Assessing Within-Task Time Course of Cognitive Interference Processing in Recreational Marijuana Users

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Abstract

Marijuana (MJ) remains the most popular illicit drug in the US; however, chronic, heavy MJ use is often associated with cognitive decrements, particularly poorer executive functioning, with earlier age of onset of MJ use associated with increased impairment. Further, neuroimaging studies have demonstrated dysfunctional activation of the cingulo-fronto-parietal attention (CFP) network, particularly within the cingulate and dorsolateral prefontal cortices (DLPFC), of MJ users.

This dissertation assesses the impact of chronic, heavy MJ use on cognitive interference, one aspect of executive function associated with attentional shifting and inhibitory control, using the Multi-Source Interference Task (MSIT). Although MJ-associated alterations in CFP activation during the MSIT have previously been reported, task performance differences have been inconsistent; however, previous studies only examined task performance and fMRI activation *averaged across the whole task*. The current research examined changes in performance and brain activation patterns over the course of the task using two-group (control vs MJ) analyses as well as three-group (control vs early MJ onset vs late MJ onset) analyses in order to assess the impact of age of MJ onset.

Results indicate that MSIT performance and brain activation are dynamic over time in both control participants and MJ users. Even though significant between-group task performance differences were not

observed, cingulate and DLPFC activation patterns were altered in MJ users. MJ users demonstrated increased activation over time, which was sustained throughout longer periods of the task relative to control subjects. However, when MJ users were divided based on age of MJ onset, the late MJ onset group demonstrated a pattern of activation more similar to the control group, with the greatest activation observed during the initial blocks, and attenuated activation over time, whereas the early MJ onset group demonstrated a more dysfunctional pattern of activation with greater activation during later blocks. Additionally, increased DLPFC activation in early MJ users and decreased cingulate activation in late MJ users were both related to greater task difficultly during cognitive interference processing, and aspects of MJ use (particularly earlier age of onset) was associated with both poorer performance as well as altered CFP activation.

Keywords: marijuana, cognitive interference, functional magnetic resonance imaging (fMRI), Multi-Source Interference Task (MSIT)

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Assessing Within-Task Time Course of Cognitive Interference Processing in Recreational Marijuana Users

1. Introduction: Marijuana

Marijuana (MJ) is an illicit drug derived from the *Cannabis sativa* plant that is currently assigned Schedule I status by the United States Drug Enforcement Administration (DEA). Schedule I is the most restrictive drug status, and drugs within this category are defined as having “no currently accepted medical use, a high potential for abuse, and no standard safety profile” (DEA, n.d.). While illegal at the federal level, the past several decades have witnessed a change in the landscape of state-level MJ legislation. Currently, twenty-two states and the District of Columbia (DC) have decriminalized MJ use, reducing the penalty for possessing small amounts of MJ for personal consumption, and nine of those states plus DC have legalized recreational MJ use for adults (National Conference of State Legislatures [NCSL], 2017a). Further, thirty states as well as DC, Guam, and Puerto Rico have passed laws allowing MJ to be used to treat medical conditions, and another seventeen states have 'limited' medical MJ law, allowing only cannabidiol (CBD)-rich products (NCSL, 2017b). A recent review of the health effects of cannabis and cannabinoids by the National Academies of Science, Engineering, and Medicine (NASEM, 2017) reported that there was "conclusive or substantial" evidence that cannabis is effective for the treatment of chronic pain, muscle spasticity associated with multiple sclerosis, and chemotherapy-induced nausea and vomiting. Since publication of the NASEM report, the authors have also added pediatric onset seizure

disorders to the list, citing recent reports from several clinical trials (e.g., Devinsky et al., 2016; Hawkes, 2017; etc.). However, in addition to these medical indications, the report also found moderate evidence that recreational MJ use is associated with impaired cognition in healthy individuals (NASEM, 2017).

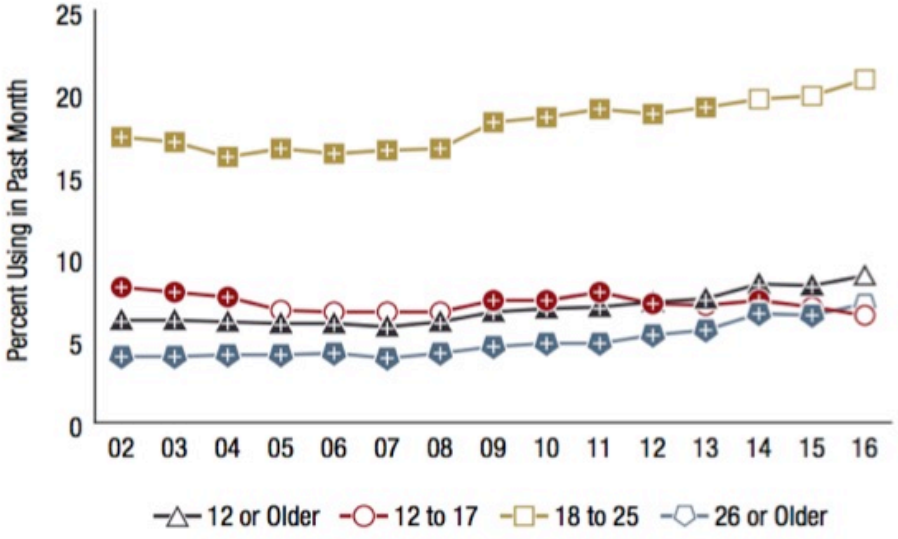
Despite recent changes in policy and in the perception of harm/benefit regarding MJ use, many questions remain concerning the short- and long-term impact of MJ use for both recreational and medical consumers. Additionally, unlike other legal substances (i.e., alcohol and tobacco), there are no accepted standards for MJ use, leaving many users uninformed about appropriate dosing, mode of use, and specific constituent composition of available products. What is undeniable is that MJ use is extremely prevalent in the US, and changes to any policy regarding MJ use have the potential to impact a large number of individuals.

1.1. Prevalence of MJ Use

MJ remains the most popular illicit drug in the US, with a recent national survey from the Substance Abuse and Mental Health Service Administration (SAMHSA) indicating that 24.0 million Americans aged 12 or over (8.9% of the population) reported current MJ use within the past month (SAMHSA, 2017; **Figure 1**). The number of current MJ users has continually increased over the past decade, and the current rate is

significantly higher than every annual report since 2002. Further, 1.6 million adolescents aged 12 to 17, representing 6.5% of the population, and 7.2 million young adults aged 18 to 25, representing a staggering 20.8% of the population, report current past-month use of MJ. These statistics are particularly concerning, considering increasing evidence that adolescence and early adulthood are times of significant neuromaturation, and substance use during these critical periods of development may increase the risk of adverse consequences (reviewed in Arain et al., 2013; Johnson, Blum, & Giedd, 2009).

Figure 1. Past month MJ use among people aged 12 or older, by age group: percentages, 2002-2016 (from SAMHSA, 2017)



Age	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
≥12	6.2+	6.2+	6.1+	6.0+	6.0+	5.8+	6.1+	6.7+	6.9+	7.0+	7.3+	7.5+	8.4+	8.3+	8.9
12-17	8.2+	7.9+	7.6+	6.8	6.7	6.7	6.7	7.4+	7.4+	7.9+	7.2+	7.1	7.4+	7.0	6.5
18-25	17.3+	17.0+	16.1+	16.6+	16.3+	16.5+	16.6+	18.2+	18.5+	19.0+	18.7+	19.1+	19.6	19.8	20.8
≥26	4.0+	4.0+	4.1+	4.1+	4.2+	3.9+	4.2+	4.6+	4.8+	4.8+	5.3+	5.6+	6.6+	6.5+	7.2

+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.

Image from SAMHSA, 2017

In order to address concerns about youth substance use, the Monitoring the Future (MTF) study, led by researchers at the University of Michigan, has collected data on drug use from American adolescents and young adults annually since 1975 (recently reviewed in Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017; Schulenberg et al., 2017). Marijuana was a relatively obscure drug in the US until the 60s, when the prevalence of MJ use dramatically increased among adolescents and continued to propagate throughout the 60s and 70s, peaking in 1979. At that time, 51% of 12th graders reported use within the past year (**Figure 2A**; Johnson et al., 2017). This peak was followed by a rapid decline in adolescent use throughout the 80s and into the early 90s before a second rise in MJ use occurred, peaking in 1997. Despite some decline in use during the mid-2000s, this rise has continued, and the most recent surveys indicate that in 2016 one in seventeen 12th graders report daily use of MJ (Johnson et al., 2017).

Recently, rates of less frequent MJ use (e.g., some MJ use within the past year or within the past 30 days) have declined somewhat, while the number of adolescents reporting *daily* MJ use has peaked and remains high with 1.3% of 8th graders in 2011; 4.0% of 10th graders in 2013; and 6.6% of 12th graders in 2011 reporting daily MJ use (Johnson et al., 2011; Schulenberg et al., 2017). These values are the highest reports of daily MJ use by adolescents in over 30 years (Schulenberg et al., 2017). In fact, 2015 marked the first time that the number of 12th graders

reporting daily MJ use (6.0%) surpassed the number reporting daily cigarette use (5.5%; Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). Taken together, these data suggest that regular MJ use is becoming more prevalent among adolescents and young adults, who are at increased risk if exposure to MJ is harmful during development.

Given the popularity of MJ and growing number of daily users, particularly adolescents and emerging adults, it is important to fully examine what factors impact the prevalence of MJ use. Over the past four decades, three social risk factors have emerged as the most important variables associated with MJ use: perceived risk of use, disapproval of use, and availability of product (reviewed in Schulenberg et al., 2017). Changes in the percentage of individuals perceiving MJ as risky or disapproving of MJ use often track with prevalence of use; as perceived risk of use declines, disapproval of use also decreases, which is often associated with increased rates of use observed soon afterwards. Over the past decade, both perceived risk (**Figure 2B**) and disapproval (**Figure 2C**) of MJ use have significantly declined, with the most recent survey from 2016 reporting levels at or near the lowest ever recorded; these data indicate that prevalence of use is likely to continue to increase (Johnson et al., 2017; Schulenberg et al., 2017).

Figure 2. Trends in annual MJ use: risk, disapproval, & availability in grades 8, 10, & 12 from 1974-2016 (from Johnson et al., 2017)

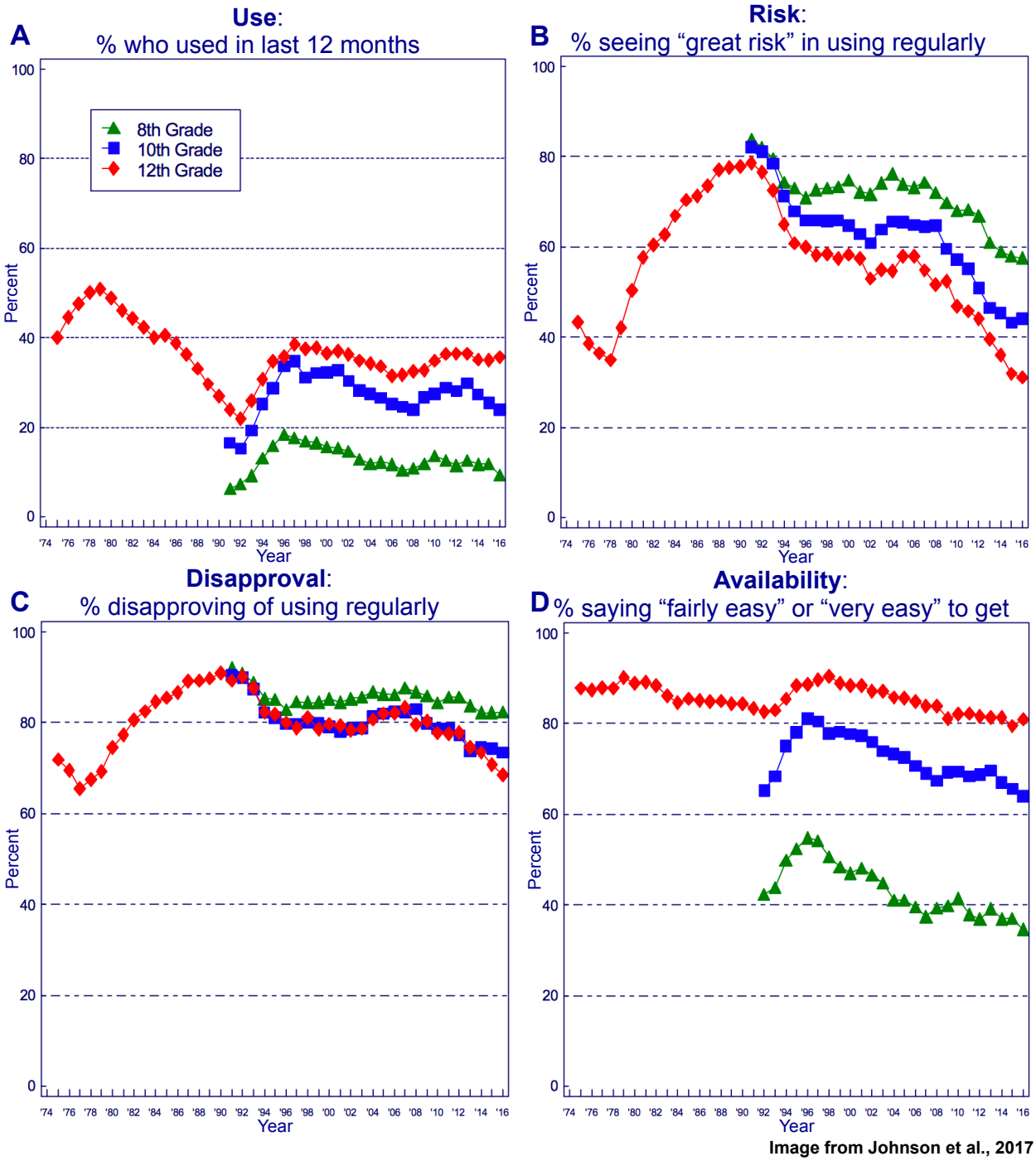


Image from Johnson et al., 2017

Additionally, availability of a drug also impacts prevalence of use: if a drug is difficult to obtain or prohibitively expensive, prevalence rates tend to decline. Marijuana remains the most accessible of all illicit drugs

monitored, and has remained the most accessible throughout the history of the MTF study. The most current survey from 2016 indicated that 81% of 12th graders, 64% of 10th graders, and 35% of 8th graders had easy access to MJ (**Figure 2D**), and although availability has declined since the mid 90s, the majority of adolescents report easy access (Johnston et al., 2017). Given the current trends towards decriminalization or legalization of MJ use, the availability of MJ is expected to remain stable or increase over the next few years.

1.2. Cannabis Use Disorder

In addition to concerns regarding MJ use during periods of critical neurodevelopment, MJ use in otherwise healthy adults can also be problematic if it interferes with typical, day-to-day functioning. The American Psychiatric Association (APA) classifies problematic substance use as a mental disorder in their *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Previous editions of the DSM categorized problematic substance use as either “abuse” (less severe) or “dependence” (more severe); however the newest version, DSM-5, has re-conceptualized the criteria of problematic substance use (reviewed in Black & Grant, 2014; Hasin et al., 2013). The DSM-5 (APA, 2013) no longer uses the terms substance “abuse” and “dependence,” replacing them with the over-arching term substance use disorder, defined as significant clinical and/or functional impairment related to alcohol or drug

use and further rated as mild, moderate, or severe according to the number of symptoms present. The removal of the terms “abuse” and “dependence” was intended to streamline diagnoses and reduce confusion, particularly since the term “dependence” can be synonymous with the pharmacological phenomena of tolerance and withdrawal (Black & Grant, 2014). Cannabis use disorder (less frequently called MJ use disorder) is the term specifically used for substance use disorder related to MJ use (see **Table 1** for detailed diagnostic criteria).

Additionally, previous versions of the DSM did not include withdrawal in the list of symptoms associated with MJ use given continued debate within the scientific community regarding its existence (Hasin et al., 2013). However, significant evidence has demonstrated that withdrawal is reliably observed following MJ discontinuation in at least subsets of chronic, heavy users, and is typically characterized by changes in emotion and behavior (e.g., irritability), reduced appetite/weight loss, and physical discomfort (reviewed in Budney, Hughes, Moore, & Vandrey, 2006). Accordingly, the DSM-5 has addressed this issue, and includes withdrawal and tolerance in the list of possible symptoms for cannabis use disorder.

Table 1. DSM-5 Diagnostic Criteria for Cannabis Use Disorder (APA, 2013)

Criterion	Symptoms
A: Impaired Control	1) Cannabis often taken in larger amounts or over a longer period than originally intended 2) Persistent desire or unsuccessful effort to cut down or control cannabis use 3) Spend a great deal of time obtaining, using, or recovering from the effects of cannabis 4) Craving, or a strong desire or urge to use cannabis
B: Social Impairment	5) Recurrent cannabis use resulting in failure to fulfill major role obligations at work, school, or home 6) Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects 7) Important social, occupational, or recreational activities given up or reduced because of cannabis use
C: Risky Use	8) Recurrent cannabis use in situations in which it is physically hazardous 9) Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis
D: Pharmacological	10) Tolerance, defined by either of the following: a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect b. Markedly diminished effect with continued use of the same amount of cannabis 11) Withdrawal, manifested by either of the following: a. Cessation of heavy and prolonged cannabis use results in at least three of the following: 1. Irritability, anger, or aggression 2. Nervousness or anxiety 3. Sleep difficulty (e.g., insomnia, disturbing dreams) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, headache b. Cannabis (or a closely related substance) is taken to avoid withdrawal symptoms

Severity Rating:
Mild: 2-3 symptoms within a 12-month period
Moderate: 4-5 symptoms within a 12-month period
Severe: 6+ symptoms within a 12-month period

The prevalence of cannabis use disorder has remained relatively stable over the past decade,[1] with some evidence suggesting a trend for a reduction in prevalence among adolescent and young adults (SAMHSA, 2017). However, the most recent national survey indicated that in 2016, approximately 4.0 million people aged 12 or over (1.5% of the population) reported cannabis use disorder within the past year (SAMHSA, 2017). This number includes approximately 585,000 adolescents between 12-17 years old (2.3% of the population) and 1.7 million young adults between 18-25 years old (5% of the population). Although rates may be decreasing slightly, these rates of prevalence underscore the fact that cannabis use disorder remains problematic, particularly among adolescents and young adults.

1.3. MJ Potency and Modes of Use

Cannabis is a plant, and as a result, cannabis or MJ is not a single, uniform product. The cannabis plant has two main species, *indica* and *sativa*, and countless thousands of strains that are hybrid blends of these species. Additionally, MJ is composed of many different chemical constituents, but specific attention has been paid to phytocannabinoids, which are compounds that naturally occur within the plant and impact the mammalian endocannabinoid system via endogenous cannabinoid receptors. Currently, 554 unique chemical constituents have been

[1] Earlier waves of the SAMHSA survey measured prevalence according to DSM-IV criteria for cannabis abuse/dependence, while current waves use DSM-5 criteria for cannabis use disorder.

[2] The vast assortment of concentrates and frequent generation of novel names and

identified in cannabis plants, of which 113 are phytocannabinoids (Aizpurua-Olaizola et al., 2016), and the effects of MJ vary depending on its cannabinoid profile. MJ products vary widely depending on a multitude of factors (e.g., cannabinoid constituent profile), and are available in a range of product types (e.g., conventional flower, hash, concentrates, edibles, topicals, etc.). As might be expected, the effects of cannabis are largely dependent on cannabinoid constituent profile, ratios of individual cannabinoids, product type, and frequency, magnitude, and mode of use (reviewed in Small, 2015).

The potency of MJ is typically classified by the amount of one particular cannabinoid: THC, the primary psychoactive constituent; however recently, increasing attention is being paid to other cannabinoids, particularly cannabidiol (CBD), a primary non-intoxicating constituent of the plant. There is evidence for a dose-dependent effect of THC, with larger blood serum THC concentrations corresponding to increased intoxication and impairment (e.g., Ramaekers et al., 2006). Further, this dose-dependent relationship is impacted by frequency and magnitude of MJ use (e.g., Ramaekers et al., 2009) as chronic, heavy MJ users less demonstrate less acute impairment relative to MJ-naïve participants after receiving the same dose of THC. Additionally, the elimination of THC in the body is relatively slow, with THC metabolites still detectable in blood serum samples even after a week or longer since last use (e.g., Odell, Frei, Gerostamoulos, Chu, & Lubman, 2015), and, as THC is highly lipid

soluble, the pharmacokinetics of its elimination can be impacted by body mass index with increased fatty tissue associated with slower elimination (e.g., Kreuz & Axelrod, 1973). Therefore, it is also important to consider the residual impact of THC potency on regular MJ users beyond periods of acute intoxication.

Over the past several decades, scientists have tracked the average potency of typically available MJ (obtained via DEA seizures) and have reported a dramatic increase in average THC potency (reviewed in Cascini, Aiello, & Di Tanna, 2012). In 1970, the earliest assessment of average THC potency of MJ indicated approximately 1% THC content, which rose throughout the next several decades; specifically, average THC potency of MJ was between 0.66-2.4% throughout the 70s; 2.40-4.75% in the 80s; 2.89-4.53% in the 90s; and 6.05-12.42% in the 2000s (Cascini et al., 2012). The most recent data from DEA seizures indicated that the average THC potency in 2014 was approximately 12% (ElSohly et al., 2016). Sevigny and colleagues (2013) calculated that the rise in THC levels between the 1970s and 2000s was statistically significant at approximately a 6- to 7-fold increase even after controlling for potential confounds. The most salient reason for this dramatic increase in THC potency has been the purposeful breeding of strains with higher potency (ElSohly et al., 2016; Sevigny, 2013).

Perhaps not surprisingly, the increasing THC potency of MJ has coincided with significant *decreases* in CBD content. Over the past

decade, average CBD content has decreased from approximately 0.5% in 2004 to less than 0.2% in 2014; subsequently, the average THC:CBD ratio of typically available MJ has risen drastically from approximately 15:1 to almost 80:1 (ElSohly et al., 2016). Cannabidiol is of particular interest as it has garnered increasing attention for its potential anticonvulsive, anxiolytic, and anti-inflammatory effects (reviewed in Mechoulam, Parker, & Gallily, 2002). Additionally, CBD appears to mitigate the impact of THC and has been shown to reduce the negative or "less desirable" effects of THC (reviewed in Mechoulam, Peters, Murillo-Rodriguez, & Hanus, 2007). ElSohly and colleagues (2016) suggest that the change in THC:CBD ratios in recreational products provides evidence of selective breeding for increased THC and therefore increased psychoactive effects.

Mode of use and preparation or processing of MJ products can also impact THC potency and the effects of MJ. Smoking the dried flower and leaves is most common mode of use, particularly rolled cigarettes ("joints"), pipes, water pipes ("bongs"), hollowed-out cigars ("blunts"), and vaporizers, which vaporize cannabis without combustion allowing for far less product to be used for the same effect; however, oral preparations in food or drink (e.g., edibles) are also popular (reviewed in Johnston et al., 2017). Most recently novel forms of MJ have become increasingly popular; concentrated MJ products (e.g., "dabs," "shatter," "wax," etc.) are created by extracting THC from flower-based MJ products resulting in final products with extremely high THC levels, which typically range from 23.7-

75.9% (Raber, Elzinga, & Kaplan, 2015) or even higher. Currently, very little is known about the prevalence of concentrate use as well as the direct long- and short-term consequences of concentrate use.

Several researchers have recently attempted to assess the prevalence of concentrate use[2] via survey studies. These studies have estimated that approximately 44-84% of MJ users have tried concentrates (Chan et al., 2017; Meier, 2017; Sagar et al., under review). Further surveys of MJ users found that 12.6% of respondents reported daily concentrate use (Loflin & Earleywine, 2014), 25.7% reported weekly use (Loflin & Earleywine, 2014), and 36.5% reported monthly use (Sagar et al., under review). Interestingly, while increased problematic use (e.g., increased tolerance and withdrawal, increased risky behavior, more numerous academic/occupational problems, etc.) have been linked to concentrate use in some of these studies (Loflin & Earleywine, 2014; Meier, 2017), increased dependence has not always been observed (Sagar et al., under review). Taken together, these studies suggest that a large percentage of MJ users have tried concentrates, but the direct long- and short-term consequences of concentrate use (or high THC potency products) on cognitive function remain unclear.

It is important to note the majority of MJ products from national THC potency analyses were flower products, and including concentrate products in these analyses is likely to generate much higher national

[2] The vast assortment of concentrates and frequent generation of novel names and products makes it difficult to quantify concentrate use; this is a burgeoning area of MJ research.

averages (Cascini et al., 2012; ElSohly et al., 2016). Interestingly, Sevigny and colleagues (2014) found that legalization of medical MJ does not lead to a significant increase in THC potency in states after legalization; potency increased an average of only 0.5% after legislation changes. However, when allowances for retail dispensaries were taken into account, the increase was significant (~1%); the authors concluded that potency increases were due to compositional shifts in products supplied by retailers, with a greater share of the market taken up by higher potency products such as concentrates (Sevigny, Pacula, & Heaton, 2014). With the recent popularity of concentrate products and growing demand for dispensaries to provide high THC products, experts believe that national THC potency will continue to increase overtime.

1.4. MJ Use and Cognitive Function

Given increasing popularity of MJ and the growing number of consumers, particularly adolescents and emerging adults, it is important to fully understand the impact of MJ use on cognition and brain function. Until recently, evidence from longitudinal studies suggested that MJ use was associated with lower IQ relative to non-using, healthy controls (Fried, Watkinson, & Gray, 2005; Meier et al., 2012); however, more recent longitudinal studies with larger sample sizes have challenged these previous findings. In a prospective cohort study examining the impact of adolescent MJ use on IQ, Mokrysz and colleagues (2016) did not observe

MJ-associated declines in IQ or education performance after controlling for potential confounds (particularly nicotine use). Further, a longitudinal study of twins found that twins' IQs remained similar over time, regardless of MJ-use status, suggesting that previously reported declines in IQ may not be due to MJ exposure but are more likely attributable to familial factors (Jackson et al., 2016). Findings from these new studies highlight the importance of continued research on the impact of MJ use on IQ.

Numerous studies have demonstrated that chronic, heavy MJ use is associated with cognitive impairment even in the absence of acute intoxication (recently reviewed in Broyd, Van Hell, Beale, Yücel, & Solowij, 2016; Gruber & Sagar, 2017). Executive function deficits, such as impaired inhibitory control and problem solving, are among the most consistently reported impairments associated with chronic, heavy MJ use (reviewed in Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crean, Crane, & Mason, 2011). Interestingly, while studies utilizing conventional neuropsychological tasks of executive function have typically reported impairment in MJ users relative to control participants (e.g., Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012a), functional neuroimaging studies using similar tasks have not consistently demonstrated performance differences despite altered brain activation patterns between-groups (e.g., Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012b).[3] Memory function also appears to be impacted by chronic heavy MJ use. Impaired verbal learning and memory (e.g., Medina et al., 2007a; Solowij

[3] This will be discussed in further detail later in this manuscript.

et al., 2011) have been consistently reported in MJ users; however impaired visual memory findings (e.g., Sneider, Gruber, Rogowska, Silveri, & Yurgelun-Todd, 2013) are less robust. Lastly, deficits in processing speed have been inconsistently reported in MJ users. Most studies have reported deficits (e.g., Auer et al., 2016; Fried et al., 2005), but some have observed faster processing speed in MJ users (e.g., Becker, Collins, & Luciana, 2014) relative to control subjects. Further, evidence suggests that higher frequency of MJ use (Lisdahl & Price, 2012) and increased lifetime MJ exposure (Auer et al., 2016) may mediate this relationship with increased MJ use and exposure associated with greater impairment of processing speed.

Over the past decade, factors characterizing MJ use (e.g., age of MJ onset, frequency and magnitude of MJ use, etc.) have emerged as important areas of investigation. Given concerns about substance use during critical periods of development (reviewed in Arain et al., 2013; Johnson, Blum, & Giedd 2009), particular attention has been paid to the impact of age of MJ onset. Earlier age of MJ onset has been associated with impaired verbal memory and learning (e.g., Pope et al., 2003; Solowij et al., 2011) and executive function (e.g., Battisti et al., 2010; Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016; Fontes et al., 2011; Gruber et al., 2012a), underscoring the need for a more comprehensive understanding of the impact of MJ use overall, and how specific cognitive domains may be affected by early versus late onset of MJ use.

1.5. Summary of MJ Background Information

MJ remains the most popular illicit drug in the US, and the prevalence of current users has continually increased over the past decade. Increased prevalence of MJ use has coincided with reduced perception of harm and disapproval of use, which may be related to recent changes in policy regarding both recreational and medical MJ use. Further, problematic MJ use such as cannabis use disorder remains a national concern, particularly for adolescents and emerging adults who use MJ during a critical period of neurodevelopmental vulnerability. Additionally, over the past several decades, the average potency of MJ, characterized by THC, the primary intoxicating constituent, has increased dramatically, and high potency MJ products termed concentrates have continued to grow in popularity. Given that chronic, heavy MJ use has been associated with cognitive impairment, particularly poorer executive functioning, even in the absence of acute intoxication, the use of higher THC products may result in increased impairment, especially among young consumers. Additionally, researchers are increasingly interested in accounting for the impact of various MJ use characteristics, such as age of MJ onset, on cognitive deficits. The primary goal of this dissertation is the exploration of the direct impact of chronic, heavy MJ use on a specific aspect of executive functioning, cognitive interference, and how MJ use

characteristics may mediate task performance and brain activation patterns.

2. Introduction: Cognitive Interference

Executive function is a complex, multidimensional psychological construct encompassing goal-driven behaviors and decision-making (for review see Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Cognitive interference, often referred to as cognitive control or executive control, is a specific component of executive function associated with attentional shifting and inhibitory control. Specifically, cognitive interference occurs when a prepotent response to a cognitive cue must be inhibited in favor of a less automatic response (Lezak et al., 2004). Cognitive interference processing relies on the principle of focal attention; target detection (focus) produces interference across the system, which slows detection of another target (reviewed in Posner & Petersen, 1990). Conflict resolution is also a key element of cognitive interference, as cognitive interference processing usually involves discriminating between different stimuli: target versus non-target, congruent versus incongruent, or automatic versus non-automatic (reviewed in Petersen & Posner, 2012; and Posner & Petersen, 1990).

Cognitive interference is critical at a low-level, basic form of attention processing (e.g., target detection, attention allocation, etc.), but it also plays an integral role in driving more complex behavior and decision-

making. Cognitive interference processes are involved in whether or not individuals check their phone while driving, decide if they should drink and drive, or make an inappropriate comment at a social gathering. Further, cognitive interference is critical aspect of emotion regulation (reviewed in Ochsner & Gross, 2005). Impaired cognitive interference, such as an inability to inhibit maladaptive behaviors and impulses, has been linked to the etiology and symptom maintenance of many psychiatric disorders, including substance use disorders (reviewed in Lubman, Yucel, & Pantelis, 2004), obsessive-compulsive disorder (reviewed in Muller & Roberts, 2005), major depressive disorder (reviewed in De Raedt & Koster, 2010), and more.

Given that cognitive interference is a multi-faceted process involving many different components, it can be challenging to measure and assess; further, the multiple subprocesses that underlie performance can also complicate interpretation of results. Neuropsychologists have developed a variety of cognitive interference tasks and assessments designed to measure different facets of this complicated process. Three widely-used, standard tasks of cognitive interference are the Stroop Color Word Test (Stroop, 1935), the Eriksen flanker task (Eriksen & Eriksen, 1974), and the Simon task (Simon & Berbaum, 1990). During the Stroop test, participants take longer to name the ink color a word is printed in when it is incongruent with the word itself (e.g., the word blue printed in green) relative to reading words printed in black ink or when colors are

presented as blocks or characters instead of words (Stroop, 1935). This task measures cognitive interference processing as it requires participants to inhibit the prepotent, automatic tendency to read words and instead name colors, which is a less automatic process. In the flanker test, participants take longer and have reduced accuracy identifying a target if it is surrounded or "flanked" by incongruent distractors (e.g., DDTDD) than when a target is surrounded by congruent, identical distractors (e.g., TTTTT; Eriksen & Eriksen, 1974). The Simon test utilizes spatial interference; participants take longer and have reduced accuracy when a target is presented in an incongruent location from the desired response (e.g., a target appears on the left and they must press a button on the right) compared to when a target is placed in a congruent location (e.g., a target appears on the left and they must press a button on the left; Simon & Berbaum, 1990).

2.1. Neural Models of Cognitive Interference

Given its complex nature, researchers have not reached a consensus on a structural and functional neural model of cognitive interference. Several regions of interest (ROIs) have been identified, but their interaction and connectivity is still widely debated. The primary ROI associated with cognitive interference is the prefrontal cortex (PFC), an area critical for goal-directed behavior, decision-making, and rule learning. The PFC is a neocortial region located in the frontal lobe, and is

comprised of interconnected areas that have connections to sensory and motor systems as well as subcortical areas (reviewed in Miller & Cohen, 2001). The top-down model of control of behavior suggests that the PFC provides bias signals to other parts of the brain in order to guide neural activity to the correct pathways necessary to complete the current task (reviewed in Miller & Cohen, 2001; Aron, 2007), but the exact pathway for this process remains unclear. Studies of humans with brain damage have demonstrated that patients with damage to the PFC have impaired performance on tasks of cognitive interference, such as the Stroop task (e.g., Perret, 1974; Vendrell et al., 1995).

The major neural network associated with cognitive interference is the cingulo-fronto-parietal (CFP) attention network (reviewed in Petersen & Posner, 2012; and Posner & Petersen, 1990). Dosenbach and colleagues (2007; 2008) proposed that the CFP network is composed of two synergistic sub-networks that interact and work in parallel: the frontoparietal and cingulo-opercular systems. The frontoparietal system is comprised of lateral regions of the frontal cortex and parietal lobe, particularly the dorsolateral PFC (DLPFC), dorsal frontal cortex, intraparietal sulcus, and inferior parietal lobule. This system has been associated with moment-to-moment task processing and task initiation/switching as well task-related adjustments over time, and is typically most active *at the beginning* of tasks or during periods of change. The cingulo-opercular system is comprised of medial regions of the

cingulate cortex and subcortex, particularly the anterior cingulate cortex (ACC), medial superior frontal cortex, thalamus, and anterior insula. This system has been associated with task set maintenance, overall performance, and is typically engaged and sustained *across the span* of an entire task. While the CFP network remains one of the most popular neural models of attention associated with cognitive interference, much remains unknown about the CFP. Currently, research is focused on the specific role(s) of each ROI as well as the interconnectivity between ROIs in order to further understand how this network functions.

Particular attention has been paid to two sub-regions of the CFP network: the cingulate and DLPFC. For the cingulate, it remains unclear whether conflict monitoring or outcome (i.e., error) monitoring is the most salient indicator for cognitive interference processing (reviewed in Botvinick, 2007). Conflict monitoring theories hypothesize that the cingulate, particularly the ACC, detects conflict during information processing; greater conflict requires increased cognitive inhibition and necessitates the recruitment of more cognitive resources to adjust performance (reviewed in Botvinick et al., 2001). Additionally, more recent work suggests that the ACC is activated in association with commission errors, a direct measure of the failure to inhibit an inappropriate response, and error detection may therefore be another form of conflict detection (reviewed in Botvinick, Cohen, & Carter, 2004). This has led to cognitive interference models suggesting that the ACC learns to predict error

likelihood in order to shape behavior (e.g., Brown & Braver, 2005); however, subsequent studies have not demonstrated modulated ACC activation under high versus low error-likelihood conditions, which weakens the argument for this hypothesis (Nieuwenhuis et al., 2007). Another model suggests that the ACC is part of an error-processing system where negative reinforcement learning signals the ACC to modify behavior through a process called hierarchical reinforcement learning (reviewed in Holroyd & Coles, 2002; Holroyd & Yeung, 2012).

The cascade of control model proposes that the DLPFC creates an attentional set of rules, and that the ACC is responsible for response selection and response evaluation (reviewed in Banich, 2009). This model suggests that there is a temporal cascade of selections processes that occur in the PFC; the DLPFC is activated first and the ACC is activated second in this cascade. However, recently, the hierarchical error representation model proposed that there is cycling between these two regions that begins in the ACC, which generates error signals in response to surprising outcomes, and these signals "train" the DLPFC, which then modulates ACC activation (Alexander & Brown, 2015).

