I, Joaquin Burciaga, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Psychology.

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The Effect of Marijuana Craving on Brain Activation and Recognition Memory in Healthy and Bipolar Adolescents

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The Effect of Marijuana Craving on Brain Activation and Recognition Memory in Healthy and Bipolar Adolescents

A dissertation submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Psychology of the College of Arts and Sciences

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Abstract

Bipolar disorder (BD) is a chronic mood disorder that is characterized by emotional dysregulation. Bipolar disorder has a higher rate of comorbidity with substance use disorders (SUD) than any other Axis I disorder and marijuana tends to be the most abused illicit drug in this population. There is evidence that SUDs are often associated with negative effects on BD treatment outcomes. Cognitive deficits are also more severe in patients who have BD and comorbid SUDs than in those with BD alone. The present study was designed to better understand the neural mechanisms associated with marijuana use in BD and the cognitive and behavioral effects of marijuana use in individuals with BD. We compared four groups of adolescents: adolescents with bipolar disorder with comorbid marijuana use (BPMJ); adolescents with bipolar disorder without comorbid marijuana use (BP); adolescents with marijuana use disorder without a comorbid mood or psychotic disorder (MJ); healthy adolescents (HA). The four groups were compared on tests of brain activation in response to a cue-reactivity task, self-reported craving and performance on a recognition memory task in order to parse the cognitive effects of bipolar disorder and the alteration in cognitive performance related to the effects of craving. We examined fMRI measures of brain activation and self-reported craving in response to a marijuana-specific cue-reactivity task in these four groups. We predicted individuals in the marijuana using groups would exhibit increased self-reported craving and increased activation in specific regions of interest in response to marijuana pictures in brain regions associated with drug craving when compared to the non-marijuana using groups. We also hypothesized that increased craving would increase recognition of marijuana-related images on a recognition task. The primary finding was that recognition memory for total combined stimuli and neutral stimuli was reduced in groups with bipolar disorder. The hypothesis that the MJ and BPMJ groups
would display enhanced recognition of marijuana images on the recognition memory test was not supported, nor did these groups demonstrate evidence of a change in craving on either the self-report measure (MCQ) or on fMRI activation in the majority of the identified regions of interest. The only significant group difference that was identified in brain activation was in the right anterior cingulate cortex, with the BPMJ group showing greater activation in response to marijuana images. These findings are in direct contrast to several studies that have found significant groups differences in activation in these regions between craving and non-craving individuals in response to drug-related cues and stimuli. It is a core problem for the present study that the cue-reactivity task did not result in increased craving as measured by the MCQ or by most of the imaging measures. The exact reason for this lack of group differences in craving and brain activation is not fully known. However, it was evident that the cue-reactivity task used in this study did not effectively elicit craving in healthy and bipolar marijuana users. Future studies may focus on developing a standardized cue-reactivity task that reliably induces craving in marijuana users.
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Chapter 1: Introduction

Bipolar disorder is a chronic, often debilitating mood disorder that is characterized by the presence of manic or mixed mood states and is often associated with depressed mood states (APA, 2000). Bipolar disorder has a higher rate of comorbidity with substance use disorders (SUD) than does any other Axis I disorder (Strakowski, DelBello, Fleck & Arndt, 2000). While alcohol is the most commonly abused substance among individuals with bipolar disorder (Regier et al., 1990), marijuana tends to be the most commonly abused illicit drug in this population (Strakowski et al., 2000; Angst, J., 1996; Cassidy, Aheard & Carrol, 2001). Moreover, the rates of marijuana use disorders in adolescents with bipolar disorder approach or exceed the rates of alcohol use disorders (Regier, 1990; Strakowski et al., 2000; Strakowski et al., 2005; Strakowski et al., 2007). Current estimates of marijuana use disorders in bipolar disorder patients range between 8% and 22%, with a lifetime prevalence between 30% and 73% (McElroy et al, 2001; Brown et al., 2001; Goldstein et al., 2008).

In addition to SUDs being common comorbidities in patients with bipolar disorder, there is evidence that they are often associated with a negative effect on bipolar disorder treatment outcomes (Strakowski et al, 2007). Patients with bipolar disorder and comorbid SUDs consistently display a more chronic type of bipolar disorder (Keller et al. 1986), an increased number of hospitalizations (Sonne et al., 1994; Tohen et al., 1990; Cassidy et al., 2001), higher rates of suicide attempts (Feinman and Dunner, 1996; Swann, Dougherty, Pazzaglia, Pham, Steinberg, and Moeller, 2005), greater rates of medication non-compliance (Warner et al., 1994), higher rates of aggression and violence during psychotic states (Scott et al., 1998), and a delay in remission from manic episodes (Strakowski et al., 2000). Cognitive deficits are also more severe
In patients who have bipolar disorder and comorbid SUDs than in those with bipolar disorder alone (van Gorp, Altshuler, Theberge & Mintz, 1999).

In light of the high rate of comorbidity between bipolar disorder and marijuana use disorders and the extensive evidence that this comorbidity conveys significant additional disease burden, the present study was designed to better understand the neural mechanisms associated with marijuana use in bipolar disorder and the cognitive and behavioral effects of marijuana use in individuals with bipolar disorder. These two are often studied independently, however, there is a potential for overlap between neural networks that maintain substance use disorders and bipolar disorder. Moreover, understanding the mechanisms that underlie substance use in adolescents with bipolar disorder may aid in early treatment or prevention efforts that will minimize the known additive burden of comorbidity on outcome. The first section describes drug craving, followed by the functional neuroimaging of craving. Then substance abuse in bipolar disorder and the cognitive deficits common in bipolar disorder will be examined. The cognitive deficits associated with marijuana use will also be examined. Finally, the effects of craving and emotional arousal will be examined.

Drug Craving

Craving is often colloquially described as a strong desire or intense longing for something specific. At some point in time, most people have experienced such an intense craving that they may have gone out of their way to satisfy it. This experience can be true in craving for everyday items such as food (Pelchat, Johnson, Chan, Valdez & Ragland, 2004), but also for more problematic substances including alcohol (Ooteman, Koeter, Vserheul, Schippers & van den Brink, 2006), cocaine (Garavan et al., 2000), and marijuana (Haughey, Marshall, Schacht, Louis & Hutchinson, 2008). Craving, or more specifically drug craving, is often considered one
of the core features of substance dependence and is known to perpetuate SUDs and relapse after periods of abstinence (Ooteman et al., 2006; Tiffany, 1990; Childress et al., 1999; Bonson et al., 2002; Brody et al., 2007; APA, 2000). Recent developments in functional neuroimaging have revealed a distributed network of brain regions that have consistently been implicated in response to craving, indicating that there is a psychobiological component to the phenomenon of craving. Research over the last 20 years has continued to focus on craving as a factor in the maintenance of substance dependence and the high relapse rate, resulting in several theoretical models of craving including how to effectively elicit and measure craving.

One of the challenges facing craving researchers is the lack of agreement in defining craving and its underlying mechanisms. One concise definition refers to the desire or urge to re-experience the effects of a previously experienced psychoactive substance (UNDCP/WHO, 1992). Nevertheless, several competing ideas have been proposed, including recurring or persistent thoughts about drugs, a lack of control over intrusive thoughts about drug use, wanting to experience relief from withdrawal symptoms, an anticipation of relief from negative affect, cue induced autonomic responses, and automatic and efficient processes that guide behavior toward drug use in the absence of awareness (Verheul, van den Brink & Geerlings, 1999; Tiffany, 1990; Kozlowski & Wilkinson, 1987; Wise, 1988, Robinson & Berridge, 1993). The last model posits that it is possible for drug craving to exist without conscious awareness. This unconscious motivational force is thought to be the result of stimuli (i.e., drug paraphernalia, environmental cues, etc.) being paired with drug administration. These stimuli become conditioned cues that can activate a motivational or drug seeking state referred to as craving (Robinson & Berridge, 1993). As a result, individuals report a subjective experience of craving, engage in drug use and experience autonomic changes without conscious awareness of the cause (Tiffany, 1997).
Given the numerous conscious and unconscious processes involved during craving, it is a construct that can prove difficult to measure objectively. The cue-reactivity paradigm has proven to be an effective method of eliciting craving, as addicts frequently report an increase in craving when they are in the presence of drug-related stimuli or cues (Niaura et al, 1988; Rohsenow, Niaura, Childress, Abrams & Monti, 1990; Drummond, Tiffany, Glautier, & Remington, 1995). This method entails the observation of participants’ verbal and physiological responses to drug-related stimuli. The theory behind this method is that neutral stimuli that are regularly associated with drug use have become conditioned stimuli that can elicit a conditioned, and often unconscious, craving response (Tiffany, 1997; Robinson & Berridge, 1993). An additional strength of the cue-reactivity paradigm is the ability to use this method in conjunction with functional brain imaging techniques (Tiffany & Conklin, 2000).

