week. This suggests that differences between our sample and past findings on Go/NoGo performance may be reflective of our more consistent moderate using sample. Behavioural measures on the Go/NoGo paradigm further support that there are no differences between groups on behavioural measures as well. Effect sizes suggest CUs may have enhanced P100 amplitudes. Given that no between-group differences were observed on behavioural measures, this enhancement in primary visual cortex activity may reflect the need for CUs to direct more cognitive resources towards the processing of the visual stimuli when compared to controls to achieve equivalent performance. While measured through different experimental designs, previous work (Hatchard et al., 2020; Nusbaum et al., 2017) has suggested that cannabis users have functional connectivity differences (e.g., CUs [vs. NUs] had decreased connectivity between the left superior temporal gyrus and the anterior cingulate cortex, and left orbitofrontal gyrus) even when behavioural measures show no group differences. Nusbaum et al. (2017) found that while their cannabis-using participants behaviourally performed at the same level as controls,

their cannabis users did not rely as heavily on typical processing modalities (top-down) suggesting additional neural networks are recruited to perform everyday tasks at the same level as non-users. Hatchard et al. (2020) found evidence of this through the use of functional magnetic resonance imaging where they found cannabis users relied on unconventional neural networks in addition to heightened processing in typically used networks to complete an attention task at the same level as controls. While we do not have imaging data to support the recruitment of additional brain networks or overactivation of standard networks, these findings do help explain what may be leading to enhanced amplitudes but equal behavioural performance in our cannabis users (vs controls).

Another possible explanation for the lack of behavioural differences and the enhanced P100 and P300 – Go amplitudes may come from the potential relationship between alcohol and these modalities. Prior work has shown that when measuring inhibitory functioning through the Go/NoGo paradigm in alcohol dependent users, these users behaviourally perform at the same level as controls, however, do not rely on conventional neural networks to process the stimuli (Czapla et al., 2017; Stein et al., 2020). Our CU group was also the group with the heaviest alcohol consumption and while their alcohol consumption was not deemed risky (as measured by the AUDIT) they did reach the intervention level on the ASSIST, suggesting they had significantly higher alcohol intake than our controls did. In addition to this our correlational findings suggest a relationship with alcohol use is present in our sample. Thus, the enhanced amplitudes found in our CUs could be due to the impact of alcohol instead of the impact of cannabis. It is also possible that where our CU participants are polydrug users, there is an

interaction between cannabis use and alcohol use that is then influencing our findings. Without being able to parse apart this relationship and control for alcohol use we are unable to fully explore this potential interaction.

To date, only one other study has measured P100 in cannabis users. This study found enhanced P100 amplitudes when THC was given to heavy users but reduced P100 when THC was given to occasional users (Theunissen et al., 2012). It is hard to compare the findings from this study to ours as we did not administer THC at the time of testing, and in fact, we had users abstain from use prior to testing. In addition, Theunnissen et al. (2012) found that the enhanced P100 amplitudes in heavy users were not statistically different from the placebo control suggesting no differences between their groups similar to our conclusions regarding lack of group differences on P100 in the context of the Go/NoGo paradigm. To our knowledge, ours is the first study to examine the P100 VEP in cannabis users using the Go/NoGo paradigm.

While the P50 and NoGo P300 inform our understanding of inhibitory network function, there are other components that have been shown to index sensory gating through other neural networks. While no differences were present in the P50 gating, there were medium-to-large effect sizes shown for between-cannabis group differences on N100 gating ratio and difference scores, suggesting CUs may be impaired on these measures of sensory gating. These findings are in line with a previous report by our lab Francis et al. (2021) that suggests this may be a characteristic of cognitive deficits caused by moderate cannabis use. This suggests that sustained moderate cannabis use may have a greater impact on the later attention triggering aspects of the stimulus filtering process as opposed to impacting the earlier sensory inhibition process (P50) as is seen in chronic

users (Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve 2000; Rentzsch et al., 2007).

Interestingly, no sex-based findings for sensory gating measures were observed, suggesting males and females in our sample did not differ on MLAER components. This is partially in line with what was found by Fuerst, Gallinat, and Boutros (2007) suggesting that sex had no impact on S2 components or gating ratios and that males had higher amplitudes for all components elicited by S1 and better (larger) difference scores. Our small effect sizes support the lack of statistical differences observed on these measures between males and females; however, given the limitations of our sample size, additional sex-based analyses would need to be completed in larger samples to fully understand the depth of this relationship and to better understand the discrepancies between our study and that of Fuerst et al. (2007).

While the P200 MLAER component showed no impact of sex, there was some indication (medium effect size) that CUs may have reduced amplitudes to the S_1 compared to NUs. This implies that CUs may have difficulty gating-in stimuli suggesting they may have difficulty inhibiting a response to S_1. These results as well as our findings surrounding the deficits in P200 amplitude are consistent with findings in those with schizophrenia, that suggests those with schizophrenia have difficulty with the later stages of sensory processing (N100, P200) which has been speculated to be a problem with the central nervous system's ability to process and act on relevant information (gating-in; Boutros et al., 2004). It is therefore possible that CUs have similar sensory gating deficits that may be arising from the same pathways. While the effect size analysis suggested differences, our null statistical findings and confidence intervals suggest these findings

need to be interpreted with caution. Further exploration of these findings is necessary to properly understand if any differences are present.

Our sex-based findings need to be interpreted with caution as we had significant sex imbalances in our CU and NU conditions, thus this imbalance may be skewing the findings. No other study has done a sex-based analysis with these ERPs of interest and thus we have very little to compare our findings to. A recent systematic review (Melynyte et al., 2018) suggests sex-based hormones are important to consider within P300 research, as hormone levels may mask any true sex-effects present between groups. While Melynyte et al. (2018) focused on the auditory P300 and we focused on the visual P300, if circulating hormone levels are influencing the auditory P300 it is possible they are also influencing the visual component. It is also possible that these circulating hormone levels are influencing the earlier components. For our study every attempt was made to ensure we had equal numbers of females in both their menstrual phase and mid-luteal phase to ensure any potential impact of hormones would be cancelled out, however, it is possible that there were natural fluctuations within our participants and within our male participants that we did not account for and that may be influencing our findings. Without a full saliva analysis of the hormone levels circulating in our participants at the time of testing we are unable to explore this possible interaction further.

Latency findings suggest that CUs and NUs were faster at responding to the S_1 than S_2 in both the N100 and P200 conditions; additionally, there was a marginal interaction where cannabis users had quicker P200 S_1 latencies when compared to NUs. Given that CUs had reduced P200 amplitudes it is not surprising that they were faster to reach peak amplitudes when compared to NUs, which may suggest a potential speed-

accuracy trade-off. Prior work has suggested that speed is usually prioritized over accuracy (Van Veen, Krug, and Carter, 2008), therefore, it may suggest that CUs are more focussed on responding to the stimuli instead of fully processing it. This finding may suggest that the later neural networks (N100, P200) are impacted by regular cannabis use even when it begins later in life while the earlier pre-processing networks (P50) may be fully developed and therefore spared, with later initiation of cannabis use. Our NoGo findings help support the speed-accuracy trade-off hypothesis such that latency negatively correlated with false alarms and misses made, suggesting that quicker responses led to more false alarms and missed targets (i.e., worse accuracy). Follow-up correlations showed that our cannabis users appeared to be more heavily impacted by this speed-accuracy trade-off in terms of false alarms, suggesting once again that they may be prioritizing fast responses at the cost of fully processing (accuracy).

In addition to the moderate use shown in our sample relative to other cannabis studies, our sample also showed a later average age of initiation of steady consistent cannabis use compared to samples in other studies (Broyd et al., 2013; Rentzsch et al., 2007, 2017). Based on brain development trajectories, our sample may be avoiding damage to neural networks during a critical developmental window by commencing cannabis use later in life. Longitudinal data has shown that subcortical structures and grey matter mature and change at different rates across adolescence depending on sex (Herting et al., 2019; Lenroot et al., 2007). These developmental processes have been documented to take place between the ages of 8-22, suggesting significant overlap with the typical onset of cannabis use described in the other studies at around 14 years of age (Broyd et al., 2013; Rentzsch et al., 2007, 2017). This, therefore, suggests that our sample should

have more developed neurological pathways by the time their cannabis use began, therefore decreasing the neurotoxic effect cannabis may have on users. This study provides evidence for how neurological functioning may be spared with later onset and moderate use of cannabis.

Our correlational findings suggest that the later MLAER components (N100, P200) may be heavily impacted by alcohol use suggesting the more our participants consumed alcohol, the more impacted their MLAER amplitudes would be. Alcohol use was also found to correlate with false alarms on the Go/NoGo paradigm suggesting consuming more alcohol was associated with better behavioural performance (fewer false alarms). Prior research (Sklar & Nixon, 2014) has shown that sensory gating, specifically the N100 is impacted by moderate alcohol use. Given our sample ranked close to the intervention level (i.e., CU ranked 6.9, intervention level is 7) for alcohol use, the deficits in later sensory processing (i.e., N100, P200) may be related to alcohol use as opposed to cannabis use. In addition to this, motivations for cannabis use appear to impact the MLAER amplitudes, such that increased use for coping reasons was related to P50 amplitude reductions, while increased use for social and coping reasons were negatively correlated with N100 amplitudes (making N100 more negative). DN100 and N100 latency were also found to correlate with the ReSUS coping subscale such that as use for coping reasons increased difference scores decreased and latency increased for the N100. This supports our findings as our sample primarily reported use for social reasons, and showed shorter N100 latencies, suggesting that use for coping but not social use would impact latency. While this helps clarify our N100 latency finding, it is contrary to our findings for the dN100, whereby CUs showed smaller difference scores when using for

coping reasons. This may suggest that reasons for use do not heavily impact dN100 or that our sample is too underpowered to examine an impact.

4.2 Study strengths

There are some strengths to the current study that should be noted. First, our study is the first study to examine the P100 VEP in otherwise healthy cannabis users in the absence of acute administration of cannabis. This alone aids in furthering our understanding of how the primary visual cortex is impacted by moderate cannabis use. Second, our study adds to the very limited knowledge surrounding the N100/P200 complex in cannabis users with only one previously published study to date in this area. Finally, we were able to replicate sensory gating effects on the paired click paradigm even when including female participants and showed stimulus by cannabis group interactions on the P200 (amplitude and latency) that were not attributed to sex.

4.3 Study Limitations

While we do believe this study adds to our current understanding of the literature surrounding MLAER and VEP components in males and females and cannabis users and non-users, the study has several important limitations reducing the confidence in our findings. First, our sample size was reduced compared to what was needed according to our *a priori* power analysis, therefore leaving the study potentially underpowered to find statistical differences. In addition, with the significant unequal sex distributions across cannabis use conditions, we did not have large enough sample sizes to conduct the full omnibus cannabis use by biological sex factorial analysis we had originally intended. Finally, we were unable to run an analysis with THC content of our participant’s preferred strain of cannabis due to inconsistent reporting by our participants.