Additionally, there is evidence that the DLPFC may modulate ACC activation. For example, Milham and colleagues (2003) demonstrated practice-related effects during multiple presentations of the Stroop task; DLPFC activation decreased gradually over time, indicating reduced cognitive load, whereas ACC activation was greatly reduced over a

shorter period of time. Stroop task performance and brain activation patterns are also affected by age, with older individuals demonstrating impaired performance with increased ACC activation and reduced DLPFC activation relative to younger participants (e.g., Milham et al., 2002). Further, an electroencephalography study examining the time course of the Stroop task demonstrated that the ACC response was dependent on DLPFC response; when DLPFC activation was low, increased ACC activation was associated with better performance (Silton et al., 2010). The authors suggest that when DLPFC activation is impaired (i.e., reduced) the ACC must increase its activity as a neurocompensatory measure to achieve successful cognitive inhibition.

Researchers continue to debate the precise role of both ACC and DLPFC function as well as how they interact. One weakness of the current models is that they are oversimplified. Recently, Sallet and colleagues (2011) reviewed the literature on the neuroanatomy of the ACC and DLPFC and provided evidence that the ACC and DLPFC are not homogenous structures, and may be further subdivided based on function. Additionally, most models have proposed unidirectional pathways of information processing between the ACC and DLPFC; however, the direction of the pathway is inconsistently reported, suggesting that unidirectional models may not accurately explain the complex process of cognitive interference (reviewed in Sallet et al., 2011). Hopefully, the advent of more sophisticated neuroimaging and computational modeling

techniques will provide more answers regarding the neural pathway of this complicated process.

2.2. MJ Use and Cognitive Interference Processing

Chronic, heavy MJ use has been associated with impaired cognitive interference processing, particularly using during the Stroop task (e.g., Battisti et al., 2010; Fontes et al., 2011; Gruber & Yurgelun-Todd, 2005; Gruber et al., 2012a; Sagar et al., 2015). Additionally, earlier age of MJ onset has been associated with increased difficulty with cognitive control (Battisti et al., 2010; Fontes et al., 2011; Gruber et al., 2012a; Sagar et al., 2015). Further, evidence suggests that the CFP network function may be altered during Stroop performance in chronic, heavy MJ users (reviewed in Batalla et al., 2013; Nader & Sanchez, 2018). Marijuana users demonstrated altered cingulate activation during the Stroop task, with larger and more diffuse midcingulate activation as well as reduced and more diffuse DLPFC activation relative to control participants (e.g., Gruber & Yurgelun-Todd, 2005; Hatchard, Fried, Hogan, Cameron, & Smith, 2014; Sagar et al., 2015). Interestingly, following 25 days of abstinence, chronic, heavy MJ users demonstrated reduced activation of both the cingulate and DLPFC during the Stroop task (Eldreth, Matochik, Cadet, & Bolla, 2004). Additionally, MJ users had poorer performance during the processing of incongruent stimuli on a

flanker task, which was associated with increased DLPFC activation (Abdullaev, Posner, Nunnally, & Dishion, 2010).

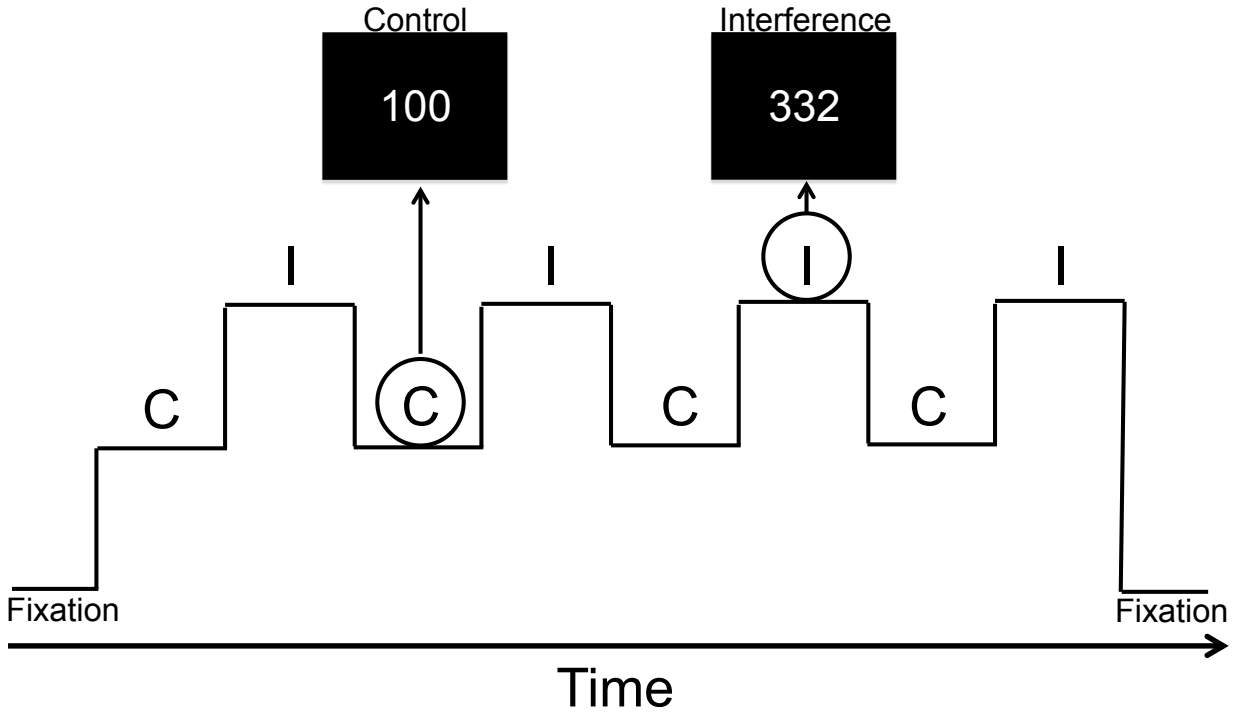
CFP network activation can also be impacted by age of MJ onset; Sagar and colleagues (2015) found that early MJ onset participants had increased cingulate activation in a more anterior aspect of the cingulate cortex as well as poorer Stroop task performance relative to control participants, while late MJ onset participants' activation and task performance was more similar to control participants. Thus far, most neuroimaging research studies of cognitive interference processing in MJ have primarily employed the Stroop task; however, a more recently developed task, the Multi-Source Interference Task (MSIT), has been gaining popularity.

2.3. The Multi-Source Interference Task (MSIT)

The current project utilizes the Multi-Source Interference Task (MSIT), which requires multiple types of cognitive interference processing and is a combination of the Stroop, flanker, and Simon tasks (Bush, Shin, Holmes, Rosen, & Vogt, 2003). The MSIT paradigm involves the presentation of stimuli sets comprised of three numbers (1, 2, 3, 0); all of the sets contain two identical distractors and a target number that differs from the distractors (e.g., 311, 100). Using a button press, participants must select the identity of the target number that is different from the others. The task consists of two conditions presented in separate

alternating blocks. During the control condition (C), the identity of the target numeral always matches its position on the button box, and the distractor numbers are always zeros (100, 020, or 003). During the interference condition (I), the target number is placed in an incongruent position relative to its location on the button box, and the distractor numbers are always other potential button box responses (e.g., 332, 212, etc.). Individuals must therefore inhibit the automatic tendency of responding to the target number's *position*, and instead report the *identity* of the target number. The MSIT was designed as a functional neuroimaging task; therefore, most studies utilize a block design format of the MSIT that begins and ends with a fixation period and includes four blocks of the C condition followed by and alternating with the I condition (**Figure 3**). Although different versions of the MSIT exist, most studies use the specific paradigm guidelines presented in Bush & Shin (2006) in which each stimulus is presented for 1.75 seconds and each block contains 24 trials each of C and I stimuli.

Figure 3. Multi-Source Interference Task (MSIT) Schematic (Image from Gruber et al., 2017)



Task performance of the MSIT is assessed by response time (RT) and task accuracy, typically expressed as either percent correct (percent accuracy) or percent wrong (percent error). Performance is usually examined within each condition (C and I separately) as well as an I-C contrast in order to assess the effects of "pure" cognitive interference processing. The I-C contrast subtracts the control (C condition) measure from the experimental (I condition) measure in order to parse out the effects of the experimental condition without the effects of background processing, and larger contrast scores are typically associated with greater difficulty with interference processing (Donders, 1969). Additionally, some studies (e.g., Gruber et al., 2012b; 2017; 2018) further examine error type: errors of omission (no response given, reflective of

slower or overloaded cognitive processing) or commission (incorrect response given, reflective of a failure to appropriately inhibit an incorrect response). To date, all studies using the MSIT have reported the expected findings of better performance (faster response times and/or better accuracy) in the C condition compared to the I condition, indicating increased cognitive load is required during the I condition, and affirming that the MSIT does in fact assess cognitive interference processing. Additionally, research utilizing healthy control twin pairs indicated a moderate level of heritability for I trials (45% of the variance was attributed to genetic factors), but not for C trials or the I-C contrast (Matthews et al., 2007). This provides evidence that genetic factors contribute to task performance, but this appears to be localized to the more difficult I condition.

In order to further investigate the impact of using multiple forms of cognitive interference in the MSIT, Stins and colleagues (2005) assessed the relative contribution of each type of cognitive interference processing during the MSIT: spatial (Simon) versus flanker interference. The authors concluded that the majority of cognitive interference processing required during the MSIT was primarily attributed to flanker interference and less to spatial interference. Stimuli incorporating multiple forms of cognitive interference (both flanker and spatial interference) required longer response times and had higher error rates than stimuli incorporating just one form of cognitive interference, suggesting an additive effect of

including multiple types of interference. Further, they emphasized the importance of engaging semantic processing during the MSIT. For example, some versions of the MSIT utilize symbols or letters (most popularly the *x*) as distractors during the C condition instead of zeros (e.g., 1xx, x2x, xx3). Stins and collaborators (2005) argued that using these symbols makes the C condition easier as these characters are from a different semantic category than numbers, which reduces the impact of flanker interference. Therefore, the two types of C conditions do not engage the exact same cognitive processing networks, and versions of the task using symbols or letters during the C condition do not require as much cognitive control as those utilizing only numbers.

2.3.1. MSIT: Neuroimaging Findings

The MSIT paradigm was specifically designed and created to robustly activate the CFP attentional network (Bush et al., 2003; 2006; 2008a). In the paper that introduced the MSIT, Bush and colleagues (2003) demonstrated that the I-C MSIT contrast produced increased activation of the medial frontal regions (particularly the dorsal ACC and right medial frontal gyrus), lateral frontal regions of the PFC (particularly the inferior and left superior frontal gyrus), superior parietal, and premotor cortex in healthy control participants. This pattern of increased CFP network activation during the MSIT has been confirmed and explored using a variety of imaging modalities in addition to functional magnetic resonance

imaging (fMRI), such as functional near-infrared spectroscopy (NIRS; Harrivel et al., 2013) and electroencephalography (EEG; e.g., Robertson et al., 2014). Further, independent component analyses (ICA) revealed increased MSIT-related medial frontal and lateral frontal connectivity, further suggesting that communication between these regions is critical during cognitive interference processing (Cocchi et al., 2012). Additionally, increased cingulate activation during the I-C contrast positively correlated with increased response time in healthy control participants and was moderately heritable, with 37% of activation variance attributed to genetic factors suggesting a potential endophenotype linking MSIT performance and cingulate activation (Matthews et al., 2007). Overall, evidence suggests that the MSIT robustly activates the CFP attentional network in healthy control samples, particularly medial and lateral frontal regions, such as the cingulate and DLPFC, as well as the parietal cortex.

MSIT performance and neural activation have also been assessed in a variety of psychiatric disorders including general anxiety disorder (GAD; Fitzgerald et al., 2013), posttraumatic stress disorder (PTSD, Shin et al., 2011), obsessive compulsive disorder (OCD; Cocchi et al., 2012; Fitzgerald et al., 2010; 2013; Yucel et al., 2007a), major depressive disorder (MDD; Davey, Yucel, Allen, & Harrison, 2012), bipolar disorder (Gruber et al., 2017), attention-deficit/hyperactivity disorder (ADHD; Bush et al., 2008b; 2013), schizophrenia/schizoaffective disorder (Harrison et

al., 2007; Heckers et al., 2004; Ikuta et al., 2012; 2014; Stern et al., 2009), and non-suicidal self-injury (Dahlgren et al., accepted 2018). Thus far, the MSIT has only been used in limited studies of substance use, which have included samples of MJ-using (Gruber et al., 2012b; Harding et al.; 2012) and opiate-using individuals (Yucel et al., 2007b).

Overall, performance differences on the MSIT have not been observed in most studies comparing healthy control and psychiatric samples (e.g., Cocchi et al., 2012; Davey et al., 2012; Gruber et al., 2012b, etc.). With regard to the neuroimaging findings, *increased* CFP activation (particularly within the cingulate) during the MSIT is commonly observed in mood and anxiety disorders as well as in substance use disorders. There are some exceptions indicating poorer MSIT performance as well as evidence for both increased and decreased CFP activation in individuals with psychiatric disorders, particularly schizophrenia (Ikuta et al., 2014) and bipolar disorder (Gruber et al., 2017); however these findings may be impacted by the use of antipsychotic medication.

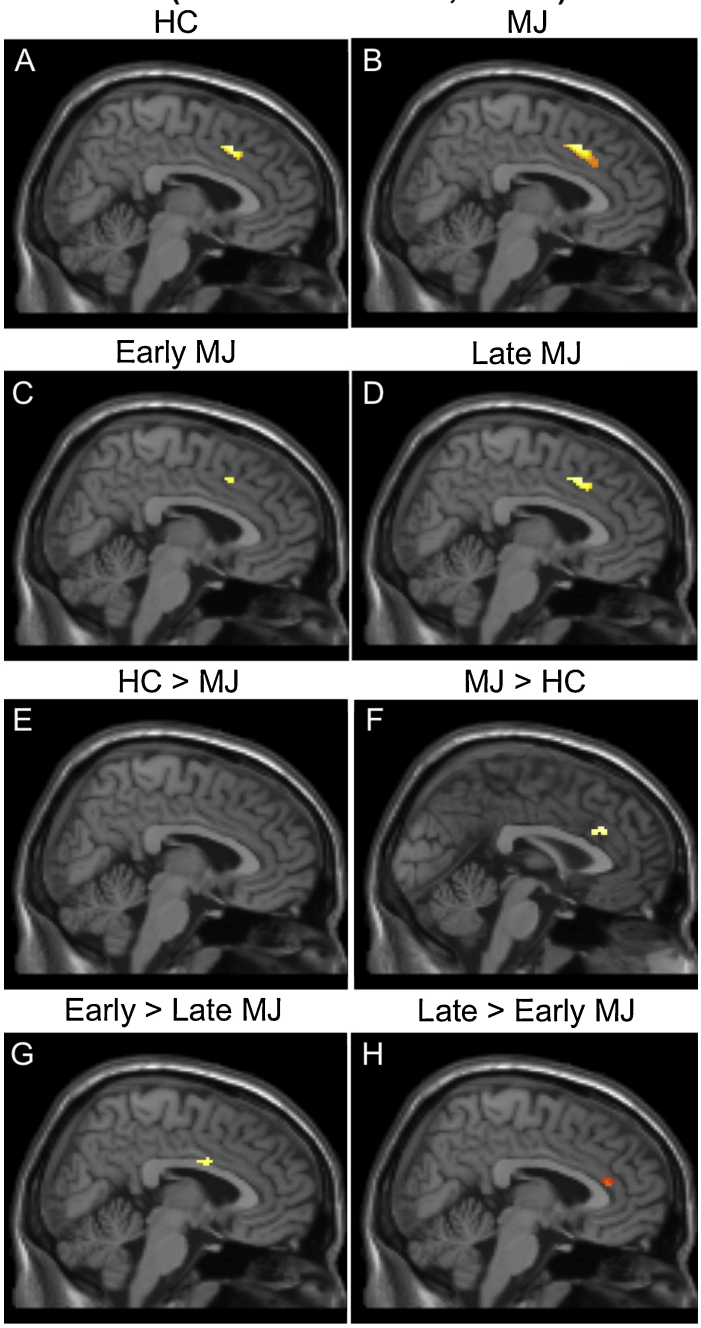
In studies of substance users, differences in MSIT performance have not been observed relative to control participants (Gruber et al., 2012b; Harding et al., 2012; Yucel et al., 2007b). Harding and colleagues (2012) did report a trend toward MJ-users demonstrating lower percent accuracy on the I condition relative to healthy control participants (p=.09); however, this was not statistically significant, and was not observed in

another study of MJ users (Gruber et al., 2012b). Differences in task performance between these two studies may be related to the total duration of MJ use in subjects (*M*>10 years in Harding et al., 2012 versus *M*=5.83 years in Gruber et al., 2012b), emphasizing the importance of assessing the impact of MJ use characteristics on MSIT performance and brain activation. Additionally, the single study examining MSIT performance in opiate-using individuals relative to healthy controls also detected no differences between the groups, including even those at trend level (Yucel et al., 2007b).

Despite a lack of performance differences on the MSIT between substance users and healthy control participants, neuroimaging data from these populations have revealed interesting findings. Gruber and colleagues (2012b) found that chronic, heavy MJ users had significantly greater cingulate activation during the I-C contrast compared to healthy control participants (**Figure 4F**). When age of onset of MJ use was accounted for, early onset MJ users (regular MJ use established prior to age 16) showed increased activation in the midcingulate as compared to late onset MJ users (regular use established at age 16 or older), who demonstrated increased activation in more anterior portions of the cingulate (**Figure 4G & 4H**). Harding et al (2012) did not report significant between-group differences in activation patterns, but connectivity analyses revealed that MJ users had increased task-related functional connectivity from frontal lobe regions, particularly the dorsal cingulate, PFC, and

insula, to the occipitoparietal cortex relative to control participants. Increased connectivity between these regions was associated with increased demand for cognitive control in MJ users, but not in control participants. Additionally, increased connectivity between the PFC and the occipitoparietal cortex positively correlated with variables related to MJ use, particularly age of onset and total lifetime exposure to MJ.

Figure 4. Functional MRI activation in MJ users during the I-C Contrast of the MSIT (from Gruber et al., 2012b)



Additionally, Gruber and colleagues (2018) recently assessed MSIT performance in a sample of patients seeking medical MJ (MMJ) treatment for a variety of health conditions (the most common indications were

chronic pain and anxiety). These patients were assessed prior to initiating MMJ treatment and again after three months of MMJ use. At baseline, the patient group had poor performance on the MSIT and very little cingulate or DLPFC activation. After three months of MMJ treatment, patients demonstrated significant improvement on task performance (both response time and percent accuracy) as well as increased cingulate and DLPFC activation, such that after MMJ treatment, fMRI activation patterns were much more similar to previous findings in control participants. Further, after MMJ treatment, patients also reported improvements in measures of depression, energy, physical limitations, quality of sleep, as well as notable reductions in conventional medication use, particularly opioids and benzodiazepines. The authors suggest that MMJ treatment was associated with improvement of clinical symptoms, overall health, and a reduction of conventional medication, resulting in improved cognitive processing. Although recreational MJ use has typically been associated with decrements in cognitive function, this study provides evidence that MMJ patients may not demonstrate the same cognitive decrements as recreational users and may, in fact, demonstrate *improvements* in cognitive processing as well as general health.

In a study of opioid-dependent individuals, fMRI data revealed significantly greater superior and inferior parietal lobe activation as well as greater DLPFC activation during the I-C contrast in opiate-users compared to healthy control participants (Yucel et al., 2007b). Although cingulate

activation during the I-C contrast was not significantly different between the groups, response errors positively correlated with cingulate activation in the control group, while no such correlation was demonstrated in the opiate-dependent group. The authors suggested that this may be reflective of self-monitoring and performance awareness in the control group, which was not detected within the opiate-dependent group. Additionally, magnetic resonance spectroscopy (MRS) data, which provides data regarding *in vivo* metabolite concentrations, indicated that opiate-dependent individuals had reduced concentrations of NAA and glutamate/glutamine in the cingulate relative to the control group, suggesting biochemical abnormalities of the cingulate may be associated with opiate use. In summary, although studies of substance users have not revealed significant differences in task performance during cognitive interference processing, they provide strong evidence for *increased* cingulate and DLPFC activation during the MSIT.

In light of these findings, the main interpretation of CFP network alterations without concomitant performance differences in psychiatric disorders is that it likely reflects neurocompensation (Fitzgerald et al., 2010; Gruber et al., 2012b; Harding et al., 2012; Harrison et al., 2007; Yucel et al., 2007a; 2007b). This neurocompensatory theory proposes that deviations from the typical healthy control CFP network activation are considered less efficient, particularly when increased activation is needed to achieve the same level of task performance. Poldrack (2015) argues

that this neural efficiency interpretation is merely another way of describing the data. Multi-modal imaging studies have attempted to clarify the underlying mechanism of activation differences (e.g., they may be related to connectivity differences), but the current interpretation continues to be the neurocompensatory theory.

Additionally, there is some evidence that CFP activation correlates with MSIT performance, and that this association may be disrupted in patients with psychiatric disorders. For example, Yucel and colleagues (2007b) found that dorsal cingulate activation during the MSIT positively correlated with performance in healthy control participants, but not in opiate users. Further, successful treatment may "normalize" brain activation patterns and restore a link between neural activation and MSIT performance. Individuals with ADHD demonstrated MSIT brain activation patterns more similar to control participants after successful treatment with methylphenidate (Bush et al., 2008b; 2013). Additionally, Ikuta and colleagues (2014) found evidence that following antipsychotic treatment, patients with psychotic disorders demonstrated decreased globus pallidus activation during the MSIT, which was associated with improved performance accuracy and reduced psychotic symptoms. However, this evidence remains limited by the paucity of significant between-group MSIT performance differences between healthy control and psychiatric samples. Fortunately, this issue may be related to the current analytic methodology used to assess MSIT behavioral data.

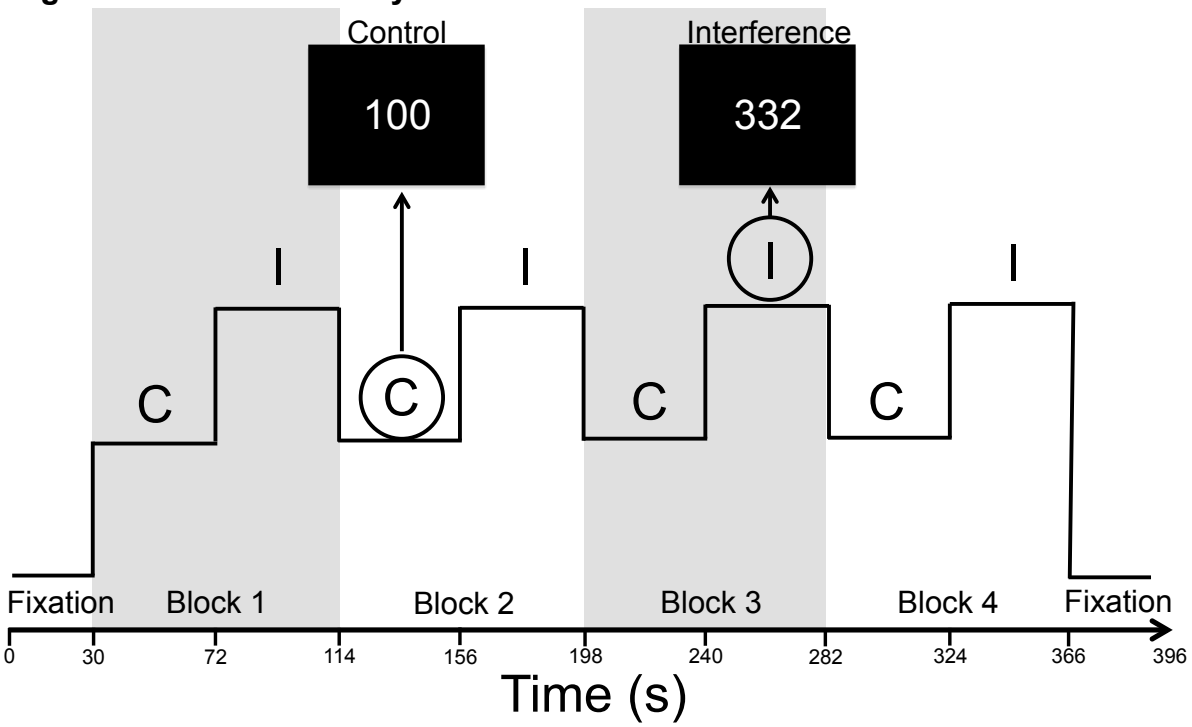
2.3.2. MSIT: A Novel Discrete Block Analysis Scheme

The current, standard method of analyzing MSIT performance involves assessing overall task performance or data averaged across the entire task (e.g., an average of all I trials or all C trials). However, task performance is often dynamic with changes over time, particularly at the initiation of tasks (reviewed in Lezak et al., 2004). If task performance changes over time, using an average of overall task performance will result in larger data variance than if performance was assessed from discrete time blocks rather than the whole task. Increased variance results in reduced power and limits the ability to detect smaller effect sizes, potentially yielding a greater number of null results. Therefore, previous studies examining MSIT performance using overall averages from the entire task may be underpowered compared to analyses that control for performance changes over time.

Given that most researchers use a block design version of the MSIT to yield greater signal and aid in the administration and analysis of neuroimaging data, one solution to the current limitation in “whole task” performance analyses is to utilize a novel, discrete block analysis scheme designed to assess performance over individual time blocks (**Figure 5**). Instead of only comparing trials averaged across the entire task for each condition, performance can also be assessed during each individual I and C block (Blocks 1, 2, 3, and 4). Block can then be used as a repeated

measures variable, which would provide an easy and reliable method of accounting for MSIT performance changes over time.

Figure 5. MSIT Schema by Block



Assessing performance over time (e.g., using Block or Trial as a repeated measures variable) is often employed in studies using neuropsychological assessments of learning or sustained attention. For example, sustained attention is required during continuous performance tasks, and task performance is likely to change over time as a result of difficulty maintaining vigilance (reviewed in Lezak et al. 2004). The typical analysis method for the Conners Continuous Performance Test (CPT) involves a block design similar to the proposed MSIT scheme described above. CPT performance is subdivided into discrete blocks, and

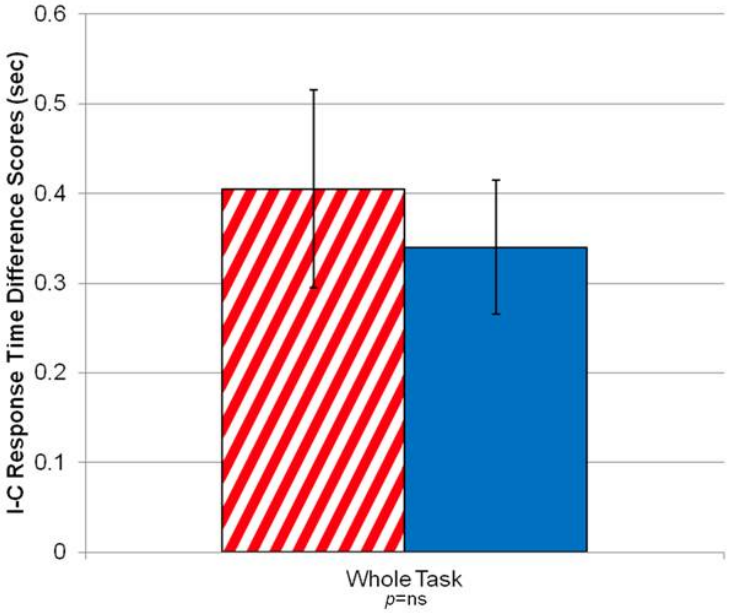
performance averages from each individual block are compared across the task to account for performance differences over time (reviewed in Conners, Epstein, Angold, & Klaric, 2003). Similarly, Dougherty and colleagues (2005) have implemented block analyses on their tasks of impulsivity (e.g., the GoStop Impulsivity Paradigm). Given the dynamic nature of executive functioning and cognitive interference processing, we propose that accounting for MSIT performance changes over time as part of the behavioral task performance analyses will reveal significant MSIT performance differences between healthy control and MJ users, which would impact previous interpretations of the MSIT neuroimaging data.

This discrete block analysis strategy was recently employed in a reevaluation of previously published (in Shin et al., 2011) MSIT task performance data in patients with PTSD. Shin and colleagues (2011) used the traditional, whole task analyses and reported a trend (p=.07) for impaired I-C response time in trauma-exposed individuals with PTSD (M=0.41s, SD=0.13) and their trauma-unexposed co-twins (M=0.40s, SD=0.09) compared to trauma-exposed individuals without PTSD (M=0.35s, SD=0.07) and their trauma-unexposed co-twins (M=0.33s, SD=0.08; **Figure 6A**). Interestingly, a reevaluation of this dataset using the new, discrete block analysis method, assessing task performance over time course with Block as a repeated measures variable, yielded significant between-group task differences, particularly during the early performance blocks (Dahlgren et al., in prep). During early MSIT trials

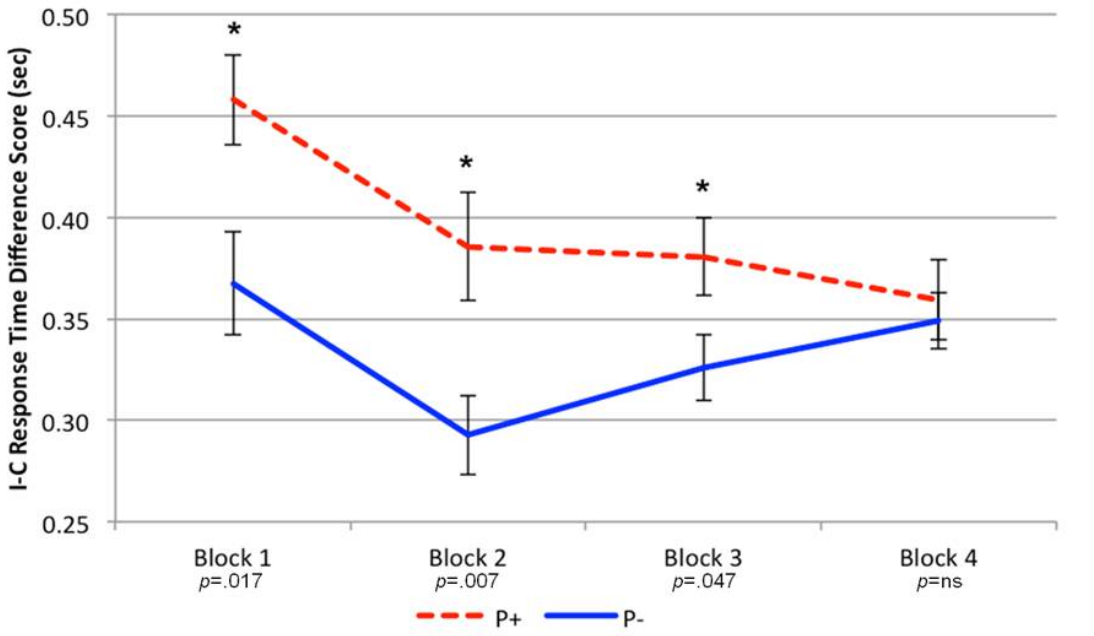
(Blocks 1-3), trauma-exposed participants with PTSD and their trauma-unexposed identical co-twins (P+ group) demonstrated significantly larger I-C contrast response times than trauma-exposed individuals without PTSD and their trauma-unexposed identical co-twins (P- group**; Figure 6B**). This difference was not observed in the last block of MSIT performance (Block 4), suggesting that impaired performance in a clinical sample may normalize over time. These results indicate that performance deficits during the initial blocks of the MSIT in individuals with PTSD and their high-risk co-twins may reflect a familial vulnerability factor for PTSD. Further supporting such an interpretation, trauma-exposed twins' PTSD symptom severity positively correlated with both their own early trial I-C response time and those of their trauma-unexposed co-twins. Additionally, the main effect of the repeated measures Block variable was significant (p=.034), indicating that MSIT performance does change over time and should therefore be assessed in statistical analyses.

Figure 6. Comparison of Conventional Whole Task vs Novel Discrete Block MSIT Analyses in Individuals with PTSD and Their Twins (P+) and Trauma-Exposed Control Participants and Their Twins (P-)

A. Conventional Analysis Scheme: Whole Task (Shin et al., 2011)



B. Novel Analysis Scheme: Discrete Blocks Over Time (Dahlgren et al., in prep)



These findings provide evidence that previous results from studies assessing MSIT performance using the traditional, whole task approach may be underpowered relative to methods that evaluate performance changes over time. Accordingly, reanalysis and reinterpretation of previous MSIT data may be necessary. Additionally, these results provide evidence that MSIT task performance does, in fact, change over time, and it is therefore prudent for neuroimaging analyses to also incorporate a method of assessing for potential activation differences over time. As most fMRI analyses currently only examine the I-C contrast using whole task averages, implementing a discrete block design analysis method as described above could yield important information regarding how activation differences may change over time.

3. The Present Research

Given the popularity of MJ and growing number of daily consumers, particularly adolescences and emerging adults, it is important to fully understand the impact of MJ use on cognition and brain function. This project extends previous research assessing cognitive interference processing in chronic, heavy MJ users during the completion of the MSIT. Marijuana-associated CFP network activation differences during the task have been previously reported, but performance differences have been inconsistent (Gruber et al., 2012b; Harding et al., 2012). However, these previous studies only examined task performance and fMRI activation

averaged across the whole task; this project examined changes over the course of the task. Since age of MJ onset was of particular interest, MSIT performance and neural activation differences were assessed over time in both two-group (control vs MJ) and three-group (control vs early MJ onset vs late MJ onset) analyses. Additionally, the impact of age of onset of MJ, frequency (episodes of use /week) and magnitude (grams/week) of use, and urinary THC concentration was also assessed in order to identify which of these variables contributes the most unique variance.

3.1. Hypotheses

With regard to MSIT performance, we hypothesized that when comparing MJ users to healthy control participants, we would observe a significant main effect of MSIT Block, with performance improving (i.e., faster response time and better performance accuracy) over time across all subjects. Previous studies of MJ users have not demonstrated a significant main effect of Group when comparing MJ users to control participants (Gruber et al., 2012b); although trends for poorer performance accuracy have been observed in MJ users relative to control participants (Harding et al., 2012). Therefore, we did not expect to find a significant main effect of Group. However, given our previous findings using the novel discrete block analysis scheme (Dahlgren et al., in prep), we hypothesized that we would observe a significant Group by Block interaction, with MJ users demonstrating impaired performance during the

beginning blocks of the MSIT relative to controls participants, and that these differences would stabilize over time resulting in no between-group differences by the last block of the task. Specifically, we expected that relative to control participants, MJ users would have faster response times, but would also demonstrate poorer performance accuracy early in the task, highlighted by increased commission errors, suggesting difficulty with inhibition of incorrect responses.

Further, in order to examine the effect of age of MJ onset, the MJ-using group was divided into early and late MJ onset groups, which has been a standard analytic procedure in previous studies (e.g., Fontes et al., 2011; Gruber et al., 2012a; 2012b; Sagar et al., 2015). When comparing MSIT performance across three groups (control, early MJ, and late MJ), we hypothesized that any impairment observed in the MJ group as a whole would be primarily driven by the early onset group. Similar to our hypotheses from the two-group analyses, we hypothesized that we would observe a significant main effect of MSIT Block with performance improving (i.e., faster response time and better performance accuracy) over time across all subjects. We did not expect to find a significant main effect of Group, but we did expect to observe a significant Group by Block interaction with the early onset MJ users demonstrating impaired performance during the initial blocks of the task relative to both the control and the late onset MJ users, and that these differences would stabilize over time resulting in no between-group differences by the last block of the

task. Specifically, we expected that relative to control participants and late onset MJ users, early onset MJ users would have faster response times, but would also demonstrate poorer performance accuracy early in the task, highlighted by increased commission errors suggesting difficulty with inhibition of incorrect responses. We expected that the control participants and the late MJ onset group would have similar MSIT performance across time.

With regard to MSIT-related brain activation changes, we expected to replicate main effects of Group previously reported (Gruber et al, 2012b). Specifically, for the two-group analyses, we expected task-related cingulate and DLPFC activation in both the control and MJ-using groups, and that comparisons between the groups would reveal increased ROI activation in the MJ group relative to the control group. For the three-group analyses, we expected task-related cingulate and DLPFC activation in all three groups, control, early MJ, and late MJ, and that comparisons between the groups would reveal increased ROI activation both the early MJ and late MJ groups relative to the control group. Specifically, we hypothesized that the early MJ group would have increased activation in the midcingulate relative to the late MJ group, while the late MJ group would have increased activation in a more frontal, anterior portion of the cingulate relative to the early MJ group.