While cue-reactivity tasks have been proven to effectively induce craving, drug craving is a subjective experience that is known to vary in intensity and frequency on an individual basis, which makes self-report an invaluable component in the study of this construct (Sayette et. al, 2000). In fact, prior to functional imaging the measurement of craving was heavily reliant on self-report measures and subjective reports. However, most self-report measures only take one aspect of craving into consideration, thereby making it difficult to differentiate between an individual craving drugs due to the desired effects of the drug versus a person craving drugs for other reasons (Kozlowski & Wilkinson, 1987). As a result, Tiffany (1992) suggested that research focused on a unidimensional approach to measuring craving might not accurately reflect all aspects of the different theoretical models of craving that have been proposed. One of the first measures to take a multidimensional approach was the Questionnaire on Smoking Urges (QSU) designed by Tiffany and Drobes (1991). The questionnaire was designed to overcome the
limitations of other craving questionnaires by combining questions about four theoretical perspectives into a single measure: desire to smoke, anticipation of positive outcome, relief of withdrawal symptoms or negative affect, and intention to smoke. The measure resulted in a two-factor model of craving: questions indicating that smoking was anticipated to be enjoyable and satisfying, and questions mainly from the relief of withdrawal category, which reflected an anticipation of relief from negative affect. The development of this multifactorial measure led researchers to pursue other questionnaires that took a similar approach.

Tiffany, Singleton, Haertzen and Henningfield (1993) expanded on the smoking questionnaire and extended the approach to the measurement of cocaine craving. The Cocaine Craving Questionnaire (CCQ) took the same four theoretical areas of craving and added a lack of control over use category to reflect the difficulty in controlling cocaine use, a common component of substance dependence. The results suggested a four-factor model of craving (compared to the two-factor model of the QSU) and led the authors to suggest that multidimensional scales allow for the measurement of craving with a higher level of reliability and sensitivity than a single-item scale.

The Marijuana Craving Questionnaire (MCQ) Heishman, Singleton and Liguori (2001), which was incorporated in the present study, was based on the research by Tiffany and colleagues (1991; 1993) and includes items that load on four factors: Compulsivity, Emotionality, Expectancy, Purposefulness and a general factor that consisted of all items that loaded onto the four factors. Similar to the QSU and CCS, the MCQ is a reliable and valid method of measuring craving in marijuana users (Singleton, Trotman, Zavahir, Taylor & Heishman, 2002; Field, Mogg & Bradley, 2004; Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Filbey et al., 2009).
**Functional Neuroimaging of Craving**

While craving is largely a subjective phenomenon, functional neuroimaging studies performed over the last decade have elucidated a distributed system of brain regions that are activated in response to craving or to cue-elicited urges for craving. The use of cue-reactivity paradigms has allowed for the successful manipulation and measurement of craving in a laboratory setting. While most of what we know about craving is based on studies of cocaine (e.g., Garavan et al., 2000; Maas et al., 1998) or alcohol dependent adults (e.g., Sayette et al., 1994; Hommer, 1999; Schneider et al., 2001; Drobes, 2002;), recent research has found a network of brain regions that is consistently activated across all types of craving. These areas include structures that mediate the cognitive functions of attention, working memory, and executive function, including the dorsolateral prefrontal cortex, orbitofrontal cortex and the anterior and posterior cingulate cortices (Maas et al., 1998; Grant et al., 1996; Garavan et al., 2000; Childress et al., 1999); areas involved in memory encoding and retrieval, including portions of the medial temporal lobe, specifically the hippocampus and parahippocampal gyrus (Park et al., 2007) and the caudate nucleus (Hommer, 1999; Garavan et al., 2000); areas involved in emotional regulation and nonconscious control of memory and attention, including the amygdala and cerebellum (Grant et al., 1996); and several structures within the reward pathway, including the insula, amygdala, anterior cingulate cortex, ventral tegmental areas, thalamus, and ventral striatum, (Hommer, 1999; Breiter et al., 1997; Heinz et al., 2004; Park et al, 2007; Filbey et al. 2009). This pattern of activation in emotional, attentional, memory, and reward systems during craving may suggest that drug users are more physiologically responsive to drug cues in their environment than are non-users. The results of these imaging findings lend support to the notion that craving is a complex phenomenon that is best measured with a multi-dimensional approach (Heishman et al., 2001; Tiffany, 1997).
"Substance Abuse and Bipolar Disorder"

Research has suggested the presence of a bidirectional relationship between SUDs and bipolar disorder, such that when a bipolar disorder diagnosis is made first, patients may have a more severe form of bipolar disorder that predisposes them to seek drugs, and are more likely to develop additional SUDs (van Rossum et al., 2009; Strakowski et al., 2007; Winokur et al, 1995). Also, the presence of an SUD has a negative impact on the course of bipolar disorder, meaning that SUDs, whether they occur before or after the onset of bipolar disorder, can present significant challenges to treatment (Strakowski et al, 2007). Specifically, the increased rates of medication non-compliance, increased number of hospitalizations and suicide attempts, and prolonged affective episodes conferred by comorbid SUDs (Strakowski et al, 1998) can result in less effective treatment and an increased demand placed on an already overburdened healthcare system. Overall, it is important to understand the role of SUDs in bipolar disorder due to their high rate of comorbidity and negative effects on treatment.

Most available research focuses on the effects of SUDs in adults with years of heavy use. However, research in adults with bipolar disorder have shown that there are also significant effects of early substance use on the course of the disorder, with the existing literature exploring alcohol use most commonly. For example, Winokur and colleagues (1995) posited that bipolar disorder patients with an alcohol use disorder that developed prior to the onset of mood symptoms had milder form of bipolar disorder that was triggered by the prolonged alcohol use. Conversely, individuals who first develop bipolar disorder and later go on to exhibit comorbid alcohol use disorders have a more severe mood disorder (Winokur et al., 1995). Strakowski, McElroy, Keck, and West (1996) found similar results, such that patients in whom bipolar disorder was diagnosed prior to the onset of an alcohol use disorder consistently displayed more affective symptoms, a slower recovery from affective symptoms and, as reported also in
Strakowski et al. (1996), an earlier onset of bipolar disorder. Additionally, in adults with bipolar disorder, the presence of an alcohol use disorder is positively correlated with the length of depressive episodes (Strakowski et al., 1998; Strakowski, et al., 2000), increased suicidal ideation (Swann et al, 2005), poorer psychosocial status following treatment (Tohen et al., 1990), and lower overall quality of life (Singh, Mattoo, Sharan & Basu, 2005).

The studies described thus far have focused on either the retrospective reports of adult patients or on prospective data from those with adult onset of their illness. Studies that examine the prevalence rates of SUDs in adolescents with bipolar disorder have found wide ranges of prevalence of SUDs, ranging between 20 and 39% of patients (Biederman et al, 2005; Findling et al., 2001; Geller et al., 2004; West et al., 1996; McElroy, Strakowski, West, Keck, & McConville, 1997; Wilens et al., 2004; Axelson et al., 2006). However, when children below the age of 13 were examined, all of these studies reported 0% prevalence rate of SUDs. In most instances of adolescent bipolar disorder, it appears that bipolar disorder develops prior to the onset of SUDs, indicating that children with bipolar disorder are at increased risk of developing SUDs during adolescence (Goldstein & Bukstein, 2010). These findings highlight the importance of early substance abuse intervention in this population, to mitigate the deleterious effects of comorbid bipolar disorder and SUDs on disease course and treatment outcome.

There is a smaller literature on comorbid marijuana use in bipolar disorder, although it too suggests a negative association between comorbid SUD and treatment outcome. A study focused on adolescents and adults in the general population found that marijuana use has been found to increase the risk for developing manic symptoms, with a higher frequency of marijuana use positively correlated with mania severity (Henquet, Krabbendam, de Graaf, ten Haave and van Os, 2006). Similar findings by Strakowski et al. (1998) determined that there was a positive
correlation between marijuana use and duration of mania in adolescent and adult patients with comorbid SUDs. In follow-up research, Strakowski et al. (2007) contrasted adolescent and adult bipolar disorder patients with premorbid marijuana use to bipolar disorder patients who began using marijuana after the onset of bipolar disorder symptoms and reported that patients who began smoking marijuana after the onset of bipolar disorder displayed longer manic episodes and a longer duration of marijuana use post-treatment, indicating a negative impact of marijuana use on the course of their pre-existing mood disorder. The results of a study by Van Rossum et al. (2009) on adults with bipolar disorder corroborated previous findings in that bipolar disorder patients with comorbid marijuana use disorders were less compliant with treatment and demonstrated a more severe course of bipolar disorder with higher mania and psychotic symptom ratings. As is common in patients with SUDs, bipolar disorder patients with comorbid marijuana use disorders are also more likely to abuse or develop dependency on alcohol and other drugs (Strakowski & DelBello, 2000; Heffner, DelBello, Fleck, Anthenelli & Strakowski, 2008). Taken together, these findings suggest that an early onset of bipolar disorder combined with early marijuana use can lead to a more severe course of the illness.