Unfortunately, the THC:CBD content was not accurately disclosed by more than half of our sample, therefore, rendering this variable unusable.

4.4 Future Directions

Due to the explained interruptions due to the COVID-19 pandemic, this study will continue to collect data to be able to perform the sex by cannabis group analysis that was originally proposed. Future work should also focus on examining the neurological correlates behind the P100 in the NoGo paradigm and why males showed marginally enhanced amplitudes relative to females. This work provided insight into how males and females may (or may not) differ on measures of inhibitory functioning as indexed through ERPs; however, continued work to investigate this is needed to fully address the question of whether biological sex impacts inhibitory functioning. Finally, more work should be done to examine how these markers of inhibition may differ based on what age cannabis users initiate heavy consistent cannabis use. The focus of the literature right now is on understanding early use as this typically intersects with brain development; however, it is also important to know how the brain may or may not be implicated if users wait until emerging adulthood to use cannabis regularly. This would be beneficial for cannabis campaigns aimed at younger populations to show that later use may not cause as many detrimental neurological deficits that early consistent use can.

4.5 Conclusions and Implications

While this study was not able to be completed as intended and largely indicated that our ERP and behavioral results did not differ based on biological sex or cannabis use, we were able to replicate main effects of stimulus type (i.e., suppression of S2 across for the P50) and regional differences (VEP) while showing no differences between groups

(CU vs. NU and Male vs. Female). Effect sizes and power analyses suggest we were underpowered to detect such effects if they did exist. Our effect sizes suggest more work needs to be done to better understand how users and non-users differ on early sensory gating and the later attention filtering and allocation mechanisms. Our sample began consistent use later than the samples in many other studies that have reported early preattentional deficits on sensory gating (Edwards et al., 2009; Patrick et al., 1999; Patrick and Struve 2000; Rentzsch et al., 2007) suggesting the moderate and later age of initiation relative to other samples may be driving these findings. Finally, our study suggests there is no difference between males and females on measures of sensory gating or behavioural inhibition. This differs from the literature which suggests females perform worse on measures of behavioural inhibition (Melynyte et al., 2017; Sowell et al., 2007). Ultimately this study provides some evidence that cannabis users who begin moderate use later in life differ from those with earlier more consistent heavy use on neural markers of inhibition and sensory gating. This thesis also further highlights the need for the inclusion of males and females in all sensory gating and behavioural inhibition research, as inconsistencies within the findings are not able to be properly interpreted due to lack of prior research including female participants. Overall, this study suggests that those who begin moderate cannabis use later in life have largely intact early sensory gating pathways while the later processing (N100 and P200) pathways may be impacted.

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Table 1.

Participant Demographic Information by Cannabis Use Group

		Cannabis users (CUs; n = 14) M (± SD)	Non-users (NUs; n = 16) M (± SD)	Signifiance
Sex M(F)				
	Male	9	4	
	Female	5	12	
Age (yrs)		21.64 (2.21)	23.87 (4.03)	$p = .07$
Education (yrs)		14.29 (1.98)	14.87 (2.75)	$p = .50$
Weekly Alcohol Consumption		2.48 (3.67)	1.30 (2.21)	$p = .30$
AUDIT[a]		6.92 (4.78)	2.31 (2.02)	$p = .004$
WHO ASSIST[b]				
	Tobacco	6.00 (6.61)	.31 (.87)	$p = .002$
	Alcohol	12.14 (8.26)	6.31 (4.06)	$p = .02$
	Cannabis	17.71 (8.98)	0.75 (1.34)	$p < .001$
	Cocaine	3.64 (6.03)	0.19 (0.75)	$p = .03$
	Amphetamines	1.21 (2.32)	0.00 (---)	-
	Inhalants	0.00 (---)	0.00 (---)	-
	Sedatives	2.64 (6.66)	0.00 (---)	-
	Hallucinogens	3.14 (4.19)	0.00 (---)	-
	Opioids	1.86 (5.33)	0.00 (---)	-
	Other drugs	.64 (2.40)	0.00 (---)	-

ReSUS[c]			
	Coping with distressing emotions and symptoms subscale	1.03 (.94)	-
	Individual enhancement	1.64 (.93)	-
	Social enhancement and intoxication	.64 (.79)	-
Years of Cannabis use		3.77 (3.03)	-
Weekly Cannabis Consumption		4.70 (2.71)	-

Note. Means and standard deviations provided for cannabis users and non-users. AUDIT - alcohol use disorders identification test; WHO ASSIST – World Health Organization, Alcohol Smoking and Substance Involvement Screening Test; ReSUS – Reasons for Substance Use Scale.

Weekly alcohol consumption measured as number of standard drinks per day. Weekly cannabis consumption measured as number of time cannabis is consumed per week. Years of cannabis use was generated based on when the user began regular consistent use.

[a] = Scores rang 0-20+ and indicate risky drinking behaviour, scores 0-7 = low risk, 8-15 = risky or hazardous, 16-19 = High risk, 20 + High risk, almost certainly dependent.

[b] = scores 0-3 suggest no intervention is needed while scores 4-26 suggest brief intervention and score 27+ suggest more intensive treatment is needed.

[c] = Average scores generated for each subscale with higher totals indicating more motivation to use for these reasons.

[d] = scores range from 5 – 15 with lower scores indicate more paranoid and suspicious feelings.

Table 2.

Frequency Rating for Cannabis Users on The Reasons for Substance Use Scale (ReSUS)

Reason for use		n (%)
Coping with Distressing Emotions and Symptoms Subscale		
When I am experiencing unpleasant thoughts		
	Never	3 (21.4)
	Sometimes	5 (35.7)
	Often	2 (14.3)
	Almost Always	4 (23.6)
When I feel ashamed or bad about myself		
	Never	4 (28.6)
	Sometimes	7 (50)
	Often	1 (7.1)
	Almost Always	2 (14.3)
When I am thinking about bad things that have happened in the past		
	Never	6 (42.9)
	Sometimes	6 (42.9)
	Often	1 (7.1)
	Almost Always	1 (7.1)
When my thoughts are racing		
	Never	6 (42.9)
	Sometimes	3 (21.4)
	Often	3 (21.4)
	Almost Always	2 (14.3)
When I want to escape from my problems and worries		
	Never	3 (21.4)
	Sometimes	3 (21.4)
	Often	5 (35.7)
	Almost Always	3 (21.4)
When I feel suspicious or paranoid		
	Never	11 (78.6)
	Sometimes	2 (14.4)
	Often	1 (7.1)
	Almost Always	0
When I am feeling depressed		
	Never	3 (21.4)
	Sometimes	3 (21.4)
	Often	5 (35.7)
	Almost Always	3 (21.4)
When I am angry at the way things have turned out		
	Never	5 (35.7)

	Sometimes	4 (28.6)
	Often	2 (14.3)
	Almost Always	3 (21.4)
When I feel anxious or tense		
	Never	4 (28.6)
	Sometimes	5 (35.7)
	Often	2 (14.3)
	Almost Always	3 (21.4)
When I start to feel guilty about something		
	Never	7 (50)
	Sometimes	5 (35.7)
	Often	2 (14.3)
	Almost Always	-
When I am feeling stressed		
	Never	1 (7.1)
	Sometimes	2 (14.3)
	Often	7 (50)
	Almost Always	4 (28.6)
When I am having trouble sleeping		
	Never	3 (21.4)
	Sometimes	4 (28.6)
	Often	3 (21.4)
	Almost Always	4 (28.6)
When I feel I have been discriminated against		
	Never	9 (64.3)
	Sometimes	4 (28.6)
	Often	1 (7.1)
	Almost Always	-
When I am hearing sounds or voices that other people can't hear		
	Never	13 (92)
	Sometimes	1 (7.1)
	Often -	
	Almost Always	-
When I am having trouble thinking or concentrating		
	Never	7 (50)
	Sometimes	5 (35.7)
	Often	2 (14.3)
	Almost Always	
When I am having trouble communicating with others		
	Never	11 (78.6)
	Sometimes	1 (7.1)
	Often	1 (7.1)
	Almost Always	1 (7.1)

When I am in pain physically		
	Never	6 (42.9)
	Sometimes	3 (21.4)
	Often	1 (7.1)
	Almost Always	4 (28.6)
When I am feeling lonely		
	Never	4 (28.6)
	Sometimes	4 (28.6)
	Often	4 (28.6)
	Almost Always	1 (7.1)
Social Enhancement & Intoxication subscale		
When I am feeling happy and content with my life		
	Never	1 (7.1)
	Sometimes	3 (21.4)
	Often	7 (50)
	Almost Always	2 (14.3)
When I want to feel good, have a laugh or be happier		
	Never	1 (7.1)
	Sometimes	1 (7.1)
	Often	4 (28.6)
	Almost Always	7 (50)
When I am with friends and we want to have a good time		
	Never	2 (14.3)
	Sometimes	-
	Often	3 (21.4)
	Almost Always	7 (50)
When I want to chill out or relax		
	Never	-
	Sometimes	1 (7.1)
	Often	4 (28.6)
	Almost Always	8 (57.1)
When I think about how good it tastes		
	Never	7 (50)
	Sometimes	1 (7.1)
	Often	1 (7.1)
	Almost Always	4 (28.6)
When I feel excited about something		
	Never	3 (21.4)
	Sometimes	5 (35.7)
	Often	3 (21.4)
	Almost Always	3 (21.4)
When I want to fit in with other people		
	Never	7 (50)

	Sometimes	4 (28.6)
	Often	3 (21.4)
	Almost Always	-
When I want to feel drunk, stoned, or high		
	Never	-
	Sometimes	1 (7.1)
	Often	7 (50)
	Almost Always	6 (42.9)
When I feel under pressure from other to use drugs/drink alcohol		
	Never	9 (64.3)
	Sometimes	3 (21.4)
	Often	1 (7.1)
	Almost Always	1 (7.1)
When I have been drinking and think about using drugs (or vice versa)		
	Never	4 (28.6)
	Sometimes	5 (35.7)
	Often	4 (28.6)
	Almost Always	1 (7.1)
When I'm bored and want something to do to pass the time		
	Never	-
	Sometimes	6 (42.9)
	Often	5 (35.7)
	Almost Always	3 (21.4)
Individual Enhancement Subscale		
When I want to feel more self-aware		
	Never	8 (57.1)
	Sometimes	2 (14.3)
	Often	3 (21.4)
	Almost Always	1 (7.1)
When I need motivation to do things		
	Never	7 (50)
	Sometimes	5 (35.7)
	Often	1 (7.1)
	Almost Always	1 (7.1)
When I want to stay awake or be more alert		
	Never	12 (85.7)
	Sometimes	2 (14.3)
	Often	-
	Almost Always	-
When I want to feel more creative		
	Never	3 (21.4)
	Sometimes	6 (42.9)
	Often	4 (28.6)

	Almost Always	1 (7.1)
When I want to feel more emotions		
	Never	4 (28.6)
	Sometimes	6 (42.9)
	Often	3 (21.4)
	Almost Always	1 (7.1)
When I want to feel sexy		
	Never	10 (71.4)
	Sometimes	3 (21.4)
	Often	1 (7.1)
	Almost Always	-
When I am experiencing medication side effects		
	Never	12 (85.7)
	Sometimes	1 (7.1)
	Often	1 (7.1)
	Almost Always	-
When I want to feel normal		
	Never	9 (64.3)
	Sometimes	3 (21.4)
	Often	-
	Almost Always	2 (14.3)
When I want to feel more confident		
	Never	6 (42.9)
	Sometimes	7 (50)
	Often	1 (7.1)
	Almost Always	-

Table 3.