Given that the proposed discrete block analysis strategy is novel, and had never been used for neuroimaging analyses of the MSIT, we did

not have specific hypotheses regarding precisely how cingulate and DLPFC activation would change over the time course of the task. Previous research using the conventional whole task analyses have demonstrated increased MSIT activation of the cingulate (Gruber et al., 2012b), which we expected to replicate in the current study; further, we proposed that any attenuation of this signal over the time course of the task would be indicative of reduced cognitive load, as participants acclimate to the task, similar to practice-related reductions in cingulate activation observed by Milham and colleagues (2002) during the Stroop task. In regard to between-group differences over time, we expected that the most impaired group (i.e., the MJ using group in the 2-group analyses and the early MJ onset group in the 3-group analyses) would demonstrate greater CFP activation relative to the control group, and that the CFP activation pattern of the early MJ group would be less similar to the control group than the late MJ group.

Lastly, given some evidence that CFP activation correlates with MSIT performance (e.g., Yucel et al., 2007b), we planned correlational analyses in order to examine whether cingulate and DLPFC activation are related to MSIT performance in each of our proposed group samples: control, MJ users as a whole, as well as early onset MJ users and late onset MJ users. Additionally, we also planned to use correlational and multiple regression techniques to assess the impact of age of onset of MJ, frequency (episodes/week) and magnitude (grams/week) of MJ use, and

urinary THC concentration. Previous research has indicated that earlier age of MJ onset, increased frequency, and greater magnitude of MJ use are all associated with increased impairment during cognitive interference processing, while urinary THC concentration is generally a less salient predictor of impairment (e.g., Dahlgren et al., 2016; Gruber et al., 2012a). We predicted that age of onset and frequency and magnitude of MJ use would contribute the most unique variance to regression modeling of MSIT performance measures and fMRI activation data, with age of MJ onset being the primary predictor.

3.2. Participants

Participants from the current study (age range: 18-44; *M*=23.26, *SD*=5.63) were recruited from the Greater Boston area, with participants from both downtown and suburban locations, and included 64 chronic, heavy MJ-smoking participants and 34 healthy nonsmoking control participants. Recruitment sites included local colleges and universities, athletic centers, and other public locations as well as internet forums. In order to ensure that the control group was similar to our MJ-using group, we enrolled control participants with similar age and education levels (both variables within ±2 year range) as our MJ-users.

In order to ensure to ensure that individuals did not meet criteria for any Axis I pathology (other than MJ abuse or dependence[4] in the MJ-

[4] Since the SCID from DSM-IV was used, MJ use is classified by the standards from that version.

using group), participants received the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P; First et al., 1994). Participants were excluded from the study if they reported drinking more than 20 alcoholic beverages per week, met criteria for binge drinking, or met diagnostic criteria for current or past alcohol dependence or any other Axis I diagnosis. In addition, participants were excluded if they reported more than 15 lifetime uses of any category of illicit drugs or recreational use of prescription drugs, or had a positive urine screen for any drug (excluding MJ for the MJ-using group). Further, exclusion criteria also included head injury with loss of consciousness; neurological disorders; current or previous use of psychotropic medications; non-native English speakers (required for the neurocognitive battery); and any MRI contraindications (e.g., metal implants, pregnancy, claustrophobia, etc.).

To qualify for study entry, MJ users were required to report a minimum of 1,500 lifetime uses of MJ, currently MJ use at least 5 times per week, and test positive for urinary cannabinoids. MJ users were also required to abstain from using MJ at least 12 hours before their study visit to ensure that they were not acutely intoxicated at the time of assessment. All participants provided a urine sample upon arrival at the laboratory, which was screened for pregnancy, which is a contraindication for neuroimaging, in female participants (QuPID® hCG pregnancy test), as well as illicit and prescription drugs including THC, amphetamines, cocaine, methamphetamine, opioids, phencyclidine (PCP),

benzodiazepines, tricyclic antidepressants, barbiturates, methadone, ecstasy (3,4-methylenedioxymethamphetamine, or MDMA), and oxycodone (Triage® Drugs of Abuse Panel: Immediate Response Diagnostics). This procedure is required to (1) ensure subjects do not test positive for other drugs, (2) to determine whether subjects have used MJ recently enough to have a positive urine screen, and (3) to encourage subjects to abstain from MJ from the previous evening as subjects were repeatedly reminded that they would be tested for MJ. For MJ users, an aliquot of urine was sent to an outside laboratory (Quest Diagnostics) for quantification of urinary THC concentration normalized to creatinine levels via gas chromatography–mass spectrometry.

3.3. Procedures

This study was part of a larger neuroimaging study designed to be completed in a single eight-hour visit to McLean Hospital or two separate four-hour visits[5] depending on each participant's preference. Participants were paid $25/hour for a total of $200 for completing the entire study. Before participation, all study procedures, including the voluntary nature of the study, were explained, and participants were required to read and sign an informed consent form approved by the McLean Hospital Institutional Review Board. Additionally, before participation in the study, participants were given information on security provisions regarding how their medical

[5] If participants preferred to split the study into two separate visits, every attempt was made to schedule these visits as close together as possible (typically within a week or sooner).

information is protected under the Health Insurance Portability and Accountability Act (HIPAA).

Study participants completed a clinical interview and battery of clinical and diagnostic assessments (approximately 2-2.5hr) in order to evaluate current state and to ensure that groups were well matched for mood, anxiety, and depression. Briefly, these measures included the Profile of Mood States (POMS; Pollock, Cho, Reker, & Volavka, 1979), which measures current mood state and provides scores for the individual domains of vigor, anger, confusion, tension, and depression, as well as a total mood disturbance score; the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); the Positive and Negative Affect Schedule (PANAS; Watson, Clark, Tellegen, & Sarason, A., & Irwin, 1988); the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979); the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959), and the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995), which provides scores for three subscales of impulsivity, attention, motor, and non-planning as well as a combined total impulsivity score. Participants also completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) in order to assess current level of nicotine use. Participants were also asked to provide information regarding their current and lifetime alcohol use during the

SCID-P including the number of days of alcohol use in the past month. Nutrition was assessed using body mass index (BMI). Finally, participants were administered either the Wechsler Abbreviated Scale of Intelligence (WASI) or an abbreviated version of the Wechsler Adults Intelligence Scale – Revised (WAIS-R), both of which provide an estimate of IQ (Wechsler, 1999; 1981).

During the SCID and a custom, proprietary MJ use questionnaire, MJ users provided information regarding their lifetime and current history of MJ use. Marijuana use variables included age of MJ onset, defined as the age at which subjects began using MJ on a routine, expected, and consistent basis (i.e., first "regular" use), duration of regular MJ use (years), and type of MJ products use. A modified Timeline Followback (TLFB; Sobell et al., 1988) procedure was employed in order to assess frequency (episodes/week) and magnitude (grams/week) of MJ use, with a specific focus on use over the previous 7–10 days as well as over the course of the past 12 months.

The ideal order of procedures[6] was 1) consent, 2) MRI safety screen, 3) urine drug/pregnancy screen, 4) self-report scales, 5) clinical interview, 6) neuropsychological testing, 7) neuroimaging, 8) payment, 9) goodbye & debrief. However, this order of procedures was often adjusted due to individual participant schedules as well limitations of the MR scanner schedule. Importantly, consent procedures were always completed prior to any other study measures at the start of visit 1 with re-

[6] Food and bathroom breaks were offered to participants throughout their visit.

consent established at the start of visit 2, if necessary. Additionally, urine screens were always performed at the beginning of the study visit, as the presence of illicit substances was exclusionary (except for THC, in the MJ-using group).

3.4. MSIT Task Parameters

The MSIT task was comprised of four blocks of C trials, which alternated with four blocks of I trails (**Figure 5**). Each trial was presented for 1750ms, and each block was comprised of 24 trials for each of the two conditions, therefore, a total of 192 number sets were presented during the entire task. All variations of number sets possible under each condition were presented randomly and an equal number of times. The task began and ended with a 30s fixation period to assist in drift correction as well as between-run assessment, and the entire task took 6 minutes and 36 seconds to complete. Immediately before scanning, participants completed a practice version of the task, and in order to ensure that all participants understood the task, the fMRI scanning did commence until participants correctly completed at least three practice trials in a row without feedback from the researchers.

3.5. Data Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 24 (Armonk, NY, USA:

IBM Corp.). Analyses of variance (ANOVAs) were used to assess between-group and within-subject differences (α=0.05). Performance outliers were identified and excluded from analyses using a 1.5x interquartile range boundary. Levene's *F* was used to confirm that the assumption of homogeneity of variance was met, and if this assumption was violated, non-parametric tests (e.g., Kruskal-Wallis *H*, etc.) were used instead. When appropriate, Scheffe (or non-parametric Mann-Whitney *U*) tests were conducted for between-group *post hoc* comparisons and Fisher's Least Significant Difference (LSD) (or non-parametric Wilcoxon-signed rank) tests were conducted for repeated measures *post hoc* comparisons.

Analyses were performed two ways. First, 2-group analyses were performed comparing the control participants to all MJ users, and then 3-group analyses were performed comparing the control participants to early MJ onset (regular MJ use before age 16; *n*= 27) and late MJ onset (regular MJ use starting at age 16 or older; *n*= 37) participants in order to assess the potential impact of age at onset on cognitive function. This method of defining and assessing age of MJ onset has previously been used in several studies (e.g., Dahlgren et al. 2016; Gruber et al., 2012a; 2012b; Sagar et al., 2015, etc.).

Demographic data (e.g., age, IQ, etc.), clinical state data (e.g., BDI, POMS, etc.), and substance use data (e.g., age of MJ onset, etc.) were assessed for between-group differences via one-way ANOVAs for the 2

group (control vs MJ user) and 3 group analyses (control vs early onset vs late onset). Chi square analyses were used to compare nominal data (e.g., sex, etc.). If groups differed significantly on any demographic variables (e.g., age, IQ, etc.), analyses of covariance (ANCOVAs) were also performed in order to control for potential confounds.

3.5.1. MSIT Performance Analyses

Performance on the MSIT was assessed for each of the task conditions (I and C) as well as a derived contrast (I-C) in order to determine the effect of cognitive interference processing without the influence of psychomotor speed. The dependent variables were response time for correct responses (ms) and percent accuracy. Additionally, if results indicated significant between-group differences for percent accuracy, analyses of error type were performed on number of omission errors, which occur when no response is given and typically reflect slower or overloaded cognitive processing, and number of commission errors, incorrect responses which typically reflect difficulty inhibiting inappropriate responses. These analyses were corrected for multiple comparisons using a Bonferroni correction ($\alpha/2$).

MSIT performance was first assessed according to whole task performance, or the average performance during each condition (I and C) as well as the I-C contrast. One-way ANOVAs were run assessing performance differences for the 2-group comparison (Group: control vs

MJ) as well as the 3-group comparison (Group: control vs early MJ vs late MJ). Next, MSIT performance was assessed over the time course of the task with Block as a repeated measures variable. Mixed-Model ANOVAs were run assessing performance differences for the 2-group comparison (Group: control vs MJ) over time (Block: 1 vs 2 vs 3 vs 4) using a 2x4 ANOVA and for the 3-group comparison (Group: control vs early MJ vs late MJ) over time (Block: 1 vs 2 vs 3 vs 4) using a 3x4 ANOVA. Power calculations performed before analyses indicated that with 34 control participants and 64 MJ users in the 2x4 ANOVA, α=.05, and power between 80-95%, we had the ability to detect effect sizes as small as *f*=0.23-0.29 for between-group effects; *f*=0.12-0.15 for repeated measures effects; and *f*=0.12-15 for the Group by Block interaction. For the 3x4 ANOVA, with 34 control, 27 early onset MJ users, and 37 late onset MJ users, α=.05, and power between 80-95%, we estimated that we could detect effect sizes as small as *f*=0.25-0.32 for between-group effects; *f*=0.12-.015 for repeated measures effects; and *f*=0.13-0.17 for the Group by Block interaction.

In order to evaluate internal consistency reliability of MSIT performance over time, we calculated Cronbach's alpha to assess the average covariance of MSIT performance across the four blocks relative to the variance of the entire task. Additionally, we also examined within-subject patterns of performance by calculating intrasubject variability (ISV), which is the average variability of response time to stimuli (see

Gruber, et al., 2017). In order to determine whether task variability differed between-groups, one-way ANOVAs for the 2-group (control vs MJ user) and 3-group analyses (control vs early MJ vs late MJ) were performed on ISV.

3.5.2. MSIT Neuroimaging Analyses

Imaging was performed on a Siemens Trio whole body 3T MRI scanner (Siemens Corporation, Erlangen, Germany) using a quadrature RF head coil; 40 contiguous coronal slices were acquired from each subject, providing whole brain coverage (5mm, 0mm skip), and images were collected every 3s using a single shot, gradient pulse echo sequence (TR=3000ms; TE=30ms, flip angle=90°, with a 20cm field of view and a 64x64 acquisition matrix; in plane resolution 3.125x3.125x3.125 mm). A total of 132 images per slice were collected.[7]

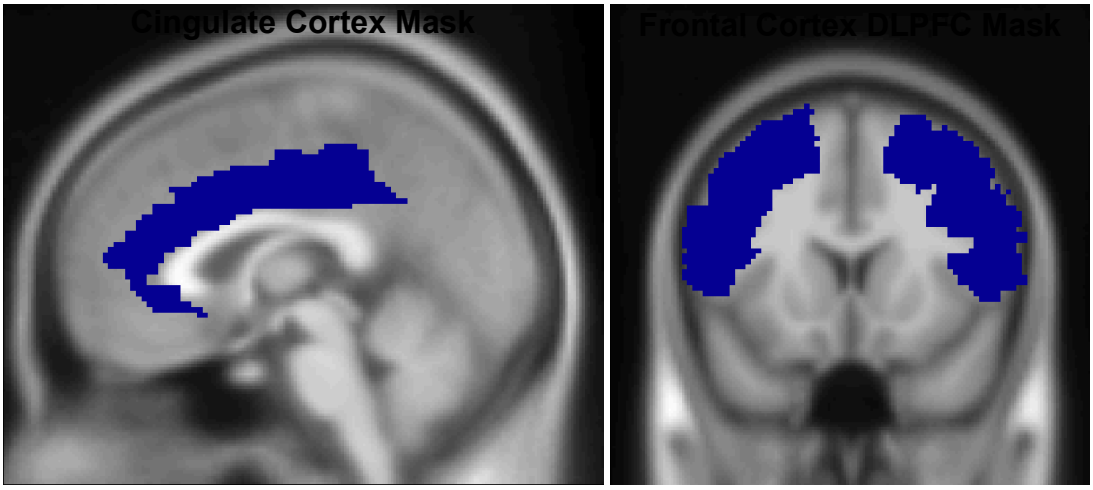
FMRI images were analyzed using SPM12 (Wellcome Trust Center for Neuroimaging, UK). Blood oxygen level dependent (BOLD) fMRI data were realigned, coregistered to a structural memprage sequence, segmented to differentiate tissue classes, normalized to Montreal Neurological Institute (MNI) stereotactic space (Collins, Neelin, Peters, & Evans, 1994), and spatially smoothed using an isotropic Gaussian kernel 6mm full width at half maximum (FWHM). Statistical parametric images were calculated individually for each subject and each task, using a

[7] Note: two participants (control=1, early MJ=1) only had 130 images per slice collected. This was corrected for during all neuroimaging analyses.

general linear model that accounted for task-related changes, with each condition modeled as a block design with a boxcar waveform. At the first level, three main regressors were fit to the data, including the baseline fixation condition, the C condition, and the I condition. At this level, movement data were included in the model to correct for each person's individual movement. However any data with movement that exceeded outlier thresholds of 3mm and/or 2° of rotation were excluded from the analyses; these movement thresholds have been utilized in several studies (e.g., Gruber et al., 2012b; 2017; Sagar et al., 2015; etc.). The C and I conditions each included four active blocks, each comprised of 42s stimulation periods. Direct contrasts between the fixation vs active condition were calculated for each subject to generate fixation vs C and fixation vs I images. Additionally, the contrast images were used to calculate a derived interference contrast image of I-C.

These contrast images were subsequently entered into second level model, subjected to a voxel-wise *t*-tests to assess statistical significance. Region of interest (ROI) masks were generated using the Wake Forest University Pickatlas utility (Maldijan et al., 2003) to restrict analyses to our ROIs: the cingulate cortex and the DLPFC (see **Figure 6**). Voxel-wise comparisons restricted to these ROIs were evaluated at $p<.05$ (uncorrected), $k\geq10$ contiguous voxels. In addition, only clusters that exceeded a false discovery rate (FDR) correction of $p<.05$ were included.

Figure 7. fMRI Region of Interest (ROI) Masks Generated by the Wake Forest University PickAtlas Toolbox (Maldijan et al., 2003)



One-sample *t*-tests were used to generate mean activation information for each condition (C, I, and I-C) for each group (control, all MJ users, early MJ, and late MJ users). Between-group differences for the two-group analyses (control vs MJ) were assessed for each condition (C, I, and I-C) using between group *t*-tests. Between-group differences for the three-group analyses (control vs early MJ vs late MJ) were assessed for each condition (C, I, and I-C) using an omnibus *F* test with *post hoc* two-group contrasts performed using *t*-tests. Additionally, individual participants' fMRI activation values from each ROI were extracted as mean voxel activations from the series of 132 images generated chronologically during the task (1 image = 3 seconds) using the MarsBaR SPM toolbox (Brett et al., 2002). The mean voxel activations were averaged for each condition (I and C) and the I-C contrast to be used in correlational analyses.

Finally, in order to assess changes in brain activation over the time course of the MSIT, one-sample *t*-tests were used to generate mean activation for each condition (C, I, and I-C) during each block (Block 1, 2, 3, 4) for each group (control, all MJ users, early onset MJ users, and late onset MJ users). Between-group differences over time for the two-group (control vs MJ) and the three-group (control vs early MJ vs late MJ) analyses were assessed for each condition (C, I, and I-C) using an omnibus *F* test with *post hoc* contrasts performed using *t*-tests.

3.5.3. MSIT Correlation and Regression Analyses

Pearson's *r* correlation analyses were performed within each individual group (control, MJ users, early MJ, and late MJ) in order to determine how MSIT performance related to MSIT-associated brain activation patterns within the cingulate and DLPFC ROIs. Separate, correlational analyses were also performed within each individual MJ-using group to assess the relationship between MSIT performance/brain activation and MJ use variables: age of MJ onset, frequency (episodes/week) and magnitude of MJ use (grams/week), duration of MJ use (yr), and urinary THC concentration. For any significant correlation results, secondary, hierarchical regression analyses were planned to determine the unique contribution of variance for each MJ use variable. For these regression analyses, each significant correlate was entered into

the regression model in order of significance; changes in R^2 were calculated to determine the contribution of each MJ use variable.

4. Results

Outlier data were *a priori* defined as response time and percent accuracy averages beyond the 1.5x interquartile range boundary. Outlier analyses were performed for MSIT performance averages for the entire task as well as by block. Participants with outliers from the whole task averages were excluded, but only participants with outliers from two or more different block averages[8] were excluded. Additionally, if any participant had an average percent accuracy equal to or below percent chance (33.33%) during any block, their data was excluded from further analyses. Using these methods, 8 control participants and 10 MJ users (early MJ=6, late MJ=4) were identified as outliers, and their data were excluded from further analyses. The total samples sizes for the final analyses of MSIT performed were: control=26, MJ=54 (early MJ=21, late MJ=33). Finally, the fMRI data were screened for movement, and data with movement of ≥3mm and/or ≥2° of rotation were excluded from the analyses. Using these outlier thresholds, 1 control participant and 3 MJ users (1 early MJ and 2 late MJ) were excluded resulting in a total sample

[8] When identifying outliers by block, we chose to include participants with outlier data in only one block because several participants in each group struggled during the first block of the task, with outlier data during block one, but not during any other part of the task. These data were related to participants' acclimation to the task, and therefore imparted important variance related to the time course of the task itself (a main effect of interest in this dissertation).

size of control=25, MJ=51 (early MJ=20 and late MJ=31) for the fMRI analyses.

Power calculations indicated that with 25 control participants and 51 MJ users in the 2x4 ANOVA, α=.05, and power between 80-95%, we had the ability to detect effect sizes as small as *f*=0.26-0.33 for between-group effects; *f*=0.14-0.17 for repeated measures effects; and *f*=0.14-0.17 for the Group by Block interaction. For the 3x4 ANOVA, with 34 control, 27 early onset MJ users, and 37 late onset MJ users, α=.05, and power between 80-95%, we estimated that we could detect effect sizes as small as *f*=0.29-0.36 for between-group effects; *f*=0.14-.017 for repeated measures effects; and *f*=0.15-0.19 for the Group by Block interaction.

4.1. Two-Group Analyses: Control versus MJ Users

Analyses of the demographic variables (**Table 2**) indicated that the control and MJ-using groups were well-matched without significant between-group differences in handedness, age, IQ, BMI, alcohol use (days of use out of past 30), and ratio of participants currently using nicotine regularly. There was a significant difference for sex, $X^2(1, N=80)=12.779$, $p<.001$, with more males in the MJ-using group and more females in the control group.

Table 2. Demographic Comparison of Control and MJ-Using Participants

Demographic Variables	Controls *n*=26	MJ Users *n*=54	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Sex[b]	**9M, 17F**	**41M, 13F**	**X^2=12.779**	**<.001**
Handedness[b]	25R, 1L	52R, 2L	X^2=0.001	.975
Age	23.85±5.89	22.96±5.56	0.426	.516 (.005)
IQ: WASI	*123.73±10.42*	*118.93±10.64*	*3.623*	*.061 (.044)*
BMI	23.09±3.32	23.27±3.82	0.043	.837 (.001)
Alcohol Use (days out of last 30)[c]	5.56±5.51	6.58±5.37	0.606	.439 (.008)
Ratio of Current Nicotine Users[d]	0/12	4/28	X^2=1.650	.199
MJ Use Variables				
Age of MJ Onset[e]	-	16.43±2.25	-	-
MJ Use Episodes/Week[f]	-	14.38±7.82	-	-
MJ Grams Used/Week[f]	-	5.17±5.42	-	-
Duration of MJ Use (yr)[e]	-	6.52±4.87	-	-
Urinary THC/Creatinine Ratio[g]	-	461.92±604.90	-	-

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Degrees of Freedom (df)=1,78 unless otherwise noted
[b] *Chi Square Analyses:* df=1, *N*=80
[c] df=1,73
[d] *Chi Square Analyses:* df=1, *N*=44
[e] *N*=54
[f] *N*=52
[g] *N*=46
Abbreviations: Analysis of Variance (ANOVA); body mass index (BMI); cannabidiol (CBD); marijuana (MJ); Tetrahydrocannabinol (THC); Wechsler Abbreviated Scale of Intelligence (WASI)

Additionally, analyses of clinical state (**Table 3**) demonstrated significant between-group differences on depressive symptoms, measured by the BDI, $F(1,74)=5.619$, $p=.020$, with MJ users reporting higher scores relative to control participants. However, it is important to note that all group means for the BDI were well below clinical significance, as scores <10 represent "no or minimal depression" (Beck, Steer, & Garbin, 1988). Additionally, MJ users reported significantly higher ratings of impulsiveness on all subscores of the BIS: attention, $F(1,78)=9.760$,

p=.003; motor, *F*(1,78)=6.749, *p*=.011; non-planning, *F*(1,78)=11.118, *p*=.001; and total impulsiveness, *F*(1,78)=15.278, *p*<.001.

Table 3. Clinical State Comparison of Control and MJ-Using Participants

Clinical Measures	Controls *n*=26	MJ Users *n*=54	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Beck Depression Inventory[b]				
Total Depression Score	**1.69±2.17**	**3.46±3.46**	**5.619**	**.020 (.071)**
Montgomery-Asberg Depression Rating Scale[b]				
Total Depression Score	1.38±1.47	2.06±2.47	1.636	.205 (.022)
Hamilton Anxiety Scale[b]				
Total Anxiety Score	1.12±1.21	1.58±1.64	1.618	.207 (.021)
State Trait Anxiety Inventory[b]				
State Anxiety	26.73±4.75	27.16±5.53	0.113	.738 (.002)
Trait Anxiety	30.85±6.34	30.68±6.31	0.012	.914 (<.001)
Positive and Negative Affect Schedule				
Positive Affect	32.92±6.39	34.13±7.71	0.477	.492 (.006)
Negative Affect[c]	10.92±1.41	12.46±3.73	*U*=566.50	.137 (.050)
Profile of Mood States				
Vigor	19.31±4.50	19.09±4.75	0.037	.847 (<.001)
Anger[c]	*2.50±3.60*	*5.20±6.46*	*U=520.00*	*.058 (.048)*
Confusion	3.92±2.95	6.87±11.41	1.670	.200 (.021)
Tension	3.89±3.19	4.72±3.16	1.223	.272 (.015)
Fatigue	3.85±3.16	4.43±3.04	0.621	.433 (.008)
Depression	2.96±3.45	4.04±4.96	0.988	.323 (.013)
Total Mood Disturbance (TMD)	*-2.19±13.70*	*6.17±22.57*	*3.021*	*.086 (.037)*
Barratt Impulsiveness Scale				
Attention	**13.89±3.88**	**16.32±2.92**	**9.760**	**.003 (.111)**
Motor	**19.77±4.31**	**22.32±4.00**	**6.749**	**.011 (.080)**
Non-Planning	**20.92±5.19**	**25.07±5.23**	**11.118**	**.001 (.125)**
Total Impulsiveness Score	**54.58±10.37**	**63.70±9.51**	**15.278**	**<.001 (.164)**

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Degrees of Freedom (df)=1,78 unless otherwise noted
[b] *df*=1,74
[c] Levene's *F* test of homogeneity of variance supported non-parametric Mann-Whitney *U* analyses; *N*=80
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ)

4.1.1. MSIT Performance Results

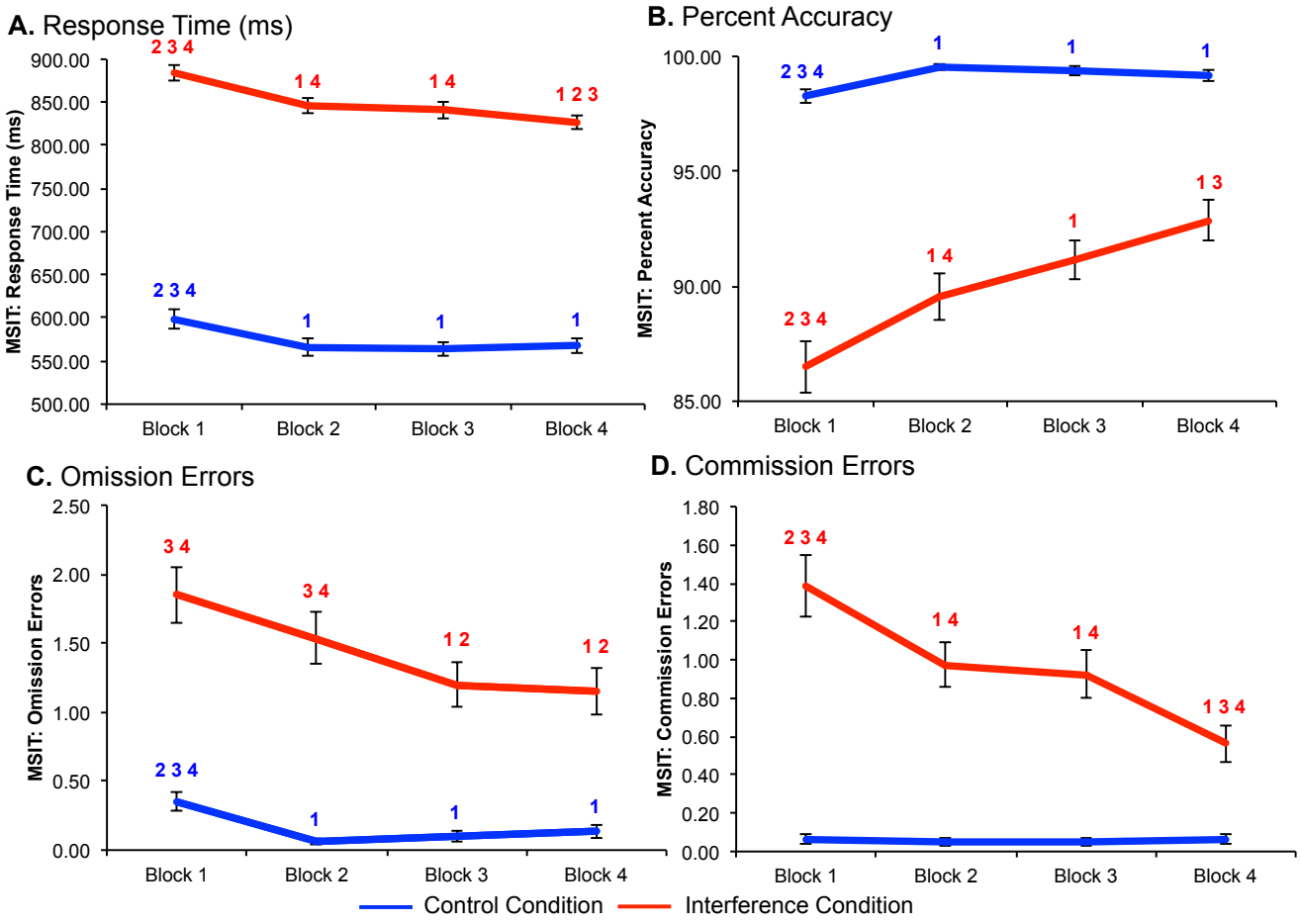
Whole task analyses of MSIT performance between the control participants and all MJ users did not reveal any significant differences between the two groups for either response time or performance accuracy (all *ps*≥.356, **Appendix A**). However, when performance over time was entered into the model using Block as a repeated measures variable, a different pattern of results emerged, with significant main effects of Block, indicating that *performance significantly improved over time for all participants* (tables presented in **Appendix B & C**). A significant main effect of Block was observed for response time during both the control condition, $F(2.02, 157.78)=6.39$, $p=.002$, and the interference condition, $F(3,234)=22.552$, $p<.001$, with a trend for significance for the I-C contrast, $F(2.39, 187.15)=2.393$, $p=.084$. *Post hoc* analyses (**Figure 8A**) indicated that for the control condition, response time decreased most significantly from Block 1 to Block 2, while during the interference condition, response time decreased significantly both from Block 1 to Block 2 and from Block 3 to Block 4.

Further, a significant main effect of Block was observed for percent accuracy during both the control condition, $F(2.21,172.05)=6.093$, $p=.002$, and the interference condition, $F(2.62, 204.47)=9.933$, $p<.001$, as well as the I-C contrast, $F(2.63, 204.97)=7.636$, $p<.001$. *Post hoc* analyses (**Figure 8B**) indicated that for the control condition, percent accuracy increased most significantly from Block 1 to Block 2 while during the

interference condition, percent accuracy increased significantly at almost every block.

As percent accuracy yielded significant results by Block, MSIT performance was further assessed by examining omission and commission errors. During the control condition, a significant main effect of Block was observed for omission, $F(2.13, 166.49)=8.653$, $p<.001$, but not commission errors ($p=.99$). During the interference condition, a significant main effect of Block was observed for both omission errors, $F(2.56, 199.75)=4.762$, $p=.005$, and commission errors, $F(3, 234)=7.581$, $p<.001$. Finally, the I-C contrast also demonstrated a significant main effect of Block for omission errors, $F(2.60, 202.64)=3.050$, $p=.036$, as well commission errors, $F(2.71, 211.64)=7.787$, $p<.001$. However, the I-C results did not survive Bonferroni correction. *Post hoc* analyses of omission errors (**Figure 8C**) indicated that during the control condition, omissions were significantly reduced from Block 1 to almost zero by Block 2. During the interference condition, omission errors declined significantly over the first 3 blocks and plateaued by Block 4. Commission errors (**Figure 8D**) were close to zero throughout the entire control condition and did not differ significantly over time. During the interference condition, commission errors significantly decreased from Block 1 to Block 2 and from Block 3 to Block 4.

Figure 8. MSIT Performance Differences Over Time in All Participants: Main Effect of Block



Note: Significant differences between Blocks at α=.05 (2-tailed) are noted by the number of the block.

For all of these analyses, the main effects of Group as well as the Group by Block interactions were all non-significant (all *ps*≥.274). Additionally, ANCOVAs covarying for potential confounding variables (i.e., sex and BDI for both the 2- and 3-group analyses as well as POMS Anger and TMD for the 3-group analyses) did not yield different findings from the original ANOVAs. However, ANCOVAs controlling for impulsivity, with BIS total score included as a covariate in the model, no longer yielded significant main effects of Block (all *ps*≥.148), except for the main effect of

Block during the interference condition demonstrating reduced omission errors over time, $F(2.50, 229.70)=4.64$, $p=.006$. Interestingly, the BIS total score covariate was not a significant contributor in any of the ANCOVAs (all $ps \geq .070$), and additional correlation analyses indicated that BIS did not significant correlate with MSIT performance in either the control or MJ-using groups (all $ps \geq .177$).

Analyses of internal consistency indicated excellent covariance across Blocks for response time during the control and interference conditions in both control ($\alpha=.895$ and $\alpha=.887$, respectively) and MJ participants ($\alpha=.849$ and $\alpha=.929$, respectively). In regard to performance accuracy, internal consistency was more moderate for both control ($\alpha=.699$ and $\alpha=.711$, respectively) and MJ participants ($\alpha=.540$ and $\alpha=.722$, respectively). Additionally, intrasubject variability analyses revealed that although ISV changed significantly over Block for both the control and interference conditions, $F(2.66, 204.68)=19.94$, $p<.001$ and $F(2.70, 207.99)=2.97$, $p=.038$, respectively, the control and MJ users reported similar ISV for both the control and interference conditions during every block (all $ps \geq .073$).

4.1.2. MSIT fMRI Conventional Whole Task Analyses

Whole Task: Individual Group Averages

Individual group averages of brain activation in the cingulate and DLPFC ROIs were created using one-sample *t*-tests. The control group

(**Figure 9**, **Appendix D**) did not demonstrate significant cingulate activation during either the control or interference conditions of the task (*k*=0), but did show significant DLPFC activation during both the control (*k*=15) and interference (*k*=100) conditions. The I-C contrast indicated significantly greater cingulate (*k*=46) and DLPFC (*k*=1309) activation during the interference condition relative to the control condition. The MJ group as a whole (**Figure 10**, **Appendix E**) demonstrated significant cingulate activation during both the control (*k*=10) and interference (*k*=20) conditions, as well as significant DLPFC activation during both the control (*k*=435) and interference (*k*=543) conditions. The I-C contrast indicated significantly greater cingulate (*k*=151) and DLPFC (*k*=930) activation during the interference condition relative to the control condition.