Cognitive Deficits in Bipolar Disorder

In addition to their heightened risk of comorbid SUDs, individuals with bipolar disorder often experience cognitive deficits in domains in executive function (Zimmerman, DelBello, Getz, Shear & Strakowski, 2006), sustained attention (Sax, Strakowski, McElroy, Keck & West, 1995; Fleck, Sax & Strakowski, 2001; Clark, Iverson & Goodwin, 2002; Fleck, Shear & Strakowski, 2005), declarative and non-declarative memory (van Gorp, Altshuler, Theberge & Mintz, 1999), verbal memory (Fleck et al., 2005), verbal fluency (Lebowitz, Shear, Steed & Strakowski, 2001) emotion regulation and interpretation of emotion (Getz, Shear & Strakowski,
2003; Pavuluri, O’Connor, Harral & Sweeney, 2007; Derntl, Seidel, Kryspin-Exner, Hasman & Dobmeier, 2009). It had been previously thought that the cognitive deficits observed in bipolar disorder were limited to manic and depressed mood states (Malhi et al., 2007). However, research has found that cognitive deficits can persist during periods of euthymia, particularly in processing speed, working memory, verbal learning and recall, and perseveration (Martinez-Aran et al., 2004, Quraishi & Frangou, 2002; Bearden, Hoffman & Cannon, 2001).

Cognitive Deficits Associated with Marijuana Use

The acute effects of marijuana use on neuropsychological performance have been well researched with adult populations. Research has revealed that chronic marijuana use can affect performance on measures of memory (Pope, Jacobs, Mialet, Yurgelun-Todd, & Gruber, 1997; Solowij et al., 2002), attention, and executive function (Pope, & Yurgelun-Todd, 1996; Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Ramaekers et al., 2006; Hunault et al., 2009; Ramaekers, Kauert, Theunissen, Toennes & Moeller, 2009), risk taking (Lane, Cherek, Tcheremissine, Lieving & Pietras, 2005) motor inhibition, manual dexterity and reaction time (Croft, Mackay, Mills, & Gruzelier, 2001; Ramaekers et al., 2006; Ramaekers et al., 2009). Though the literature is somewhat inconsistent, in that other researchers did not find significant deficits in attention (O’Leary et al., 2002), reaction time and recognition memory (Heishman, Arasteh & Stitzer, 1997) or executive functioning (Hart, van Gorp, Haney, Foltin, & Fischman, 2001) during acute marijuana intoxication.

There are also mixed findings about the long-term effects of marijuana use in adults. Some research with adults has failed to find persisting deficits related to marijuana use. One study found that the verbal learning deficits present among marijuana users during 3 evaluations in the 7 days following use were not detectable after a 28-day abstinence period (Pope, Gruber,
Hudson, Huestis, & Yurgelun-Todd, 2001; Pope et al., 2002). Consistent with this result, another study found impairments in attention, psychomotor speed and short-term memory during the 12-24 hour period following marijuana use, but these impairment subsided after the 24-hour period (Pope, Gruber & Yurgelun-Todd, 1995). In contrast, others have documented persisting deficits after periods of one day up to 2 months of abstinence in several areas of cognitive function including: learning and memory (Grant, Gonzalez, Carey, Natarajan & Wolfson, 2003; Nestor, Roberts, Garavan & Hester, 2008), sustained and divided attention, reaction time, visual scanning and executive functioning (Pope & Yurgelun-Todd, 1996; Ehrenreich et al., 1999), visual memory, visuoperception, psychomotor speed, and manual dexterity (Croft, Mackay, Mills & Gruzeiler, 2001; Bolla, Brown, Eldreth, Tate & Cadet, 2002; Schweinsburg et al., 2008).

Much less is known about the acute and long-term cognitive effects of marijuana use in adolescents. Chronic marijuana use in adolescents is associated with deficits in spatial working memory (Schweinsburg et al., 2005; Harvey, Sellman, Porter and Frampton, 2007), and memory (Harvey et al., 2007; Millsaps, Azrin & Mittenberg, 1994) and with increases in perseveration (Lane, Cherek, Tcheremissine, Steinberg, & Sharon, 2007) within a few days of use.

Adolescent marijuana use is of particular concern given findings that adolescence is a period of significant neurodevelopmental change (Sowell, Trauner, Gamst & Jernigan, 2002; Gogtay et al., 2004; Hua et al., 2009). This is of significant concern given findings in animal studies that suggest the brain may be vulnerable to the effects of regular marijuana use (Loeber & Yurgelun-Todd, 1999). Additionally, the use of MJ during adolescence has been associated with increased morphometric and cognitive abnormalities in adult marijuana users (Ehrenreich et al., 1999; Pope et al., 2003; Wilson et al., 2000) suggesting that adolescents may be more vulnerable to the effects of chronic marijuana use than adults. Medina and colleagues (2007) found deficits in
memory, complex attention, psychomotor speed and sequencing ability in adolescents who were regular users of marijuana, which were still detectable after a month of abstinence. Other studies have shown similar deficits in learning and memory after 6 weeks of abstinence (Schwartz, Gruenwald, Klitzner, Fedio, 1989). Furthermore, adults who begin using marijuana before age 17 demonstrate lower verbal IQ compared to marijuana users who began after age 17. This decrement was still evident after a 28-day abstinence period, suggesting a greater vulnerability to the effects of marijuana during adolescence either by virtue of the associated neurodevelopmental or neurocognitive effects or by the impact of early use of the quality of their educational experience (Pope et al., 2003).

Chronic marijuana use during adolescence has also been associated with abnormal brain structure. One study found that individuals who began using marijuana prior to age 17 had smaller whole brain volumes, a smaller percentage of cortical gray matter volume and a larger percentage of white matter volume than non-users (Wilson, et al., 2000). Volume abnormalities have also been found in adolescent marijuana users in the hippocampus (Medina, Schweinsburg, Cohen-Zion, Nagel, and Tapert, 2007), prefrontal cortex (Medina et al., 2009) and cerebellum (Medina, Nagel & Tapert, 2010).

These structural changes are consistent with functional imaging studies in adolescents who use marijuana which exhibit abnormalities in brain activation during tests of spatial working memory (Schweinsburg, et al., 2005; Padula, et al., 2007; Harvey, et al., 2007), auditory verbal working memory (Jacobsen, et al., 2004), verbal learning (Harvey, et al., 2007; Millsaps, et al., 1994), executive function (Lane, et al., 2007), and inhibitory processing (Tapert, et al., 2007). These findings suggest that early marijuana use may not only be associated with reductions in
the volumes of specific brain structures, but also with abnormal brain activation as measured by functional neuroimaging.

Thus far, this literature includes strong evidence that the presence of bipolar disorder (especially during abnormal mood states) and marijuana use each confer risk for cognitive dysfunction. There are few studies that examine possible additive effects of these two conditions. It is known that adults who have bipolar disorder and comorbid alcohol abuse have poorer verbal memory than those with bipolar disorder alone (van Gorp et al., 1999). We were able to identify only a single study that has examined possible additive effects of bipolar disorder and comorbid marijuana use on cognition. Ringen and colleagues (2010) studied adult marijuana users with schizophrenia, bipolar I, bipolar II and bipolar NOS. Their findings suggested that marijuana use in bipolar disorder actually improved executive functioning, attention and memory. However, their study did not differentiate between mood states, contained a small group of marijuana users and considered marijuana use to be any use in the previous six months. Clearly, further research in this area is needed.

Cognitive Effects of Craving and Emotional Arousal

The cognitive effects that may accompany bipolar disorder and comorbid marijuana abuse are further complicated by the known relationship between craving and cognition. First, it is well documented that craving can affect performance on cognitive tasks. More specifically, research has demonstrated performance on tasks of working memory, reaction time and language comprehension to be negatively impacted during craving (Kemps, Tiggeman, & Grigg, 2008; Sayette & Hufford, 1994; Cepeda-Benito & Tiffany, 1996; Sayette et al., 1994; Zwaan & Truitt, 1998; Zwaan, Stanfield, & Madden, 2000; Cox, Yeates & Regan, 1999). These findings lend support to Tiffany’s (1990) view that, although the processes initiating craving can be an
unconscious phenomenon, the act of craving is a non-automatic process that competes for limited cognitive resources and interferes with cognitive performance. Perhaps consistent with this hypothesis of limited resources, it is known that certain types of cognitive tasks can attenuate craving. For example, when craving is induced in participants through a visual cue-reactivity task, craving is effectively attenuated by having participants engage in visuospatial tasks (May, Andrade, Panabokke & Kavanagh, 2010; Kemps, Tiggemann & Hart, 2005; Kemps, Tiggemann, Woods, & Soekov, 2004).