Mean Amplitude and Latency for the paired click paradigm

		Paired Click Paradigm	
		CU (± SD)	NU (± SD)
P50 (Cz)			
	S1	1.75 µV[a] (1.14)	1.54µV[a] (1.20)
	S2	0.55 µV[a] (.59)	0.64 µV[a] (.76)
	RP50	0.32 µV (.36)	0.72 µV (1.37)
	DP50	1.20 µV (1.38)	0.90 µV (1.07)
	Latency S1	108.86 ms (7.47)	105.88 ms (5.44)
	Latency S2	108.00 ms (8.01)	104.63 ms (4.11)
N100 (Cz)			
	S1	-1.86 µV (2.28)	-2.80 µV (3.31)
	S2	-2.60 µV (2.40)	-1.78 µV (1.84)
	RN100	1.20 µV (1.83)	.36 µV (.82)
	DN100	.74 µV (2.98)	-1.01 µV (2.63)
	Latency S1	112.43 ms[a] (28.07)	129.75 ms[a] (33.47)
	Latency S2	177.57 ms[a] (27.65)	181.88 ms[a] (19.66)
P200 (Cz)			
	S1	0.01 µV[b] (3.32)	2.93 µV[b] (3.45)
	S2	1.25 µV (2.87)	1.19 µV (2.23)
	RP200	.71 µV (2.25)	-.70 µV (2.56)
	DP200	-1.24 µV (3.62)	2.71 µV (5.34)
	Latency S1	142.14 ms[b] (50.44)	190.38 ms[b] (57.38)
	Latency S2	227.71 ms (45.36)	234.75 ms (32.36)

Note. µV = Microvolts ; ms = milliseconds

[a]= Stimulus Main Effect $p < .05$

[b]= Group Main Effect $p < .05$

Table 4.

Main and interaction effects of the paired click paradigm CU vs NU

		df	F statistic	Significance (*p* – value)	Hedges' g
				Amplitude	
P50					
	Stimulus	1,28	22.23	*p* < .001	g = 1.09
	Group	1,28	.05	*p* = .82	g = .05
	Stimulus*Group	1,28	.45	Overall: *p* = .51	S_1: g =.18
				S1: *p* = .62	S_2: g =.12
				S2: *p* = .73	
N100					
	Stimulus	1,28	.074	*p* = .79	g = .079
	Group	1,28	.007	*p* = .94	g = .02
	Stimulus*Group	1,28	2.92	Overall: *p* = .098	S_1: g =.30
				S1: *p* = .38	S_2: g =.38
				S2: *p* = .30	
P200					
	Stimulus	1,28	.118	*p* = .73	g = .011
	Group	1,28	3.04	*p* = .09	g = .48
	Stimulus*Group	1,28	4.14	Overall: *p* = .05	S_1: g = .86
				S1: *p* = .02	S_2: g = .02
				S2: *p* = .95	
				Latency	
P50					
	Latency	1,28	1.88	*p* = .18	g = .16
	Group	1,28	1.93	*p* = .18	g = .47
	Latency*Group	1,28	.065	Overall: *p* = .80	S_1: g = .46
				S1: *p* = .22	S_2: g = .50
				S2: *p* = .18	
N100					
	Latency	1,28	91.09	*p* < .001	g = 2.09
	Group	1,28	1.81	*p* = .19	g = .40
	Latency*Group	1,28	1.12	Overall: *p* = .30	S_1: g =.55
				S1: *p* = .14	S_2: g =.18
				S2: *p* = .62	
P200					
	Latency	1,28	39.56	*p* < .001	g = .01
	Group	1,28	3.96	*p* = .06	g = .60
	Latency*Group	1,28	3.98	Overall: *p* = .06	S_1: g =.61
				S1: *p* = .02	S_2: g =.17
				S2: *p* = .63	

Note. F-statistic and p-values are based on the Greenhouse-Geiser correction to account for sphericity violations in our data.

Table 5.

Main effects of ratio and difference scores across the Paired Click Paradigm

		df	F statistic	Significance (*p* – value)	Hedges' g
P50					
	rP50	1,28	1.14	*p* = .30	g = .40
	dP50	1,28	.45	*p* = .51	g = .24
N100					
	rN100	1,28	2.70	*p* = .11	g = .80
	dN100	1,28	2.92	*p* = .098	g = .63

Note. F-statistic and p-values are based on the Greenhouse-Geiser correction to account for sphericity violations in our data.

Table 6.

Main and interaction effects of the paired click paradigm Male vs Female covarying for weekly cannabis use

		df	F statistic	Significance (p – value)	Hedges' g
				Amplitude	
P50					
	Stimulus	1,27	7.00	p = .01	g = 1.11
	Sex	1,27	.66	p = .42	g = .22
	Stimulus*Sex	1,27	2.67	Overall p = .13 S1: p = .08 S2: p = .46	S_1: g =.41 S_2: g =.10
N100					
	Stimulus	1,27	1.12	p = .29	g = .079
	Sex	1,27	.22	p = .64	g = .14
	Stimulus*Sex	1,27	.399	Overall: p = .29 S1: p = .92 S2: p = .22	S_1: g =.10 S_2: g =.20
P200					
	Stimulus	1,27	1.48	p = .23	g = .11
	Sex	1,27	.05	p = .83	g = .023
	Stimulus*Sex	1,27	1.39	Overall: p = .25 S1: p = .49 S2: p = .24	S_1: g = .17 S_2: g = .19
				Latency	
P50					
	Stimulus	1,27	3.25	p = .082	g = .16
	Sex	1,27	.20	p = .66	g = .09
	Stimulus*Sex	1,27	.006	Overall: p = .94 S1: p = .99 S2: p = .97	S_1: g = .04 S_2: g = .14
N100					
	Stimulus	1,27	38.06	p < .001	g = 2.08
	Sex	1,27	1.39	p = .25	g = .28
	Stimulus*Sex	1,27	1.32	Overall: p = .26 S1: p = .36 S2: p = .73	S_1: g =.38 S_2: g =.14
P200					
	Stimulus	1,27	11.11	p = .002	g = 1.28
	Sex	1,27	2.67	p = .11	g = .33
	Stimulus*Sex	1,28	1.71	Overall: p = .20 S1: p = .30 S2: p = .81	S_1: g =.41 S_2: g =.23

Note. F-statistic and p-values are based on the Greenhouse-Geiser correction to account for sphericity violations in our data.

Weekly cannabis use has been added to the model as a covariate.

Table 7.

Main effects of ratio and difference scores across the Paired Click Paradigm Males vs Females

		df	F statistic	Significance (p – value)	Hedges' g
P50					
	rP50	1,27	.54	p = .59	g = .18
	dP50	1,27	1.46	p = .25	g = .45
N100					
	rN100	1,28	1.43	p = .26	g = .47
	dN100	1,28	.68	p = .51	g = .009
P200					
	rP200	1,28	2.07	p = .14	g = .63
	dP200	1,28	2.78	p = .08	g = .47

Note. F-statistic and p-values are based on the Greenhouse-Geiser correction to account for sphericity violations in our data.
Weekly cannabis use has been added to the model as a covariate.

Table 8.

Means and Standard deviations in addition to main effects of the behavioural measures of the Go/NoGo paradigm

	CU M (± SD)	NU M (± SD)	F	Significance (*p* – value)
Percent Correct	97.16 (2.77)	97.81 (1.47)	.64	p = .43
RT Correct response	360.54 ms (53.68)	361.81 (51.07)	.004	p = .95
False Alarm	35.08 (17.90)	35.31 (14.41)	.002	p = .97
RT False Alarm	361.10 ms (63.38)	363.05 (50.94)	.009	p = .93
Miss	12.77 (12.50)	9.88 (6.63)	.64	p = .43
	Male M (± SD)	Female M (± SD)	F	Significance (*p* – value)
Percent Correct	97.17 (2.38)	97.77 (1.98)	.54	p = .47
RT Correct response	376.31 (49.92)	350.60 (51.02)	1.82	p = .19
False Alarm	34.67 (15.67)	35.59 (16.31)	.023	p = .88
RT False Alarm	374.82 (57.84)	353.26 (54.25)	1.05	p = .31
Miss	12.75 (10.75)	10.06 (8.92)	.54	p = .46

Note. ms = Milliseconds, RT = Reaction time
RT for correct responses and false alarms are proportional to the number of correct responses and false alarms per block of the task.
Percent correct represents the correct responses made across all four blocks of the task.

Table 9.

Main and interaction effects of cannabis users versus non-users on the Go/NoGo paradigm

		df	F statistic	Significance (p – value)	Hedges' g
		Amplitude			
P100 (Go)					
	Region	1,27	14.05	p = .001	g = .52
	Region*Group	1,27	1.10	p = .30	g = .50
P300 (Go)					
	Region	1,27	33.08	p < .001	g = .03
	Region*Group	1,27	.28	p = .60	g = .50
P100 (NoGo)					
	Region	1,27	21.14	p < .001	g = .60
	Region*Group	1,27	1.19	p =.28	g = .52
P300 (NoGo)					
	Region	1,27	38.98	p < .001	g = .74
	Region*Group	1,27	.43	p = .52	g = .01
		Latency			
P100 (Go)	Group	1,28	.20	p = .66	g = .16
P300 (Go)	Group	1,28	.44	p = .52	g = .25
P100 (NoGo)	Group	1,28	.007	p = .93	g = .03
P300 (NoGo)	Group	1,28	.60	p = .43	g = .28

Note. F-statistic and p-values are based on the Greenhouse-Geiser correction to account for sphericity violations in our data. Latency was only examined between groups at the site of maximal amplitude.

Figure 1.

P50 Amplitudes for Stimulus 1and Stimulus 2 in cannabis users (a) and non-users (b).