Figure 9. CONTROL GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT

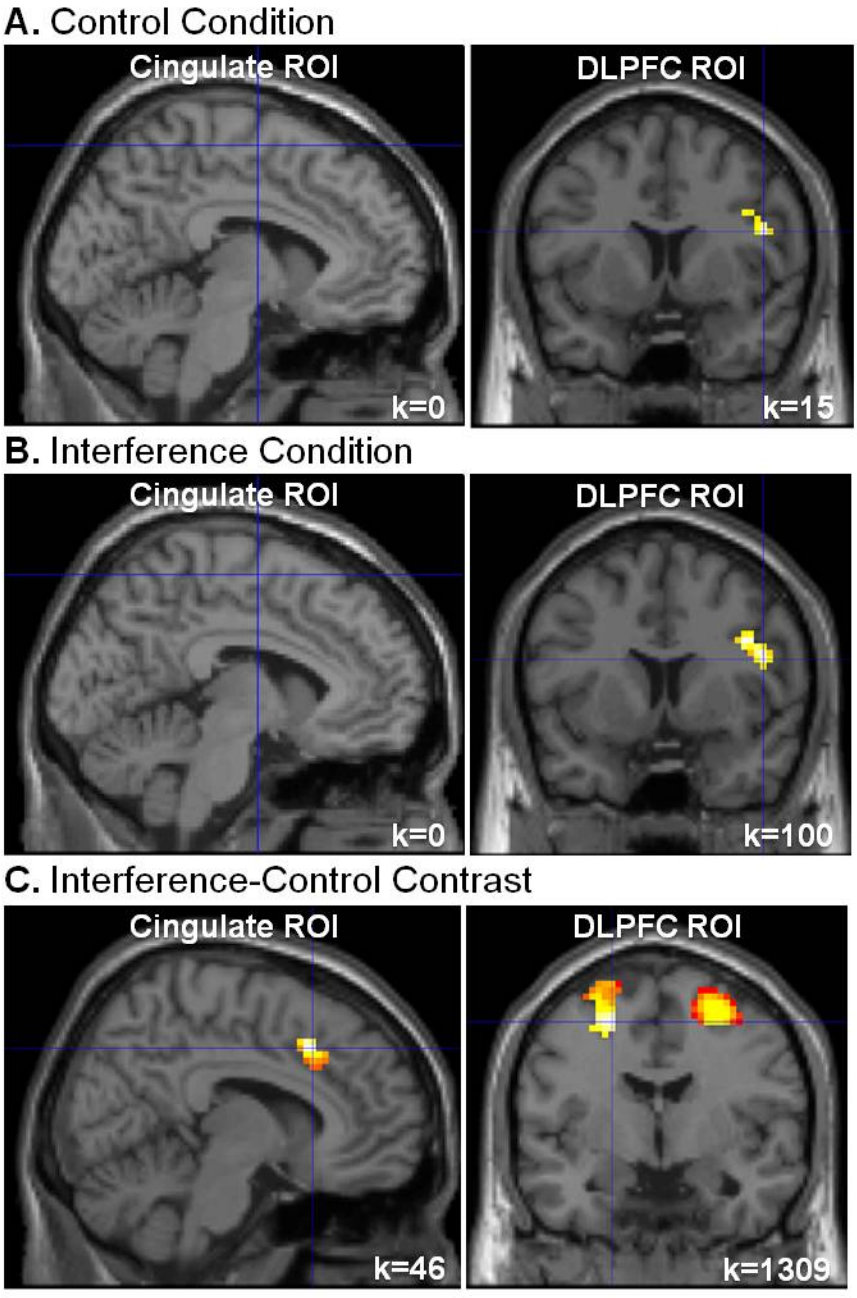
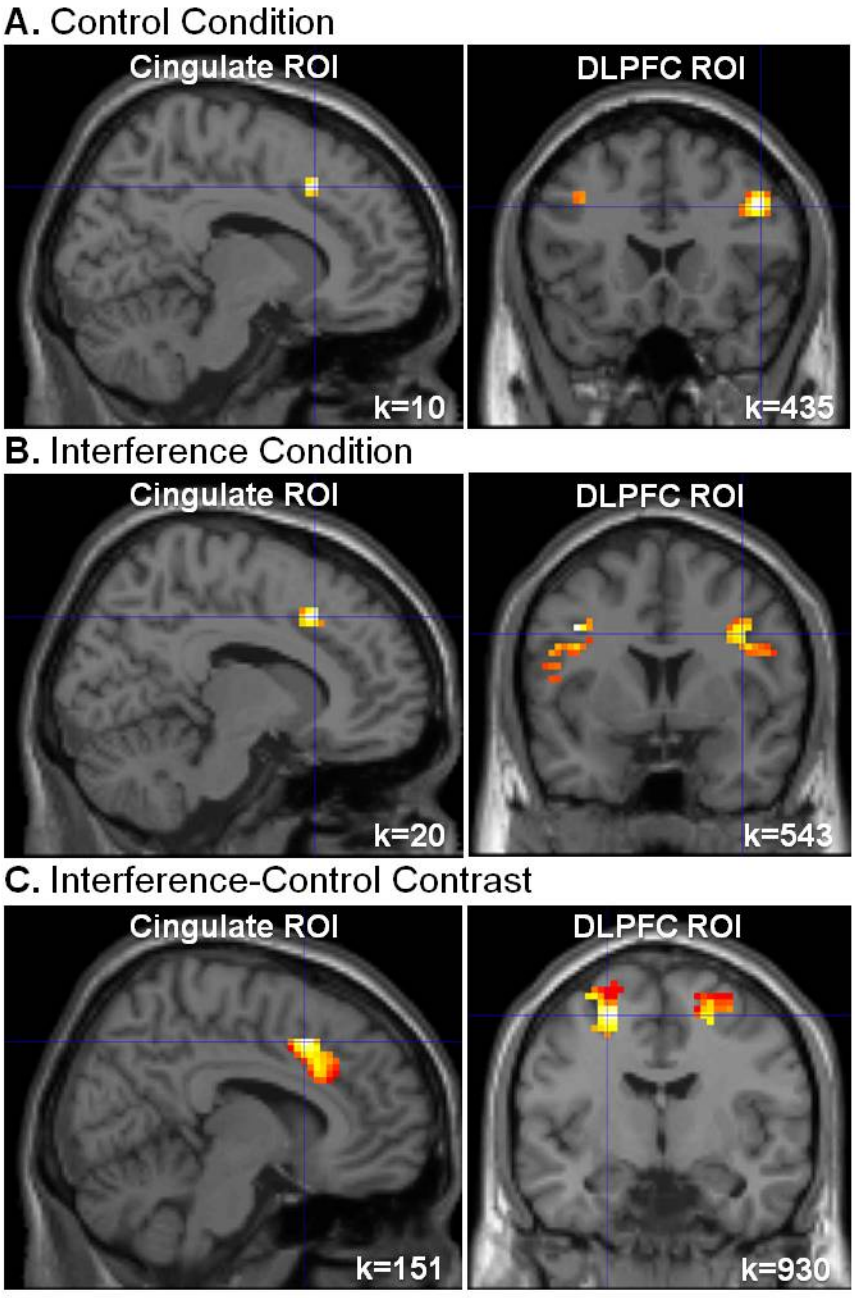


Figure 10. MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT



Whole Task: Two-Group Analyses

Next, differences in patterns of brain activation between the two groups (control vs MJ) were assessed using two-group *t*-tests (**Appendix**

F) which identifies activation in one subject group relative to another (i.e., MJ >HC; HC>MJ).

Cingulate (**Figure 11**): The MJ group demonstrated increased activation during both the control (*k*=152) and interference (*k*=102) task conditions relative to the control group. The control group did not demonstrate any activation greater than the MJ group during either the control or interference conditions (both *ks*=0). The I-C contrast indicated significantly greater (*k*=244) activation during the interference condition relative to the control condition in the HC group relative to the MJ group; the MJ group did not have any significantly larger I-C contrast activations relative to the control group (*k*=0).

DLPFC (**Figure 12**): The MJ group demonstrated increased activation during both the control (*k*=602) and interference (*k*=375) conditions relative to the control group. The control group did not demonstrate any activation greater than the MJ group during the control condition (*k*=0), but did demonstrate a small locus of increased activation during the interference condition (*k*=21). The I-C contrast indicated significantly greater cingulate (*k*=470) activation during the interference condition relative to the control condition in the HC group relative to the MJ group and a much smaller locus of activation in the MJ group relative to the control group (*k*=16).

Figure 11. CONTROL vs MJ GROUP: Two-Group *t*-Test of fMRI Activation During the MSIT in the Cingulate Cortex

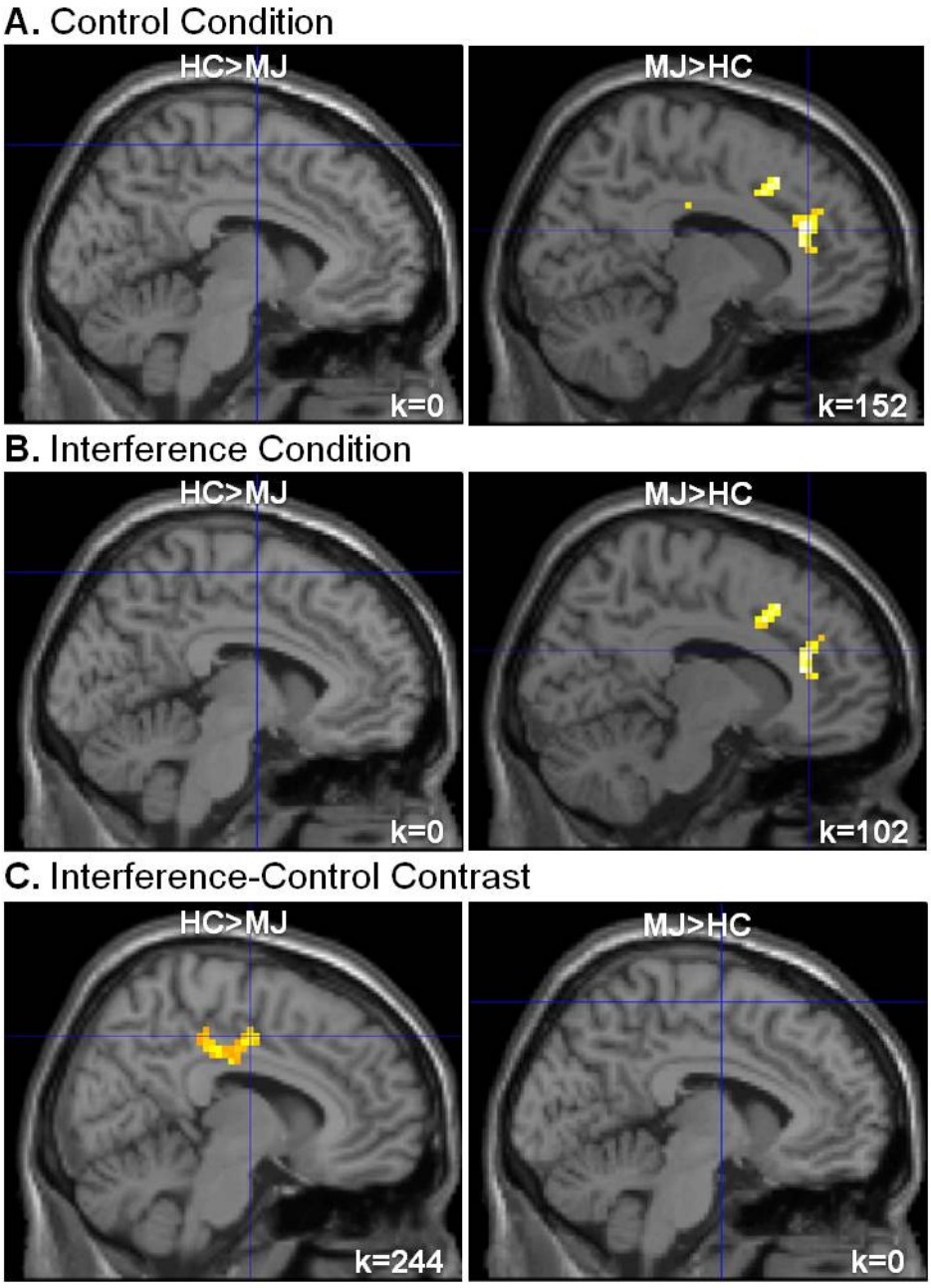
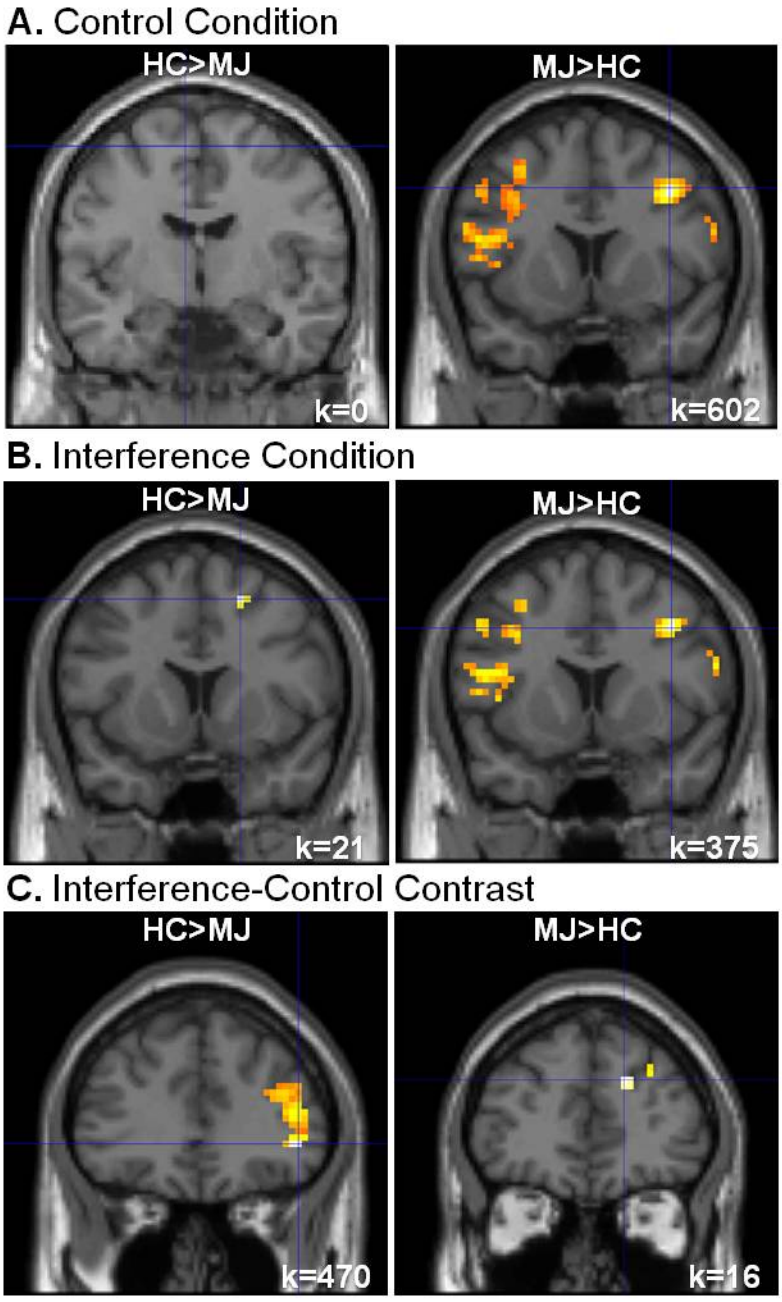


Figure 12. CONTROL vs MJ GROUP: Two-Group *t*-Test of fMRI Activation During the MSIT in the DLPFC



4.1.3. MSIT fMRI Novel Block Analyses

Block Analyses: Individual Group Averages

Individual group averages of brain activation over time were assessed using one-sample *t*-tests for both the interference and control conditions across each of the four blocks of the MSIT.

*Cingulate: T*he control group (**Appendix G**) did not significantly activate any clusters above threshold for any block during the control condition (all *ks*=0; **Figure13A**). During the interference condition (**Figure 13B**), the control group demonstrated significant activation during Block 1 (*k*=16) and Block 2 (*k*=20), but no clusters were significant during Block 3 or 4 (all *ks*=0). The MJ group (**Appendix I**) demonstrated a pattern of increasing activation during Block 1 (*k*=11), Block 2 (*k*=126), and Block 3 (*k*=258) of the control condition (**Figure 14A**), but by Block 4, no clusters were significant (*k*=0). During the interference condition (**Figure 14B**), the MJ group had significant clusters of activation for all 4 blocks, but activation was greatest during Block 1 (*k*=116) and Block 2 (*k*=138) with decreased activation demonstrated in Block 3 (*k*=75) and Block 4 (*k*=14). Overall, relative to the control group, the MJ group demonstrated greater cingulate activation during both the control and interference conditions, but the increased activation during the control condition was the most different from the pattern of activation observed in the control group.

Figure 13. CONTROL GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the Cingulate by Block

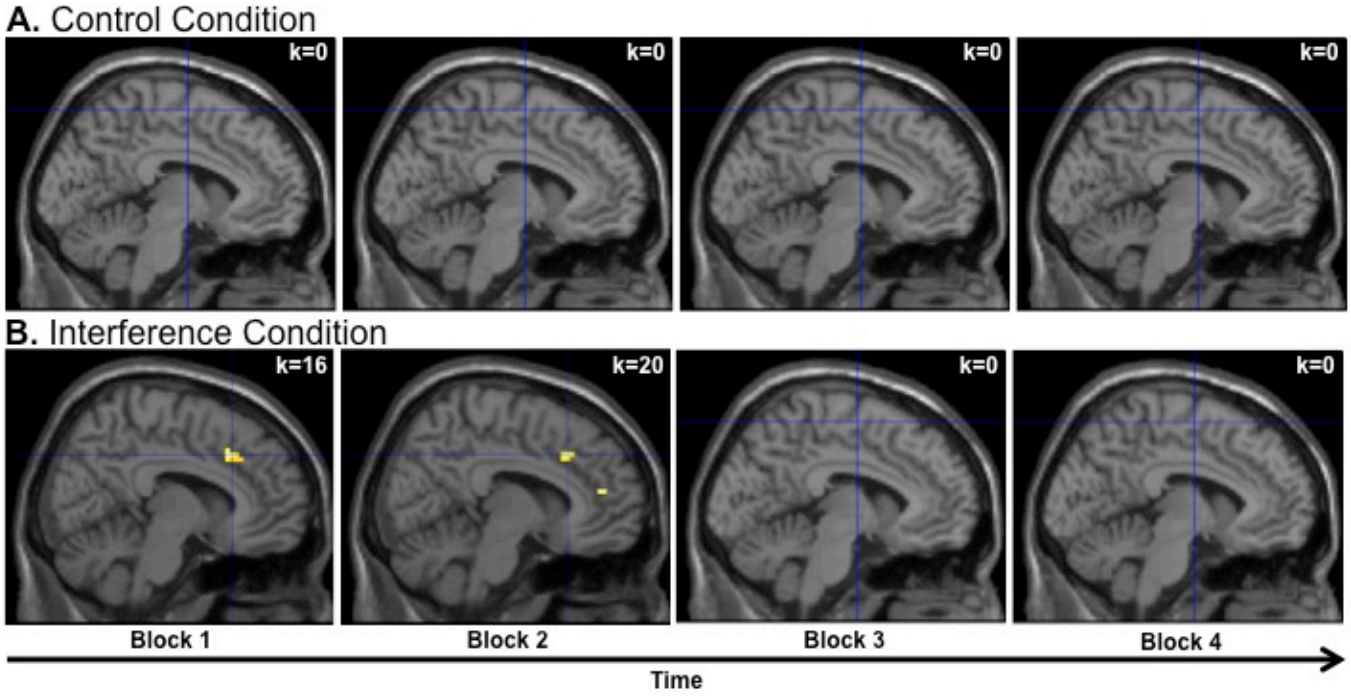
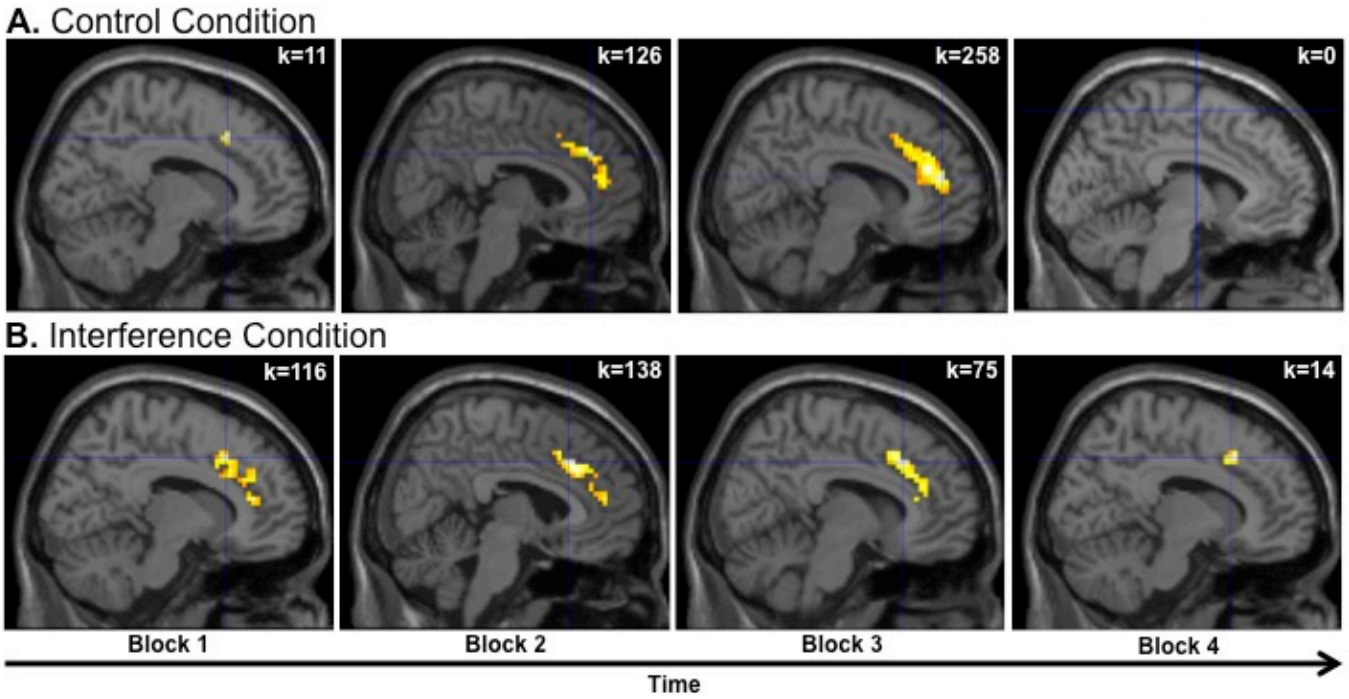


Figure 14. MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the Cingulate by Block



DLPFC: The control group (**Appendix H**) had greater activation during Block 1 (*k*=183) and Block 2 (*k*=359) of the control condition (**Figure 15A**) relative to Block 3 (*k*=0) and Block 4 (*k*=13). During the interference condition (**Figure 15B**), the control group had the greatest level of activation during Block 1 (*k*=659), which decreased over every subsequent block (Block 2 *k*=310, Block 3 *k*=114, Block 4 *k*=14). The MJ group (**Appendix J)** demonstrated overall greater activation in the DLPFC during the control condition (**Figure 16A**); Block 1 (*k*=627), Block 2 (*k*=1008), and Block 3 (*k*=807) demonstrated greater levels of activation, with lower levels of activation only observed in Block 4 (*k*=89). During the interference condition (**Figure 16B**), the MJ group displayed a similar pattern of activation as the control condition with greater activation observed in Block 1 (*k*=828), Block 2 (*k*=863), and Block 3 (*k*=613), and relatively lower activation only observed in Block 4 (*k*=114). Overall, the control subjects demonstrated increased DLPFC activation during the initial blocks of the MSIT for both the control and interference conditions, with decreased or no activation observed in later blocks, whereas the MJ group typically demonstrated greater activation overall relative to the control group as well as increased activation sustained through later blocks (i.e., Block 3).

Figure 15. CONTROL GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the DLPFC by Block

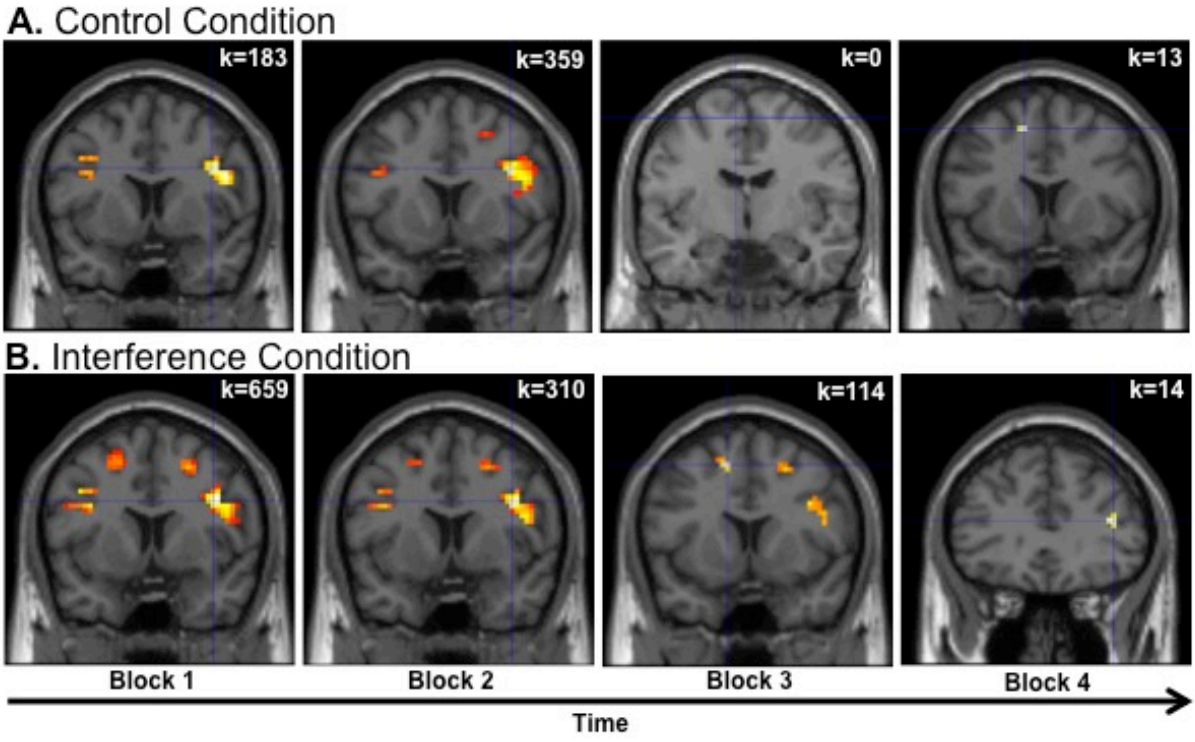
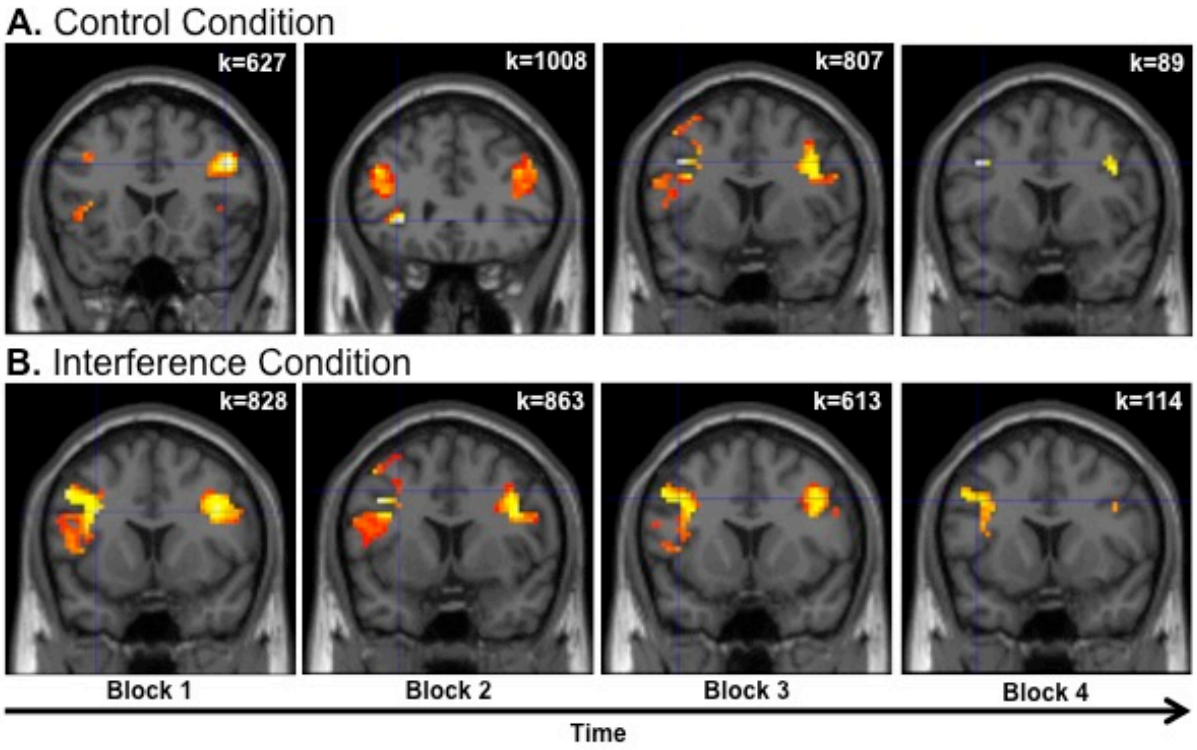


Figure 16. MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the DLPFC by Block



4.2. Three-Group Analyses: Control versus Early MJ Onset versus Late MJ Onset

Analyses of the demographic variables (**Table 4**) indicated that the control, early onset MJ, and late onset MJ groups were well-matched without significant between-group differences in handedness, age, IQ, BMI, alcohol use (days of use out of past 30), and ratio of participants currently using nicotine regularly. There was a significant difference between sex, $X^2(2,N=80)=12.780$, $p=.002$, with more males in both the early and late MJ onset groups relative to the control group; there was not a significant difference in the male:female ratio between the early and late onset MJ groups. Additionally, the MJ-using groups were well-matched with regard to MJ use with similar frequency (episodes/week) and magnitude (grams/week) of MJ use, duration of MJ use (yr), and urinary THC quantification. Age of MJ onset was the only MJ use variable that was significantly different between the early and late MJ onset groups[9], $U=0.00$, $p<.001$.

[9] A Mann-Whitney U value equal to zero signifies that all values in one group are lager than all the values in the other group, which is expected given that age of onset is how the groups were defined.

Table 4. Demographic Comparison of Control, Early Onset MJ, and Late Onset MJ Participants

Demographic Variables	Controls *n*=26	Early Onset MJ *n*=21	Late Onset MJ *n*=33	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Sex[b]	**9M, 17F*^**	**16M, 5F***	**25M, 8F^**	**X^2=12.780**	**.002**
Handedness[b]	25R, 1L	19R, 2L	33R, 0L	X^2=3.226	.199
Age	23.85±5.89	21.95±5.80	23.60±5.39	0.760	.471 (.019)
IQ: WASI	123.73±10.42	118.57±11.13	119.15±10.49	1.808	.171 (.045)
BMI	23.09±3.32	22.54±2.59	23.74±4.41	0.701	.499 (.018)
Alcohol Use (days out of last 30)[c]	5.56±5.51	5.98±3.91	7.00±6.21	*H*=0.886	.642 (.014)
Ratio of Current Nicotine Users[d]	*0/12*	*3/9*	*1/19*	*X^2=5.280*	*.071*
MJ Use Variables					
Age of MJ Onset[e]	-	**14.38±0.74**	**17.72±1.88**	***U*=0.00**	**<.001 (.538)**
MJ Use Episodes/Week[f]	-	14.06±6.09	14.60±8.90	0.057	.812 (.001)
MJ Grams Used/Week[f]	-	5.04±3.84	5.25±6.33	0.019	.891 (<.001)
Duration of MJ Use (yr)[g]	-	7.57±5.65	5.85±4.26	1.625	.208 (.030)
Urinary THC/Creatinine Ratio[h]	-	291.22±163.34	396.80±431.46	*U*=285.00	.856 (.020)

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
* and ^ indicate significant differences between groups at α<.05
[a] Degrees of Freedom (df)=2,77 unless otherwise noted
[b] *Chi Square Analyses:* df=2, *N*=80
[c] Levene's *F* test of homogeneity of variance supported non-parametric Kruskal-Wallis *H* analyses; *N*=75
[d] *Chi Square Analyses:* df=2, *N*=44
[e] Levene's *F* test of homogeneity of variance supported non-parametric Mann-Whitney *U* analyses; *N*=54
[f] df=1,50
[g] df=1,52
[h] Levene's *F* test of homogeneity of variance supported non-parametric Mann-Whitney *U* analyses; *N*=46
Abbreviations: Analysis of Variance (ANOVA); body mass index (BMI); cannabidiol (CBD); marijuana (MJ); Tetrahydrocannabinol (THC); Wechsler Abbreviated Scale of Intelligence (WASI)

Additionally, analyses of clinical state (**Table 5**) demonstrated significant between-group differences on depressive symptoms measured by the BDI, $F(2, 73)=3.880$, $p=.025$, with the early onset MJ users reporting significantly higher ratings than the control participants; no differences were detected for the late onset MJ users relative to the early onset MJ users or the control participants. POMS anger and total mood disturbance (TMD) scores were also statistically significant, $H(2)=9.451$, $p=.009$ and $F(2, 77)=3.269$, $p=.043$ respectively. For the POMS anger subscore, early onset MJ users reported significantly higher scores

relative to both control participants and late onset MJ users; no differences were detected between control participants and late onset MJ users. For the POMS TMD, early onset MJ users reported significantly higher scores relative to control participants, but late onset MJ users did not report significantly different levels of TMD from either early onset MJ users or control participants. Again, it is important to note that all group means on the BDI and POMS were well below clinical significance (Beck, Steer, & Garbin, 1988; Pollock et al., 1979).

Additionally, all subscores of the BIS were statistically significant: attention, $F(2, 77)=4.985$, $p=.009$; motor, $F(2, 77)=4.095$, $p=.020$; non-planning, $F(2, 77)=6.243$, $p=.003$; and total impulsiveness, $F(2, 77)=8.545$, $p<.001$. For the attention, non-planning, and total impulsiveness subscores, both the early and late onset MJ users reported significantly higher levels of impulsiveness relative to the control participants, but the early and late onset MJ users did not differ from each other. For the motor subscore, the early onset MJ users reported significantly higher levels of impulsiveness compared to control participants, but the late onset MJ users were not statistically different from either the control participants or the early onset MJ users.

Table 5. Clinical State Comparison of Control, Early Onset MJ, and Late Onset MJ Participants

Clinical Measures	Controls *n*=26	Early Onset MJ *n*=21	Late Onset MJ *n*=33	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Beck Depression Inventory[b]					
Total Depression Score	**1.69±2.17***	**4.19±4.00***	**2.93±2.98**	**3.880**	**.025 (.096)**
Montgomery-Asberg Depression Rating Scale[b]					
Total Depression Score	*1.39±1.47*	*2.81±3.19*	*1.52±1.64*	*3.088*	*.052 (.078)*
Hamilton Anxiety Scale[b]					
Total Anxiety Score	1.12±1.21	1.71±1.82	1.48±1.53	0.943	.394 (.025)
State Trait Anxiety Inventory[b]					
State Anxiety	26.73±4.75	26.86±5.15	27.38±5.88	0.115	.892 (.003)
Trait Anxiety	30.85±6.34	31.05±6.50	30.41±6.28	0.066	.936 (.002)
Positive and Negative Affect Schedule					
Positive Affect	32.92±6.39	32.76±8.11	35.00±7.45	0.842	.435 (.021)
Negative Affect[c]	10.92±1.41	14.05±4.97	11.46±2.21	*H*=4.215	.122 (.155)
Profile of Mood States					
Vigor	19.31±4.50	18.62±4.38	19.39±5.01	0.194	.824 (.005)
Anger[c]	**2.50±3.60***	**7.24±7.25*^**	**3.91±5.65^**	***H*=9.451**	**.009 (.101)**
Confusion[c]	*3.92±2.95*	*9.52±17.90*	*5.18±2.83*	*H=4.846*	*.089 (.054)*
Tension	3.89±3.19	4.62±3.12	4.79±3.24	0.622	.540 (.016)
Fatigue	3.85±3.16	4.67±3.04	4.27±3.09	0.411	.664 (.011)
Depression	2.96±3.45	5.00±5.24	3.42±4.76	1.278	.284 (.032)
Total Mood Disturbance (TMD)	**-2.19±13.70***	**12.43±28.05***	**2.18±17.58**	**3.269**	**.043 (.078)**
Barratt Impulsiveness Scale					
Attention	**13.89±3.88*^**	**16.62±3.03***	**16.12±2.88^**	**4.985**	**.009 (.115)**
Motor	**19.77±4.31***	**23.14±4.40***	**21.79±3.71**	**4.095**	**.020 (.096)**
Non-Planning	**20.92±5.19*^**	**26.10±4.95***	**24.42±5.36^**	**6.243**	**.003 (.140)**
Total Impulsiveness Score	**54.58±10.37*^**	**65.86±9.42***	**62.33±9.45^**	**8.545**	**<.001 (.182)**

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
* and ^ indicate significant differences between groups at α<.05
[a] Degrees of Freedom (df)=2,77 unless otherwise noted
[b] *df*=2,73
[c] Levene's *F* test of homogeneity of variance supported non-parametric Kruskal-Wallis *H* analyses; *N*=80
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ)

4.2.1. MSIT Performance Results

Whole task analyses of MSIT performance between the control, early, and late onset MJ participants did not reveal any significant differences between the two groups for either RT or performance accuracy

(all *ps*≥.282, **Appendix K**). However, when performance over time was entered into the model using Block as a repeated measures variable, once again, a different pattern of results emerged (tables presented in **Appendix L & M**), with significant main effects of Block indicating that performance significantly improved over time for all participants. Specifically, significant main effects of Block were observed for response time during both the control condition, $F(2.01, 154.73)=7.39$, $p=.001$, and the interference condition, $F(3, 231)=27.75$, $p<.001$, and for percent accuracy during both the control, $F(2.22, 170.60)=35.43$, $p<.001$, and interference condition, $F(2.61, 201.23)=12.07$, $p<.001$. As differences were detected for percent accuracy, error type was examined by analyzing omission and commission errors. Significant main effects of Block were observed for omission errors during both the control condition, $F(2.14, 164.47)=10.28$, $p<.001$, and the interference condition, $F(2.55, 196.28)=5.39$, $p=.003$, and for commission errors during the interference condition, $F(3, 231)=10.08$, $p<.001$, but not the control condition. Given that these main effects of Block were based on overall means of each performance variable for each Block, the *post hoc* analyses for the 3-group analyses were exactly the same as the 2-group analyses (see **Figure 8**).