Given findings that craving consistently activates brain areas involved in memory and attention (Grant et al., 1996; Maas et al., 1998; Childress et al., 1999; Hommer, 1999; Garavan et al., 2000; Park et al., 2007), it is plausible that craving could negatively impact memory encoding and retrieval. However, despite the fact that previous studies have shown deficits in cognition as a result of craving, none of them have examined the interaction between cue-induced craving and memory for the stimuli used in the cue-reactivity tasks. This is of interest in light of research that consistently demonstrates an increased attentional bias for drug-related stimuli in abusers of alcohol (Cox, Brown & Rowlands, 2003; Stormark, Field, Hugdahl & Horowitz, 1997), nicotine (Wertz & Sayette, 2001), heroin (Franken, Kroon, Wiers & Jansen, 2000), cocaine (Hester, Dixon & Garavan, 2006) and marijuana (Field et al., 2004; Field & Cox, 2008; Wölfling, Flor & Grüsser, 2008). The results of these studies suggest that drug-related stimuli are more salient during craving and support the hypothesis posited by Robinson and Berridge (2003) that part of the substance dependence process involves an alteration in attentional processes which favor environmental drug cues. It is feasible that increased attending to the cue-reactivity stimuli and the observed activation in the medial temporal lobe (MTL) in response to craving may actually aid in increasing memory for the stimuli as opposed to
negatively impacting performance as previous studies showed. In fact, activation in the MTL has been shown to predict a person’s ability to retrieve information not only during intentional study, but also during incidental exposure (Stark & Okado, 2003). Additionally, activation in areas responsible for emotional processing during cue-induced craving may lead to enhanced encoding of the images (Garavan, 2010; Wölfing, Flor & Grüsser, 2008), considering that research has shown that increased amygdala-mediated emotional arousal during encoding of information can enhance memory (Dougal, Phelps & Davachi, 2007; Phelps, 2004; Cahill, Prins, Weber, & McGaugh, 1994; Cahill, Bablinsky, Markowitsch, & McGaugh, 1995). These findings suggest the need for additional study on the effect of acute craving on cognition, most specifically on the information being processed at the time that craving is induced.
Specific Aims and Hypotheses

The current study was designed to compare four groups of adolescents: adolescents with bipolar disorder with comorbid marijuana use (BPMJ); adolescents with bipolar disorder without comorbid marijuana use (BP); adolescents with marijuana use disorder without a comorbid mood or psychotic disorder (MJ); healthy adolescents (HA). The four groups were compared on tests of brain activation in response to a cue-reactivity task, self-reported craving and performance on a recognition memory task in order to parse the cognitive effects of bipolar disorder and the alteration in cognitive performance related to the effects of craving.

To our knowledge, this study is the first to look at recognition memory for the images used in a cue-reactivity task and may help determine the effect craving has on recognition memory.

Hypothesis: Using fMRI during a cue-reactivity task (consisting of neutral and marijuana images), it was hypothesized that medial temporal and limbic brain regions, including the Amygdala, Hippocampus, Parahippocampal Gyrus, Anterior Cingulate Cortex, Insula and Caudate, would be activated differentially in the BP, BPMJ, MJ and HA groups. We also hypothesized that increased craving in response to a cue reactivity task would be associated with enhanced recognition of images shown during the cue reactivity task.

Prediction 1: Increased activation in the aforementioned brain regions during the presentation of marijuana images will be observed in the BPMJ and MJ groups compared to the HA and BP groups.
Prediction 2: As craving increases, as measured by a craving questionnaire and brain activation in the aforementioned areas, the number of marijuana images recognized during a post-scan forced-choice recognition task will also increase.

Prediction 3: We predicted that an interaction between group and image type (marijuana or neutral) would occur, with the MJ and BPMJ groups showing enhanced memory for marijuana images, while the HA group would display comparable performance across image type. Conversely, the BP group would display poorer recognition memory for both image types when compared to the BPMJ, MJ and HA groups.
Chapter 2: Method

Participants

Participants were recruited from two studies: 1) Quetiapine Plus Topiramate or Placebo for Bipolar Mania and Cannabis Use in Adolescents (1 R01 DA022221-01; PI: DelBello) and 2) Neuroimaging of Adolescents with and without Cannabis Use, and of Adolescents with Bipolar Disorder without Cannabis Use (3 R01 DA022221-02S1; PI: DelBello).

For this present study, participants were categorized into four groups. The group of healthy adolescents (HA) with no marijuana use consisted of 8 participants who did not meet criteria for an SUD for the previous 12 months or any Axis I mood or psychotic disorder, as assessed by raters applying the WASH-U-KSADS. The marijuana group (MJ) consisted of 6 participants who met DSM-IV criteria for marijuana abuse or dependence over the previous 12 months and used marijuana at least twice per week during the 28 days prior to screening, but did not meet criteria for any other mood or psychotic disorder. The bipolar adolescents without marijuana use group (BP) consisted of 9 participants who met DSM-IV criteria for bipolar disorder, type I (currently manic or mixed), and did not have an SUD. The 10 bipolar adolescents with comorbid marijuana use (BPMJ) met criteria both for bipolar disorder, type I (currently manic or mixed) and marijuana abuse or dependence during the previous 12 months and used marijuana at least twice per week during the 28 days prior to screening. Individuals in the non-marijuana groups were included even if they had used marijuana at some point in the past but never met criteria for substance abuse or dependence; that is, these groups were not entirely drug-naive.

Inclusion criteria for all participants included being fluent in English and being 12 to 22 years of age and either providing informed consent if over 18, or providing assent and having a
parent or legal guardian provide informed consent if participant was a minor. Participants were excluded from this study for any of the following: diagnosis of any other substance use disorder (with the exception of nicotine dependence); a known history of mental retardation (IQ < 70); arriving acutely intoxicated and impaired; manic or depressive symptoms are the result of acute intoxication or withdrawal from substances and not bipolar disorder; a history of significant head trauma (injury resulting in a loss of consciousness greater than 5 minutes); a positive serum pregnancy test or lactating; any unstable medical or neurological condition; treatment of substance use during the 28 days prior to screening (excluding peer support groups); court-ordered substance use treatment; claustrophobia; wearing braces, implants or any metal object that cannot be removed. Finally, potential participants in the HA and MJ group with an Axis I mood disorder or with a first-degree relative with a history of an Axis I mood disorder were excluded from the study.

Recruitment

Potential participants were recruited from both inpatient and outpatient settings. Inpatient bipolar participants were recruited from CCHMC Adolescent Medicine Psychiatry Service. Outpatient bipolar adolescents were recruited from the CCHMC Psychiatry outpatient clinic and from ongoing, IRB-approved clinical trial protocols within the Division of Bipolar Disorders Research that involve bipolar and control participants. Participants in the HA and MJ groups were also recruited from the community via recruitment flyers, and newspaper and Internet advertisements.

Measures

Semi-Structured clinical interview: The Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Orvaschel & Puig-
Antich, 1987; Geller et al., 2001) was administered to all participants to establish the presence or absence of a DSM-IV Axis I disorder. This measure was administered by raters with an excellent symptom and diagnostic reliability (kappa>0.9).

Self report measure of marijuana craving: The Marijuana Craving Questionnaire (MCQ; Heishman, Singleton & Liguori, 2001) was administered to all participants before and immediately after the MRI scan to assess the presence and severity of marijuana craving. The MCQ is a self-rated instrument on which each item is rated on a likert-scale ranging from 1 (strongly disagree) to 7 (strongly agree). The MCQ was modified from the original form to include only the 17 items that are known to load on the 5 factors scales that are relevant to marijuana craving. These five factors include: compulsivity (an inability to control marijuana use); emotionality (use of marijuana in anticipation of relief from withdrawal or negative mood); expectancy (anticipation of positive outcomes from smoking marijuana); purposefulness (intention and planning to use marijuana for positive outcomes); the general factor which consists of all 17 items on the scale. Moderate to high reliability and validity estimates have been established for these five factors (Singleton et al., 2002). The initial administration of the craving questionnaire allowed for a baseline craving profile to be established. The post-scan administration of the questionnaire allowed for a comparison in marijuana craving from baseline to post-scan. Participants who demonstrated an increase of more than 20% in craving after the MRI scan were asked to stay for an additional 10-minutes and were re-administered the MCQ to ensure that craving returned to baseline before their study session was ended.

Mania rating scale: All participants were administered the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, Meyer, 1978) to quantify the degree of mania symptomatology at the time of the assessment. Previous research has found that the YMRS is a reliable measure

*Depression rating scale:* All participants were administered the Children’s Depression Rating Scale-Revised (CDRS-R; Poznanski, Cook, Carroll, & Corzo, 1983). This scale has been found to be both a valid and reliable measure of depression in children and adolescents (Poznanski et al., 1984).

*Estimate of intellectual functioning:* All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) to estimate intelligence, in order to explore possible intellectual differences across the study groups. The WASI is a brief test that consists of four subtests: Vocabulary, Matrix Reasoning, Block Design, and Similarities. This measure has been found to reliably provide a valid intelligence quotient estimate for research purposes (Psychological Corporation, 1999).

*Cue reactivity task:* All participants were administered a novel cue reactivity task specifically designed to induce marijuana craving in participants while in an MRI scanner. This task consists of 60 images: 30 neutral images (see Figure 1) and 30 marijuana images (see Figure 2). Similar to a method used by Grüsser, Heinz and Flor (2000), the images were selected so that those in the neutral condition created three groups: people interacting with neutral objects, neutral objects alone, and plants. The marijuana images have three similar groups: people interacting with marijuana, marijuana paraphernalia alone, and marijuana in different forms (e.g., plants, in bags, in a joint, etc.). The neutral images of people were selected from the International Affective Picture System (IAPS; Lang, Öhman & Vaitl, 1988) to the extent possible. The remaining images, including all those depicting marijuana, were drawn from Internet sources.
Within each set (neutral or marijuana images), the stimuli were arranged in a quasi-random order such that there were never more than three images of any category in a row. The order remained fixed for every participant. Participants were administered this task while in the MRI scanner. The 30 neutral images were always presented first, in order to compare activation in response to neutral images to activation in response to marijuana images. All participants received instructions to focus on the images that were presented. The images were presented in five blocks of six images. Every image was displayed for 4750ms with a 250ms inter-stimulus delay. Between each block, there was a 20 second rest period. During the rest period, a blinking cross hair was presented on the screen, serving as a fixation point. Following the presentation of the neutral images, the marijuana images were presented in the same format as the neutral images. A red number 1 also appeared in the top center of random images. In order to ensure that the participants were attending to all aspects of the images on their display, participants were asked to press the button on their response box to indicate that they saw the number on the image. Button presses were also recorded to assess accuracy and attention.