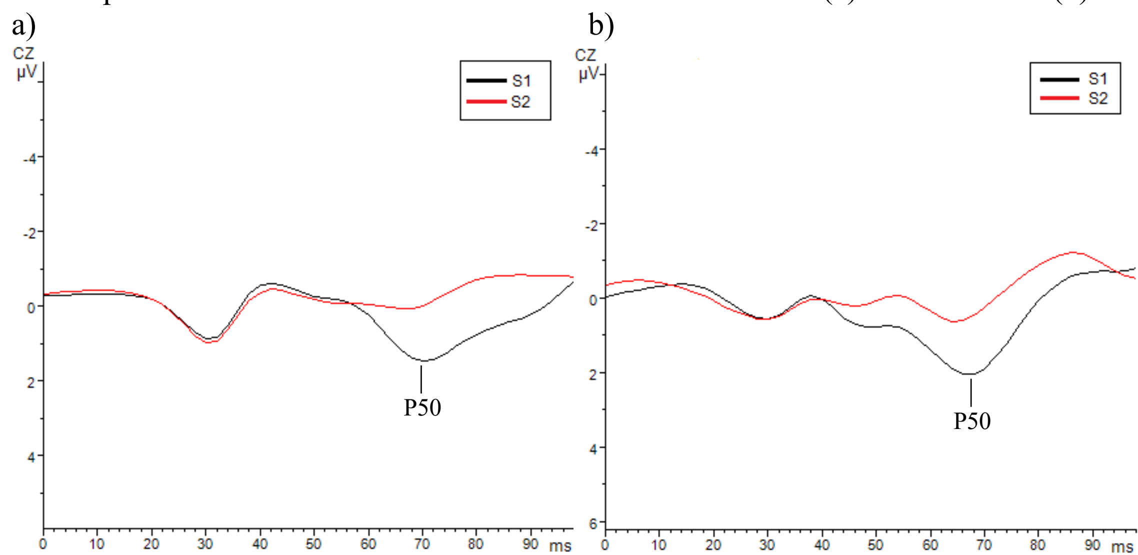
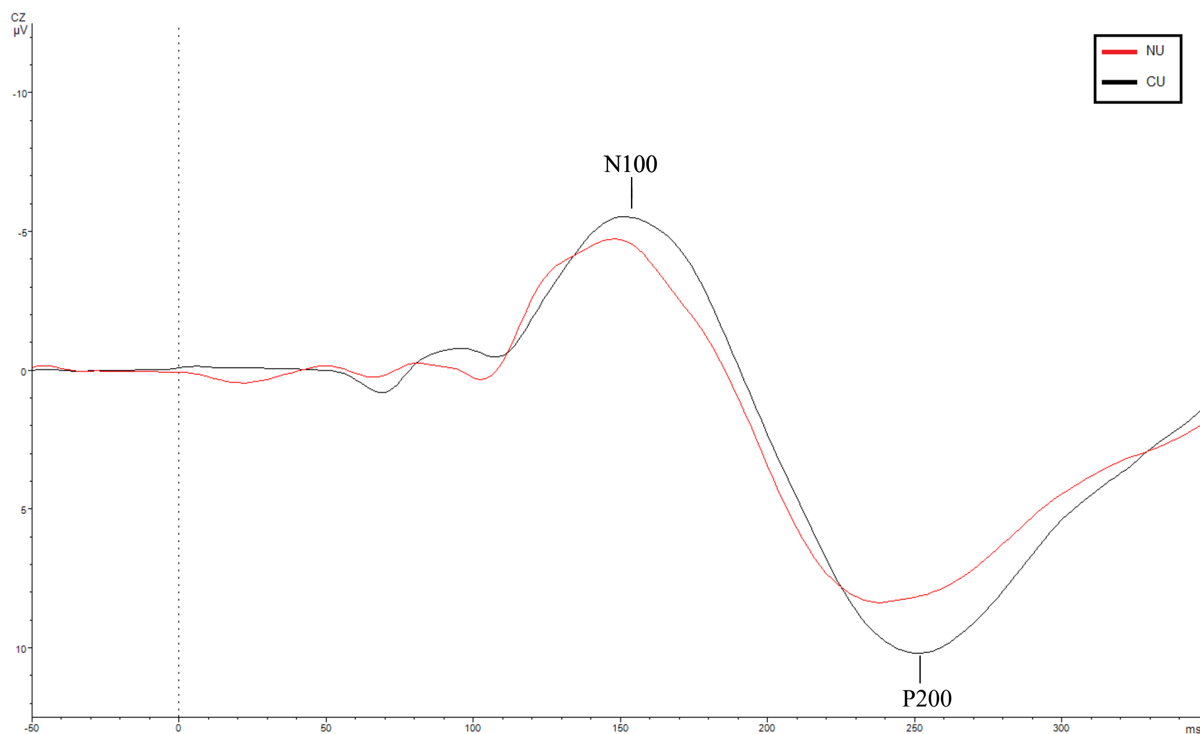


Figure 2.

N100/P200 amplitudes to the Paired Click paradigm (Stimulus 1 (a), and Stimulus 2 (b)) between cannabis users and non-users

a)



b)

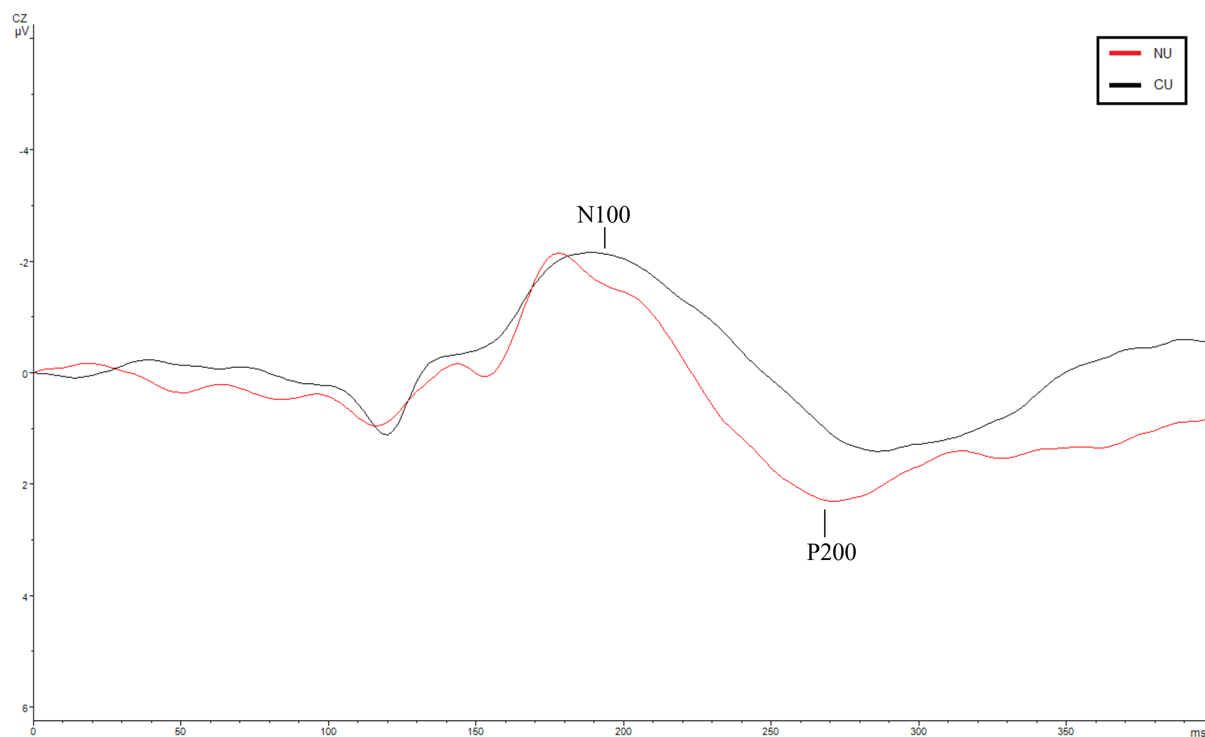


Figure 3.

Difference (dN100) and ratio (rN100) measures of N100-indexed sensory gating in cannabis users and non-users

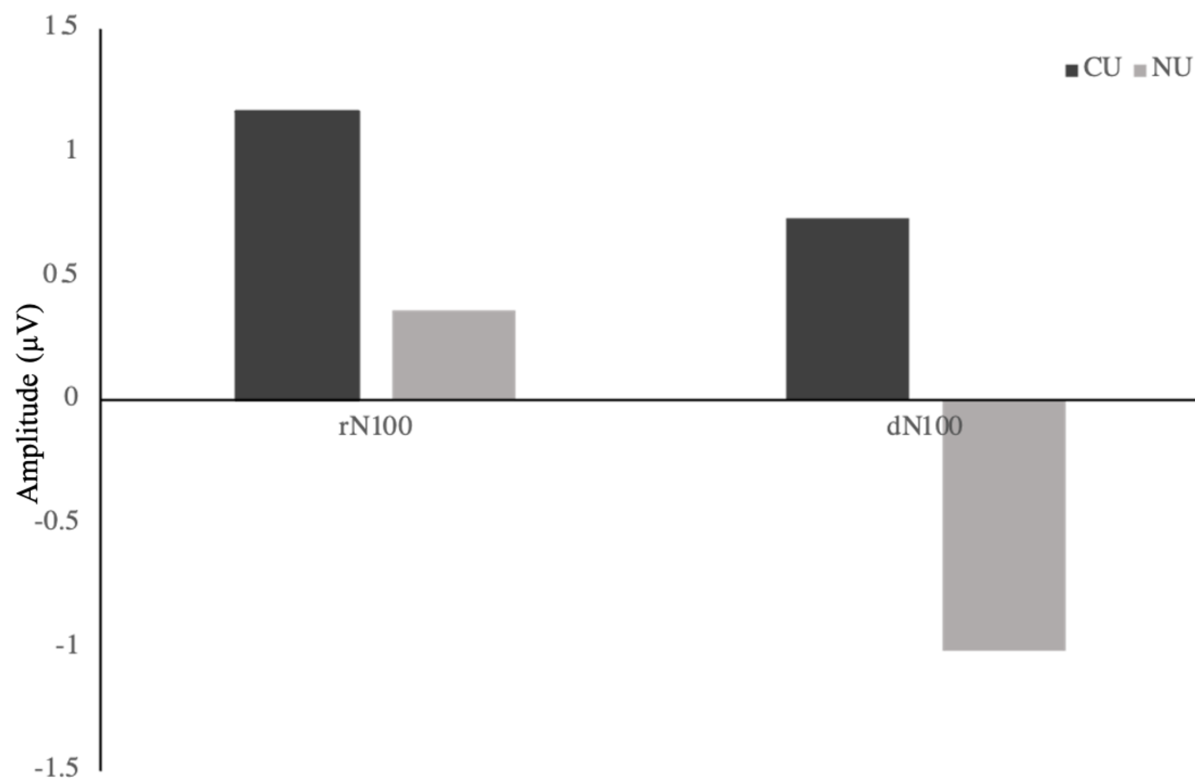


Figure 4.