For all of these analyses, the main effects of Group as well as the Group by Block interactions were all non-significant (all *ps*≥.452). Additionally, ANCOVAs covarying for potential confounding variables (i.e.,

sex and BDI for both the 2- and 3-group analyses as well as POMS Anger and TMD for the 3-group analyses) did not yield different findings from the original ANOVAs. However, ANCOVAs controlling for impulsivity, with BIS total score included as a covariate in the model, no longer yielded significant main effects of Block (all *ps*≥.144), except for the main effect of Block during the interference condition demonstrating reduced omission errors over time, $F(2.50, 226.47)=4.60$, $p=.007$. Interestingly, the BIS total score covariate was not a significant contributor in any of the ANCOVAs (all *ps*≥.086). Additional correlation analyses indicated that BIS did not significant correlate with MSIT performance in control participants or early MJ users (all *ps*≥.177), but increased impulsivity was associated with poorer performance in late MJ users. Specifically, lower interference percent accuracy, $r(34)=-.441$, $p=.007$, increased omission errors, $r(34)=.330$, $p=.049$, and increased commission errors, $r(34)=.453$, $p=.006$, all significantly correlated with increased impulsivity in late MJ users.

Analyses of internal consistency indicated excellent covariance across Blocks for response time during the control and interference conditions in both control (α=.895 and α=.887, respectively), early MJ (α=.855 and α=.897, respectively), and late MJ participants (α=.847 and α=.941, respectively). In regard to performance accuracy, internal consistency was more moderate for both control (α=.699 and α=.711, respectively), early MJ (α=.644 and α=.653, respectively), and late MJ participants (α=.640 and α=.757, respectively). Additionally, intrasubject

variability analyses revealed that although ISV changed significantly over Block for both the control and interference conditions, $F(2.66, 204.68)=19.94$, $p<.001$ and $F(2.70, 207.99)=2.97$, $p=.038$, respectively, the control and MJ users reported similar ISV for both the control and interference conditions during every block (all $ps \geq .073$).

4.2.2. MSIT fMRI Conventional Whole Task Analyses

Whole Task: Individual Group Averages

Individual group averages of brain activation in the cingulate and DLPFC ROIs were created using one-sample *t*-tests. As presented previously, the control group (**Figure 9**, **Appendix D**) did not demonstrate significant cingulate activation during either the control or interference conditions ($k=0$), but did show significant DLPFC activation during both the control ($k=15$) and interference ($k=100$) conditions. The I-C contrast indicated significantly greater cingulate ($k=46$) and DLPFC ($k=1309$) activation during the interference condition relative to the control condition. The early MJ group (**Figure 17**, **Appendix N**) did not demonstrate significant cingulate activation during either the control or interference conditions ($k=0$), but did show significant DLPFC activation during both the control ($k=174$) and interference ($k=117$) conditions. The I-C contrast indicated significantly greater cingulate ($k=36$) and DLPFC ($k=392$) activation during the interference condition relative to the control condition. The late MJ group (**Figure 18**, **Appendix O**) demonstrated significant

cingulate activation during both the control (*k*=17) and interference conditions (*k*=36), as well as significant DLPFC activation during both the control (*k*=347) and interference (*k*=481) conditions. The I-C contrast indicated significantly greater cingulate (*k*=117) and DLPFC (*k*=900) activation during the interference condition relative to the control condition.

Figure 17. EARLY ONSET MJ GROUP: One-Sample *t*-Test of Average fMRI Activation During the MSIT

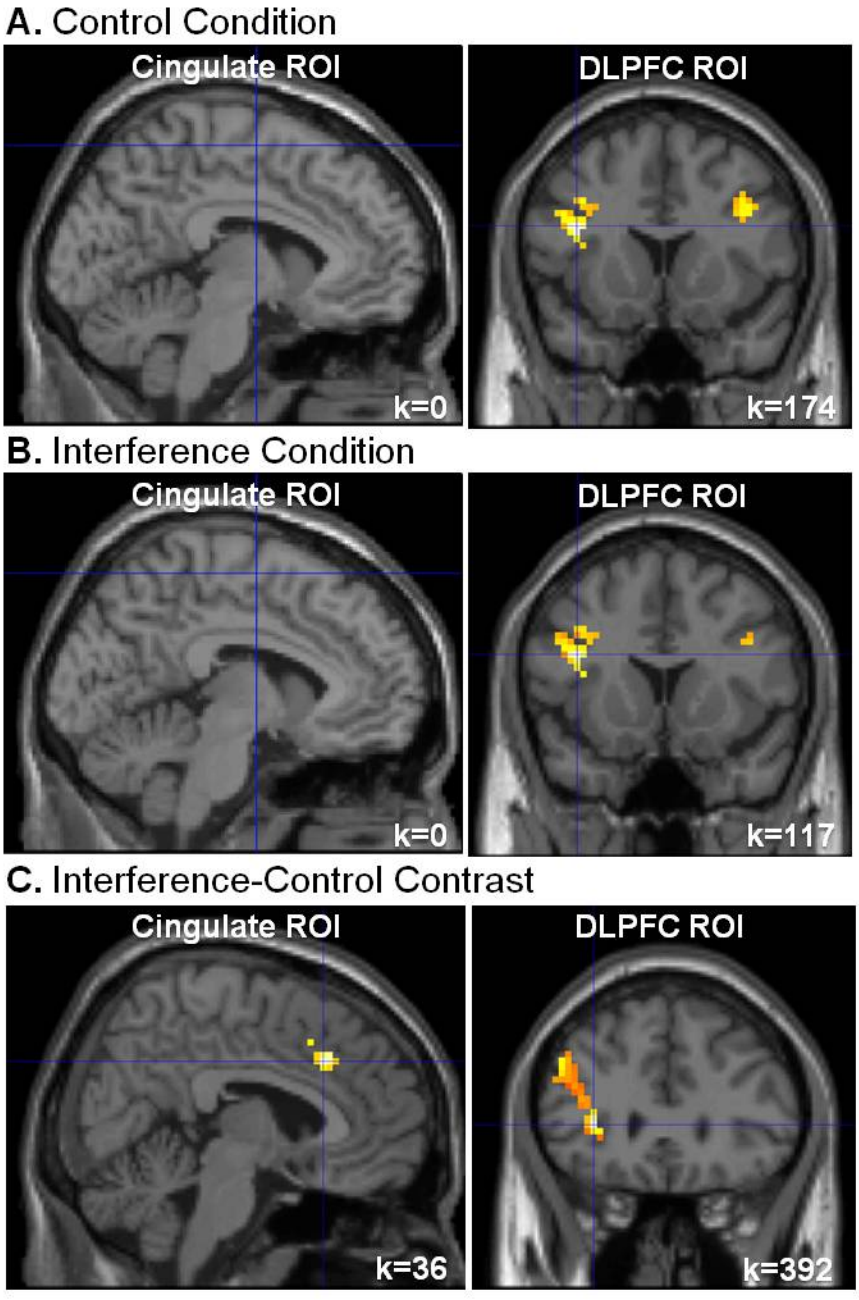
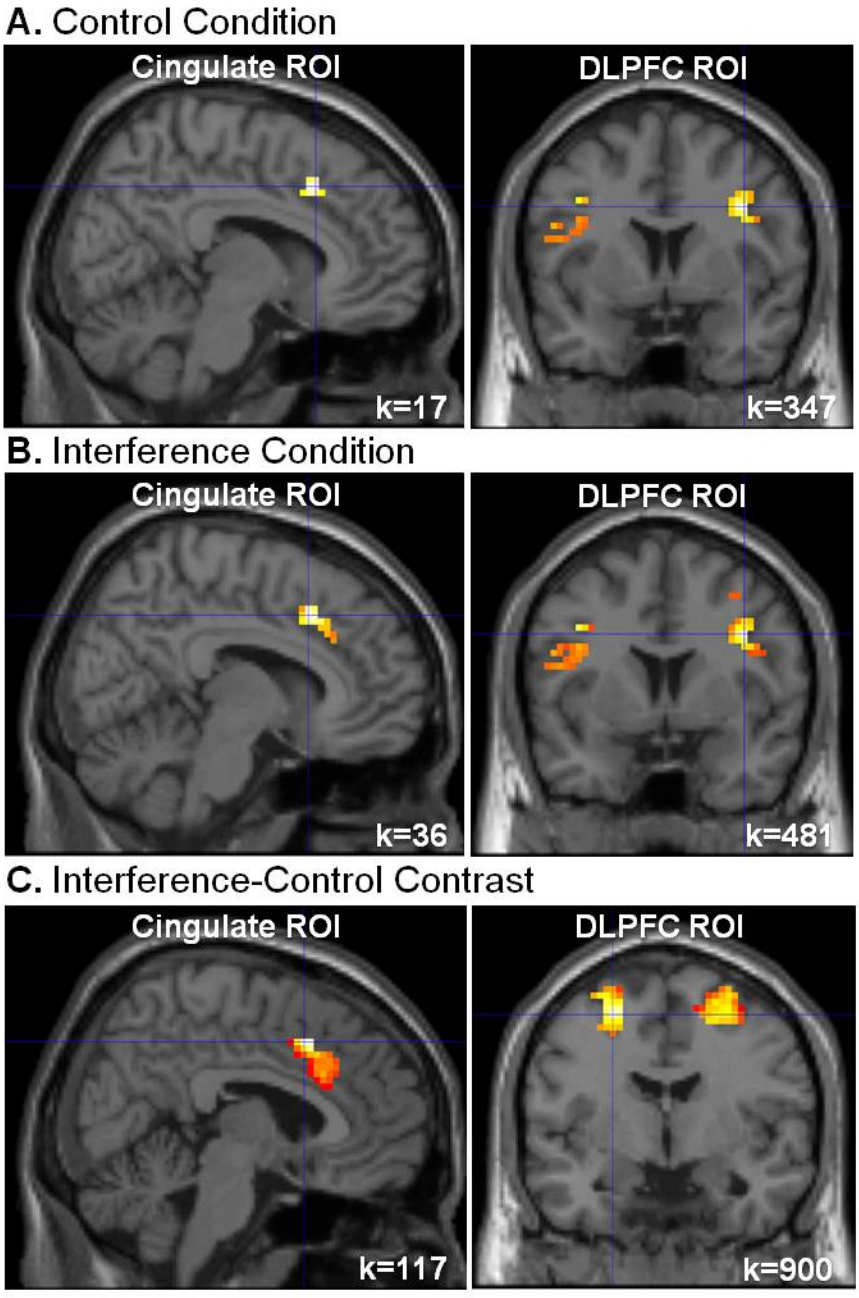


Figure 18. LATE ONSET MJ GROUP: One-Sample *t*-Test of Average fMRI Activation During the MSIT



Whole Task: Three-Group Analyses

Next, activation differences between the three groups (control vs early MJ vs Late MJ) were assessed next using an omnibus *F*-test

(**Appendix P**). In order to interpret the findings from the *F*-test, *post hoc t*-test comparisons of each unique two-group contrast were performed.

Control Condition

Cingulate (**Figure 19**, **Appendix Q**): Both the early MJ and late MJ groups demonstrated increased cingulate activation relative to the control group (*k*=39 and *k*=172, respectively). The control group did not exhibit any activation that was greater than the early MJ or late MJ groups (all *ks*=0). Additionally, the late MJ group had a small locus of increased activation in the posterior cingulate relative to the early MJ group (*k*=15). The early MJ group did not have any activation greater than the late MJ group (*k*=0).

DLPFC (**Figure 20**, **Appendix R**): Again, both the early MJ and late MJ groups demonstrated increased DLPFC activation relative to the control group (*k*=346 and *k*=618, respectively). The control group did not exhibit any activation that exceeded the early MJ or late MJ groups (all *ks*=0). Additionally, the late MJ group demonstrated increased activation relative to the early MJ group (*k*=252) while the early MJ group demonstrated only a small locus of increased activation relative to the late MJ group (*k*=39).

Figure 19. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Control Condition in the Cingulate

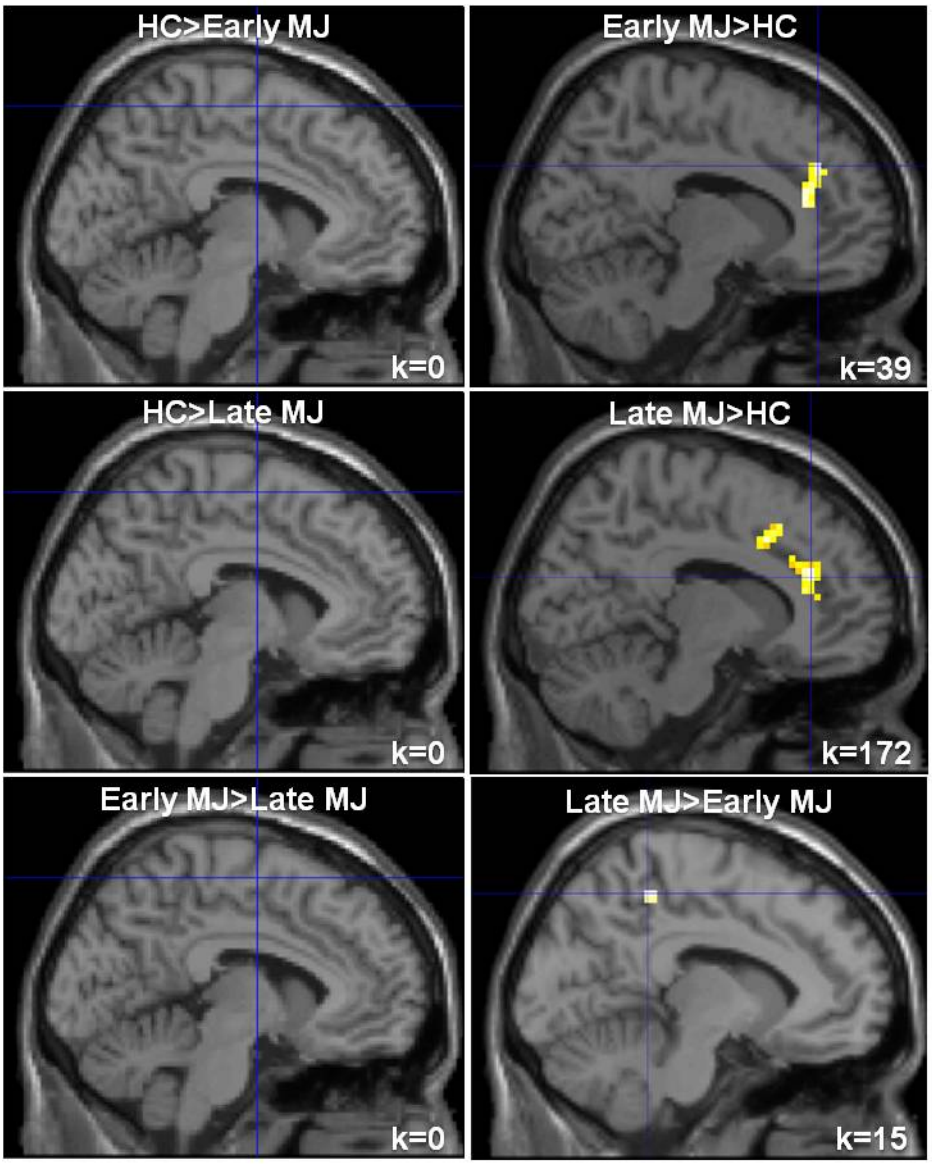
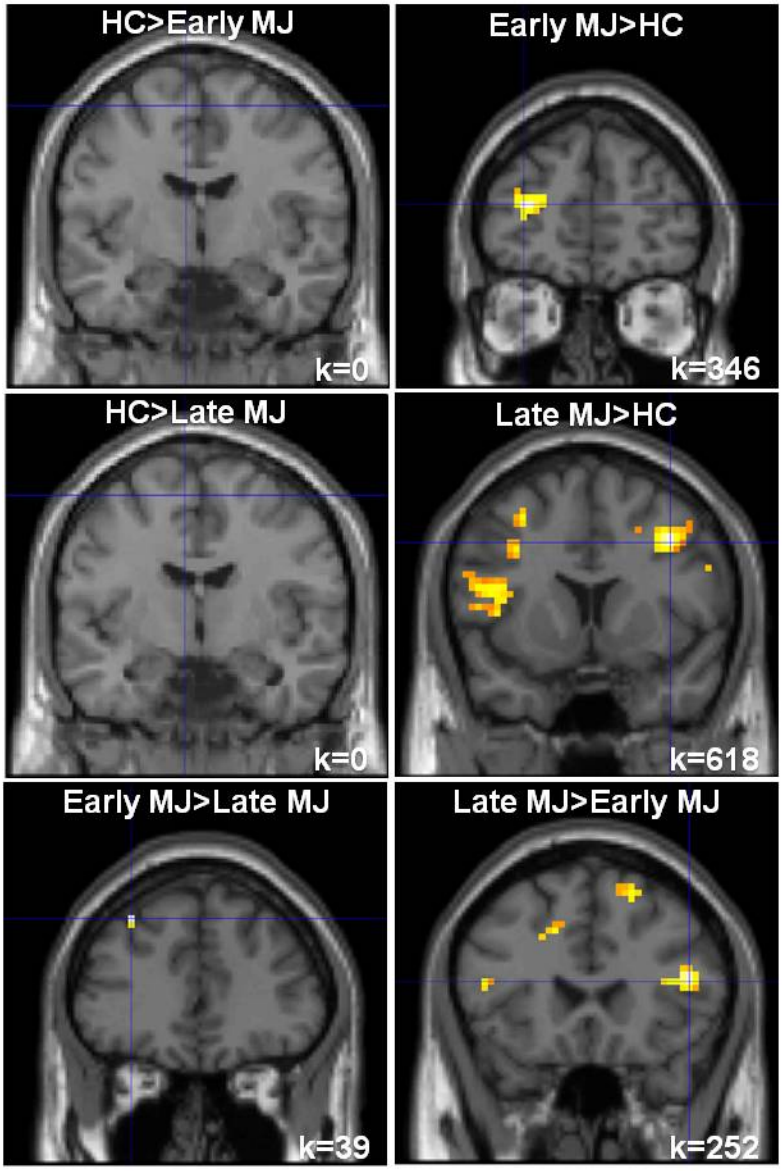


Figure 20. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Control Condition in the DLPFC



Interference Condition

Cingulate (**Figure 21**, **Appendix S**): Both the early MJ and late MJ groups demonstrated increased cingulate activation relative to the control group (*k*=23 and *k*=126, respectively). Further, the control group

demonstrated a small cluster of increased activation in the posterior cingulate relative to the early MJ group (*k*=19), but did not have any activation in that exceeded the late MJ group (*k*=0). Additionally, the late MJ group demonstrated increased activation relative to the early MJ group (*k*=51), while the early MJ group did not have any activation that exceeded the late MJ group (*k*=0). Notably, activation was increased in both the early MJ and late MJ groups relative to the control group, while both the control group and the late MJ group showed elevated activation in the posterior portion of the cingulate relative to early MJ users.

DLPFC (**Figure 22**, **Appendix T**): Both the early MJ and late MJ groups demonstrated elevated DLPFC activation relative to the control group (*k*=184 and *k*=470, respectively). While the control group did show some areas of increased activation compared to both the early MJ and late MJ groups (*k*=42 and *k*=10, respectively), the magnitude of these activations was not as great. Additionally, the late MJ group demonstrated increased activation relative to the early MJ group (*k*=293), while the early MJ group demonstrated a much smaller magnitude of increased activation relative to the late MJ group (*k*=55). Interestingly, the maxima of activation in the late MJ group was in a more lateral and posterior area of the DLPFC, while the maxima of increased activation in the early MJ group was in a more frontal anterior area.

Figure 21. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Interference Condition in the Cingulate

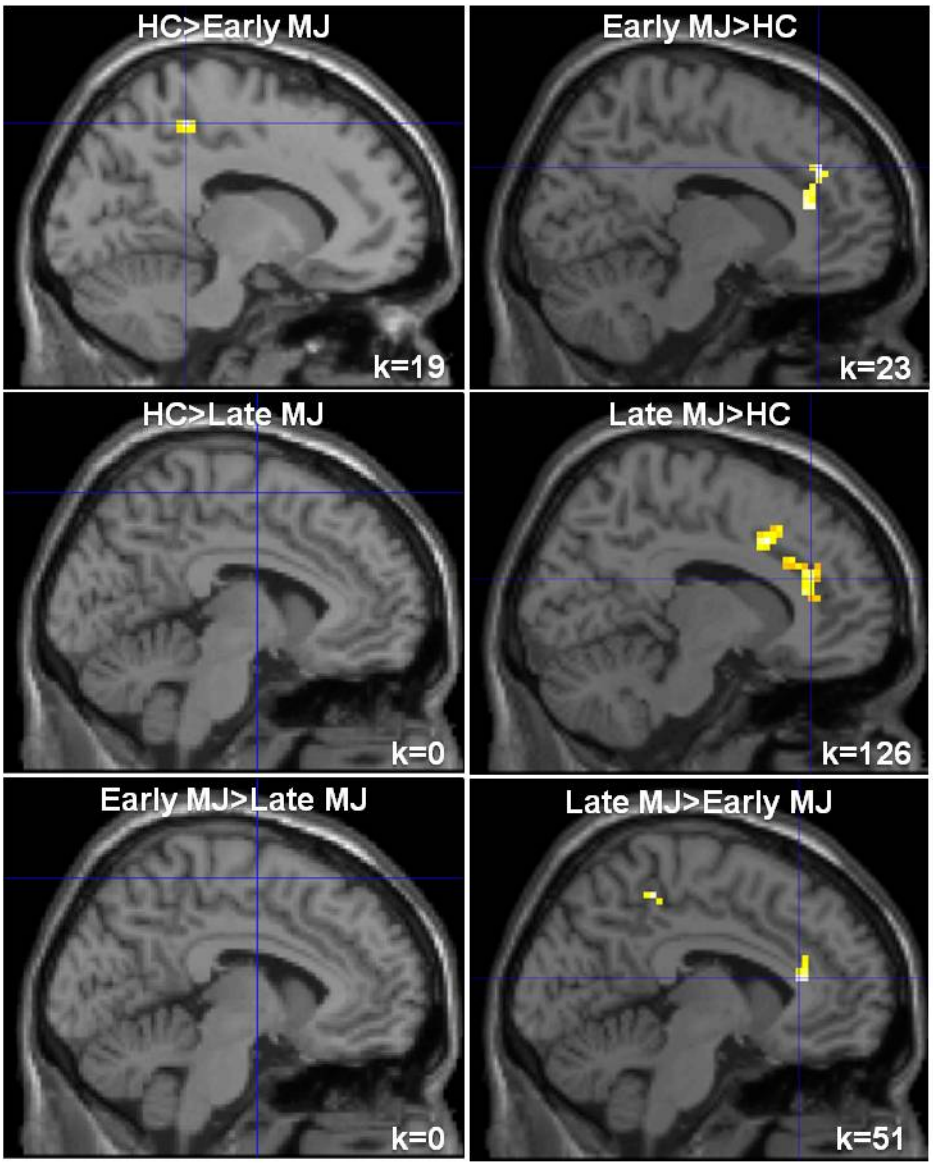
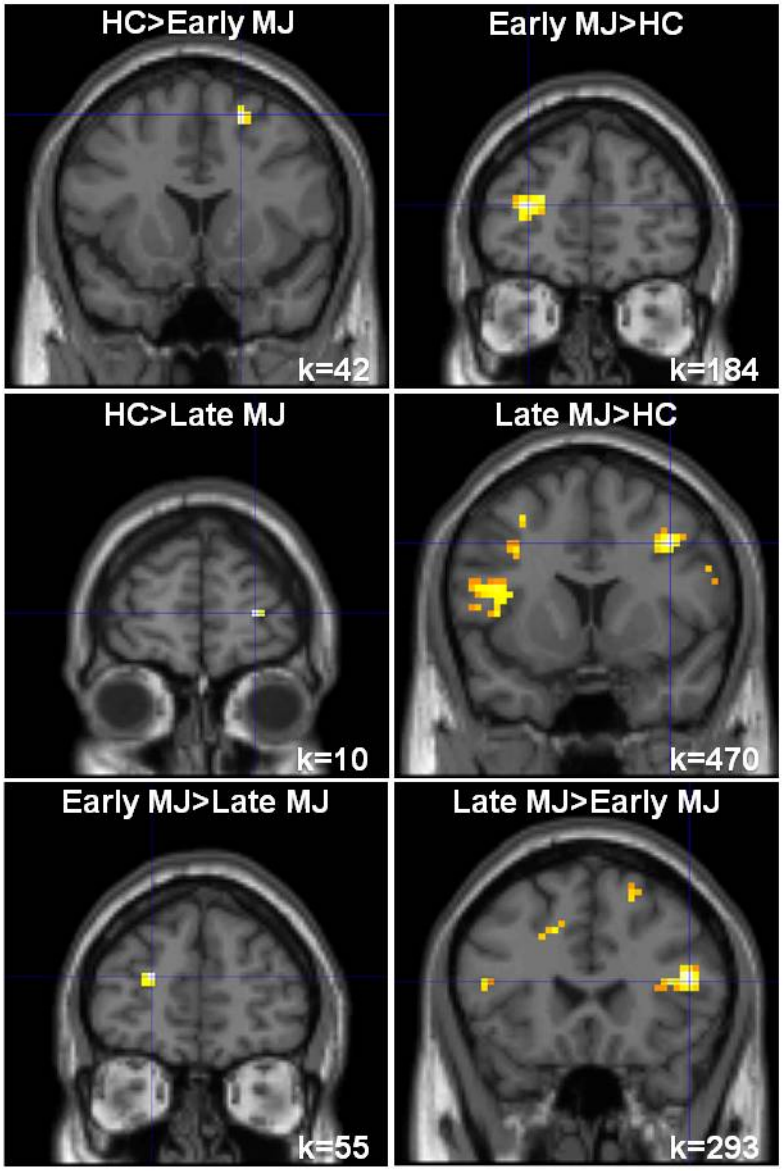


Figure 22. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Interference Condition in the DLPFC



Interference-Control Contrast

Cingulate (**Figure 23**, **Appendix U**): The control group demonstrated increased cingulate activation relative to both the early MJ and late MJ groups (*k*=157 and *k*=223, respectively). The late MJ group

had a small locus of increased activation relative to the control group (*k*=18), but the early MJ group did not have any activation greater than the control group (*k*=0). Additionally, the late MJ group showed increased activation relative to the early MJ group (*k*=126). The early MJ group did not have any activation greater than the late MJ group (*k*=0).

DLPFC (**Figure 24**, **Appendix V**): Again, the control group demonstrated increased DLPFC activation relative to both the early MJ and late MJ groups (*k*=665 and *k*=316, respectively). The early MJ group had a small locus of increased activation relative to the control group (*k*=14), and the late MJ group had a slightly larger locus of increased relative to the control group (*k*=60). Further, the late MJ group had increased activation relative to the early MJ group (*k*=263), while the early MJ group demonstrated a much smaller magnitude of increased activation relative to the late MJ group (*k*=87).

Figure 23. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Interference-Control Contrast in the Cingulate

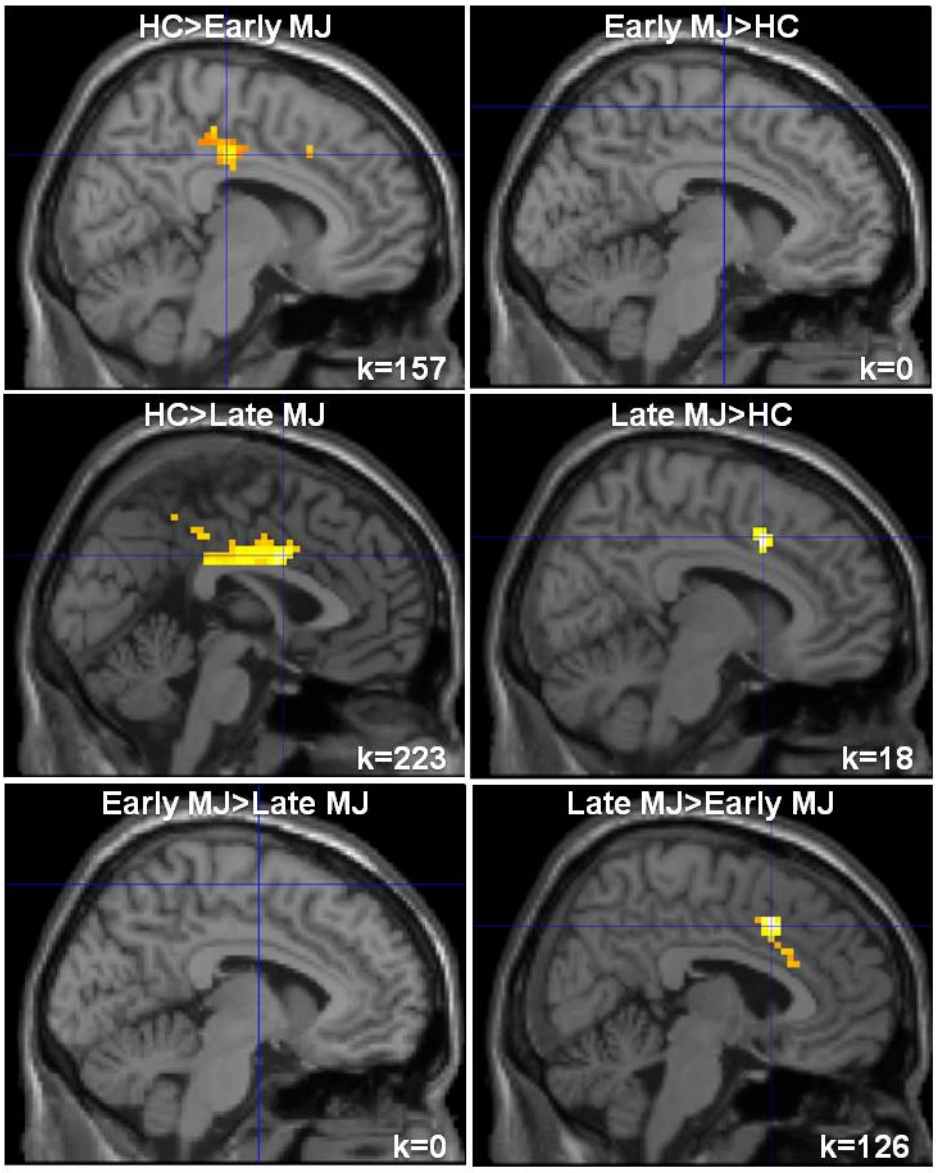
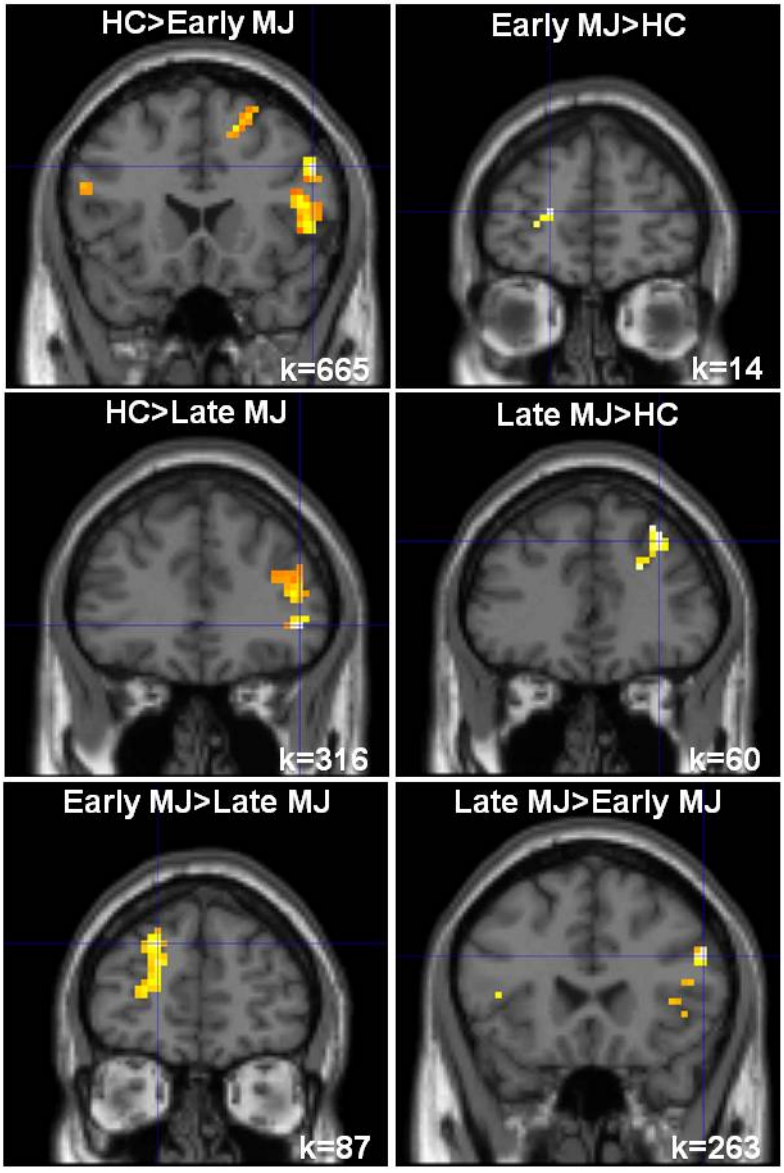


Figure 24. CONTROL vs EARLY MJ vs LATE MJ: *Post Hoc* Two-Group *t*-Tests of fMRI Activation During the MSIT Interference-Control Contrast in the DLPFC



4.2.3. MSIT fMRI Novel Block Analyses

Block Analyses: Individual Group Averages

Individual group averages of brain activation over time were assessed using one-sample *t*-tests for both the interference and control conditions across each of the four blocks of the MSIT.

Cingulate: During the control condition (**Figure 25A**), the early MJ group (**Appendix W**) did not activate any clusters above threshold during Block 1 (*k*=0), but they did demonstrate increased activation during later blocks, with activation peaking in Block 3 (*k*=116). During the interference condition, (**Figure 25B**), the greatest levels of activation were observed during Block 2 (*k*=57) and Block 3 (*k*=51), with little or no activation during Block 1 (*k*=10) and Block 4 (*k*=0).

The late MJ group (**Appendix Y**) demonstrated relatively lower levels of activation during Block 1 (*k*=34) of the control condition (**Figure 26A**), which increased during Block 2 (*k*=124) and Block 3 (*k*=149), but decreased to no activation by Block 4 (*k*=0). During the interference condition (**Figure 26B**), the late MJ group had the greatest activation during Block 1 (*k*=132), which decreased over each subsequent block (Block 2 *k*=92, Block 3 *k*=40, Block 4 *k*=20). Relative to the control group (**Figure 13**), the late MJ group followed a more similar pattern of activation during the interference condition, with greatest activation during the initial blocks that decreased over time. In contrast, the early onset group

demonstrated an altered pattern of activation, with increased cingulate activation during later blocks, (i.e., through Block 3).