**Recognition memory task:** A recognition memory task (MT) was developed to test the participants’ incidental recognition memory for the images they viewed in the scanner. Participants were not informed in advance that they would need to remember the images they were shown in the scanner. The task consisted of a total of 80 images presented individually 10 minutes after the image collection. Forty of the images in the MT were targets that they had seen while in the MRI scanner (20 neutral, 20 marijuana) and 40 were foils (20 neutral, 20 marijuana). The foils for the recognition memory task were gathered from various Internet sources and carefully selected to be as similar to the original images as possible. The images were arranged in quasi-random order such that there were never more than three images from any category
(neutral or marijuana) presented consecutively. The order of presentation for the images was fixed for every individual. The participants were asked to press a key labeled “yes” if they remember being presented with the image while in the scanner or to press a key labeled “no” if they did remember seeing the image while in the scanner. These images were presented without a time limit, but response latency was recorded.

Procedure

Research assistants screened potential study participants during inpatient hospitalizations at a local children’s medical center or over the phone by using a study-specific questionnaire to assess symptoms of bipolar and substance use disorders. If a potential study participant was under 18 years of age, verbal permission from their legal guardian was obtained prior to prescreening. If the potential participant was found to be appropriate for additional screening, informed consent and assent (under age 18) were obtained. Specifically, if the potential participant was under 18 years of age, written informed consent was obtained from their legal guardian and written and verbal assent from the adolescent for study participation. If the potential participant was 18 – 22 years old, written informed consent was obtained from participant.

Potential participants who met the prescreening criteria came in for a study visit, during which they completed a structured interview to ensure they met all inclusion/exclusion criteria. The mood and intellectual function measures were then administered to the participants, followed by the imaging procedures. The recognition memory task was administered 10 minutes after the end of the image acquisition at a computer in the scanner control room.
**fMRI Procedure & Acquisition**

Imaging data was collected using a 4 Tesla Varian Unity INOVA Whole Body MRI/MRS System (Varian Inc., Palo Alto, CA) at the University of Cincinnati’s Center for Imaging Research. A radiofrequency (RF) coil was placed over the participants’ heads, and foam padding was used to control head movement. Participants wore headphones and non-ferromagnetic, high-resolution goggles. They were allowed to listen to music or view a movie during the anatomical scan and prior to the administration of the cue-reactivity fMRI task.

An initial alignment scan was done in 3 orthogonal planes simultaneously using a 3D fast gradient echo multi-slice sequence developed for the scanner [TE=10ms, TR=20 ms, field of view (FOV)= 25.6cm, matrix=128 x 256, flip angle=20 degrees, slice thickness=4 mm]. This scan took approximately 8 seconds and provided a quick view of the subject's head position. A high-resolution T1-weighted 3-D neuroanatomic scan was also obtained using a modified driven equilibrium Fourier transform (MDEFT) pulse sequence (TE=6ms, TR=13ms FOV=25.6cm x 19.2cm x 15cm, matrix=256 x 192 x 96 pixels, flip angle=22 degrees, 96 slices) in order to provide a high quality anatomic template.

The cue reactivity task was then presented during the fMRI portion of the scan. Participants viewed the stimuli through goggles, and the task was controlled by E-prime. Data were collected using a T2-weighted gradient-echo planar imaging pulse sequence (TR/TE=3000/30 ms, FOV =20.8 x 20.8 cm, matrix 64 x 64 pixels, slice-thickness = 4 mm, flip angle = 75 degrees). Data were continuously acquired during each run. Participants were in the scanner for a total of 60 – 90 minutes.

The MCQ was administered prior to placement of the participant in the scanner and again after they were removed from the scanner and had a brief break. Ten minutes after the scan, the
recognition memory task was administered in the scanner control room on a computer using E-Prime. Participants were asked to sit at a chair with their feet touching a marked line on the floor. This line was used to ensure that all participants viewed the images on the display from the same distance. They were read the directions displayed on their screen and instructed to begin when they were ready. After completion of the recognition memory task, participants were debriefed.

**fMRI Preprocessing**

Images acquired from the scanner were reconstructed with software that has been developed using Interactive Data Language (IDL) into Analysis of Functional Neuro Images (AFNI) compatible images. The functional data (echo planar images, EPI) was originally acquired with 4mm voxels. Hamming filtering was used during the reconstruction to smooth the images by a factor of 1.8, creating an effective Gaussian filter width of 7.2 mm. The first two acquisitions of each run were discarded to avoid non-equilibrium intensity modulation effects. The images were then visually inspected by the experimenter to ensure that the EPI data were properly aligned with the anatomical data. In instances in which the EPI data did not overlap anatomic markers appropriately, they were manually nudged using 3drefit by inputting x, y, and z coordinates obtained by the 3dNudge program in the AFNI viewer window. Motion correction of the EPI time series was achieved by using 3dvolreg to correct for small head motion during the scan. Then, a mask was created using 3dAutomask to remove areas of activation outside of the brain, ensuring that variance from non-brain activation would not confound the statistical analyses. A censor file was created, reflecting time points in which there was excessive movement that was unable to be corrected by the movement correction algorithm. The time series data were visually inspected to identify images depicting excessive movement. Finally, using a deconvolution procedure, the time series data were correlated with a task-specific (marijuana or neutral images).
reference function. This step included input of the censor file to remove the aforementioned time points. This multiple linear regression yielded a fit coefficient that represented the fit between the observed and hypothesized signal for the two conditions (e.g., neutral or marijuana) to prepare for group-level analyses. All further fMRI data analyses were performed using AFNI and SPSS.

Data Analysis

Regions of Interest (ROI) were chosen a priori from published studies that found significant groups differences in peak activation between craving and non-craving participants. The studies selected looked at craving in response to marijuana (Filbey et al., 2009), alcohol, (Park et al., 2007; Schneider et al., 2001), cocaine (Breiter et al., 1997) and food (Pelchat et al., 2004). A total of 12 regions (6 ROIs across the two hemispheres of the brain) were anatomically defined using Talairach coordinates from published studies. Then, 8mm radius spherical ROIs were created for each region. Mean activation for each region of interest was extracted for each participant. These values were then imported into SPSS to test for statistical significance between groups.

Bivariate correlations were conducted in order to determine whether age, years of education or IQ were correlated with performance on the recognition memory task. These variables were selected due to the age range of the sample. It was thought that these variables could contribute to performance on the recognition memory task due to developmental differences. In the presence of a significant correlation, efforts to control for these variables were carried out by using the variables as a covariate. An analysis of variance (ANOVA) was performed to examine group differences in performance and reaction time on the recognition task across image type (marijuana or neutral) and group differences on the MCQ. All post hoc
analyses were performed using the Bonferonni post hoc criterion for significance at the $p \leq .05$ level. Paired sample t-tests examined self-reported craving from pre- to post-scan. Bivariate correlations were performed to assess the relationship between the selected regions of interest and performance on the recognition memory task, self-reported craving, CDRS score, YMRS score, the number of marijuana joints smoked during the previous 30 days, the number of alcoholic drinks consumed during the previous 30 days and the number of times alcohol was consumed to intoxication in the previous 30 days.

Secondary analyses were also performed using AFNI and SPSS. For the secondary analyses, all groups were combined, and T-tests were performed in AFNI for activation in response to neutral images compared to baseline; activation in response to marijuana images compared to baseline; and activation for marijuana compared to neutral images. All groups were combined to test for the effect of viewing the images on brain activation across all groups to examine what areas were consistently activated across all groups to test for group differences. A Monte Carlo simulation was performed using AFNI’s AlphaSim program with alpha set at 0.005 for activation intensity threshold and $p = .05$ cluster size threshold to control for family-wise error, which defined clusters of 37 or more voxels to be included in the secondary analyses. Peak activation values for each of the surviving clusters were used to identify a total of 29 regions of interest. 8mm spherical ROIs were created based on peak activation for all 29 surviving clusters. Mean activation for each functional region of interest was extracted for each participant. These values were then imported into SPSS to test for statistical significance between groups. All decisions about statistical significance were made at the $p \leq .05$ level.
Chapter 3: Results

Cue-Reactivity Task Attention Performance

Performance accuracy on the attentional task that participants completed during stimulus presentation in the scanner did not differ significantly across groups $F(3, 29) = .159, p = .923$. There was a mean hit rate of 92.5% in the HA, an 88.33% hit rate in the MJ group, an 87.5% hit rate in the BP group and a 90% hit rate in the BPMJ group. Thus, the hit rates suggest that participants in all groups attended well to the stimulus presentation during the cue-reactivity task.