Interaction between group and stimulus type on P200 amplitude (paired click paradigm)

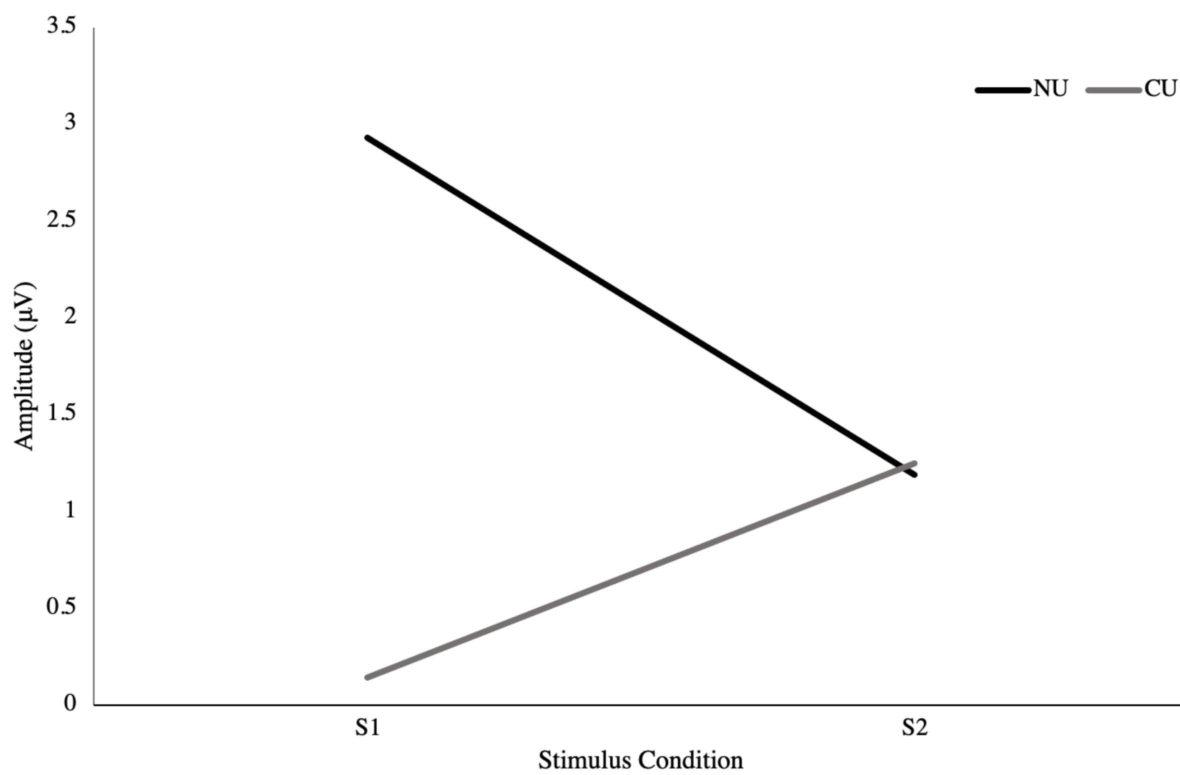


Figure 5.

Main effect of P200 latency showing trend level interactions between stimulus type and group for the paired click paradigm.

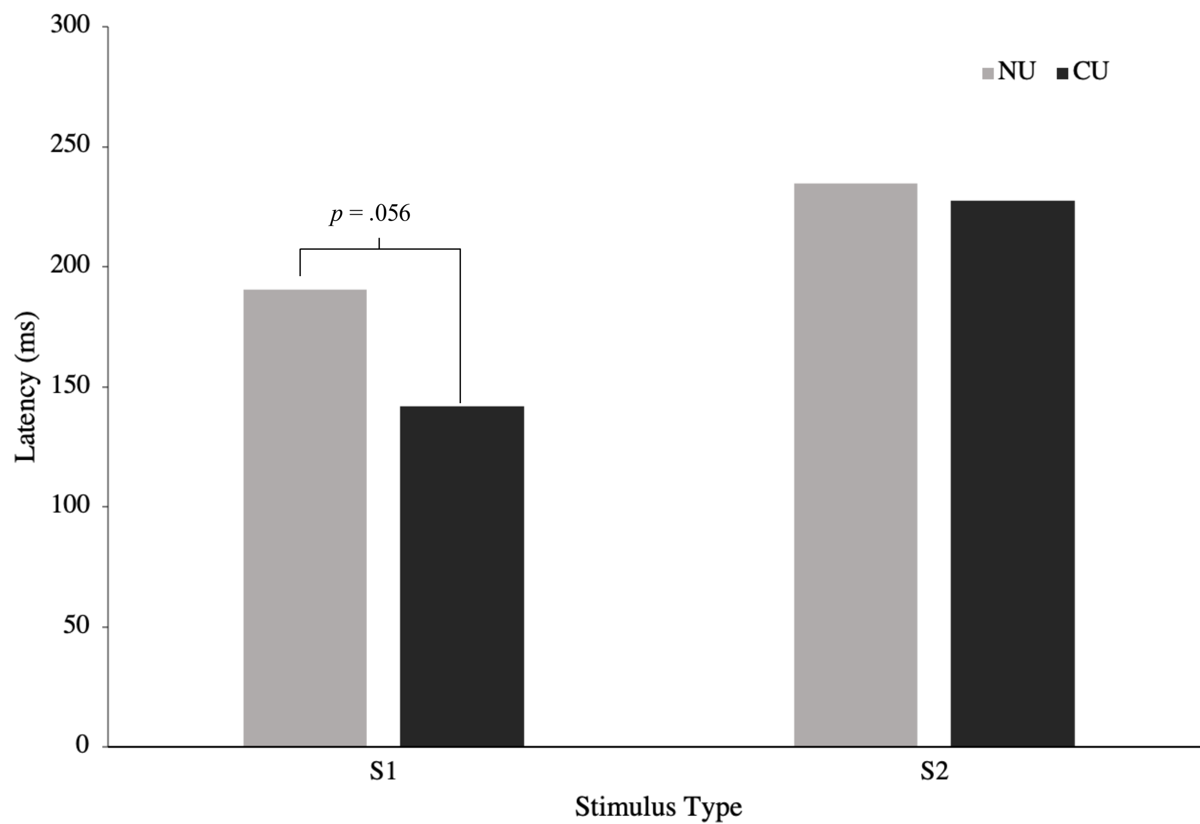


Figure 6.

P50 amplitudes for the paired click paradigm for stimulus 1 and 2 in females (a) and males (b).

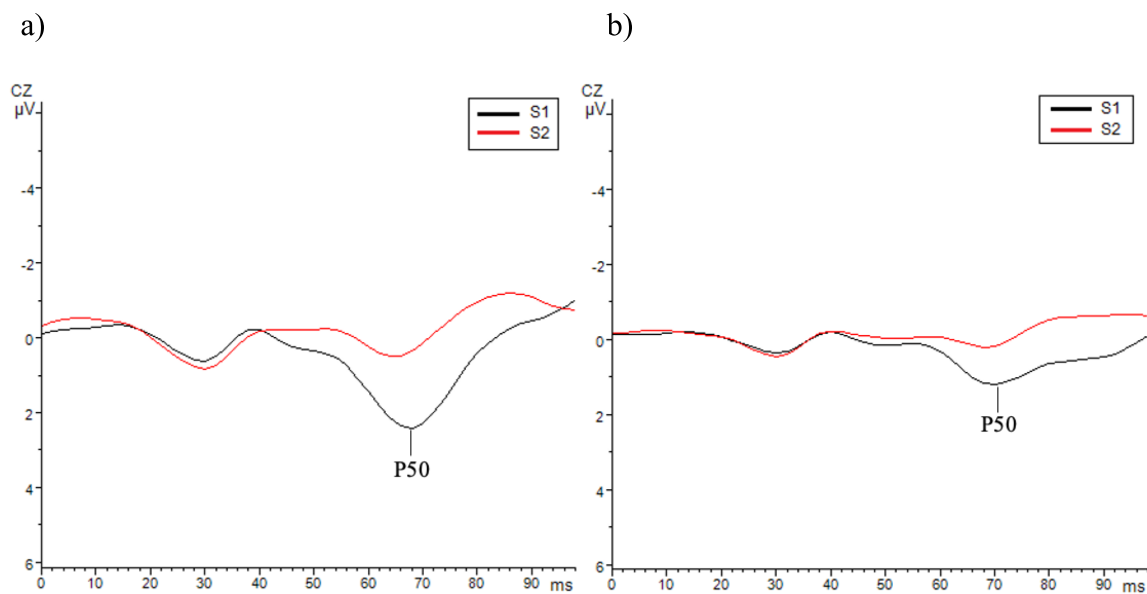


Figure 7.

N100/P200 amplitudes to the Paired Click paradigm (Stimulus 1 (a), and Stimulus 2 (b)) between males and females.

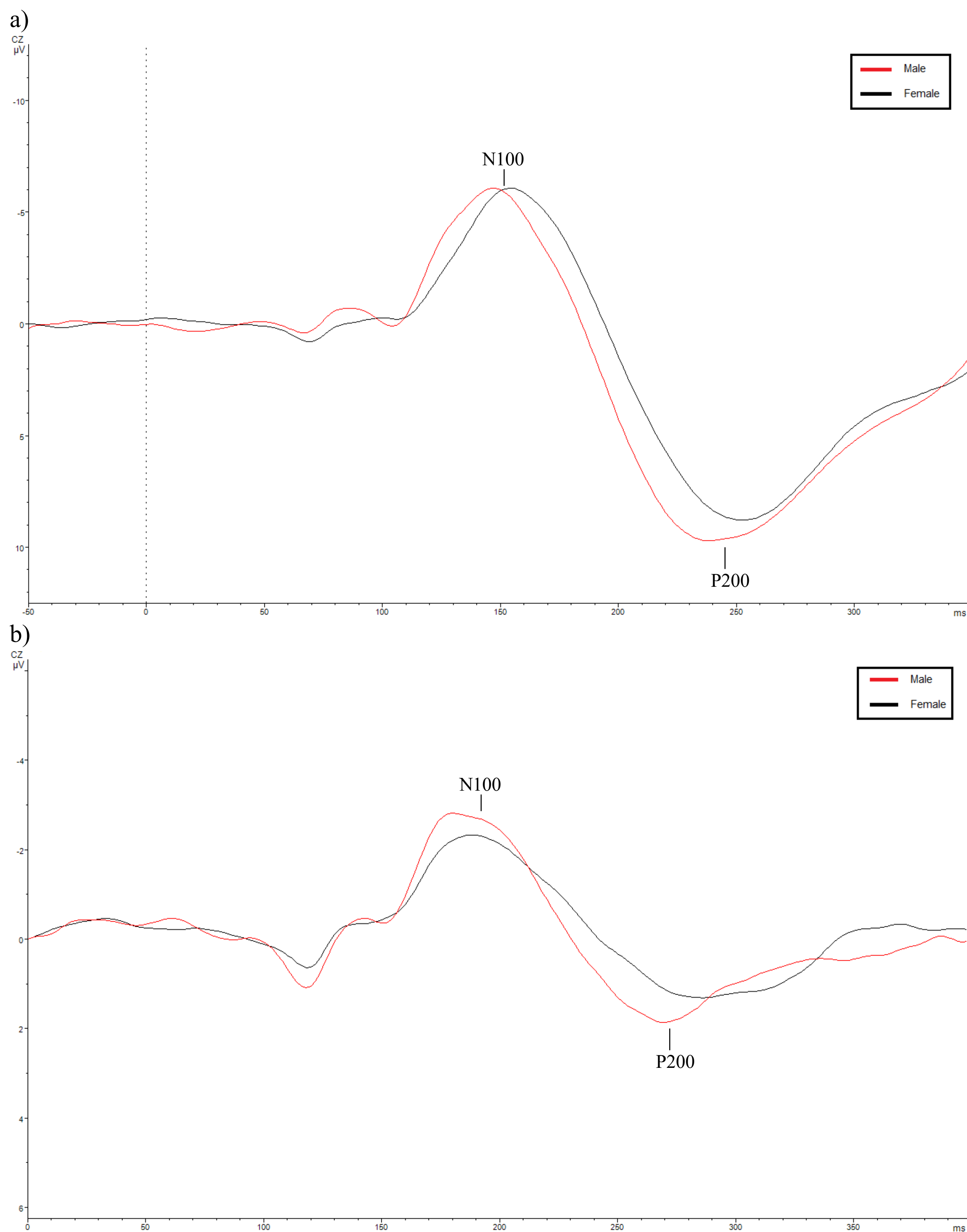
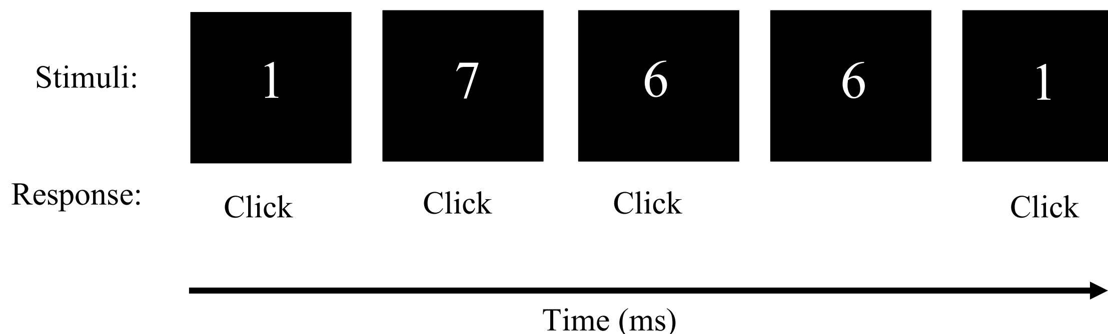