Figure 25. EARLY MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the Cingulate by Block

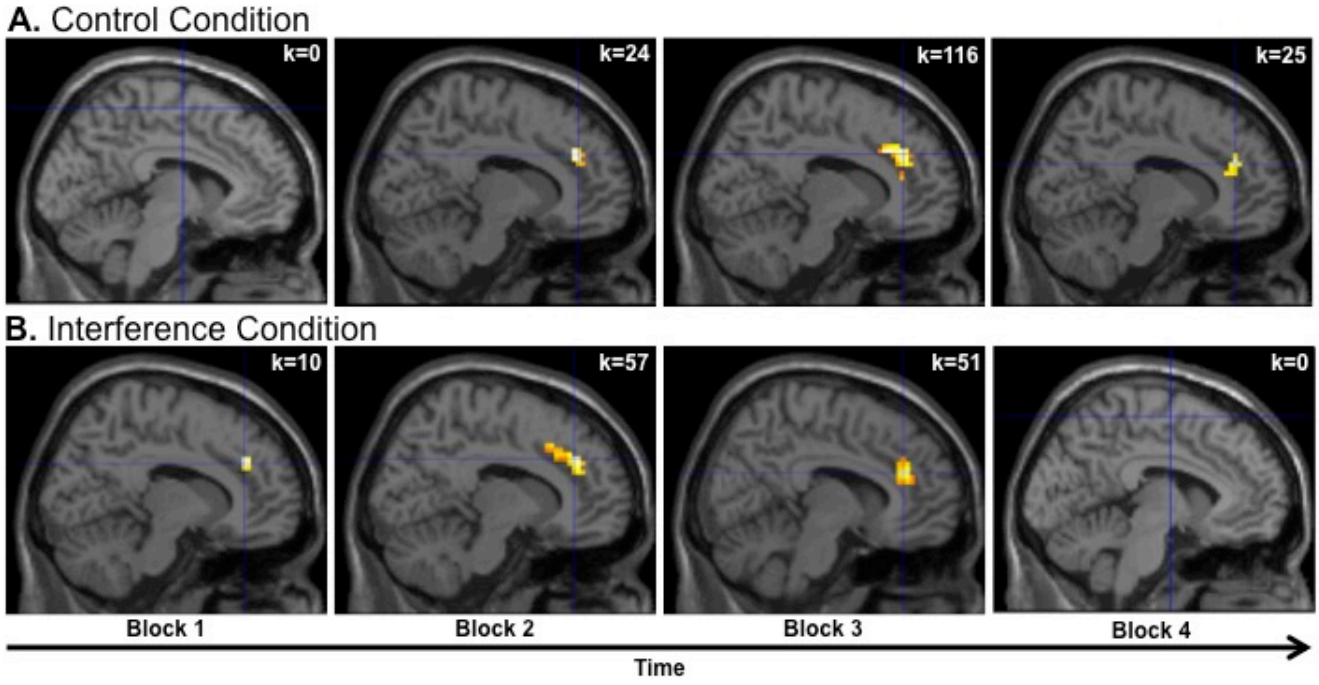
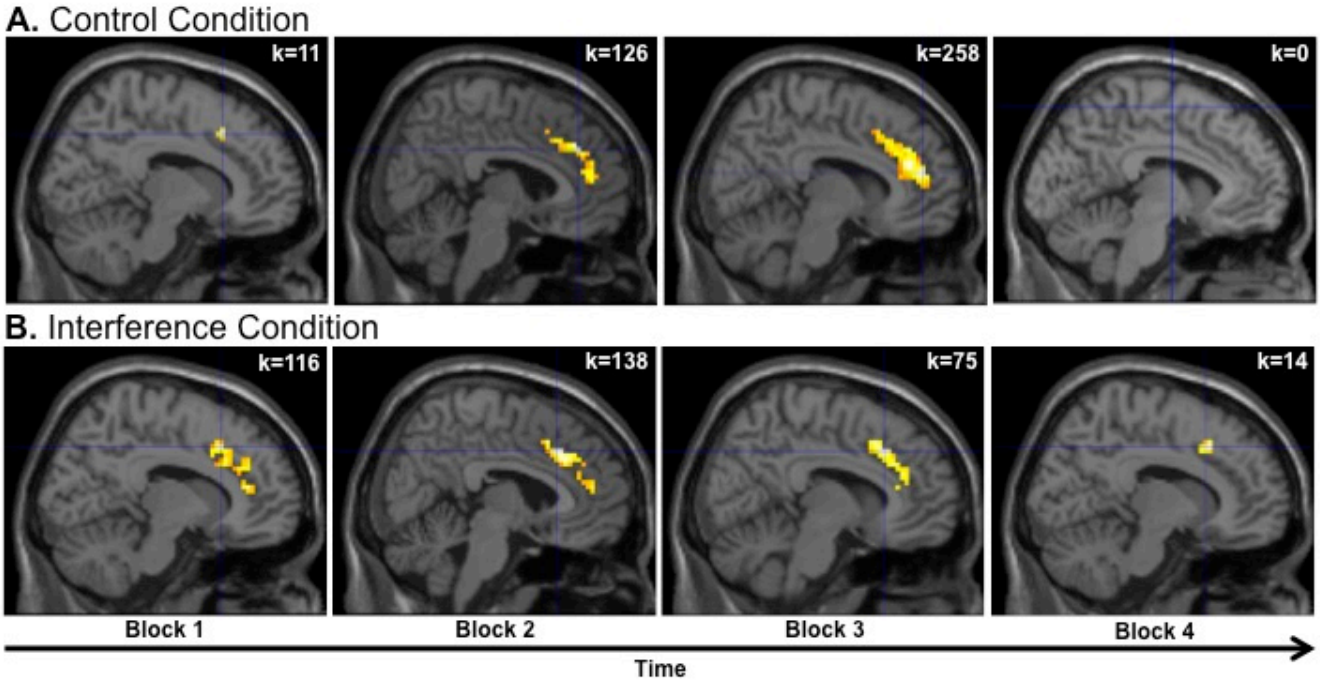


Figure 26. LATE MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the Cingulate by Block



DLPFC: The early MJ group (**Appendix X**) demonstrated significant activation during all blocks of the control condition (**Figure 27A**). The greatest activation was observed during the early blocks (Block 1 *k*=279, Block 2 *k*=383, and Block 3 *k*=793), with peak activation occurring during Block 3; however, activation significantly decreased during Block 4 (*k*=93). During the interference condition (**Figure 27B**), the early MJ group demonstrated significant activation during early blocks (Block 1 *k*=284, Block 2 *k*=526, Block 3 *k*=498), which peaked during Block 2 and Block 3. Activation significantly decreased by Block 4 (*k*=49).

The late MJ group (**Appendix Z**) demonstrated significant activation during all blocks of the control condition (**Figure 28A**). The greatest activation was observed during early blocks (Block 1 *k*=577, Block 2 *k*=1053, Block 3 *k*=441), with peak activation occurring during Block 2; however, activation significantly decreased by Block 4 (*k*=45). During the interference condition (**Figure 28B**), activation was the greatest during early blocks (Block 1 *k*=799 and Block 2 *k*=725) and decreased during subsequent blocks (Block 3 *k*=348 and Block 4 *k*=96). Overall, both the early and late MJ groups demonstrated altered patterns of activation during the control condition relative to the control group (**Figure 15**). Interestingly, during the interference condition, the late MJ group demonstrated a pattern of activation more similar to the control group (**Figure 15B**), with greater activation observed during initial blocks and decreased activation in later blocks. In contrast, the early onset group

demonstrated an altered pattern of activation with increased DLPFC activation during later blocks (i.e., through Block 3).

Figure 27. EARLY MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the DLPFC by Block

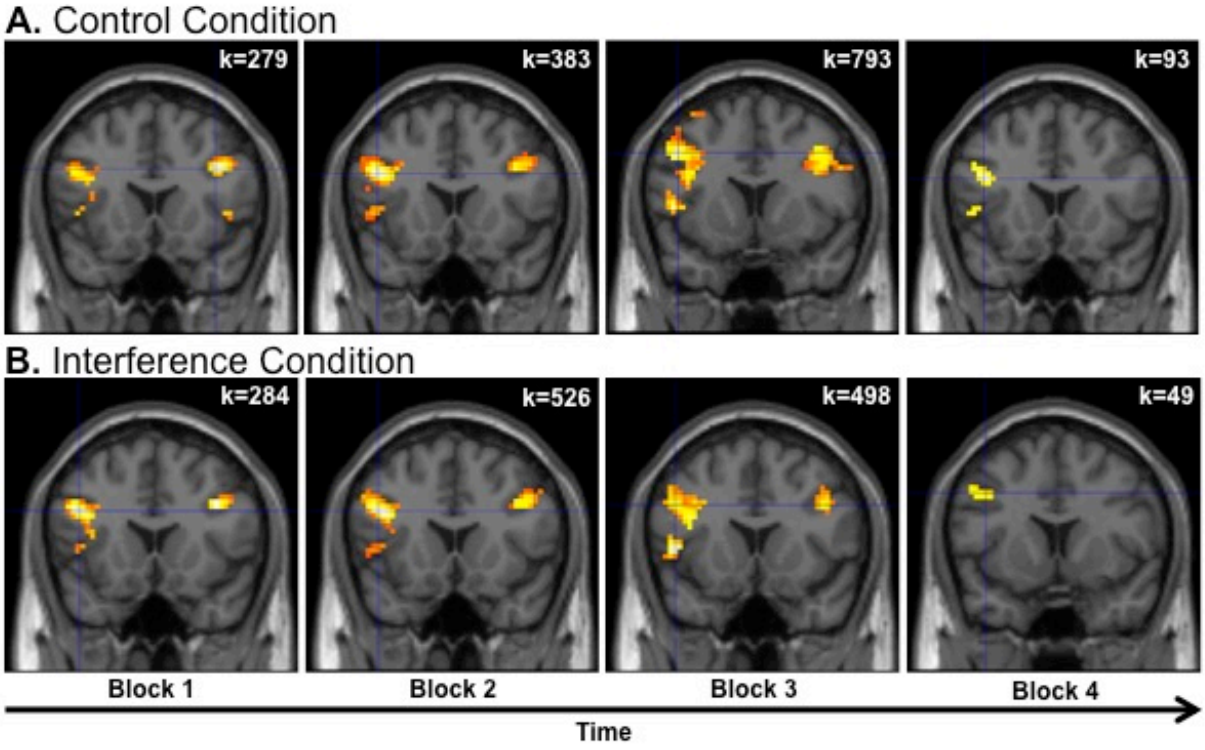
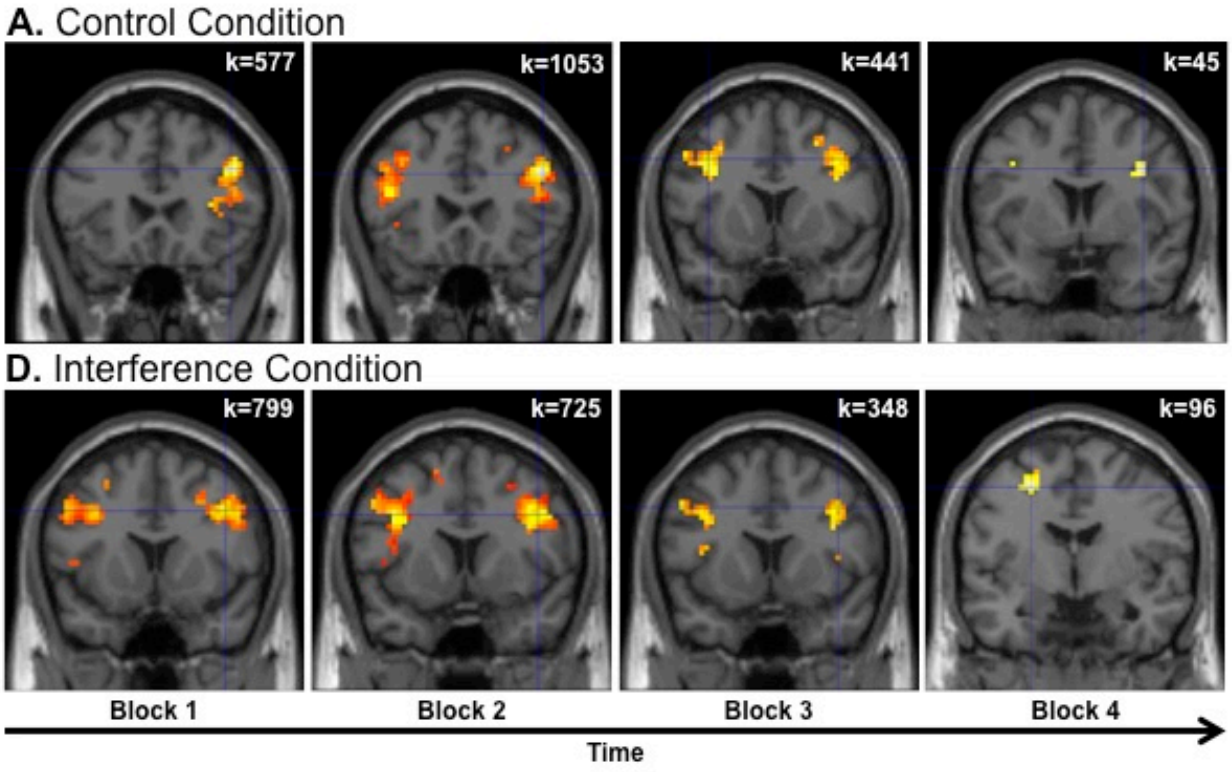


Figure 28. LATE MJ GROUP: One-Sample *t*-Test Average fMRI Activation During the MSIT in the DLPFC by Block



4.3. Correlation and Regression Analyses

4.3.1. Two-Group Analyses

MSIT Performance versus fMRI Activation

Correlation analyses indicated that within the control group, MSIT performance did not correlate with either cingulate or DLPFC activation. Within the MJ group, there was a trend for a negative correlation for increased control condition accuracy to be associated with reduced cingulate activation, $r(49)=-.245$, $p=.083$.

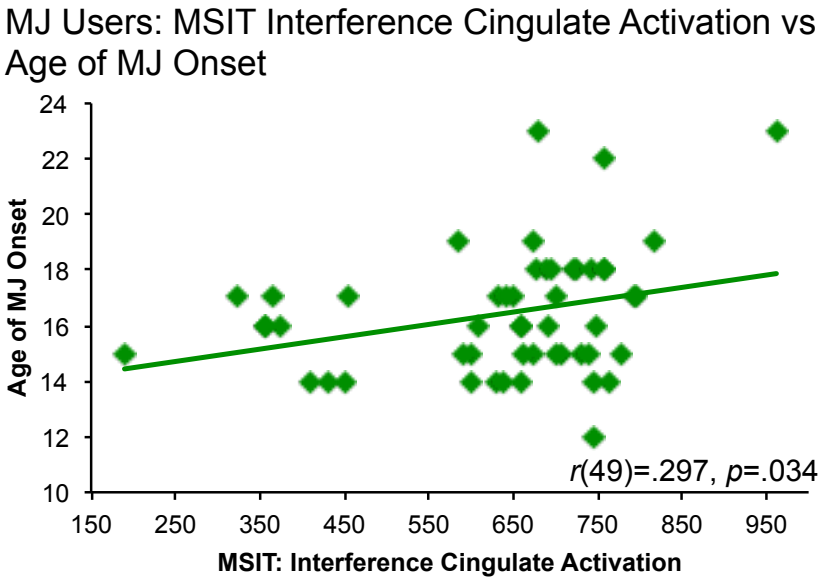
MSIT Performance versus MJ Use Variables

With regard to the impact of MJ use variables on MSIT performance, there was a trend for duration of MJ use to correlate with control condition response time, $r(52)=.265$, $p=.052$, but this was not significant. MJ episodes/week, MJ grams/week, and urinary THC concentration were not significantly correlated with MSIT performance (all $ps \geq .148$).

MSIT fMRI Activation versus MJ Use Variables

MJ use variables were also associated with fMRI activation during the MSIT. Age of MJ onset positively correlated with cingulate activation during both the control, $r(49)=.298$, $p=.034$ (**Figure 29**) and interference conditions, $r(49)=.297$, $p=.034$. This was the only MJ use variable to significantly correlate with fMRI activation; frequency (episodes/week) and magnitude (grams/week) of MJ use, duration of use (yr), and urinary THC concentration (all $ps \geq .162$).

Figure 29. MJ Use Variables Correlate with MSIT fMRI Activation: MJ Group



4.3.2. Three-Group Analyses

MSIT Performance versus fMRI Activation

Correlation analyses indicated that, within the control group, MSIT performance did not correlate with either cingulate or DLPFC activation. Within the early MJ group, interference condition response time significantly correlated with DLPFC activation, $r(18)=.473$, $p=.035$ (**Figure 30A**), and within the late MJ group, interference commission errors significantly correlated with cingulate activation, $r(29)=.372$, $p=.039$ (**Figure 30B**).

MSIT Performance versus MJ Use Variables

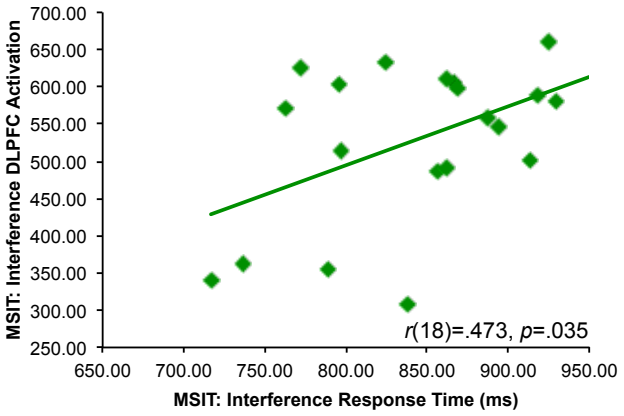
Within the early and late MJ group, MJ use variables did not highly correlate with MSIT performance. Within the early MJ group, none of the MJ use variables (age of onset, episodes/week, grams/week, duration of use, and urinary THC concentration) correlated with MSIT performance (all *ps*≥.102). Within the late MJ group, trends emerged for age of MJ duration to correlate with control commissions, $r(31)=.334$, $p=.057$, and for both urinary THC concentration, $r(25)=.373$, $p=.056$, and age of MJ onset, $r(31)=.327$, $p=.063$, to correlate with interference commissions, but these did not reach significance.

MSIT fMRI Activation versus MJ Use Variables

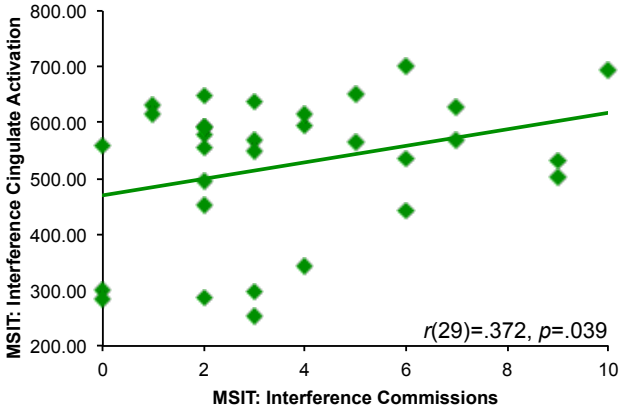
Additionally, within the late MJ group, age of MJ onset positively correlated with cingulate activation during both the control, $r(29)=.477$, $p=.007$, and interference conditions, $r(29)=.477$, $p=.007$ (**Figure 30C**). Further, duration of MJ use also correlated with cingulate activation during both the control, $r(29)=.392$, $p=.029$, and interference conditions, $r(29)=.393$, $p=.029$ (**Figure 30D**). Regression analyses indicated that age of MJ onset contributed the most unique variance to the model; adding MJ duration did not produce a significant change in the model, $\Delta R^2=.037$, $\Delta F(1,28)=1.330$, $p=.259$. Within the early MJ group, none of the MJ use variables (age of onset, episodes/week, grams/week, duration of use, and urinary THC concentration) correlated with MSIT fMRI activation (all *ps*≥.173).

Figure 30. MJ Use Variables Correlate with MSIT Performance and fMRI Activation: Early and Late MJ Groups

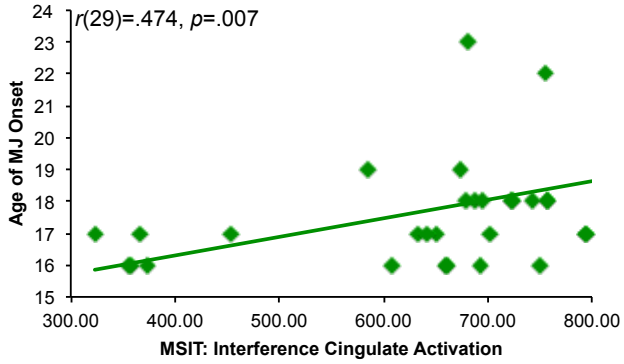
A. Early MJ: MSIT Interference Response Time vs DLPFC Activation



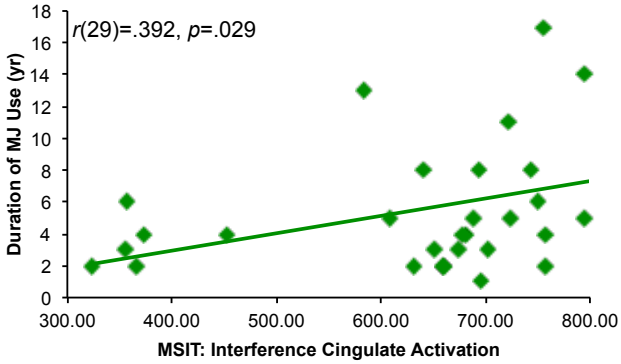
B. Late MJ: MSIT Interference Commissions vs Cingulate Activation



C. Late MJ: MSIT Interference Cingulate Activation vs Age of MJ Onset



D. Early MJ: MSIT Interference Response Time vs DLPFC Activation



5. Discussion

The primary goal of this project was to compare "whole task" analyses of the MSIT, based on *overall averages* of task performance and brain activation, to novel "discrete block" analyses, which used task Block as a repeated measures variable to assess performance and brain activation *differences over time*. Specifically, we were interested in assessing MSIT performance and brain activation changes over time in MJ users relative to healthy control participants. Gruber and colleagues

(2012b) previously used whole task analyses of the MSIT and observed altered patterns of activation within the cingulate cortex without concurrent performance deficits in MJ users relative to control participants. Further, age of onset of MJ use appeared to impact cingulate activation, as early onset MJ users (who began using MJ prior to age 16) demonstrated a more diffuse pattern of activation in the midcingulate relative to control participants, while late MJ users (MJ onset after age 16) demonstrated a more focal pattern of activation in a more anterior aspect of the cingulate, which was more similar to control participants.

Given previous work demonstrating significant performance improvements over the course of the task (Dahlgren et al., in prep), we hypothesized that in the current project, MSIT performance and brain activation would be dynamic, and would significantly change over time in all groups (control, MJ users, early MJ users, and late MJ users). Additionally, Dahlgren and colleagues (in prep) observed a significant Group by Block interaction, as individuals with PTSD and their "high risk" co-twins demonstrated greater performance decrements during earlier blocks of the MSIT task, which normalized over time. Previous whole task analyses of this data (Shin et al., 2011) reported only a trend for group differences, suggesting that discrete block analyses may be more sensitive than whole task analyses at identifying between-group differences, particularly in task performance. For this project, we hypothesized that discrete block analyses would reveal significant

differences between the groups that have not been observed in the whole task analyses (Gruber et al., 2012b; Harding et al., 2012). Specifically, we expected MJ users to demonstrate impaired MSIT performance and altered cingulate and DLPFC activation over time relative to control participants, and that these differences would be driven by age of MJ onset, with the early onset MJ group exhibiting the most impairment and the late MJ group more closely resembling to the control group.

Lastly, increased attention is now focused on the ways in which MJ use characteristics may impact cognitive function, as evidence suggests that increased cognitive impairment is related to increased MJ use, particularly earlier age of MJ onset (Battisti et al., 2010; Dahlgren et al., 2016; Fontes et al., 2011; Gruber et al., 2012a; Pope et al., 2003; Solowij et al., 2011). Therefore, the current research planned to evaluate how MJ use characteristics (e.g., age of MJ onset, frequency of MJ use, magnitude of MJ use, etc.) correlate with MSIT performance and brain activation. We hypothesized that age of MJ onset would have the most impact on the MSIT, with earlier age of onset associated with poorer performance and more altered patterns of brain activation.

5.1. MSIT Performance Results

Consistent with previous studies of MSIT performance in MJ users (Gruber et al., 2012b; Harding et al., 2012), when assessing whole task performance, we did not observe any significant performance differences

in our two-group analyses (control vs MJ) or in our three-group analyses (control, early MJ onset, and late MJ onset). Further, when MSIT performance was examined over time, performance remained similar between the groups, with no significant main effects of Group and no significant Group by Block interactions. We had hypothesized that we would observe impaired MSIT performance over time in the MJ users, particularly in early onset MJ users, relative to control participants; however these differences were not observed in the current research.

Despite a lack of significant between-group differences over time, significant main effects of Block did emerge as hypothesized, indicating that MSIT performance changed over time across all participants. Specifically, during the control condition, performance differences were localized to Block 1 with slower response time and poorer performance accuracy relative to the other three blocks. Control condition performance approached ceiling level accuracy (100%) by Block 2, which was sustained throughout the rest of the task. This pattern of performance over time suggests that all participants acclimated to the control condition of the task during Block 1 with near-perfect performance sustained thereafter.

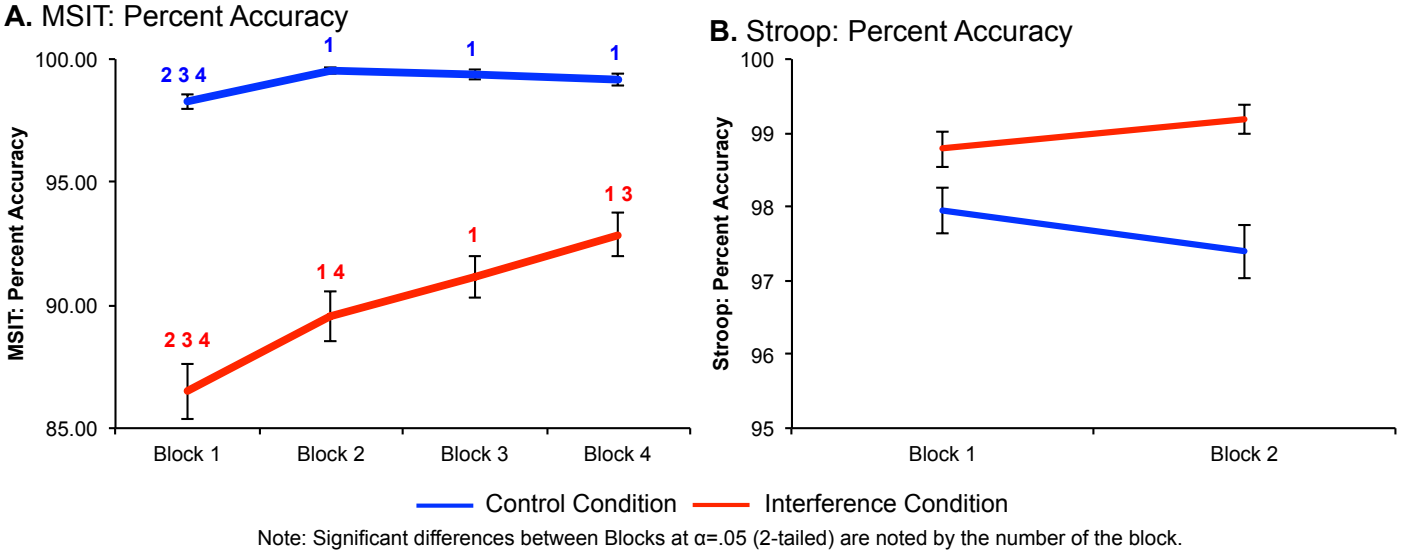
During the interference condition however, change over time was more dynamic; both response time and percent accuracy continually improved throughout the task, with significant improvements observed even in the last block of the task. However, it is unclear how interference

condition performance might change over a longer period of time. Future studies could address this question using longer versions of the MSIT; some studies already use a longer version of the task (e.g., Yucel et al., 2007b), but have employed whole task analysis schemes not designed to evaluate performance differences over time. Performance during the interference condition may continue to improve until the accuracy ceiling is reached, or alternatively, the cognitive load of sustained attention may prevent participants from reaching near-perfect accuracy. Evidence suggests that MJ users may have difficulty with sustained attention (e.g., Mathias et al., 2011; Scholes & Martin-Iverson, 2009); therefore, longer versions of the task may also be more sensitive to identifying group differences, as sustaining attention may be more difficult for MJ users relative to control participants during longer tasks.

Furthermore, in order to determine whether cognitive interference performance differences over time were limited to the MSIT task, we performed pilot analyses on Stroop interference performance data using block as a repeated measures variable utilizing the same participant pool as the current MSIT analyses (control=25, MJ=49, early MJ=18, and late MJ=31 after controlling for Stroop performance outliers). Both two-group (control vs MJ) and three-group (control vs early MJ vs late MJ) analyses did not return any significant main effects (neither Group nor Block) or any significant Group by Block interactions (**Figure 31**). However, it should be noted that each condition of the Stroop task consisted of only two

separate (30s) of experimental trials, which were interleaved with 30s fixation blocks. Conversely, each condition of the MSIT (**Figure 5**) consisted of four alternating blocks of experimental trials (42s). These results suggest that the MSIT may be better suited to assess performance changes over time.

Figure 31. Comparison of MSIT and Stroop Performance Over Time



Note: Significant differences between Blocks at α=.05 (2-tailed) are noted by the number of the block.

Overall, the results of the current study confirm that MSIT performance is dynamic over time in both control participants and MJ users, but the data did not reveal any group differences, either between the overall group means or between-groups over time. Importantly, evidence of MSIT performance differences over time has now been confirmed in two different studies. Dahlgren and colleagues (in prep) previously demonstrated changes over Block in a small sample of trauma-exposed individuals with and without PTSD. That study also reported a

significant Group by Block interaction where trauma-exposed individuals (and their trauma-unexposed co-twins) performed more poorly during Blocks 1-3 of the MSIT relative to trauma-exposed individuals without PTSD (and their trauma-unexposed co-twins), but there were no between-group differences during Block 4. These results indicate that performance deficits during the initial blocks of the MSIT in individuals with PTSD and their high-risk co-twins may reflect a familial vulnerability factor for PTSD, but that performance normalizes over time, with no differences between-groups by the last block of the task. However, when comparing Dahlgren et al. (in press) to the current study, it is important to note the clinical difference between the study samples. In the current study, participants were mostly healthy, young college students without any major medical or psychiatric conditions. In the PTSD study, participants were mostly Vietnam War veterans, and as such were older men with a variety of other health issues in addition to their PTSD diagnosis. Future studies should examine MSIT performance differences over time in other clinical populations, as group differences may emerge in samples of individuals with greater clinical symptomatology.

While the hypothesized between-group differences over time were not observed in the current study, it is important to note that previous studies using whole task analyses of MSIT performance also did not report significant differences between MJ users and healthy controls (Gruber et al., 2012b; Harding et al., 2012). It is possible that the current

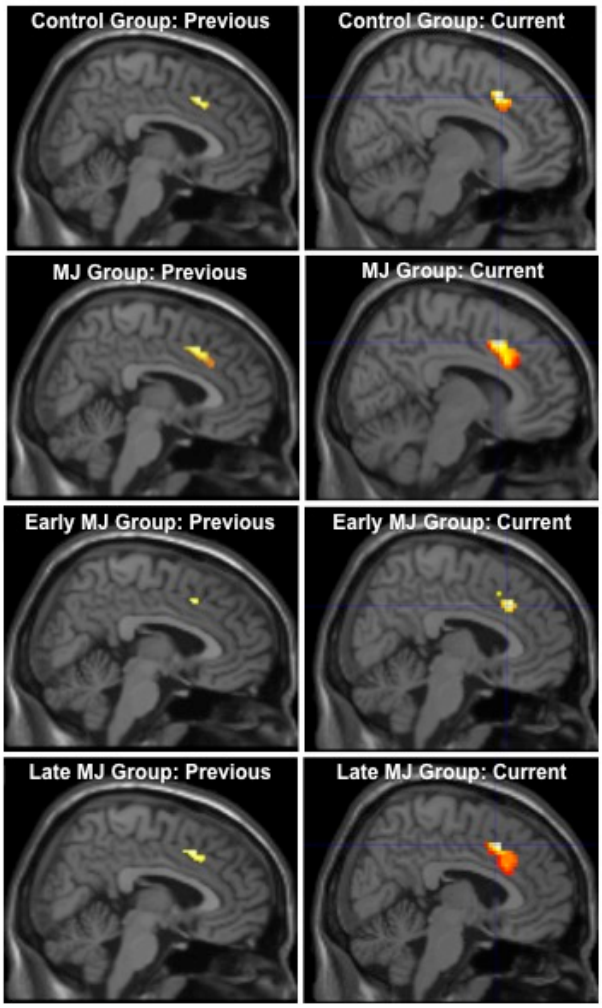
findings represent true null results, meaning that MJ users and healthy controls perform equally well on this task; however, it is also possible that the current results represent a Type II error, and a false null has been inappropriately retained. Interestingly, the current sample of MJ users also did not demonstrate significantly poorer performance on the Stroop interference task relative to control participants, but previous studies have consistently reported Stroop impairment in MJ users (e.g., Battisti et al., 2010; Fontes et al., 2011; Gruber & Yurgelun-Todd, 2005; Gruber et al., 2012a; Sagar et al., 2015). The fact that the current sample of MJ users did not demonstrate the expected Stroop performance differences suggests that the null results observed in the current study may not be due to other confounding factors. For example, these non-significant results may be attributable to the fact that the MJ-using cohort and control subjects are high-functioning, intelligent young adults; this point is further discussed in the "Limitations and Future Directions" section.

5.2. MSIT fMRI Conventional Whole Task Results

The current study replicated previous whole task analyses of the MSIT comparing MJ users to control participants; **Figure 32** provides a side-by-side comparison of the I-C contrast images from the current study versus Gruber et al. (2012b). Both studies demonstrated increased cingulate activation during the MSIT in MJ users relative to control participants. Additionally, in both studies, the three-group comparison

(control vs early MJ vs late MJ) revealed that the late MJ users had the greatest activation within the cingulate cortex, followed by control participants and finally the early MJ users, who exhibited the lowest level of cingulate activation of the three groups.

Figure 32. MSIT I-C Contrast fMRI Activation of the Cingulate ROI: Comparison of Previous Findings (Gruber et al., 2012b) with the Current Study



Further, the current study extended previous research by examining MSIT-related activation within the DLPFC. Abdullaev and

colleagues (2010) previously reported increased cingulate and DLPFC activation in chronic, heavy MJ users relative to control participants during incongruent trials on a flanker task. We observed similar neural activation patterns between control and MJ participants during the interference condition of the MSIT. Interestingly, results from the MSIT more closely resemble results from the flanker task (Abdullaev et al., 2010) relative to results from the Stroop task (Gruber & Yurgelun-Todd, 2005; Hatchard et al., 2014; Sagar et al., 2015). Given that flanker interference has been determined to be the primary contributor of cognitive interference during the MSIT (Stins et al., 2005), the similarity of the results is not unexpected. Additionally, in the current study, three-group analyses revealed that the late MJ users had the greatest DLPFC activation, which was diffuse and bilateral, during the interference condition. The control participants and early MJ users displayed smaller levels of DLPFC activation, which were relatively similar in magnitude but contralateral.

When interpreting the findings of the fMRI activation contrasts, it is important to consider the group activation averages. The control group (**Figure 9**) activated a relatively small, focal locus of the cingulate for the I-C contrast; however, no significant clusters of cingulate activation emerged during either the control or interference condition individually. In regard to DLPFC activation, control participants demonstrated large, diffuse, bilateral activation of the DLPFC during the I-C contrast; this was due to the comparatively minor activation during the control condition

relative to much greater activation during the interference condition. These results confirm the standard finding in healthy control samples: greater CFP activation is necessary during the interference condition of the MSIT relative to the control condition (e.g., Bush et al., 2003). Additionally, our sample of control subjects exhibited relatively little cingulate cortex activation relative to DLPFC activation during the entire task, but this difference was greatest during the interference condition. Interestingly, Milham and colleagues (2002) provided evidence that cingulate activation is modulated by the DLPFC, with increased cingulate activation necessary when DLPFC activation is low. In the current study, low cingulate activation may be related to the large magnitude of DLPFC activation in control participants.

In regard to the entire MJ group (**Figure 10**), smaller, more focal activation within both the cingulate and DLPFC was observed during the control condition, with larger activations in both ROIs apparent during the interference condition; this resulted in large, diffuse activation patterns for the I-C contrast. Overall, the entire MJ group revealed significantly increased cingulate activation relative to the control group; additionally, the MJ group demonstrated a similar pattern of DLPFC activation as the control group, but with larger local maxima for both task conditions.