Sample Characteristics

Table 1 includes demographic information for all groups. Groups were not significantly different in age, $F(3, 29) = .244, p = .865$, education, $F(3, 29) = .764, p = .524$ or gender, $\chi^2(1, N = 33) = 0.30, p = 0.86$. The groups differed in CDRS score, $F(3, 29) = 11.31, p = .000$. Post hoc analyses using the Bonferroni post hoc criterion for significance indicated that the BP and BPMJ groups exhibited similar levels of depression, but displayed higher scores when compared to HA and MJ groups, $p < .05$. The groups also differed on YMRS score, $F(3, 29) = 61.96, p = .000$, with post hoc analyses indicating that the BP and BPMJ groups differed significantly from each other with the BP group endorsing significantly more manic symptoms $p \leq .05$ level. In addition, both groups exhibited significantly more manic symptoms than the HA and BMPJ groups which did not differ amongst themselves, $p < .05$. Groups also differed significantly in IQ, $F(3, 25) = 3.52, p = .029$, post hoc analyses indicated that the HA group was significantly more intelligent than the BP and BPMJ, but not the MJ group, $p < .05$. Additionally, the MJ group was significantly more intelligent that the BP group, $p < .05$. The groups differed in the number of marijuana joints smoked over the last 30 days, $F(3, 29) = 8.13, p = .000$. While all groups including the HA and BP groups reported marijuana use, post hoc analyses indicated that the MJ...
and BPMJ groups did not significantly differ from each other. However, both groups smoked significantly more joints that the HA and BP groups, $p < .05$. There was a significant difference between groups in the number of alcoholic drinks consumed over the last 30 days, $F(3, 29) = 4.06$, $p = .016$. Post hoc analyses using the Bonferroni post hoc criterion for significance indicated that the MJ group consumed significantly more drinks than the HA group, $p < .05$.

Finally, the groups differed on the number of times they drank to intoxication during the last 30 days, $F(3, 29) = 8.51$, $p = .000$. Post hoc analyses using the Bonferroni post hoc criterion for significance revealed that the MJ group had significantly more periods of intoxication compared all other groups, but the other groups did not differ significantly from each other, $p \leq .05$. 
<table>
<thead>
<tr>
<th></th>
<th>Healthy Adolescent Group</th>
<th>Marijuana Group</th>
<th>Bipolar Group</th>
<th>Comorbid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age M (SD), Range</td>
<td>17.75 (2.66), 12 – 20</td>
<td>18 (1.10), 16 – 19</td>
<td>17 (3.00), 12 – 22</td>
<td>17.60 (2.17), 15 – 20</td>
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<tr>
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<td>50</td>
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<td>5</td>
<td>9</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No Response</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<td>Years of Education (SD)</td>
<td>11.63 (2.61), 6 – 14</td>
<td>11.67 (1.37), 10 – 13</td>
<td>10.33 (2.70), 6 – 16</td>
<td>10.70 (1.50), 9 – 13</td>
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<td>Range</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IQ M (SD) Range*</td>
<td>113.38 (16.32), 83 – 128</td>
<td>110 (4.94), 104 – 118</td>
<td>97.29 (7.57), 87 – 107</td>
<td>96.62 (15.20), 77 – 120</td>
</tr>
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<td>CDRS Score M (SD)</td>
<td>17.5 (.76), 17 – 19</td>
<td>19.67 (2.65), 17-23</td>
<td>34.44 (10.57), 21-48</td>
<td>35.10 (10.14), 21 – 58</td>
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<tr>
<td>Range***</td>
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<td>YMRS Score M (SD)</td>
<td>1.37 (2.07), 0 – 5</td>
<td>2.17 (3.43), 0 – 9</td>
<td>29.56 (7.38), 15 – 39</td>
<td>22.60 (5.23), 17 – 32</td>
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<tr>
<td>Range***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Marijuana joints used last 30 days M (SD)</td>
<td>.38 (1.06), 0 – 3</td>
<td>29.00 (18.28), 4 – 60</td>
<td>.06 (.167), 0 – 1</td>
<td>58.10 (51.36), 4 – 144</td>
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<td>Range***</td>
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</tr>
<tr>
<td># of Alcoholic drinks consumed last 30 days M (SD) Range*</td>
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<td>8.40 (14.44), 0 – 40</td>
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<tr>
<td># Times alcohol used to intoxication last 30 days M (SD) Range***</td>
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<td>7 (6.20), 0 – 15</td>
<td>.78 (1.72), 0 – 5</td>
<td>.70 (1.57), 0 – 5</td>
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</tbody>
</table>

*p ≤ .05, ***p ≤ .001
Prediction 1

It was hypothesized that groups would differ in activation in medial temporal and limbic brain regions, including the insula, amygdala, hippocampus, anterior cingulate cortex, parahippocampal gyrus, and caudate, in response to the presentation of marijuana images. Table 2 displays mean activation values in these regions of interest. When examining differences in activation for the neutral and marijuana images individually, a significant group difference in activation was found in response to marijuana images in the right anterior cingulate cortex, $F(3, 29) = 3.19, p = .038$. Post hoc analyses using the Bonferroni post hoc criterion for significance indicated that the BPMJ group showed significantly greater activation in this region when compared to the HA group, $p < .05$. There were no significant group differences in activation to neutral images or in the difference between activation to marijuana and neutral images. The results do not support the hypothesis that groups differ in response to image type. Figures 3-14 display activation maps for each group across image type.
<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy Adolescent Group</th>
<th>Marijuana Group</th>
<th>Bipolar Group</th>
<th>Comorbid Group</th>
<th>Tailarach Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>L Insula</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Marijuana</td>
<td>.000 (.015)</td>
<td>-.003 (.010)</td>
<td>-.002 (.011)</td>
<td>.000 (.009)</td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>-.004 (.013)</td>
<td>-.003 (.010)</td>
<td>.005 (.008)</td>
<td>-.004 (.010)</td>
<td></td>
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<tr>
<td>Marijuana vs. Neutral</td>
<td>.003 (.009)</td>
<td>.000 (.013)</td>
<td>-.007 (.013)</td>
<td>.004 (.015)</td>
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<tr>
<td>R Insula</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Marijuana</td>
<td>-.004 (.010)</td>
<td>-.002 (.002)</td>
<td>-.007 (.017)</td>
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<tr>
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<td>-.006 (.014)</td>
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<tr>
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<td>.006 (.021)</td>
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<td></td>
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<tr>
<td>Marijuana</td>
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<td>.014 (.009)</td>
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<tr>
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<tr>
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<td>.013 (.015)</td>
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<tr>
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<td>.005 (.019)</td>
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<tr>
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<td>.010 (.013)</td>
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<tr>
<td>Marijuana vs. Neutral</td>
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<td>.002 (.010)</td>
<td>.006 (.017)</td>
<td>.008 (.018)</td>
<td></td>
</tr>
</tbody>
</table>

p < .05
**Prediction 2**

It was expected that increased craving as measured by the MCQ and increased brain activation in the regions of interest would result in group differences on the post-scan forced-choice recognition task. Table 3 displays mean index scores for the five factors of the MCQ by group. Groups differed significantly in their level of craving on all factors both pre- and post-scan: Compulsivity factor pre-scan, $F(3, 29) = 7.18, p = .001$ and post-scan, $F(3, 29) = 8.08, p = .000$; Emotionality factor pre-scan, $F(3, 29) = 5.38, p = .005$ and post-scan, $F(3, 29) = 6.96, p = .001$; Expectancy factor pre-scan, $F(3, 29) = 10, p = .000$, and post-scan, $F(3, 29) = 10.94, p = .000$; Purposefulness factor pre-scan, $F(3, 29) = 24.09, p = .000$, and post-scan, $F(3, 29) = 31.53, p = .000$. However, no group showed a significant increase in craving from pre-scan to post-scan. Figures 15 - 19 display mean index scores on the MCQ by groups for both pre- and post-scan.

Table 4 displays both performance and reaction time on the recognition memory task. Significant group differences were found on the total images (neutral and marijuana images combined) correctly recognized $F(3, 29) = 3.00, p = .047$. Post hoc analyses using the Bonferroni post hoc criterion for significance indicated that the MJ group recognized significantly more images than the BP group, $p < .05$. Groups also differed significantly on total neutral images correctly recognized $F(3, 29) = 5.02, p = .006$. Post hoc analyses indicated that the HA and MJ groups did not differ significantly from each other, however both groups recognized significantly more images than the BP group, $p < .05$. The differences in performance did not appear to be related to craving, as there were no significant correlations between performance and craving as measured by the MCQ (both pre- and post-scan) or with brain activation in the regions of interest. The hypothesis that increased craving would be associated with enhanced recognition of the images shown during the cue-reactivity task was not supported.
Table 3
Marijuana Craving Questionnaire Index Scores