Figure 8.

The NoGo visual paradigm.



Note. Go/NoGo paradigm depicting the ‘go’ stimuli (click) and ‘NoGo’ stimuli (no click/click inhibition). The stimuli in this paradigm are white numbers presented on a black computer screen. A response in the form of a click indicates a ‘Go’ trial while no-click indicates a ‘NoGo’ or inhibition trial. Participants only inhibit the response if the number presented is a duplicate of that preceeding it (e.g., 6,6).

Figure 9.

P100 amplitudes for cannabis users and non-users to the Go stimuli in the Go/NoGo paradigm

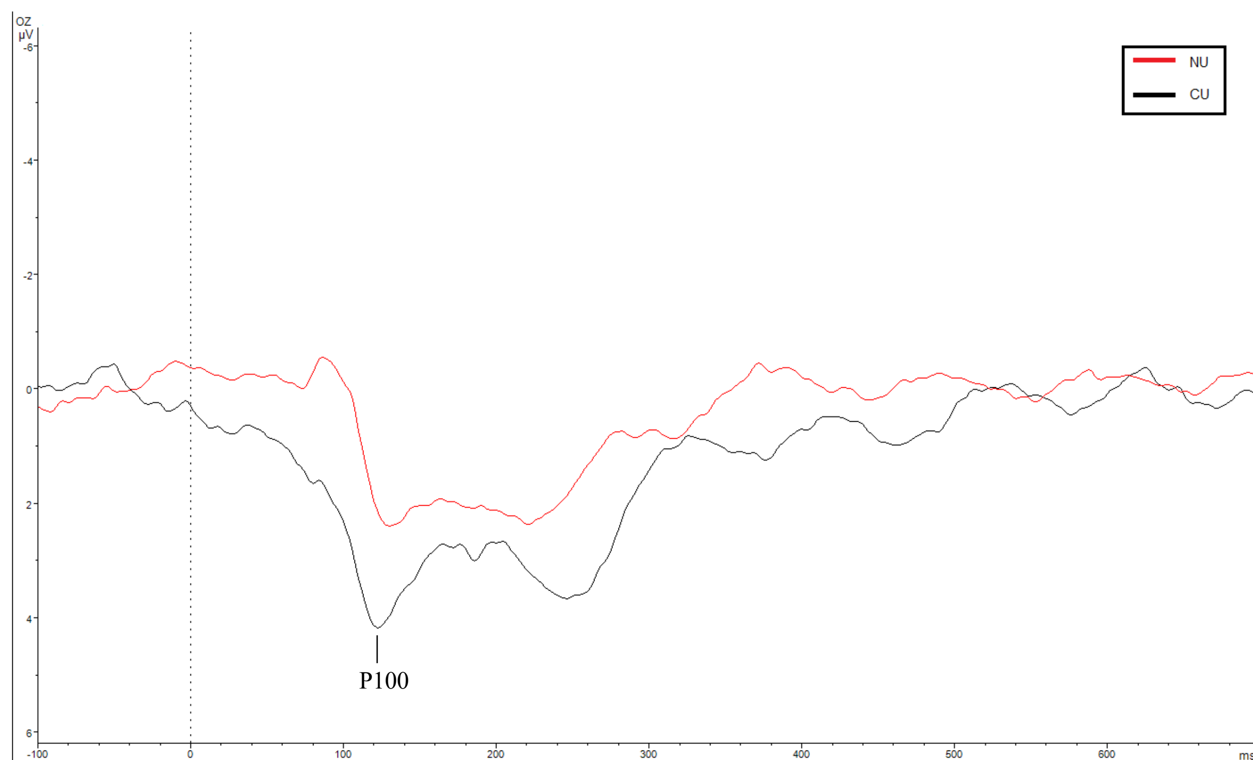
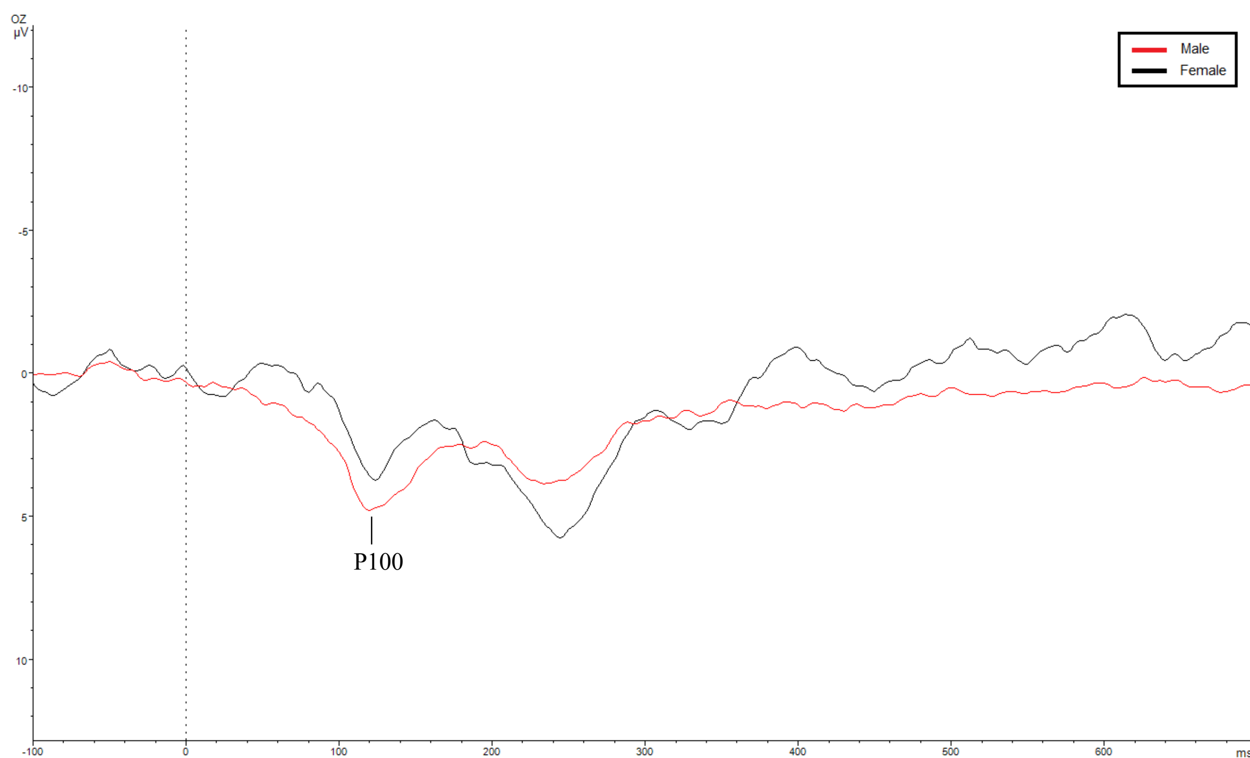


Figure 10.

P100 amplitudes for cannabis users and non-users to the NoGo stimuli in the Go/NoGo paradigm

Figure 11.

P100 amplitudes for males and females to the Go stimuli in the Go/NoGo paradigm.



Appendix A : Invitation to participate and consent

<u>Cannabis users and non-users needed for a research study on brain function</u>

If you are a regular cannabis user or a cannabis non-user, you may be eligible to participate in a research study investigating how cannabis affects brain function in males and females.

Each participant will attend two 2-hour visits where they will complete questionnaires and computer-based tasks. Electroencephalography (EEG) will be recorded in order to measure brain function during performance of the computer tasks.

You will be reimbursed for your participation in the study.

Contact Information

If you are interested and want more information, please contact the lab of Dr. Derek Fisher at 902.457.6441 or derek.fisher@nshealth.ca.

Informed Consent Form Non-Interventional Study

STUDY TITLE:	Differential Effects of Cannabis Use on Event-Related Potential (ERP)-Indexed Brain Function in Males and Females
PRINCIPAL INVESTIGATOR:	Dr. Derek Fisher, Psychiatry EVR427-166 Bedford Highway Halifax, Nova Scotia, B3M2J6 (902)457-5503
SUB-INVESTIGATORS:	Candice Crocker, Ph.D. Departments of Psychiatry & Radiology Sherry Stewart, Ph.D., C.Psych. Department of Psychiatry Philip Tibbo, M.D., Department of Psychiatry
FUNDER:	This study is being funded by a Catalyst Grant from the Canadian Institutes of Health Research

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Introduction
You have been invited to take part in a research study. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study. You may take as much time as you wish to decide whether or not to participate.

Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:
Discuss the study with you
Answer your questions
Be available during the study to deal with problems and answer questions
Keep any information which could personally identify you confidential

You are being asked to consider participating in this study because you have volunteered to participate as a) a regular cannabis user; or b) a cannabis non-user.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. Why Is This Study Being Conducted?