When the MJ group was divided into early and late MJ users, different patterns of activation emerged. Within the early MJ group (**Figure 17**), cingulate activation was strikingly similar to the control group,

with no significant clusters of activation apparent during either the control or interference conditions, but a small, focal local maxima of activation was revealed in the I-C contrast. However, activation patterns within the DLPFC were very different, with the early MJ group demonstrating more DLPFC activation during the control condition relative to the interference condition. Within the late MJ group (**Figure 18**), both cingulate and DLPFC activation was increased relative to the control group, and followed the typical pattern expected, with increased activation during the interference condition relative to the control condition. When comparing the two MJ groups, the late MJ group had increased cingulate and DLPFC activation relative to all other groups, but the early MJ group displayed the most altered activation patterns with increased bilateral DLPFC activation, particularly within the middle frontal gyrus, during the control condition relative to the interference condition.

Interestingly, the cingulate cortex results from the current study, demonstrating higher levels of activation within the late MJ group relative to the early MJ group during the MSIT, are the *opposite* of reported activation patterns during the Stroop interference condition in similar populations. Sagar and colleagues (2015) observed that all MJ users demonstrated less cingulate activation relative to control participants, and while early MJ participants displayed greater anterior cingulate activation during the Stroop task relative to late MJ users, this activation was in a more anterior region of the cingulate. Late MJ users demonstrated less

cingulate activation than both control and early MJ users, but the location of activation, in the posterior cingulate, was more similar to activation patterns within the control group. However, this study also reported impaired Stroop performance in MJ users relative to control participants, with early MJ users demonstrating poorer performance relative to both control subjects and late MJ users; the control and late MJ users performance was not significantly different. This pattern of altered cingulate activation with concurrent performance differences is different from the current study. Additionally, Sagar and colleagues (2015) did not report activation patterns within the DLPFC. If cingulate activation is modulated by the DLPFC, as suggested by Milham and colleagues (2002), then DLPFC dysfunction is also likely implicated in both Stroop and MSIT activation patterns and differences detected. For example, reduced DLPFC activation in early MJ users may result in increased cingulate activation during the Stroop task relative to late MJ users. Overall, evidence suggests that CFP activation during cognitive interference processing is altered in MJ users with early onset users demonstrating the most dysfunctional activation patterns relative to non-MJ using control subjects.

Additionally, the current results demonstrating CFP network alteration during the MSIT without concomitant performance differences are consistent with previous findings in a variety of subject populations (e.g., Fitzgerald et al., 2010; Gruber et al., 2012b; Harding et al., 2012;

Harrison et al., 2007; Silton et al., 2010; Yucel et al., 2007a; 2007b), and have been interpreted as being related to neurocompensatory mechanisms. The neurocompensatory theory proposes that deviations from the typical pattern of healthy control CFP network activation are considered less efficient, particularly when increased activation is needed to achieve the same level of task performance. The precise mechanisms underlying the need for increased CFP network activation for MJ users to complete the MSIT are not completely understood. Harding and colleagues (2012) reported that MJ users demonstrated altered connectivity between CFP attention network ROIs, particularly the DLPFC, during the MSIT. Additionally, evidence suggests that recreational MJ use is also associated with structural alterations relative to control participants, particularly reduced white matter integrity, which has also been associated with earlier onset of use (e.g., Gruber et al., 2014; Orr, Paschall, & Banich, 2016), increased impulsivity (e.g., Gruber et al., 2014), impaired executive functioning (e.g., Gruber et al., 2015), and increased clinical symptomatology, such as depressive symptoms (e.g., Medina et al., 2007b) in MJ users. Future research should explore the potential contribution of alterations in regional connectivity and white matter integrity in MJ users, particularly with regard to how they relate to outcome measures such as MSIT performance.

5.3. MSIT fMRI Novel Block Analyses Results

Overall the MJ groups demonstrated greater activation in both the cingulate and DLPFC ROIs relative to the control group, which supports the neurocompensatory theory that greater activation is necessary for clinical groups to perform the MSIT (e.g., Gruber et al., 2012b; Yucel et al., 2007b). In regard to cingulate activation over time, the MJ group as a whole demonstrated greater cingulate activation during both the control and interference conditions relative to the control group, but the increased activation during the control condition was the most different from the pattern of activation observed in the control group. Additionally, during the interference condition, the late MJ group demonstrated a pattern of activation more similar to the control group, with the greatest activation observed during the initial blocks and reduced activation over time, whereas the early onset group demonstrated an altered pattern of activation with increased cingulate activation during latter blocks (i.e., through Block 3).

Interestingly, the control group did not demonstrate any cingulate activation throughout the control condition, and only exhibited cingulate activation during the initial blocks of the interference condition. Dosenbach and colleagues (2007; 2008) suggested that the cingulo-opercular system of the CFP attentional network, which includes the cingulate, is responsible for task set maintenance. Further, conflict monitoring theories hypothesize that the cingulate, particularly the ACC,

detects cognitive conflict, (a form of cognitive interference), and greater cingulate activation is therefore required during increased cognitive conflict in order to adjust performance (reviewed in Botvinick et al., 2001). Additionally, the error detection theory suggests that cingulate activation is associated with commission errors, with increased cingulate activation occurring in response to error, which then shapes behavior to improve performance (reviewed in Botvinick, Cohen, & Carter, 2004). The current research supports each of these theories, as no significant cingulate activation was observed during the control condition, which has little cognitive conflict, and participants' performance was close to perfect. During the interference condition, cingulate activation was observed during initial blocks of the task, but not during later blocks; this decrease in cingulate activation occurred as participants' performance significantly improved and may represent acclimation to the task as participants achieved set.

In regard to DLPFC activation over time, the control subjects demonstrated increased DLPFC activation during the initial blocks of the MSIT for both the control and interference conditions, with decreased or no activation observed in later blocks, while the MJ group typically demonstrated greater activation overall relative to the control group, as well as increased activation, which was sustained through later blocks (i.e., Block 3). When the MJ group was split into early and late MJ onset groups, both the early and late MJ groups demonstrated altered patterns

of activation during the control condition relative to the control group. Interestingly, however, during the interference condition, the late MJ group demonstrated a pattern of activation more similar to the control group, with larger activation observed during initial blocks and decreased activation in latter block, while the early onset group demonstrated an altered pattern of activation with increased DLPFC activation during latter blocks (i.e., through Block 3).

These results are consistent with practice-related effects reported by Milham and colleagues (2003) demonstrating attenuation of both cingulate and DLPFC activation over time, which the authors suggested was due to reduced cognitive load over time. Interestingly, the authors also reported that attenuation of activation within the cingulate was reduced over a shorter period of time, while DLPFC activation decreased more gradually over time; we observed a similar pattern of attenuation over time in the current study. Further, this pattern of activation supports work by Silton and colleagues (2010), who suggested that cingulate activation is modulated by DLPFC activation, with greater DLPFC activation associated with reduced cingulate activation.

Overall, DLPFC activation was sustained throughout all blocks of the MSIT during the interference condition, but not during the control condition suggesting that the DLPFC may be involved in sustained attention during the task during the more difficult condition. Dosenbach and colleagues (2007; 2008) proposed that the DLPFC is associated with

moment-to-moment task processing, and the current results support this theory. Increased, sustained DLPFC activation throughout the interference condition may be necessary for sustained cognitive load during cognitive interference processing. Future studies should examine DLPFC activation over a longer time course to further access activation differences over time.

5.4. MSIT Correlation and Regression Results

Correlation analyses indicated a relationship between MSIT performance and fMRI activation within the MJ groups. Within the MJ group as a whole, a trend emerged for higher accuracy during the control condition in conjunction with reduced cingulate activation. Additionally, within the early MJ group, slower reaction time for interference condition was significantly related to increased DLPFC activation, and within the late MJ group, increased interference commission errors were positively associated with increased cingulate activation. In both MJ groups, poorer performance was associated with increased CFP activation. However, within the control group, MSIT performance was not related to fMRI activation. This was unexpected given that previous studies have demonstrated a positive correlation between cingulate activation and slower response time and increased errors in control participants (e.g., Matthews et al., 2007; Yucel et al., 2007b), but the low levels of cingulate

activation in control participants may explain why we did not observe these correlations in the current study.

Additionally, MJ use variables were significantly associated with both MSIT performance and fMRI activation. Within the late MJ group, trends emerged for earlier age of MJ onset, longer duration of MJ use, and higher urinary THC concentration to correlate with increased commission errors. Interestingly, Harding and colleagues (2012) have also shown that earlier age of MJ onset and increased lifetime MJ use are associated with increased cognitive interference demand during the MSIT. These results are consistent with previous reports of increased cognitive impairment related to increased MJ use, particularly earlier age of MJ onset (Battisti et al., 2010; Dahlgren et al., 2016; Fontes et al., 2011; Gruber et al., 2012a; Pope et al., 2003; Solowij et al., 2011).

Lastly, MJ use variables also correlated with fMRI activation during the MSIT. Within the MJ group as a whole, earlier age of MJ onset was significantly related to lower cingulate activation during both the control and interference conditions; this result was replicated within the late MJ group, but not the early MJ group, indicating that the late MJ group drove this finding. Within the late MJ group, longer duration of use was also associated with increased cingulate activation during both the control and interference conditions, but regression analyses indicated that age of MJ onset was the more salient factor associated with increased activation. Within the early MJ group, none of the MJ use variables correlated with

fMRI activation. This finding was unexpected, as previous studies typically report significant correlations between MJ use variables, particularly age of MJ onset, and altered brain function (e.g., Gruber et al., 2014; Harding et al., 2012). However, these null results may be related to the relatively low frequency and magnitude of use (particularly within the early MJ group) relative to studies reporting significant correlations; this is further discussed in the Limitations.

Taken together, these results suggest that for MJ users, increased CFP activation is related to the greater difficulty encountered during the MSIT, and that MJ use, particularly earlier age of onset, is associated with both poorer performance as well as altered CFP activation patterns.

5.5. Limitations and Future Directions

This is a case-control study, and as such, the independent variable (MJ use) was not under control of the researcher. As participants were not randomly assigned to groups, there may have been other confounding variables related to MJ use that could have also impacted cognitive performance and brain activation. In order to control for this possibility, we adopted strict inclusion/exclusion criteria for this study in order to reduce the likelihood of potential confounding variables. Additionally, demographic questionnaires and a comprehensive clinical state battery were performed in order to determine whether groups differed on these variables. Results indicated that groups differed on the ratio of male and

female participants, depressive symptoms measured by the BDI, and the anger and total mood disturbance subscores of the POMS. Subsequently, these potential confounds were controlled for in secondary ANCOVAs; however, the initial findings remained unchanged, indicating that these group differences did not significantly impact performance or brain activation patterns exhibited during the MSIT.

Interestingly, MJ users also reported significantly greater levels of impulsivity compared to control participants, and when impulsivity scores were controlled for in the ANCOVAs, almost all results were no longer significant. Only the main effect of Block demonstrating reduced omission errors over time in all participants during the interference condition remained significant after controlling for impulsivity. Omission errors typically reflect cognitive overload and are associated with psychomotor slowing, while commission errors, which reflect difficulty inhibiting incorrect responses, are associated with increased impulsivity and decreased inhibition. It is therefore unsurprising that the variable least associated with impulsivity remained significant following analyses of covariance. Additionally, increased impulsivity may be a characteristic of MJ use and more generally substance use, with evidence suggesting that increased impulsivity and poorer inhibitory control may represent both a pre-existing vulnerability to as well as a consequence of substance use (reviewed in Yucel & Lubman, 2007c). Given that increased impulsivity may be a trait of the MJ using group, it should not be considered a confounding variable.

Additionally, for this study, participants completed a practice version of the MSIT and trained until performance met a criterion level (three correct responses without feedback) before completing the experimental run of the task with concurrent imaging. As the purpose of this study was to assess cognitive interference processing and not learning, this procedure was implemented in order to ensure that participants completely understood the task before beginning the experimental run. Accordingly, this training protocol resulted in variable levels of exposure to the task before experimental data was collected. It is therefore possible that increased training could have affected the results of the study.

It is also important to note that the MJ-using participants were not required to meet specific DSM-IV requirements of MJ abuse or dependence for entry into this study, and instead had to meet minimum MJ use requirements: a minimum of 1,500 lifetime uses of MJ, current MJ use at least 5 times per week, and a positive urinary cannabinoid screen. Further, our samples of MJ participants were mostly comprised of high-functioning, young college students who did not endorse negative effects related to MJ use. Therefore, findings from this study may be limited to chronic MJ users who do not experience problematic MJ use. Additionally, all participants were screened for any comorbid psychiatric disorders, which were exclusionary for this study. While these inclusion and exclusion criteria controlled for potential psychiatric confounds, it is

possible that MJ-users with more problematic MJ use would display more impairment. Importantly, within the past year, 24.0 million Americans aged 12 or over reported current MJ use within the past month, but only 4.0 million people aged 12 or over reported cannabis use disorder (SAMHSA, 2017), suggesting that the majority of monthly MJ users do not experience problematic MJ use. While the current study provides information on heavy MJ use in healthy individuals, future research should also investigate individuals with problematic MJ use.

Furthermore, recruitment for this study included a large number of subjects from top-tier, Boston-based colleges and universities; as a result, both the control and MJ-using groups are comprised of high-functioning, young adults with above average IQ (control *M*=123.73; MJ *M*=118.93). Studies of participants more representative of average intelligence may yield different results. Interestingly, previous longitudinal studies reporting MJ-related decreases in IQ (Fried et al, 2005; Meier, 2012) have been challenged by more recent findings suggesting that other variables such as nicotine use and familial factors may explain these deficits (Jackson et al., 2015; Mokrysz et al., 2016). In fact, it is possible that higher IQ or other factors found to be associated with higher IQ (e.g., higher childhood socioeconomic status, fewer childhood behavioral problems, etc.; Mokrysz et al., 2016) may be *protective* against potential MJ-related decrements; future studies should explore this potential association.

In addition, previous studies have demonstrated that increased frequency and magnitude of MJ use are associated with cognitive impairment (e.g. Dahlgren et al., 2016; Gruber et al., 2012a; Sagar et al., 2015; Solowij, et al., 2011). Frequency (*M*=14.38 episodes/week) and magnitude (*M*=5.17 grams/week) of MJ use in the current study was relatively low compared to the frequency and of MJ use reported in previous studies (e.g., *M*=19.54 episodes/week and *M*=11.77 grams/week in Dahlgren et al., 2016). Further, one of the most comprehensive studies demonstrating neurocognitive deficits in early MJ users relative to late MJ users across a broad battery of neuropsychological tasks also reported significantly higher rates of frequency and magnitude of MJ use in the early MJ relative to late MJ onset group (Gruber et al., 2012a). However, in the current study, the early and late MJ onset groups were not significantly different with regard to any MJ use variables other than age of MJ onset. Accordingly, the relative homogeneity of MJ use within the entire MJ sample may have reduced the effect size of cognitive differences between the groups. This may also explain why we did not observe the task performance differences expected between early and late MJ groups.

Lastly, all MJ users were required to abstain from MJ for a minimum of 12 hours before study procedures in order to eliminate any effects of acute intoxication, although we cannot be certain participants fulfilled this requirement. However, all MJ users were comprehensively

queried about their MJ use (including last use); any participants who reported use within 12 hours of their study visit were rescheduled. Further, none of the MJ subjects endorsed clinical ratings of acute intoxication, and all MJ subjects were able to successfully complete a full neurocognitive battery and a lengthy study visit. Additionally, the neuroimaging portion of the experimental protocol occurred later in the study visit (typically several hours after arrival at the research facility). Given these considerations, we are confident that MJ users were not acutely intoxicated during data collection. Further, the naturalistic design of the study, in which participants are not required to complete an extended period of abstinence, is a more ecologically valid method of assessing chronic, heavy MJ users.

5.6. Conclusions

Previous studies of cognitive interference processing using the MSIT have only examined task performance and fMRI activation *averaged across the whole task*. The current study employed a discrete block schema of analyses in order to examine changes in performance and brain activation over the time course of the task in control participants and MJ users. Results provided evidence that MSIT performance and brain activation are dynamic over time in all subjects. Even though between-group task performance differences were not demonstrated, group

differences may emerge in samples of individuals with greater clinical symptomatology and more problematic MJ use.

Additionally, fMRI activation patterns were altered in MJ users, who demonstrated increased cingulate and DLPFC activation relative to control participants. Interestingly, the control group did not demonstrate cingulate activation during the control condition, while the MJ-using groups did. When MJ users were subdivided based on age of MJ onset, the late onset MJ group demonstrated increased activation in all ROIs across both task conditions, while the early onset MJ group exhibited dysfunctional patterns of DLPFC activation, with increased activation during the control condition relative to the interference condition. Analyses of brain activation over time revealed that MJ users demonstrated greater activation that was sustained longer throughout the task relative to control participants. Further, the late MJ group demonstrated a pattern of activation more similar to the control group, with the greatest activation observed during the initial blocks and reduced activation over time, whereas the early onset group demonstrated an altered pattern of activation with increased cingulate activation during latter blocks. Increased DLPFC activation in early MJ users and decreased cingulate activation in late MJ users were both related to greater difficulty during cognitive interference processing. Additionally, earlier age of MJ use onset was associated with both poorer task performance and altered CFP activation, consistent with previous studies.

Chronic, heavy MJ use has consistently been associated with cognitive impairment, particularly poorer executive functioning, even in the absence of acute intoxication. While the current study did not report between-group performance differences on a task requiring cognitive control, patterns of activation within both the cingulate and DLPFC were altered in MJ users, and those with earlier age of MJ onset demonstrated the greatest alterations. Given increased MJ use across the nation, and the growing number of daily consumers, it is important to fully understand the impact of MJ use on cognition and brain function. Despite recent changes in state-level legislation and shifting opinions on the perception of harm and potential benefit associated with MJ use, many questions remain concerning the short- and long-term impact of MJ use for both recreational and medical consumers, which require further investigation. This is especially important given the prevalence of MJ use across the globe, and the growing number of consumers, particularly those in late adolescence or early adulthood who are more vulnerable to the potential deleterious effects related to recreational MJ use.

Appendices

Appendix A. MSIT Performance Comparison of Control and MJ-Using Participants

MSIT: Whole Task	Controls *n*=26	MJ Users *n*=54	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Control (C) Condition				
Response Time (ms)	565.99±74.95	577.78±71.84	0.460	.500 (.006)
Percent Accuracy	99.00±1.60	99.13±1.34	0.154	.696 (.002)
Number of Omissions	0.69±1.26	0.63±1.05	0.055	.816 (.001)
Number of Commissions	0.27±0.60	0.20±0.49	0.269	.606 (.003)
Interference (I) Condition				
Response Time (ms)	849.55±66.02	848.31±74.49	0.005	.943 (<.001)
Percent Accuracy	90.58±6.20	89.74±6.60	0.300	.585 (.004)
Number of Omissions	5.50±5.17	5.85±4.89	0.088	.768 (.001)
Number of Commissions	3.54±3.25	4.00±3.07	0.381	.539 (.005)
I-C Contrast				
Response Time (ms)	283.56±53.07	270.53±61.32	0.861	.356 (.011)
Percent Accuracy	-8.41±5.74	-9.39±6.27	0.453	.503 (.006)
Number of Omissions	4.81±4.83	5.22±4.65	0.136	.713 (.002)
Number of Commissions	3.27±3.13	3.80±2.95	0.537	.466 (.007)

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Degrees of Freedom (df)=1,78 unless otherwise noted
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix B. MSIT Performance Over Block Comparison of Control and MJ-Using Participants: Control Condition

MSIT: Block Analyses Control (C) Condition	Controls *n*=26	MJ Users *n*=54	Mixed-Model ANOVA (2-tailed)[a]		
			Effects	*F*	*p* (η^2)
Response Time (ms)					
Block 1	589.05±96.97	602.83±100.08	Group	0.45	.503 (.006)
Block 2	558.76±78.27	568.92±91.72	**Block**[b]	**6.39**	**.002 (.076)**
Block 3	550.72±82.77	570.78±75.19	Interaction[b]	0.31	.733 (.004)
Block 4	566.25±85.36	569.12±76.63			
Percent Accuracy					
Block 1	98.40±2.91	98.23±2.87	Group	0.15	.696 (.002)
Block 2	99.36±1.53	99.61±1.22	**Block**[c]	**6.09**	**.002 (.072)**
Block 3	99.36±1.93	99.38±1.70	Interaction[c]	0.38	.709 (.005)
Block 4	98.88±2.22	99.31±2.10			
Omission Errors					
Block 1	0.35±0.63	0.35±0.56	Group	0.06	.816 (.001)
Block 2	0.08±0.27	0.06±0.23	**Block**[d]	**8.65**	**<.001 (.100)**
Block 3	0.08±0.27	0.11±0.37	Interaction[d]	0.32	.739 (.004)
Block 4	0.19±0.49	0.11±0.42			
Commission Errors					
Block 1	0.04±0.20	0.07±0.26	Group	0.27	.606 (.003)
Block 2	0.08±0.27	0.04±0.19	Block	0.03	.992 (<.001)
Block 3	0.08±0.27	0.04±0.19	Interaction	0.46	.711 (.006)
Block 4	0.08±0.27	0.06±0.23			

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Unless otherwise noted, Degrees of Freedom (df)=1,78 for Group and df=3,234 for Block and the Group*Block Interaction
[b] Greenhouse-Geisser corrected; df=2.02,157.78 for Block and the Interaction
[c] Greenhouse-Geisser corrected; df=2.21,172.05 for Block and the Interaction
[d] Greenhouse-Geisser corrected; df=2.13,166.49 for Block and the Interaction
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix C. MSIT Performance Over Block Comparison of Control and MJ-Using Participants: Interference Condition

MSIT: Block Analyses Interference (I) Condition	Controls *n*=26	MJ Users *n*=54	Mixed-Model ANOVA (2-tailed)[a]		
			Effects	*F*	*p* (η^2)
Response Time (ms)					
Block 1	880.43±71.99	885.64±82.46	Group	<0.01	.954 (<.001)
Block 2	885.64±83.46	838.68±78.07	**Block**	**22.55**	**<.001 (.224)**
Block 3	847.94±73.74	837.19±87.58	Interaction	1.30	.274 (.016)
Block 4	833.44±80.09	823.27±75.44			
Percent Accuracy					
Block 1	88.14±10.32	85.73±10.10	Group	0.30	.585 (.004)
Block 2	89.26±8.00	89.66±9.53	**Block**[b]	**9.93**	**<.001 (.113)**
Block 3	91.67±7.73	90.90±7.81	Interaction[b]	0.50	.654 (.006)
Block 4	93.27±7.55	92.67±8.13			
Omission Errors					
Block 1	1.73±2.01	1.91±1.73	Group	0.09	.768 (.001)
Block 2	1.53±1.68	1.54±1.68	**Block**[c]	**4.76**	**.005 (.058)**
Block 3	1.15±1.52	1.22±1.48	Interaction[c]	0.06	.979 (.001)
Block 4	1.08±1.50	1.19±1.58			
Commission Errors					
Block 1	1.12±1.31	1.52±1.50	Group	0.38	.539 (.005)
Block 2	1.04±1.00	0.94±1.09	**Block**	**7.58**	**<.001 (.089)**
Block 3	0.85±1.08	0.96±1.12	Interaction	0.86	.463 (.001)
Block 4	0.54±0.99	0.57±0.86			

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Unless otherwise noted, Degrees of Freedom (df)=1,78 for Group and df=3,234 for Block and the Group*Block Interaction
[b] Greenhouse-Geisser corrected; df=2.62,204.47 for Block and the Interaction
[c] Greenhouse-Geisser corrected; df=2.56,199.75 for Block and the Interaction
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix D. One-Sample *t*-Test of fMRI Activation During the MSIT: Control Group

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI (total *k*=0)						
None	-	-	-	-	-	-
DLPFC Frontal Cortex ROI (total *k*=15)						
Right Inferior Frontal Gyrus	15	48	8	20	2.85	.004
Interference Condition						
Cingulate Cortex ROI (total *k*=0)						
None	-	-	-	-	-	-
DLPFC Frontal Cortex ROI (total *k*=100)						
Right Inferior Frontal Gyrus	49	48	8	20	3.25	.002
Right Middle Frontal Gyrus	41	42	38	23	2.82	.005
Left Middle Frontal Gyrus	10	-24	-4	47	2.67	.007
Interference-Control Contrast						
Cingulate Cortex ROI (total *k*=46)						
Right Anterior Cingulate	46	9	20	41	4.48	<.001
DLPFC Frontal Cortex ROI (total *k*=1309)						
Left Middle Frontal Gyrus	301	-21	-4	53	6.54	<.001
Right Superior Frontal Gyrus	326	18	8	59	6.26	<.001
Left Precentral Gyrus	390	-39	5	35	5.84	<.001
Right Inferior Frontal Gyrus	111	39	5	29	5.81	<.001
Right Middle Frontal Gyrus	158	42	35	23	3.89	<.001
Right Insula	23	48	11	2	3.39	.001

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix E. One-Sample *t*-Test of fMRI Activation During the MSIT: MJ Group

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI (total *k*=10)						
Right Anterior Cingulate	10	12	20	41	3.11	.002
DLPFC Frontal Cortex ROI (total *k*=435)						
Right Middle Frontal Gyrus	243	48	20	32	4.48	<.001
Left Precentral Gyrus	145	-39	5	35	4.18	<.001
Left Inferior Frontal Gyrus	10	-33	29	-1	3.14	<.001
Left Middle Frontal Gyrus	22	-30	-4	50	2.82	.003
Left Middle Frontal Gyrus	15	-39	29	17	2.31	.012
Interference Condition						
Cingulate Cortex ROI (total *k*=20)						
Right Anterior Cingulate	20	12	20	41	3.81	<.001
DLPFC Frontal Cortex ROI (total *k*=543)						
Left Precentral Gyrus	268	-39	5	35	5.04	<.001
Left Inferior Frontal Gyrus	12	-33	29	-1	4.09	<.001
Right Precentral Gyrus	138	39	5	32	4.01	<.001
Left Middle Frontal Gyrus	52	-30	-4	50	3.63	<.001
Right Middle Frontal Gyrus	56	42	38	20	3.20	.001
Right Insula	17	39	17	8	3.16	.001
Interference-Control Contrast						
Cingulate Cortex ROI (total *k*=151)						
Right Anterior/Midcingulate	151	9	14	44	7.15	<.001
DLPFC Frontal Cortex ROI (total *k*=930)						
Left Middle Frontal Gyrus	173	-24	-7	56	7.23	<.001
Right Middle Frontal Gyrus	205	30	-1	59	6.29	<.001
Right Insula	44	33	23	11	6.24	<.001
Left Insula	373	-36	17	11	5.70	<.001
Right Middle Frontal Gyrus	100	33	41	32	3.59	<.001
Left Superior Frontal Gyrus	11	-12	14	47	3.58	<.001
Right Precentral Gyrus	24	42	5	35	3.03	.002

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix F. Two-Group *t*-Test of fMRI Activation During the MSIT: Control vs MJ Group Comparison

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI						
HC>MJ (total *k*=0)						
None	-	-	-	-	-	-
MJ>HC (total *k*=152)						
Right Anterior Cingulate	68	12	35	20	2.97	.001
Left Midcingulate	18	-12	-7	41	2.83	.002
Right Anterior Cingulate	14	12	20	44	2.85	.003
Right Midcingulate	15	9	-22	32	2.59	.005
Left Anterior Cingulate	14	-6	17	23	2.52	.007
Right Midcingulate	10	3	-10	29	2.41	.009
Left Midcingulate	13	-3	-22	44	2.15	.017
DLPFC Frontal Cortex ROI						
HC>MJ (total *k*=0)						
None	-	-	-	-	-	-
MJ>HC (total *k*=602)						
Right Middle Frontal Gyrus	202	39	11	41	4.09	<.001
Right Inferior Frontal Gyrus	30	45	17	2	3.39	.001
Left Inferior Frontal Gyrus	109	-36	32	-1	3.33	.001
Left Middle Frontal Gyrus	186	-36	20	35	3.13	.001
Left Medial Frontal Gyrus	18	-18	35	26	2.62	.005
Right Superior Frontal Gyrus	13	15	17	44	2.53	.007
Right Superior Frontal Gyrus	15	27	56	17	2.40	.009
Left Middle Frontal Gyrus	17	-51	14	32	2.21	.015
Left Middle Frontal Gyrus	12	-27	5	62	2.14	.018
Interference Condition						
Cingulate Cortex ROI						
HC>MJ (total *k*=0)						
None	-	-	-	-	-	-
MJ>HC (total *k*=102)						
Left Anterior/Midcingulate	25	-12	8	41	2.96	.002
Right Anterior Cingulate	54	12	32	14	2.80	.003
Right Anterior/Midcingulate	13	12	14	38	2.71	.004
Left Anterior Cingulate	10	-6	17	23	2.29	.012
DLPFC Frontal Cortex ROI						
HC>MJ (total *k*=21)						
Right Superior Frontal Gyrus	11	21	11	53	2.70	.004
Left Superior Frontal Gyrus	10	-18	62	20	2.28	.013
MJ>HC (total *k*=375)						
Right Precentral Gyrus	82	39	11	38	3.61	<.001
Left Inferior Frontal Gyrus	39	-36	32	-1	3.43	<.001
Right Inferior Frontal Gyrus	25	45	17	2	3.32	.001
Left Superior Frontal Gyrus	40	-27	50	14	3.19	.001
Left Precentral Gyrus	44	-33	14	35	2.93	.002
Left Insula	68	-39	14	17	2.91	.002
Right Middle Frontal Gyrus	25	36	-1	59	2.54	.007
Left Medial Frontal Gyrus	14	-18	35	26	2.49	.007
Right Inferior Frontal Gyrus	13	60	11	20	2.39	.010
Left Middle Frontal Gyrus	12	-51	11	38	2.21	.015
Left Middle Frontal Gyrus	13	-30	11	50	2.11	.019

Interference-Control Contrast						
Cingulate Cortex ROI						
HC>MJ (total *k*=244)						
Right Midcingulate	206	6	-16	29	3.30	.001
Left Posterior Cingulate	23	-15	-43	53	3.17	.001
Left Posterior Cingulate	15	-12	-43	32	2.69	.004
MJ>HC (total *k*=0)						
None	-	-	-	-	-	-
DLPFC Frontal Cortex ROI						
HC>MJ (total *k*=470)						
Right Inferior Frontal Gyrus	254	48	35	-1	4.06	<.001
Right Superior Frontal Gyrus	117	21	11	50	3.50	<.001
Left Middle Frontal Gyrus	29	-24	56	20	2.76	.004
Left Middle Frontal Gyrus	37	-21	8	47	2.47	.008
Right Superior Frontal Gyrus	20	21	2	68	2.44	.008
Left Middle Frontal Gyrus	13	-33	5	53	2.09	.020
MJ>HC (total *k*=16)						
Right Superior Frontal Gyrus	16	18	44	29	2.70	.004

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix G. One-Sample *t*-Test of Cingulate Activation During the MSIT By Block: Control Group

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=0)						
None	-	-	-	-	-	-
Block 2 (total *k*=0)						
None	-	-	-	-	-	-
Block 3 (total *k*=0)						
None	-	-	-	-	-	-
Block 4 (total *k*=0)						
None	-	-	-	-	-	-
Interference Condition						
Block 1 (total *k*=16)						
Right Anterior/Midcingulate	16	9	23	38	3.00	.003
Block 2 (total *k*=20)						
Right Anterior/Midcingulate	10	9	23	38	2.50	.010
Right Anterior Cingulate	10	12	41	14	2.36	.013
Block 3 (total *k*=0)						
None	-	-	-	-	-	-
Block 4 (total *k*=0)						
None	-	-	-	-	-	-

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix H. One-Sample *t*-Test of DLPFC Activation During the MSIT By Block: Control Group

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=183)						
Right Inferior Frontal Gyrus	83	39	8	29	4.22	<.001
Right Middle Frontal Gyrus	77	42	38	23	3.34	.001
Left Precentral Gyrus	10	-36	5	35	2.62	.008
Left Precentral Gyrus	13	-33	5	29	2.54	.009
Block 2 (total *k*=359)						
Right Middle Frontal Gyrus	283	39	11	29	6.16	<.001
Left Inferior Frontal Gyrus	34	-45	29	17	3.01	.003
Left Precentral Gyrus	18	-36	2	26	2.99	.003
Left Inferior Frontal Gyrus	13	-36	44	-1	2.93	.004
Right Superior Frontal Gyrus	11	24	14	50	2.62	.008
Block 3 (total *k*=0)						
None	-	-	-	-	-	-
Block 4 (total *k*=13)						
Left Superior Frontal Gyrus	13	-12	11	53	2.56	.009
Interference Condition						
Block 1 (total *k*=659)						
Right Inferior Frontal Gyrus	305	39	8	29	5.88	<.001
Left Precentral Gyrus	206	-36	2	26	4.04	<.001
Left Middle Frontal Gyrus	74	-24	-4	47	3.76	<.001
Right Superior Frontal Gyrus	74	24	11	50	3.44	.001
Block 2 (total *k*=312)						
Right Inferior Frontal Gyrus	211	39	8	29	5.19	<.001
Left Inferior Frontal Gyrus	34	-39	5	26	3.61	.001
Right Middle Frontal Gyrus	32	27	-1	50	2.94	.004
Left Middle Frontal Gyrus	33	-27	-1	47	2.85	.004
Block 3 (total *k*=114)						
Left Superior Frontal Gyrus	13	-12	11	53	3.98	<.001
Right Middle Frontal Gyrus	24	27	-1	50	3.12	.002
Left Middle Frontal Gyrus	14	-24	-7	50	2.65	.007
Right Inferior Frontal Gyrus	35	39	8	29	2.56	.009
Right Middle Frontal Gyrus	28	33	38	14	2.52	.009
Block 4 (total *k*=14)						
Right Middle Frontal Gyrus	14	42	32	17	2.46	.011

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix I. One-Sample *t*-Test of Cingulate Activation During the MSIT By Block: MJ Group

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=11)						
Right Anterior/Midcingulate	11	12	20	41	3.05	.002
Block 2 (total *k*=126)						
Right Anterior Cingulate	107	6	38	32	3.40	.001
Left Anterior Cingulate	19	-9	32	20	3.21	.001
Block 3 (total *k*=258)						
Right Anterior Cingulate	258	9	47	17	3.81	<.001
Block 4 (total *k*=0)						
None	-	-	-	-	-	-
Interference Condition						
Block 1 (total *k*=116)						
Right Anterior/Midcingulate	84	12	20	41	3.42	.001
Left Anterior Cingulate	16	-9	32	20	3.41	.001
Right Anterior Cingulate	16	12	38	14	2.87	.003
Block 2 (total *k*=138)						
Right Anterior/Midcingulate	120	6	23	38	3.41	.001
Left Anterior Cingulate	18	-9	32	20	3.07	.002
Block 3 (total *k*=75)						
Right Anterior/Midcingulate	75	9	23	38	2.98	.002
Block 4 (total *k*=14)						
Right Anterior/Midcingulate	14	12	17	41	3.25	.001

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix J. One-Sample *t*-Test of DLPFC Activation During the MSIT By Block: MJ Group