<table>
<thead>
<tr>
<th></th>
<th>Healthy Adolescent Group</th>
<th>Marijuana Group</th>
<th>Bipolar Group</th>
<th>Comorbid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Pre-Scan Compulsivity Index***</td>
<td>1.79 (.35)</td>
<td>2.83 (.36)</td>
<td>1.52 (.24)</td>
<td>3.57 (.45)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1 – 3.71</td>
<td>1.57 – 4</td>
<td>1 – 2.71</td>
<td>1.71 – 6.14</td>
</tr>
<tr>
<td>Post-Scan Compulsivity Index***</td>
<td>1.66 (.34)</td>
<td>3.57 (.57)</td>
<td>1.57 (.20)</td>
<td>3.54 (.49)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1 – 3.57</td>
<td>2.14 – 6</td>
<td>1 – 2.71</td>
<td>1.43 – 6</td>
</tr>
<tr>
<td>Pre-Scan Emotionality Index**</td>
<td>4.09 (.47)</td>
<td>5.88 (.57)</td>
<td>3.80 (.51)</td>
<td>5.90 (.51)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>2.50 – 6.50</td>
<td>4.75 – 7</td>
<td>1.25 – 5.75</td>
<td>2.50 – 7</td>
</tr>
<tr>
<td>Post-Scan Emotionality Index***</td>
<td>4.03 (.72)</td>
<td>5.88 (.33)</td>
<td>3.56 (.59)</td>
<td>6.43 (.33)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1.25 – 7.00</td>
<td>4.50 – 7</td>
<td>1 – 5.50</td>
<td>4 – 7</td>
</tr>
<tr>
<td>Pre-Scan Expectancy Index***</td>
<td>2.25 (.37)</td>
<td>5.83 (.45)</td>
<td>3.18 (.63)</td>
<td>5.03 (.44)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1 – 3.67</td>
<td>4.33 – 7</td>
<td>1 – 5.67</td>
<td>1.67 – 6</td>
</tr>
<tr>
<td>Post-Scan Expectancy Index***</td>
<td>1.91 (.40)</td>
<td>6.11 (.46)</td>
<td>3.18 (.75)</td>
<td>5.23 (.43)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1 – 3.67</td>
<td>4.67 – 7</td>
<td>1 – 7</td>
<td>2.33 – 7</td>
</tr>
<tr>
<td>Pre-Scan Purposefulness Index***</td>
<td>1.79 (.54)</td>
<td>6.56 (.20)</td>
<td>2.19 (.46)</td>
<td>5.60 (.48)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1 – 5.00</td>
<td>5.67 – 7</td>
<td>1 – 5</td>
<td>3 – 7</td>
</tr>
<tr>
<td>Post-Scan Purposefulness Index***</td>
<td>1.83 (.55)</td>
<td>6.33 (.42)</td>
<td>1.89 (.31)</td>
<td>5.60 (.37)</td>
</tr>
<tr>
<td>M (SD), Range</td>
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<td>5 – 7</td>
<td>1 – 3</td>
<td>3.67 – 7</td>
</tr>
<tr>
<td>Pre-Scan General Index***</td>
<td>2.41 (.25)</td>
<td>4.74 (.17)</td>
<td>2.47 (.26)</td>
<td>4.74 (.31)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1.71 – 3.76</td>
<td>4.18 – 5.41</td>
<td>1.12 – 3.82</td>
<td>3.29 – 6.06</td>
</tr>
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<td>Post-Scan General Index***</td>
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<td>2.38 (.23)</td>
<td>4.88 (.23)</td>
</tr>
<tr>
<td>M (SD), Range</td>
<td>1.35 – 3.41</td>
<td>3.88 – 6.59</td>
<td>1.18 – 3.12</td>
<td>3.82 – 5.88</td>
</tr>
</tbody>
</table>

**p ≤ .01, ***p ≤ .001
Table 4

*Mean Recognition Memory Test Performance and Reaction Time*

<table>
<thead>
<tr>
<th></th>
<th>Healthy Adolescent Group</th>
<th>Marijuana Group</th>
<th>Bipolar Group</th>
<th>Comorbid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Overall Total Correct (80 possible) M (SD)*</td>
<td>68.50 (4.94)</td>
<td>74 (2.97)</td>
<td>61.33 (8.90)</td>
<td>64.30 (11.88)</td>
</tr>
<tr>
<td>Correct Neutral Images (out of 40) M (SD)**</td>
<td>35.63 (2.20)</td>
<td>37 (2.61)</td>
<td>30 (4.58)</td>
<td>31.70 (5.19)</td>
</tr>
<tr>
<td>Correct Marijuana Images (out of 40) M (SD)</td>
<td>32.88 (3.68)</td>
<td>37 (1.67)</td>
<td>31.33 (4.95)</td>
<td>32.60 (7.18)</td>
</tr>
<tr>
<td>Total Reaction Time (seconds) M (SD)</td>
<td>1.58 (.26)</td>
<td>1.44 (.16)</td>
<td>1.48 (.34)</td>
<td>1.48 (.37)</td>
</tr>
<tr>
<td>Neutral Images Reaction Time (seconds) M (SD)</td>
<td>1.44 (.20)</td>
<td>1.39 (.16)</td>
<td>1.52 (.39)</td>
<td>1.45 (.34)</td>
</tr>
<tr>
<td>Marijuana Images Reaction Time (seconds) M (SD)</td>
<td>1.75 (.37)</td>
<td>1.54 (.22)</td>
<td>1.51 (.40)</td>
<td>1.55 (.44)</td>
</tr>
</tbody>
</table>

*p ≤ .05, **p ≤ .01

**Prediction 3**

It was predicted that there would be an interaction between group and image type, with the BPMJ and MJ groups showing enhanced memory for marijuana images and the HA group displaying comparable performance across image type. However, when the MJ and BPMJ groups were combined, there was no significant increase in recognition of marijuana images $F(1, 29) = 2.18, p = .151$. As predicted, the HA group displayed comparable performance across image type $t(7) = 2.2, p = .064$. The BP group also displayed comparable performance across image type $t(8) = 1.17, p = .277$; however, when compared to the MJ and HA groups, the BP group displayed significantly lower recognition of the neutral images. The HA and MJ (non-bipolar) groups were combined and compared to BP and BPMJ (bipolar) groups combined. When combined, the non-bipolar groups recognized significantly more total images $F(1,31) =$
6.99, \( p = .013 \) and significantly more neutral images \( F(1,31) = 14.20, p = .001 \) than the bipolar groups. Figures 20-22 display mean performance on the recognition memory test for the bipolar groups combined and the non-bipolar groups combined.

![Figure 20](image-url)

*Figure 20. Mean total images correctly recognized for both the BP and BPMJ groups combined compared to the HA and MJ groups combined.*
Figure 21. Mean neutral images correctly recognized for both the BP and BPMJ groups combined compared to the HA and MJ groups combined.
Figure 22. Mean neutral images correctly recognized for both the BP and BPMJ groups combined compared to the HA and MJ groups combined.

Secondary Results

Given previous craving research that consistently found significant activational differences between groups, post-hoc analyses were performed using a larger number of regions of interest. All groups were combined to examine what areas were consistently activated across all groups to test for group differences. A total of 29 regions of interest, not including the regions selected a priori, were used to compare group differences in activation in response to image type. Examining activation to neutral and marijuana images separately, there were no significant group
differences in response to either marijuana or neutral images. Similarly, in examining differences in activation in response to marijuana compared to neutral images, there were no significant group differences in any of the regions of interest. Figures 23-25 display group activation maps in response to image type for these secondary regions of interest.
Chapter 4: Discussion

This study was conducted to explore the effects of cue-induced craving on brain activation and recognition memory of drug-related imagery in healthy adolescents, marijuana-using adolescents, bipolar adolescents and marijuana-using, bipolar adolescents. To our knowledge, this is the first study to examine the effect of cue-induced craving on recognition memory for the images that were used in the cue-reactivity task. The primary significant finding was that recognition memory for the total stimuli combined and the neutral stimuli presented during the cue-reactivity task was reduced in those groups that had bipolar disorder alone or in combination with a comorbid MJ use disorder, relative to those who did not have bipolar disorder. These results are consistent with the literature that shows deficits in memory in individuals with bipolar disorder (van Gorp, Altshuler, Theberge & Mintz, 1999; Fleck et al., 2005). More specifically, Fleck and colleagues (2005) found specific impairments in recognition memory in adults with bipolar disorder. Because these patients were all experiencing manic or mixed episodes at the time of testing, it is possible that mood state, in addition to diagnosis of a mood disorder, contributed to the findings.

The hypothesis that the MJ and BPMJ groups would display enhanced performance on aspects of the recognition memory test that involved marijuana images was not supported in the present sample, nor did these groups demonstrate the anticipated craving response during completion of the cue-reactivity task. Specifically, there was no evidence of a change in craving on either the self-report measure (MCQ) or on fMRI activation in the majority of the identified regions of interest. The only significant group difference that was identified in brain activation was in the right anterior cingulate cortex, with the BPMJ showing the greater activation in response to marijuana images when compared to the HA group. Despite expectations, there were
no significant differences between the MJ group and the HA and BP groups in any of the regions of interest. These findings are in direct contrast to several studies (Maas et al., 1998; Grant et al., 1996; Garavan et al., 2000; Childress et al., 1999; Park et al., 2007; Hommer, 1999; Garavan et al., 2000; Grant et al., 1996; Hommer, 1999; Breiter et al., 1997; Heinz et al., 2004; Park et al., 2007; Filbey et al. 2009), which have found significant groups differences in activation in these regions between craving and non-craving individuals in response to drug-related cues and stimuli.