Cannabis use within the previous 12 months in the Canadian population was reported at 12.3% in 2015. The typical age of initiation of cannabis is between 13-15 years of age; cannabis use at this time point and through adolescence overlaps with changes in the structure and function of the brain that may be influenced by cannabis. This appears to produce changes in the way the brain works. What is unclear, however, is whether cannabis use produces different effects in males and females. Therefore, our research question is whether the changes that have been seen in brain activity in people who use cannabis can be seen in males only, in females only, or in both. By better understanding sex-based differences in brain activity following cannabis user, this work will tell us more about how cannabis effects the brain and possibly eventually influence public health guidelines.

3. How Long Will I Be In The Study?

You will be in this study for two 2-hour sessions (i.e. 4 hours total).

4. How Many People Will Take Part In This Study?

It is anticipated that about 60 regular cannabis users (30 male and 30 female) and 60 cannabis non-users (30 male and 30 female) will participate in this study throughout Nova Scotia. All people will participate in this study at the QEII Health Sciences Centre or at Mount Saint Vincent University.

5. How Is The Study Being Done?

We can study how the brain reacts to incoming information, such as sounds, by measuring the brain's electrical activity. This can be done by placing electrodes on the surface of the scalp, a procedure called an electroencephalogram (EEG). An EEG is a non-painful procedure that allows us to examine brain function during the processing of sounds in a quick and easy way.

This study is being conducted using EEG recording equipment at the Neuroimaging Research Lab located at the QEII Health Sciences Centre and the EEG lab at Mount Saint Vincent University. There will also be some questionnaires that each participant will be required to complete asking about your use of cannabis, alcohol and nicotine, as well as aspects of mental health.

6. What Will Happen If I Take Part In This Study?

If you agree to participate and sign the consent form and you are eligible to participate, you will be required to come to the Neuroimaging Research Lab for two, 2-hour session.

You will be asked to not use alcohol, cannabis products (such as marijuana), illegal drugs and over-the-counter drugs beginning at midnight prior to the test session. Participants should still take any prescribed drugs as they normally would. Upon arrival, a urine test will be conducted to ensure you did not use alcohol, cannabis or other drugs prior to the test session. If it is determined that you were unable to abstain from these substances, the test session will be cancelled and rebooked. The test session will usually take place between 10:00 a.m. – 12:00 p.m. In the test session, sensors will be placed on your scalp and around your eyes to monitor electrical activity of the brain. In order to properly place the sensors, we will put an EEG cap on your head; the cap is made of a stretchy nylon-like material and fits snugly to your head. Once the sensors are in place, your brain activity will be recorded while you are watching a silent, neutral video (for example, a nature film like "Planet Earth"). At the same time as you are watching the film, sounds will be presented through headphones. The process of setting up the sensors and recording brain activity will take approximately 1.5 hours. Small breaks in the recording process will be integrated into the test session. Five (5) questionnaires asking you about your cannabis use (such as how often you use, when you started using, etc…), general drug consuming behaviour, and about specific thoughts and experiences (such as hearing voices or feeling like your thoughts are being controlled) will also be completed so we can better understand how these might affect your brain activity. You will also be asked to provide a saliva sample to assess circulating hormone levels (such as estradiol and testosterone). You have a right to skip any questions you do not wish to answer. A member of the study team will always be with you.

If at any point you change your mind and you no longer wish to participate in the study you can withdraw from the study. Your decision to withdraw will not affect your health care in any way.

7. Are There Risks To The Study?

There are risks with this, or any study. To give you the most complete information available, we have listed some *possible* risks. We want to make sure that if you decide to try the study, you have had a chance to think about the risks carefully. Please be aware that there may be risks that we don't yet know about.

EEG
You will be required to wear an electrode cap; though unlikely, wearing the cap may produce a headache. The electrode sensors may result in temporary redness and irritation of the skin that will disappear in a few hours. Additionally, you will be asked to sit for 2 hours during the test session.

QUESTIONNAIRES
You may find the interviews and questionnaires you receive during the course of the study upsetting or distressing. You may not like all of the questions that you will be asked. You do not have to answer those questions you find too distressing.

IDENTIFICATION

To protect your information, we will not keep your name or other information that may identify you with your study data, only a code number. Files that link your name to the code number will be kept in a secure place. Although no one can absolutely guarantee confidentiality, using a code number makes the chance much smaller that someone other than the research staff or other authorized groups or persons (discussed later in the consent form) will ever be able to link your name to your study data.
8. Are There Benefits Of Participating In This Study?
We cannot guarantee or promise that you will receive any benefits from this research. However, possible benefits include a sense of contributing to a greater understanding of how cannabis affects the brain. There are no direct medical benefits to participating in this study.

9. What Happens at the End of the Study?

Once you have completed the study procedures your participation in the study is over.

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

You may leave your mailing/email address with a member of the study team if you wish to receive a copy of the results and/or any publications that result from the study. The results will be forwarded to you once the study has been completed and all the data has been analyzed.

10. What Are My Responsibilities?

As a study participant you will be expected to:
Follow the directions of the research team;
Report all medications being taken or that you plan on taking;
Report any changes in your health to the research team;
Report any problems that you experience that you think might be related to participating in the study;
Not consume alcohol, cannabis (such as marijuana), caffeine (including coffee, tea and cola), illegal drugs and over-the-counter drugs beginning at midnight before each test session

11. Can My Participation in this Study End Early?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare. If you decide to withdraw from the study, the information collected up to that time will continue to be used by the research team. It may not be removed.

Also, the Nova Scotia Health Authority Research Fund, the Nova Scotia Health Authority Research Ethics Board and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

You do not follow the directions of the research team;
There is new information that shows that being in this study is not in your best interests;

If you are withdrawn from this study, Dr. Derek Fisher will discuss the reasons with you and plans will be made for your continued care outside of the study, if needed.

12. What About New Information?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

13. Will It Cost Me Anything?

There is no fee for participating in the study, although you may need to pay for medications to treat the side effects that you may experience as a result of participating in this study. Your private health care insurer may not pay for any or all of these added costs

You will not be paid to be in the study. You will be compensated $25 for each session to cover meals and transportation costs on the study visit day.

<u>Research Related Injury</u>

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

14. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records.

If you decide to participate in this study, the research team will collect personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;
Name,
Address,
Telephone number,
Age or month/year of birth (MM/YY),
Information from the study interviews and questionnaires;

<u>Access to Records</u>

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB because they oversee the ethical conduct of research studies within the Nova Scotia Health Authority.

These people will view your study records at this institution and will not take identifying information away with them.

<u>Use of Your Study Information</u>

The research team and the other people listed above will keep the information they <u>see</u> or <u>receive</u> about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal health information about you in a secure and confidential location for 7 years after the publication of data and then destroy it according to NSHA policy. This information will initially be held in the PI's private, locked office at Mount Saint Vincent University and will be transferred to locked storage at the QEII Centre for Clinical Research once the study data is published. Your personal health information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent. Additionally, we may want to follow your progress and to check that the information we collected is correct.

You have the right to be informed of the results of this study once the entire study is complete.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your access to records

You have the right to access, review, and request changes to your study data. You may access these records at any time until the records are destroyed, however changes to study data may not be possible once the study data has been analyzed and published.

15. Declaration of Financial Interest

The Canadian Institutes of Health Research is reimbursing the principal investigator and/or the principal investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study. The PI has no vested financial interest in conducting this study.

16. What About Questions or Problems?

For further information about the study you may call the principal investigator, who is the person in charge of this study and/or any other research team member listed below.

The principal investigator is Dr. Derek Fisher.
Telephone: 902.457.5503.
Email: derek.fisher@msvu.ca

If you experience any symptoms or possible side effects or other medical problems, please let the principal investigator or research coordinator know immediately.

17. What Are My Rights?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study. You have the right to withdraw your consent at any time.

If you have any questions about your rights as a research participant, contact Patient Relations at (902) 473-2133 or healthcareexperience@nshealth.ca

In the next part you will be asked if you agree (consent) to join this study. If the answer is "yes", please sign the form.

Consent Form Signature Page

I have reviewed all of the information in this consent form related to the study called:

Differential Effects of Cannabis Use on Event-Related Potential (ERP)-Indexed Brain Function in Males and Females

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time.

_______________________________ ____________________ _____ / ____ / ___
Signature of Participant Name (Printed) Year Month Day*

________________________ ________________________ ______/____ /_____
Signature of Investigator Name (Printed) Year Month Day*

______________________________ ________________________ _____ / ____/ ____
Signature of Person Conducting Consent Discussion Name (Printed) Year Month Day*

I Will Be Given a Signed Copy Of This Consent Form

Thank you for your time and patience!

ROMEO File #1024305
SMU REB # 21-077

Appendix B: Questionnaires

CANNABIS AND SEX STUDY

Screening Questionnaire

Date: ___________________________ ID# :_________________________

Name: ___________________________ Age: _____ DOB (dd/mm/yyyy): _____________

Sex: _____

Education:

Grade school	0 1 2 3 4 5 6 7 8
High school	9 10 11 12
Trade/College	13 14
University	13 14 15 16
Master’s level	17 18
Ph.D. level	19 20 21

Classification: *CF / CM / NF / NM*

Handedness: *Left / Right* Normal hearing: *Y / N* Vision: *Normal / Corrected*

Telephone: (h) ____________________ (w) __________________ (c)___________________

What is your first language? _____________ Other languages you are fluent in? ___________

Are you employed? Y / N If yes, what is your occupation? _____________ F/T or P/T?

If no, why? (retired / disability / let go / by choice)

EXCULSION CRITERIA

Are you currently on medication on a regular basis for any physical condition? Y / N
Are you currently using any pain medication on a regular basis? Y / N
Have you had any steroid use within the past 3 months? Y / N
Do you have a condition that effects estrogen/progesterone or testosterone levels in your body? Y / N
If they do exclude. – only if confirmed otherwise test and note.
Have you ever been diagnosed with a psychiatric or mental illness (e.g. depression, anxiety)? Y / N
If yes, what disorder was diagnosed? _________________________
Are you currently being seen for treatment? ___________________

Do you currently receive medication for these illnesses? ______________
Have you ever been diagnosed with a learning disability? Y / N
If yes, what disorder was diagnosed? _________________________
Have you had a head of brain injury in the past 6 months? Y / N
If yes, did you lose consciousness for one or more hours? _________

To the best of your knowledge:
Do you have any neurological disorders such as epilepsy, dementia, Parkinson's disease? Y / N
If yes, which? _____________________

What is your daily (or weekly) alcohol consumption? ________________________
Have you ever smoked cigarettes? Y / N
If yes, do you currently smoke? ______________________
If no, when did you quit? _____________________
How many years have you been a smoker? _____________
How many cigarettes/day? __________________
How long at this rate? ______________________
Have you ever used cannabis? Y / N
If yes, do you currently use it? _______________________
If no, when did you quit? _____________________
How many times in your life have you used it? ___________
If yes, what is the THC/CBD content of your favourite strain?_____________
How many years have you smoked cannabis? __________________
How many times each week do you smoke? ____________________

Timeline follow-back (TFB) of cannabis use.
TFB Week Start Date (mm/dd/yyyy) ________/________/______

Please indicate which of the following days cannabis was consumed over the past week, check each day that cannabis was consumed and report the date in the space provided.