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=627)						
Right Middle Frontal Gyrus	353	45	20	32	5.09	<.001
Left Precentral Gyrus	211	-39	5	35	4.27	<.001
Left Middle Frontal Gyrus	27	-18	-1	50	3.00	.002
Right Insula	17	33	23	11	2.77	.004
Left Superior Frontal Gyrus	19	-27	50	11	2.60	.006
Block 2 (total *k*=1008)						
Left Inferior Frontal Gyrus	562	-33	29	-1	6.06	<.001
Right Middle Frontal Gyrus	377	42	11	32	5.11	<.001
Left Middle Frontal Gyrus	69	-30	56	5	2.83	.003
Block 3 (total *k*=807)						
Left Middle Frontal Gyrus	531	-42	8	35	5.16	<.001
Right Inferior Frontal Gyrus	264	42	8	29	4.08	<.001
Left Middle Frontal Gyrus	12	-33	59	5	2.58	.006
Block 4 (total *k*=89)						
Left Precentral Gyrus	20	-39	8	35	2.80	.004
Right Precentral Gyrus	19	39	5	32	2.52	.007
Left Middle Frontal Gyrus	20	-30	35	14	2.43	.009
Left Middle Frontal Gyrus	20	-42	32	26	2.28	.013
Left Middle Frontal Gyrus	10	-24	-4	47	2.24	.015
Interference Condition						
Block 1 (total *k*=828)						
Left Inferior Frontal Gyrus	409	-33	29	-1	5.11	<.001
Right Middle Frontal Gyrus	293	39	14	32	4.51	<.001
Left Middle Frontal Gyrus	61	-21	-4	50	4.26	<.001
Right Insula	18	33	23	11	4.03	<.001
Left Middle Frontal Gyrus	10	-33	-1	65	2.94	.003
Right Middle Frontal Gyrus	15	33	-4	62	2.54	.007
Left Middle Frontal Gyrus	22	-27	47	11	2.32	.012
Block 2 (total *k*=863)						
Left Inferior Frontal Gyrus	568	-30	29	-1	6.28	<.001
Right Inferior Frontal Gyrus	270	42	8	29	5.21	<.001
Left Middle Frontal Gyrus	12	-42	47	-1	2.36	.011
Left Middle Frontal Gyrus	13	-27	47	11	2.15	.018
Block 3 (total *k*=613)						
Left Middle Frontal Gyrus	368	-42	8	35	5.06	<.001
Left Middle Frontal Gyrus	52	-24	-4	50	4.06	<.001
Right Inferior Frontal Gyrus	127	42	8	29	3.93	<.001
Right Precentral Gyrus	10	42	14	8	2.89	.003
Right Middle Frontal Gyrus	56	39	32	29	2.66	.005
Block 4 (total *k*=114)						
Left Precentral Gyrus	45	-39	5	35	3.82	<.001
Left Middle Frontal Gyrus	39	-24	-4	50	3.30	.001
Right Precentral Gyrus	18	39	5	32	2.71	.005
Left Middle Frontal Gyrus	12	-42	32	26	2.23	.015

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix K. MSIT Performance Comparison of Control, Early MJ, and Late MJ Participants

Clinical Measures	Controls *n*=26	Early Onset MJ *n*=21	Late Onset MJ *n*=33	ANOVA (2-tailed)[a] *F*	*p* (η^2)
Control (C) Condition					
Response Time (ms)	565.99±74.95	582.74±73.36	574.63±71.82	0.306	.737 (.008)
Percent Accuracy	99.00±1.60	99.26±0.88	99.05±1.57	0.205	.815 (.005)
Number of Omissions	0.69±1.26	0.52±0.60	0.70±1.26	0.179	.837 (.005)
Number of Commissions	0.27±0.60	0.19±0.51	0.21±0.48	0.143	.867 (.004)
Interference (I) Condition					
Response Time (ms)[b]	849.55±66.02	840.71±62.33	853.15±81.85	*H*=0.631	.729 (.005)
Percent Accuracy	90.58±6.20	90.08±5.95	89.52±7.06	0.196	.823 (.005)
Number of Omissions	5.50±5.17	4.81±3.71	6.52±5.46	0.802	.452 (.020)
Number of Commissions	3.54±3.25	4.71±3.54	3.55±2.69	1.096	.339 (.028)
I-C Condition					
Response Time (ms)	283.56±53.07	257.97±56.46	278.52±63.77	1.223	.300 (.031)
Percent Accuracy	-8.41±5.74	-9.18±5.93	-9.53±6.57	0.245	.783 (.006)
Number of Omissions	4.81±4.83	4.29±3.73	5.82±5.12	0.750	.476 (.019)
Number of Commissions	3.27±3.13	4.52±3.39	3.33±2.59	1.287	.282 (.032)

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
* and ^ indicate significant differences between groups at α<.05
[a] Degrees of Freedom (df)=2,77 unless otherwise noted
[b] Levene's *F* test of homogeneity of variance supported non-parametric Kruskal-Wallis *H* analyses; *N*=80
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix L. MSIT Performance Over Block Comparison of Control, Early MJ, and Late MJ Participants: Control Condition

MSIT: Block Analyses Control (C) Condition	Controls *n*=26	Early Onset MJ *n*=21	Late Onset MJ *n*=33	Mixed-Model ANOVA (2-tailed)[a]		
				Effects	*F*	*p* (η^2)
Response Time (ms)						
Block 1	589.05±96.97	612.19±109.39	596.87±94.95	Group	0.30	.740 (.008)
Block 2	558.76±78.27	564.14±90.53	571.96±93.74	**Block**[b]	**7.39**	**.001 (.088)**
Block 3	550.72±82.76	578.62±73.20	565.79±77.12	Interaction[b]	0.41	.802 (.011)
Block 4	566.25±85.36	576.40±73.40	564.48±79.38			
Percent Accuracy						
Block 1	98.40±2.91	98.02±2.83	98.36±2.94	Group	0.21	.815 (.005)
Block 2	99.36±1.53	99.80±0.91	99.50±1.38	**Block**[c]	**35.43**	**<.001 (.095)**
Block 3	99.36±1.93	99.60±1.25	99.24±1.94	Interaction[c]	0.46	.784 (.012)
Block 4	98.88±2.22	99.60±1.25	99.12±2.50			
Omission Errors						
Block 1	0.35±0.63	0.38±0.50	0.33±0.60	Group	0.18	.837 (.005)
Block 2	0.08±0.27	0.00±0.00	0.09±0.29	**Block**[d]	**10.28**	**<.001 (.118)**
Block 3	0.08±0,27	0.10±0.30	0.12±0.42	Interaction[d]	0.39	.825 (.010)
Block 4	0.19±0.49	0.05±0.23	0.15±0.51			
Commission Errors						
Block 1	0.04±0.20	0.10±0.30	0.06±0.24	Group	0.14	.867 (.004)
Block 2	0.08±0.27	0.05±0.22	0.03±0.17	Block	0.12	.947 (.002)
Block 3	0.08±0.27	0.00±0.00	0.06±0.24	Interaction	0.46	.841 (.012)
Block 4	0.08±0.27	0.05±0.22	0.06±0.24			

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Unless otherwise noted, Degrees of Freedom (df)=2,77 for Group, df=3,231 for Block, and df=6,231 for the Group*Block Interaction
[b] Greenhouse-Geisser corrected; df=2.01,154.73 for Block and df=4.02,154.73 for the Interaction
[c] Greenhouse-Geisser corrected; df=2.22,170.60 for Block and df=4.43,170.60 for the Interaction
[d] Greenhouse-Geisser corrected; df=2.14,164.47 for Block and df=4.27,164.47 for the Interaction
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix M. MSIT Performance Over Block Comparison of Control, Early MJ, and Late MJ Participants: Interference Condition

MSIT: Block Analyses Interference (I) Condition	Controls *n*=26	Early Onset MJ *n*=21	Late Onset MJ *n*=33	Mixed-Model ANOVA (2-tailed)[a]		
				Effects	*F*	*p* (η^2)
Response Time (ms)						
Block 1	880.43±71.99	881.98±76.88	887.97±86.91	Group	0.22	.804 (.006)
Block 2	838.68±78.07	846.16±75.59	853.12±88.72	**Block**	**27.75**	**<.001 (.265)**
Block 3	847.94±73.74	821.05±67.62	847.46±97.81	Interaction	0.98	.439 (.025)
Block 4	833.44±80.09	814.91±62.45	828.59±83.15			
Percent Accuracy						
Block 1	88.14±10.32	85.12±10.99	86.11±9.64	Group	0.20	.823 (.005)
Block 2	89.26±8.01	91.07±6.36	88.76±11.10	**Block**[b]	**12.07**	**<.001 (.135)**
Block 3	91.67±7.73	91.87±6.38	90.28±8.63	Interaction[b]	0.61	.697 (.016)
Block 4	93.27±7.55	92.26±9.34	92.93±7.40			
Omission Errors						
Block 1	1.73±2.01	1.71±1.49	2.03±1.88	Group	0.80	.452 (.020)
Block 2	1.54±1.68	1.19±1.21	1.75±1.90	**Block**[c]	**5.39**	**.003 (.065)**
Block 3	1.15±1.52	0.81±0.87	1.48±1.72	Interaction[c]	0.27	.939 (.007)
Block 4	1.08±1.50	1.10±1.76	1.24±1.48			
Commission Errors						
Block 1	1.12±1.31	1.86±1.74	1.30±1.31	Group	1.10	.339 (.028)
Block 2	1.04±1.00	0.95±0.67	0.93±1.30	Block	**10.08**	**<.001 (.116)**
Block 3	0.85±1.08	1.14±1.42	0.85±0.87	Interaction	0.78	.591 (.020)
Block 4	0.54±0.99	0.76±1.00	0.46±0.62			

Notes:
Bold numbers are significant at α<.05 (2-tailed)
Italicized numbers are trends towards significance at α<.10 (2-tailed)
[a] Unless otherwise noted, Degrees of Freedom (df)=2,77 for Group, df=3,231 for Block, and df=6,231 for the Group*Block Interaction
[b] Greenhouse-Geisser corrected; df=2.61,201.23 for Block and df=5.23,201.23 for the Interaction
[c] Greenhouse-Geisser corrected; df=2.55,196.28 for Block and df=5.10,196.28 for the Interaction
Abbreviations: Analysis of Variance (ANOVA); marijuana (MJ); Multi-Source Interference Task (MSIT)

Appendix N. One-Sample *t*-Test of fMRI Activation During the MSIT: Early MJ Group

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI (total *k*=0)						
None	-	-	-	-	-	-
DLPFC Frontal Cortex ROI (total *k*=174)						
Left Middle Frontal Gyrus	70	-39	14	23	3.32	.002
Right Middle Frontal Gyrus	51	39	17	29	3.08	.003
Left Middle Frontal Gyrus	12	-39	29	17	2.44	.007
Right Middle Frontal Gyrus	25	51	32	26	2.53	.010
Left Inferior Frontal Gyrus	16	-57	11	20	2.43	.013
Interference Condition						
Cingulate Cortex ROI (total *k*=0)						
None	-	-	-	-	-	-
DLPFC Frontal Cortex ROI (total *k*=117)						
Left Middle Frontal Gyrus	96	-39	14	23	3.59	.001
Left Middle Frontal Gyrus	16	-39	29	17	2.59	.005
Right Middle Frontal Gyrus	15	39	17	29	2.81	.006
Left Superior Frontal Gyrus	15	-21	47	17	2.49	.006
Left Inferior Frontal Gyrus	24	-57	11	20	2.69	.007
Right Middle Frontal Gyrus	11	42	44	23	2.49	.011
Interference-Control Contrast						
Cingulate Cortex ROI (total *k*=36)						
Right Anterior Cingulate	36	6	23	35	3.03	.003
DLPFC Frontal Cortex ROI (total *k*=392)						
Left Inferior Frontal Gyrus	198	-33	29	5	4.43	<.001
Left Middle Frontal Gyrus	95	-27	-10	59	4.18	<.001
Right Middle Frontal Gyrus	83	21	-1	53	3.69	.001
Left Inferior Frontal Gyrus	16	-48	5	26	3.03	.003

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix O. One-Sample *t*-Test of fMRI Activation During the MSIT: Late MJ Group

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI (total *k*=17)						
Right Anterior Cingulate	17	9	20	41	2.82	.004
DLPFC Frontal Cortex ROI (total *k*=347)						
Right Precentral Gyrus	227	39	5	32	4.21	<.001
Left Precentral Gyrus	87	-39	5	35	3.08	.002
Left Middle Frontal Gyrus	33	-21	-1	50	2.57	.008
Interference Condition						
Cingulate Cortex ROI (total *k*=36)						
Right Anterior Cingulate	36	9	17	41	3.85	<.001
DLPFC Frontal Cortex ROI (total *k*=481)						
Right Precentral Gyrus	129	39	5	32	4.71	<.001
Left Middle Frontal Gyrus	76	-24	-4	53	3.79	<.001
Left Precentral Gyrus	125	-39	5	35	3.75	<.001
Right Insula	88	33	23	11	3.64	.001
Left Inferior Frontal Gyrus	10	-33	29	-1	3.43	.001
Left Middle Frontal Gyrus	30	-42	32	26	3.36	.001
Right Middle Frontal Gyrus	23	33	-4	53	3.00	.003
Interference-Control Contrast						
Cingulate Cortex ROI (total *k*=117)						
Right Anterior/Midcingulate	177	6	14	44	7.60	<.001
DLPFC Frontal Cortex ROI (total *k*=900)						
Left Middle Frontal Gyrus	192	-24	-4	56	7.54	<.001
Right Middle Frontal Gyrus	217	27	-1	59	6.28	<.001
Right Insula	54	33	23	11	5.92	<.001
Left Insula	304	-36	17	11	5.14	<.001
Right Middle Frontal Gyrus	86	33	44	32	3.71	<.001
Right Precentral Gyrus	47	42	5	35	3.28	.001

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix P. Omnibus *F*-Test of fMRI Activation During the MSIT: Control vs Early MJ vs Late MJ Group Comparison

Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*F*	Voxel *p* Uncorrected
Control Condition						
Cingulate Cortex ROI						
Midcingulate Cortex	1010	0	-34	47	19.48	<.001
	Total *k*=1010					
DLPFC Frontal Cortex ROI						
Left Superior Frontal Gyrus	347	-21	38	44	12.73	<.001
Right Precentral Gyrus	51	21	-13	74	8.43	<.001
Right Superior Frontal Gyrus	333	21	26	47	7.67	<.001
Left Precentral Gyrus	23	-39	5	35	6.70	<.001
Left Inferior Frontal Gyrus	27	-45	32	8	6.64	<.001
Right Inferior Frontal Gyrus	72	39	8	29	6.37	.001
Right Inferior Frontal Gyrus	15	48	23	14	4.92	.004
Right Middle Frontal Gyrus	18	42	38	20	4.75	.004
Right Middle Frontal Gyrus	13	36	-1	53	4.60	.005
Left Superior Frontal Gyrus	10	-30	50	14	4.16	.009
Left Insula	18	-39	14	17	4.07	.010
Left Middle Frontal Gyrus	14	39	14	53	3.69	.016
	Total *k*=941					
Interference Condition						
Cingulate Cortex ROI						
Midcingulate Cortex	1134	0	-34	47	28.52	<.001
	Total *k*=1134					
DLPFC Frontal Cortex ROI						
Left Superior Frontal Gyrus	465	-18	38	47	19.09	<.001
Right Superior Frontal Gyrus	482	24	26	47	13.72	<.001
Left Precentral Gyrus	68	-39	5	35	11.26	<.001
Left Inferior Frontal Gyrus	53	-48	32	5	10.17	<.001
Right Precentral Gyrus	41	21	-13	74	9.38	<.001
Right Inferior Frontal Gyrus	54	42	8	29	8.47	<.001
Right Inferior Frontal Gyrus	125	54	29	8	8.00	<.001
Left Middle Frontal Gyrus	24	-24	-4	50	5.90	.001
Left Inferior Frontal Gyrus	14	-57	8	23	5.39	.002
	Total *k*=1326					
Interference-Control Contrast						
Cingulate Cortex ROI						
Right Posterior Cingulate	903	3	-46	38	39.11	<.001
Right Anterior/Midcingulate	123	9	17	41	20.70	<.001
Right Anterior Cingulate	68	9	47	20	6.12	.001
	Total *k*=1094					
DLPFC Frontal Cortex ROI						
Left Middle Frontal Gyrus	190	-24	-4	53	27.13	<.001
Right Middle Frontal Gyrus	1297	30	-1	59	23.30	<.001
Left Superior Frontal Gyrus	683	-18	29	56	19.86	<.001
Left Precentral Gyrus	362	-39	5	35	19.50	<.001
	Total *k*=2532					

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix Q. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Control Condition in the Cingulate ROI

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
HC>E (total *k*=0)						
None	-	-	-	-	-	-
HC>L (total *k*=0)						
None	-	-	-	-	-	-
E>HC (total *k*=39)						
Right Anterior Cingulate	39	12	38	32	2.46	.008
L>HC (total *k*=172)						
Right Anterior Cingulate	70	12	35	20	2.99	.002
Left Anterior Cingulate	10	-15	35	20	2.92	.002
Left Anterior/Midcingulate	20	-12	8	41	2.84	.003
Right Anterior/Midcingulate	20	12	14	38	2.82	.003
Left Anterior Cingulate	14	-6	17	23	2.43	.007
Left Midcingulate	25	-6	-22	44	2.40	.009
Right Midcingulate	13	3	-10	29	2.39	.010
E>L (total *k*=0)						
None	-	-	-	-	-	-
L>E (total *k*=15)						
Right Posterior Cingulate	15	-9	-43	53	2.19	.016

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix R. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Control Condition in the DLPFC ROI

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
HC>E (total *k*=0)						
None	-	-	-	-	-	-
HC>L (total *k*=0)						
None	-	-	-	-	-	-
E>HC (total *k*=346)						
Left Superior Frontal Gyrus	54	-30	50	14	3.33	.001
Right Middle Frontal Gyrus	82	42	14	41	3.11	.001
Left Middle Frontal Gyrus	106	-39	14	20	3.05	.002
Right Inferior Frontal Gyrus	21	48	17	2	2.98	.002
Left Middle Frontal Gyrus	19	-39	32	17	2.73	.003
Left Middle Frontal Gyrus	17	-30	8	53	2.55	.005
Left Middle Frontal Gyrus	14	-45	8	53	2.49	.008
Left Inferior Frontal Gyrus	18	-39	32	-1	2.38	.009
Left Inferior Frontal Gyrus	15	-57	11	20	2.39	.010
L>HC (total *k*=618)						
Right Precentral Gyrus	160	39	11	38	3.55	<.001
Left Middle Frontal Gyrus	40	-36	20	35	3.33	.001
Left Inferior Frontal Gyrus	160	-45	29	8	3.31	.001
Right Inferior Frontal Gyrus	25	48	20	14	3.05	.002
Left Middle Frontal Gyrus	41	-15	23	38	3.03	.002
Right Inferior Frontal Gyrus	25	45	17	2	2.87	.003
Right Medial Frontal Gyrus	20	15	29	44	2.76	.003
Left Premotor Cortex	16	-18	-1	50	2.53	.006
Left Middle Frontal Gyrus	21	-27	50	8	2.52	.006
Left Middle Frontal Gyrus	28	-30	11	50	2.47	.007
Right Superior Frontal Gyrus	11	21	23	56	2.43	.007
Right Superior Frontal Gyrus	24	27	44	17	2.42	.009
Left Superior Frontal Gyrus	15	-27	-1	65	2.41	.009
Right Middle Frontal Gyrus	17	39	32	29	2.30	.010
Right Inferior Frontal Gyrus	15	57	20	23	2.33	.011
E>L (total *k*=39)						
Left Middle Frontal Gyrus	10	-30	38	44	2.70	.004
Left Middle Frontal Gyrus	29	-45	17	26	2.60	.006
L>E (total *k*=252)						
Left Middle Frontal Gyrus	12	-15	11	59	3.55	<.001
Right Inferior Frontal Gyrus	53	48	23	14	3.27	.001
Left Inferior Frontal Gyrus	21	-45	32	8	2.83	.003
Right Middle Frontal Gyrus	11	27	14	44	2.73	.004
Left Superior Frontal Gyrus	44	-21	35	32	2.63	.005
Right Superior Frontal Gyrus	54	18	29	47	2.63	.005
Right Middle Frontal Gyrus	13	36	2	53	2.44	.009
Right Middle Frontal Gyrus	26	27	32	35	2.28	.013
Left Insula	18	-39	11	11	2.22	.013

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix S. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Interference Condition in the Cingulate ROI

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Interference Condition						
HC>E (total *k*=19)						
Left Posterior Cingulate	19	-12	-40	53	2.75	.004
HC>L (total *k*=0)						
None	-	-	-	-	-	-
E>HC (total *k*=23)						
Right Anterior Cingulate	23	12	38	32	2.30	.012
L>HC (total *k*=126)						
Right Anterior/Midcingulate	26	12	14	38	3.10	.001
Left Anterior/Midcingulate	16	-12	8	41	2.83	.003
Left Anterior Cingulate	10	-15	35	20	2.71	.003
Right Anterior Cingulate	61	12	32	14	2.55	.005
Left Anterior Cingulate	13	-6	17	23	2.22	.013
E>L (total *k*=0)						
None	-	-	-	-	-	-
L>E (total *k*=51)						
Left Anterior Cingulate	10	-6	29	14	2.67	.005
Left Posterior Cingulate	20	-9	-43	53	2.54	.007
Right Anterior/Midcingulate	11	9	14	38	2.48	.008
Right Midcingulate	10	12	-1	44	2.33	.011

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix T. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Interference Condition in the DLPFC ROI

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Interference Condition						
HC>E (total *k*=42)						
Right Superior Frontal Gyrus	21	21	14	56	2.75	.004
Left Superior Frontal Gyrus	10	-15	35	35	2.61	.005
Right Middle Frontal Gyrus	11	42	26	14	2.16	.017
HC>L (total *k*=10)						
Right Superior Frontal Gyrus	10	27	59	5	2.55	.006
E>HC (total *k*=184)						
Left Superior Frontal Gyrus	55	-27	50	14	3.36	.001
Left Middle Frontal Gyrus	69	-45	20	26	2.68	.004
Left Middle Frontal Gyrus	14	-39	32	17	2.69	.004
Right Middle Frontal Gyrus	32	42	20	32	2.64	.005
Left Precentral Gyrus	14	-51	8	11	2.08	.020
L>HC (total *k*=470)						
Right Precentral Gyrus	82	39	11	38	3.55	<.001
Left Inferior Frontal Gyrus	120	-45	29	8	3.26	.001
Left Inferior Frontal Gyrus	15	-36	32	-1	3.24	.001
Right Middle Frontal Gyrus	37	36	2	53	3.13	.001
Left Middle Frontal Gyrus	30	-15	23	38	3.05	.002
Right Inferior Frontal Gyrus	30	45	17	2	3.05	.002
Left Middle Frontal Gyrus	29	-36	17	35	2.92	.002
Right Medial Frontal Gyrus	16	15	32	41	2.88	.003
Right Inferior Frontal Gyrus	36	48	20	14	2.83	.003
Left Superior Frontal Gyrus	14	-27	50	11	2.37	.009
Left Middle Frontal Gyrus	10	-30	11	50	2.30	.012
Left Superior Frontal Gyrus	30	-27	-1	65	2.28	.013
Right Superior Frontal Gyrus	11	27	44	17	2.25	.014
Left Superior Frontal Gyrus	10	-39	35	26	2.07	.021
E>L (total *k*=55)						
Left Superior Frontal Gyrus	19	-21	50	17	2.63	.005
Left Middle Frontal Gyrus	10	-30	38	44	2.61	.005
Left Middle Frontal Gyrus	26	-45	17	26	2.56	.006
L>E (total *k*=293)						
Right Inferior Frontal Gyrus	85	48	23	14	3.54	<.001
Right Middle Frontal Gyrus	23	36	2	53	2.81	.003
Left Inferior Frontal Gyrus	18	-45	32	8	2.63	.004
Right Medial Frontal Gyrus	45	15	32	44	2.65	.005
Right Middle Frontal Gyrus	11	27	14	44	2.56	.006
Left Superior Frontal Gyrus	41	-21	35	32	2.47	.008
Left Insula	17	-39	11	11	2.37	.010
Right Middle Frontal Gyrus	22	27	32	25	2.27	.013
Left Middle Frontal Gyrus	20	-24	-13	59	2.26	.013
Left Middle Frontal Gyrus	11	-36	32	29	2.19	.016

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix U. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Interference-Control Contrast in the Cingulate ROI

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Interference-Control Contrast						
HC>E (total *k*=157)						
Left Posterior Cingulate	61	-12	-43	53	3.63	<.001
Right Midcingulate	61	6	-13	29	3.55	<.001
Left Midcingulate	11	-6	-1	35	2.73	.004
Left Anterior Cingulate	14	-6	29	17	2.67	.005
Right Anterior/Midcingulate	10	6	17	41	2.48	.008
HC>L (total *k*=223)						
Left Posterior Cingulate	33	-9	-40	32	3.12	.001
Left Midcingulate	162	-9	-1	35	2.93	.002
Right Midcingulate	13	6	-10	44	2.22	.015
Left Midcingulate	15	-15	-25	41	2.09	.020
E>HC (total *k*=0)						
None	-	-	-	-	-	-
L>HC (total *k*=18)						
Right Anterior/Midcingulate	18	9	11	41	2.78	.003
E>L (total *k*=0)						
None	-	-	-	-	-	-
L>E (total *k*=126)						
Right Anterior/Midcingulate	87	6	14	41	3.30	.001
Right Midcingulate	24	12	-22	44	2.67	.005
Left Posterior Cingulate	15	-12	-40	50	2.23	.010

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix V. Control vs Early MJ vs Late MJ Group Contrasts: *Post Hoc* Two-Group *t*-Test of fMRI Activation During the MSIT Interference-Control Contrast in the DLPFC ROI

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Interference-Control Contrast						
HC>E (total *k*=665)						
Right Middle Frontal Gyrus	421	54	20	32	3.96	<.001
Right Superior Frontal Gyrus	173	21	11	50	3.47	<.001
Left Medial Frontal Gyrus	12	-21	38	23	2.45	.008
Left Inferior Frontal Gyrus	13	-39	41	5	2.26	.013
Left Middle Frontal Gyrus	18	-36	44	17	2.25	.014
Left Inferior Frontal Gyrus	12	-54	20	23	2.17	.017
Left Middle Frontal Gyrus	16	-33	5	56	1.99	.025
HC>L (total *k*=316)						
Right Inferior Frontal Gyrus	93	48	35	-1	3.83	<.001
Left Superior Frontal Gyrus	64	-24	56	23	3.06	.002
Right Middle Frontal Gyrus	69	30	11	53	3.01	.002
Right Middle Frontal Gyrus	10	42	50	11	2.62	.005
Right Precentral Gyrus	19	42	2	26	2.55	.006
Left Middle Frontal Gyrus	40	-21	8	47	2.49	.007
Right Superior Frontal Gyrus	21	27	62	17	2.02	.023
E>HC (total *k*=14)						
Left Medial Frontal Gyrus	14	-18	53	11	2.37	.010
L>HC (total *k*=60)						
Right Middle Frontal Gyrus	50	33	38	38	2.89	.003
Left Insula	10	-36	11	14	2.02	.023
E>L (total *k*=87)						
Left Superior Frontal Gyrus	13	-15	29	56	3.16	.001
Left Superior Frontal Gyrus	74	-18	50	32	2.81	.003
L>E (total *k*=263)						
Right Middle Frontal Gyrus	70	54	23	26	3.22	.001
Right Inferior Frontal Gyrus	102	51	17	14	3.04	.002
Right Middle Frontal Gyrus	26	33	2	53	3.01	.002
Right Middle Frontal Gyrus	27	33	41	35	2.43	.009
Left Middle Frontal Gyrus	12	-36	44	17	2.21	.015
Left Inferior Frontal Gyrus	12	-42	23	8	2.19	.016
Right Precentral Gyrus	14	24	-13	68	2.09	.020

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix W. One-Sample *t*-Test of Cingulate Activation During the MSIT By Block: Early MJ Group

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=0)						
None	-	-	-	-	-	-
Block 2 (total *k*=24)						
Right Anterior Cingulate	24	12	38	29	3.49	.001
Block 3 (total *k*=116)						
Right Anterior/Midcingulate	116	12	26	32	3.81	.001
Block 4 (total *k*=25)						
Right Anterior Cingulate	25	12	38	23	2.95	.004
Interference Condition						
Block 1 (total *k*=10)						
Right Anterior Cingulate	10	12	35	29	2.84	.005
Block 2 (total *k*=57)						
Right Anterior Cingulate	57	12	35	32	3.64	.001
Block 3 (total *k*=51)						
Right Anterior Cingulate	51	9	35	23	3.73	.001
Block 4 (total *k*=0)						
None	-	-	-	-	-	-

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix X. One-Sample *t*-Test of DLPFC Activation During the MSIT By Block: Early MJ Group

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=279)						
Right Middle Frontal Gyrus	111	39	17	29	4.22	<.001
Left Middle Frontal Gyrus	129	-45	17	26	3.06	.003
Left Middle Frontal Gyrus	13	-39	29	17	2.86	.005
Right Inferior Frontal Gyrus	11	48	14	14	2.77	.006
Right Middle Frontal Gyrus	15	51	32	26	2.59	.009
Block 2 (total *k*=383)						
Left Middle Frontal Gyrus	181	-45	17	26	4.66	<.001
Left Middle Frontal Gyrus	23	-36	32	20	4.13	<.001
Right Middle Frontal Gyrus	143	51	35	26	4.11	<.001
Left Inferior Frontal Gyrus	10	-33	29	-1	3.25	.002
Left Inferior Frontal Gyrus	26	-48	14	2	2.55	.010
Block 3 (total *k*=793)						
Left Middle Frontal Gyrus	485	-45	5	56	4.43	<.001
Right Middle Frontal Gyrus	95	48	35	29	4.32	<.001
Right Inferior Frontal Gyrus	131	42	5	23	3.93	<.001
Left Precentral Gyrus	72	-48	11	5	3.83	.001
Left Superior Frontal Gyrus	10	-18	44	29	2.47	.012
Block 4 (total *k*=93)						
Left Inferior Frontal Gyrus	15	-51	38	5	2.78	.006
Left Middle Frontal Gyrus	54	-42	17	23	2.70	.007
Left Precentral Gyrus	12	-48	14	5	2.56	.010
Right Middle Frontal Gyrus	12	42	32	41	2.47	.011
Interference Condition						
Block 1 (total *k*=284)						
Right Middle Frontal Gyrus	80	39	17	32	4.30	<.001
Left Middle Frontal Gyrus	181	-42	20	26	4.09	<.001
Left Middle Frontal Gyrus	23	-39	32	17	3.74	.001
Block 2 (total *k*=516)						
Left Middle Frontal Gyrus	264	-45	17	26	4.52	<.001
Left Middle Frontal Gyrus	11	-45	5	56	4.25	<.001
Right Middle Frontal Gyrus	29	51	35	26	4.03	<.001
Left Inferior Frontal Gyrus	14	-30	29	-1	3.92	<.001
Right Middle Frontal Gyrus	101	42	14	32	3.83	.001
Left Superior Frontal Gyrus	35	-21	53	20	3.14	.003
Left Middle Frontal Gyrus	33	-30	44	8	2.82	.005
Left Precentral Gyrus	39	-48	11	11	2.82	.006
Block 3 (total *k*=498)						
Left Precentral Gyrus	42	-48	14	5	4.03	<.001
Left Middle Frontal Gyrus	323	-42	8	35	4.02	<.001
Right Middle Frontal Gyrus	41	51	35	26	3.24	.002
Right Middle Frontal Gyrus	69	42	14	29	3.10	.003
Left Middle Frontal Gyrus	11	-45	50	5	2.67	.008
Left Middle Frontal Gyrus	12	-24	-4	47	2.32	.016
Block 4 (total *k*=49)						
Left Middle Frontal Gyrus	16	-42	8	35	3.05	.003
Left Inferior Frontal Gyrus	20	-39	17	23	2.77	.006
Left Superior Frontal Gyrus	13	-27	44	14	2.53	.010

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix Y. One-Sample *t*-Test of Cingulate Activation During the MSIT By Block: Late MJ Group

Cingulate Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=34)						
Right Anterior/Midcingulate	22	9	17	41	2.92	.003
Right Anterior Cingulate	12	15	38	14	2.58	.007
Block 2 (total *k*=124)						
Right Anterior/Midcingulate	98	9	17	44	2.99	.003
Left Anterior Cingulate	26	-9	32	20	2.74	.005
Block 3 (total *k*=149)						
Right Anterior Cingulate	149	9	47	17	3.34	.001
Block 4 (total *k*=0)						
None	-	-	-	-	-	-
Interference Condition						
Block 1 (total *k*=132)						
Right Anterior/Midcingulate	113	9	17	44	4.61	<.001
Left Anterior Cingulate	19	-9	32	17	3.48	.001
Block 2 (total *k*=92)						
Right Anterior/Midcingulate	53	6	17	44	3.60	.001
Left Anterior/Midcingulate	20	-15	32	26	2.94	.003
Right Anterior Cingulate	19	9	47	17	2.64	.006
Block 3 (total *k*=40)						
Right Anterior/Midcingulate	40	9	23	38	2.97	.003
Block 4 (total *k*=20)						
Right Anterior/Midcingulate	20	9	17	41	3.15	.002

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

Appendix Z. One-Sample *t*-Test of DLPFC Activation During the MSIT By Block: Late MJ Group

DLPFC Frontal Cortex Region of Interest (ROI)	Cluster Size *k* (Voxels)	x	y	z	*t*	Voxel *p* Uncorrected
Control Condition						
Block 1 (total *k*=577)						
Right Middle Frontal Gyrus	399	45	23	32	4.41	<.001
Left Inferior Frontal Gyrus	11	-30	29	-1	3.59	.001
Left Precentral Gyrus	108	-39	5	35	3.24	.001
Left Middle Frontal Gyrus	43	-21	-4	50	3.04	.002
Left Middle Frontal Gyrus	16	-36	41	5	2.83	.004
Block 2 (total *k*=1053)						
Right Middle Frontal Gyrus	490	48	23	29	5.19	<.001
Left Inferior Frontal Gyrus	85	-33	29	-1	5.16	<.001
Left Middle Frontal Gyrus	452	-45	29	29	3.97	<.001
Right Superior Frontal Gyrus	11	24	56	14	2.75	.005
Right Middle Frontal Gyrus	15	36	53	-1	2.71	.005
Block 3 (total *k*=441)						
Right Precentral Gyrus	101	39	5	32	3.88	<.001
Left Middle Frontal Gyrus	109	-36	20	35	3.80	<.001
Left Inferior Frontal Gyrus	14	-33	32	-1	3.46	.001
Right Inferior Frontal Gyrus	84	45	26	14	3.29	.001
Left Middle Frontal Gyrus	29	-24	-4	50	2.82	.004
Left Middle Frontal Gyrus	65	-42	32	26	2.71	.006
Right Superior Frontal Gyrus	11	21	56	14	2.33	.013
Left Inferior Frontal Gyrus	17	-39	44	2	2.23	.017
Left Superior Frontal Gyrus	11	-18	35	32	2.16	.019
Block 4 (total *k*=45)						
Right Precentral Gyrus	13	39	5	32	2.56	.008
Left Middle Frontal Gyrus	11	-24	-4	50	2.14	.016
Left Middle Frontal Gyrus	11	-30	41	11	1.98	.028
Left Precentral Gyrus	10	-39	8	35	1.90	.033
Interference Condition						
Block 1 (total *k*=799)						
Left Middle Frontal Gyrus	262	-21	-4	50	4.90	<.001
Left Inferior Frontal Gyrus	55	-33	29	-1	4.74	<.001
Right Precentral Gyrus	339	39	5	32	4.25	<.001
Right Middle Frontal Gyrus	55	36	-4	56	3.36	.001
Left Middle Frontal Gyrus	88	-42	32	26	3.15	.002
Block 2 (total *k*=725)						
Left Inferior Frontal Gyrus	18	-33	29	-1	5.44	<.001
Right Precentral Gyrus	308	42	8	32	4.92	<.001
Left Middle Frontal Gyrus	382	-39	11	31	4.20	<.001
Left Inferior Frontal Gyrus	17	-39	44	2	2.44	.010
Block 3 (total *k*=348)						
Left Inferior Frontal Gyrus	14	-33	29	-1	4.03	<.001
Right Precentral Gyrus	56	39	5	32	3.99	<.001
Left Precentral Gyrus	47	-39	5	35	3.68	<.001
Left Middle Frontal Gyrus	45	-42	29	26	3.64	.001
Left Middle Frontal Gyrus	54	-24	-4	50	3.54	.001
Right Insula	28	33	23	11	3.41	.001
Right Precentral Gyrus	11	42	14	8	2.95	.003
Right Middle Frontal Gyrus	30	39	32	29	2.74	.005
Left Middle Frontal Gyrus	35	-33	44	11	2.59	.007

Right Middle Frontal Gyrus	17	36	-4	56	2.46	.010
Left Insula	11	-36	17	11	2.38	.012
Block 4 (total *k*=96)						
Left Middle Frontal Gyrus	50	-24	-4	50	3.53	.001
Right Precentral Gyrus	24	39	5	32	3.42	.001
Left Precentral Gyrus	12	-39	5	35	2.52	.009
Left Insula	10	-36	14	14	2.27	.015

SPM 12, $p \leq .05$, $k \geq 10$ continuous voxels

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