☐ Sunday: __________
☐ Monday: _________
☐ Tuesday: _________
☐ Wednesday: ________
☐ Thursday: __________
☐ Friday: ____________
☐ Saturday: ____________

Do you use any street drugs (cocaine, MDMA)? _______________
If yes, What drugs? _________________
How often? _________________

FOR FEMALES:
Do you have a regular menstrual cycle? Y / N
Relatively regular cycle.
Do you use oral contraceptives/ have you ever used oral contraceptives in the past 3 months? Y/ N

What brand? _____________
Have you ever been pregnant? Y / N
If yes, how many times (including births, miscarriages and abortions)? ______
***Note: We do not need to know how many of each, just total # of pregnancies*

Participant: ______________ Date: ____________
WHO ASSIST Questionnaire

INTRODUCTION ***(Please read to patient)***

Thank you for agreeing to take part in this brief interview about alcohol, tobacco products and other drugs. I am going to ask you some questions about your experience of using these substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills (show drug card).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please let me know. While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO PATIENT

Question 1
(if completing follow-up please cross check the patient's answers with the answers given for Q1 at baseline. Any differences on this question should be queried)

In your life, which of the following substances have you ever used? *(NON-MEDICAL USE ONLY)*	**No**	**Yes**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3
d. Cocaine (coke, crack, etc.)	0	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
j. Other - specify:	0	3

Probe if all answers are negative:
"Not even when you were in school?"

If "No" to all items, stop interview.

If "Yes" to any of these items, ask Question 2 for each substance ever used.

Question 2

In the <u>past three months</u>, how often have you used the substances you mentioned *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d. Cocaine (coke, crack, etc.)	0	2	3	4	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	2	3	4	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for <u>each substance</u> used.

Question 3

During the <u>past three months</u>, how often have you had a strong desire or urge to use *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d. Cocaine (coke, crack, etc.)	0	3	4	5	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3	4	5	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the <u>past three months</u>, how often has your use of *(FIRST DRUG, SECOND DRUG, ETC)* led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d. Cocaine (coke, crack, etc.)	0	4	5	6	7
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	4	5	6	7
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the <u>past three months</u>, how often have you failed to do what was normally expected of you because of your use of *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d. Cocaine (coke, crack, etc.)	0	5	6	7	8
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	5	6	7	8
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6

Has a friend or relative or anyone else ever expressed concern about your use of *(FIRST DRUG, SECOND DRUG, ETC.)?*	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 7

Have you ever tried and failed to control, cut down or stop using *(FIRST DRUG, SECOND DRUG, ETC.)?*	**No, Never**	**Yes, in the past 3 months**	**Yes, but not in the past 3 months**
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 8

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you ever used any drug by injection? *(NON-MEDICAL USE ONLY)*	0	2	1

IMPORTANT NOTE:

Patients who have injected drugs in the last 3 months should be asked about their pattern of injecting during this period, to determine their risk levels and the best course of intervention.

PATTERN OF INJECTING		INTERVENTION GUIDELINES
Once weekly or less or **Fewer than 3 days in a row**	→	**Brief Intervention including "risks associated with injecting" card**
More than once per week or **3 or more days in a row**	→	**Further assessment and more intensive treatment***

HOW TO CALCULATE A SPECIFIC SUBSTANCE INVOLVEMENT SCORE.

For each substance (labelled a. to j.) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: **Q2c + Q3c + Q4c + Q5c + Q6c + Q7c**

Note that Q5 for tobacco is not coded, and is calculated as: **Q2a + Q3a + Q4a + Q6a + Q7a**

THE TYPE OF INTERVENTION IS DETERMINED BY THE PATIENT'S SPECIFIC SUBSTANCE INVOLVEMENT SCORE

	Record specific substance score	no intervention	receive brief intervention	more intensive treatment *
a. tobacco		0 - 3	4 - 26	27+
b. alcohol		0 - 10	11 - 26	27+
c. cannabis		0 - 3	4 - 26	27+
d. cocaine		0 - 3	4 - 26	27+
e. amphetamine		0 - 3	4 - 26	27+
f. inhalants		0 - 3	4 - 26	27+
g. sedatives		0 - 3	4 - 26	27+
h. hallucinogens		0 - 3	4 - 26	27+
i. opioids		0 - 3	4 - 26	27+
j. other drugs		0 - 3	4 - 26	27+

Reasons for Substance use Scale (ReSUS)
Participant Code: _________

Please answer the following questions regarding when you typically feel like using cannabis:

1: When I am experiencing unpleasant thoughts.

Never
Sometimes
Often
Almost always

2: When I feel ashamed or bad about myself.

Never
Sometimes
Often
Almost always

3: When I am thinking about bad things that have happened in the past.

Never
Sometimes
Often
Almost always

4: When my thoughts are racing.

Never
Sometimes
Often
Almost always

5: When I want to escape from my problems and worries.

Never
Sometimes
Often
Almost always

6: When I am feeling suspicious or paranoid.

Never
Sometimes
Often
Almost always

7: When I am feeling depressed.

Never
Sometimes
Often
Almost always

8: When I am angry at the way things have turned out.

Never
Sometimes
Often
Almost always

9: When I feel anxious or tense.

Never
Sometimes
Often
Almost always

10: When I start to feel guilty about something.

Never
Sometimes
Often
Almost always

11: When I am feeling stressed.

Never
Sometimes
Often
Almost always

12: When I am having trouble sleeping.

Never
Sometimes
Often
Almost always

13: When I feel I have been discriminated against.

Never
Sometimes
Often
Almost always

14: When I am hearing sounds or voices that other people can't hear.

Never
Sometimes
Often
Almost always

15: When I am having trouble thinking or concentrating.

Never
Sometimes
Often
Almost always

16: When I am having trouble communicating with others.

Never
Sometimes
Often
Almost always

17: When I am in pain physically.

Never
Sometimes
Often
Almost always

18: When I am feeling lonely.
Never
Sometimes
Often
Almost always

19: When I am feeling happy and content with my life.

Never
Sometimes
Often
Almost always

20: When I want to feel good, have a laugh or be happier.

Never
Sometimes
Often
Almost always

21: When I am with friends and we want to have a good time.

Never
Sometimes
Often
Almost always

22: When I want to chill out or relax.

Never
Sometimes
Often
Almost always

23: When I think about how good it tastes.
Never
Sometimes
Often
Almost always

24: When I feel excited about something.

Never
Sometimes
Often
Almost always

25: When I want to fit in with other people.

Never
Sometimes
Often
Almost always

26: When I want to feel drunk, stoned or high.

Never
Sometimes
Often
Almost always

27: When I feel under pressure from others to use drugs/drink alcohol.

Never
Sometimes
Often
Almost always

28: When I have been drinking and think about using drugs (or vice versa).

Never
Sometimes
Often
Almost always

29: When I am bored and want something to do to pass the time.

Never
Sometimes
Often
Almost always

30: When I want to feel more self aware.

Never
Sometimes
Often
Almost always

31: When I need motivation to do things.

Never
Sometimes
Often
Almost always

32: When I want to stay awake or be more alert.

Never
Sometimes
Often
Almost always

33: When I want to feel more creative.

Never
Sometimes
Often
Almost always

34: When I want to feel more emotions.

Never
Sometimes
Often
Almost always

35: When I want to feel sexy.

Never
Sometimes
Often
Almost always

36: When I am experiencing medication side effects.

Never
Sometimes
Often
Almost always

37: When I want to feel normal.

Never
Sometimes
Often
Almost always

38: When I want to feel more confident.

Never
Sometimes
Often
Almost always

Alcohol Use Disorders Identification Test (AUDIT)

1. How often do you have a drink containing alcohol?

   Never   Monthly or less   Two to four times a month   Two to three times a week   Four or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

   1 or 2   3 or 4   5 or 6   7 or 9   10 or more

3. How often do you have six or more drinks on one occasion?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

4. How often during the last year have you found that you were not able to stop drinking once you had started?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

   Never   Less than monthly   Monthly   Weekly   Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?

   No   Yes, but not in the last year   Yes, during the last year

10. Has a relative or friend, or doctor or other health worker been concerned about your drinking or suggested you cut down?

    No   Yes, but not in the last year   Yes, during the last year

Appendix C: Study Timeline

Timeline

Participant code: ________________________ Date: _____________________ _______

Session: 1 / 2 Recording tech: _________________________ _______

_______ Arrival and Consent (turn cell phone off)
_______ Urine Sample Obtained
_______ Questionnaires (ReSUS, AUDIT, ASSIST, FTND& cannabis preference)
_______ Saliva sample
_______ EEG set up

_______ Optimal MMN Filename: _________________ _______

(3 blocks)

_______Paired 50 Click Filename: _________________ _______

_______ Eyes-Closed Resting (3 minutes) Filename: _________________ _______

_______ NoGo P300 Filename: _________________ _______

(4 blocks)

_______Eyes-Open Resting (3 minutes) Filename: ________________________

_______ Novelty P3 Filename: _________________ _______

(4 blocks)

_______ Clean up electrodes/cap
_______ Turn off amplifier

Notes:

Appendix D: COVID Limitations

Unfortunately, during the first year of this study, the global COVID-19 pandemic halted all data collection for my thesis. Data collection for this study began in early December 2019 after troubleshooting equipment and paradigms and obtaining ethical clearance for the study. On March 15th, 2020, data collection was shut down due to country-wide lockdowns to stop the spread of the virus. Unfortunately, the lockdowns lasted longer than originally anticipated and face-to-face research was unable to reopen at Mount Saint Vincent University (the site of the laboratory) until March 14th, 2021. When the lab was given the clearance to reopen, we had participants booked in on the first day possible day to ensure an adequate sample size for this study. Unfortunately, recruitment was not as easy as it had been pre-pandemic as students (a significant pool of participants) were now dispersed across the province, country, and world doing online learning. In addition, those who were interested in participating in our study often chose to wait until case numbers were 0 for a period of 2 weeks or longer before agreeing to come within 6-feet of another individual for our study. Due to the nature of EEG, it was not possible to complete testing from 6-feet away, and while approved protective measures were put in place by our laboratory, some participants were not comfortable with this and therefore chose to wait to participate. With recruitment looking better towards the end of March, at the beginning of April, it appeared as though the study would reach enough participants for a sex by cannabis group analysis. Unfortunately, this is when the province was hit with another wave of COVID-19 and was forced to go into a full provincial lock-down once again closing face-to-face research and forcing us to close the lab and rebook all scheduled participants. Therefore, with all of these lockdowns and interruptions in data collection, I had a total of 5.5 months to collect my full sample of

participants, 1.5 of which I was only able to run one participant per day due to the modified COVID-19 testing protocol. For the remaining 4 months, I was able to run a maximum of 2 participants per day to abide by our study guidelines.