It is a core problem for the present study that the cue-reactivity task did not result in increased craving as measured by the MCQ or by most of the imaging measures. One possible explanation is that the MJ and BPMJ groups exhibited significantly higher pre-scan craving scores than the HA and BP groups, at times scoring so near maximum on the pre-scan measure that there was no possibility of a significant post-scan increase in score. As a result, it is difficult to ascertain if the cue-reactivity task actually elicited craving in the MJ and BPMJ groups. The absence of activational changes that are well documented in the craving literature, however, suggests that there was indeed not an increase in craving that was detectable in this sample. Further evidence that craving may not have been elicited comes from bivariate correlations that failed to find any significant relationships between pre- and post-scan craving and recognition memory. It was also thought that craving, as measured by the MCQ, would be positively correlated with brain activation. Again, bivariate correlations did not reveal significant correlations with pre- or post-scan craving.

The heightened pre-scan craving levels in the BP and BPMJ groups could have resulted in habituation and a reduction in response in these individuals. Research has consistently found that the amygdala plays a critical role in affective processing in humans (Pessoa, 2010; Zald, 2003), particularly during the processing of fearful and happy stimuli. However, the amygdala
also habituates to frequently presented emotional stimuli. This finding has been replicated in studies that examined the presentation of emotionally valenced visual (Breiter et al., 1996) and auditory (Wiethoff, Wildgruber, Grodd & Ethofer, 2009) stimuli. The results of the MCQ prescan questionnaire suggest that the MJ and BPMJ participants arrived to the study while in a state of heightened craving. These groups could have exhibited an attenuated response to the craving stimuli due to the frequency with which these individuals engaged in marijuana use, resulting in a habituation of brain regions that would normally activate in response to drug-related stimuli. This habituation of response could contribute to the lack of expected activation patterns in the MJ groups, although it is unclear why the present sample would have exhibited habituation to a greater degree than others in the published literature.

Although there were differences in recognition memory associated with bipolar diagnosis, no significant differences in activation were found that were predictive of these performances. After the initial analyses were performed, it was thought that the lack of significant differences between groups in brain activation could be the result of a narrowed focus on six bilateral regions of interest. Visual inspection of the images initially indicated the possibility of an effect of bipolar status on activation similar to the effect of performance on the recognition memory test. Additional analyses were performed which expanded the regions of interest to a total of 29 regions in an attempt to capture any differences that may actually have existed between groups. Despite increasing the number of regions of interest, no significant differences were found between groups.

There are several limitations that could have contributed to the present negative findings. Among them, a large limitation was the sample size and unbalanced groups. The current sample is a subset of a larger data set that featured balanced groups sizes and evenly matched groups.
While an imaging paradigm often inherently limits the amount of participants that can be recruited for a particular study, a larger sample would have provided a more representative sample and allowed for better matching across groups.

In addition, individuals with severe mental illnesses, including bipolar disorder, are typically excluded from imaging studies that examine drug craving. This is often done in an effort to avoid confounds related to severe mental illness. Research has demonstrated both structural and functional differences between individuals with and without bipolar disorder. Bearden and colleagues (2008) found that adolescents with bipolar disorder evidenced reduced hippocampal volume relative to healthy controls. Jarvis and colleagues (2008) also examined adolescents with bipolar disorder with and without a marijuana use disorder. They found evidence of structural abnormalities in frontal and temporal cortical regions in both marijuana-using and non-using groups. However, the structural abnormalities were more pronounced in the marijuana-using group. Jarvis and colleagues (2008) also found evidence of subcortical differences, specifically in the caudate and fusiform gyrus, both areas often linked to craving (Breiter et al. 1997). Sax and colleagues (1998) also found decreased prefrontal volumes in bipolar patients. Moreover, all subjects in the BP groups in the present study were in a manic or mixed state during the time of the scan. Differences in activation patterns have been found between patients with bipolar disorder during a manic phase and healthy controls. These differences have been seen in prefrontal regions (Strakowski, Delbello, Adler, Cecil & Sax, 2000; Rubinsztein et al. 2001; Strakowski, 2002; Blumberg et al. 2003), and temporal regions (Blumberg et al, 2000; Yurgelun-Todd et al., 2000). It is possible that differences in morphology and activation patterns could exist within the BP and BMPJ groups and could have negatively affected inferences that could be made comparing the MJ and BPMJ groups.
The study was also limited by the presence of differences in severity of mood state between bipolar groups, with the BP group endorsing significantly more symptoms on the YMRS compared to the BPMJ group. Thus, in the bipolar disorder groups, symptom severity was confounded with comorbidity. In addition, some participants in the BP group were on a sub-therapeutic dose of a mood-stabilizing medication at the time of the scan, while the BPMJ participants were not on any medication at the time of the scan. The presence of potential medication effects further limits the inferences that could be drawn from performance on the MT and brain activation between the BP groups.

Intelligence was found to be a contributor to performance on the recognition memory test. While the larger study that this subset of participants was drawn from did not display differences in IQ, this subset of the data suffered from significant IQ differences. While all efforts to control for IQ were made, the concern about IQ as a contributor to performance remains. Future studies could control for this by requiring a higher IQ (e.g., IQ > 85) in order to participate in the study in an effort to control for IQ differences and its contribution to performance on these subtests.

Another limitation presented by this study is the comparison of adolescents as young as 12-years-old to adults as old as 22. Neuromaturation continues through adolescence and young adulthood (Sowell et al., 2002). Therefore, while not examined in this study, the differences in brain development between a 12-year-old and a 22-year-old participant could have contributed to the lack of group differences.

Finally, this study examined groups who are known to have both structural and functional abnormalities in their brains. Individuals with bipolar disorder have shown abnormal activation
patterns (Strakowski, Delbello, Adler, Cecil & Sax, 2000; Rubinsztein et al. 2001; Strakowski, 2002; Blumberg et al. 2003). Similarly, marijuana use during adolescence has been associated with increased morphometric and cognitive abnormalities in regular marijuana users (Ehrenreich et al., 1999; Pope et al., 2003; Wilson et al., 2000). A recent study by Medina and colleagues (2010) with adolescent, chronic marijuana users found significant changes in cerebellar volume compared to controls. In addition, despite 28 days of monitored abstinence, deficits in executive functions were found and attributed to the changes in cerebellar volume. It is feasible that structural changes and abnormal activations could have affected our ability to find significant group differences. Longitudinal studies are needed to examine brain development and activation patterns in regular marijuana-using adolescents and marijuana-using bipolar adolescents.

In summary, those groups that had bipolar disorder alone or in combination with a comorbid MJ use disorder displayed reduced recognition memory for both the neutral and marijuana stimuli combined and the neutral stimuli presented during the cue-reactivity task relative to those who did not have bipolar disorder. Additionally, the only group difference that was identified in brain activation was in the right anterior cingulate cortex, with the BPMJ group showing the greater activation in response to marijuana images when compared to all other groups. Craving was not effectively induced in the marijuana using groups and there were no observed group differences in brain activation in response to marijuana and neutral images. These findings are in direct contrast to the literature that consistently found group differences in craving and brain activation between drug users and non-users. The exact reason for this lack of group differences in craving and brain activation is not fully known. However, it was evident that the cue-reactivity task used in this study did not effectively elicit craving in healthy and bipolar marijuana users. Future studies may focus on developing a standardized cue-reactivity
task that reliably induces craving in marijuana users. In the absence of a clear craving effect from the cue-reactivity task, it was unfortunately not possible in this study to effectively examine the hypothesis that craving competes for available cognitive resources by administering cognitive measures that are known to be mediated by areas involved in craving.
Figure 1. Example of neutral images displayed during the cue-reactivity task administered during the fMRI data collection.
Figure 2. Example of marijuana mages displayed during the cue-reactivity task administered during the fMRI data collection.
Figure 3. Activation map of areas activated in response to neutral images in the HA group. Warm colors note increased activation to neutral images while cool colors indicate decreased activation in response to neutral images. A = left insula, B = right insula, C = left amygdala, D = right amygdala, E = left anterior cingulate, F = right anterior cingulate, G = left parahippocampal gyrus, H = right parahippocampal gyrus, I = left hippocampus, J = right hippocampus, K = left caudate, L = right caudate.
Figure 4. Activation map of areas activated in response to marijuana images in the HA group. Warm colors note increased activation to marijuana images while cool colors indicate decreased activation in response to marijuana images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 5. Activation map showing the differences in activation in response to both marijuana and neutral images in the HA group. Warm colors note increased activation to marijuana images while cool colors indicate increased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 6. Activation map of areas activated in response to neutral images in the MJ group. Warm colors note increased activation to neutral images while cool colors indicate decreased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 7. Activation map of areas activated in response to marijuana images in the MJ group. Warm colors note increased activation to marijuana images while cool colors indicate decreased activation in response to marijuana images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I= left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 8. Activation map showing the differences in activation in response to both marijuana and neutral images in the MJ group. Warm colors note increased activation to marijuana images while cool colors indicate increased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 9. Activation map of areas activated in response to neutral images in the BP group. Warm colors note increased activation to neutral images while cool colors indicate decreased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 10. Activation map of areas activated in response to marijuana images in the BP group. Warm colors note increased activation to marijuana images while cool colors indicate decreased activation in response to marijuana images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 11. Activation map showing the differences in activation in response to both marijuana and neutral images in the BP group. Warm colors note increased activation to marijuana images while cool colors indicate increased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 12. Activation map of areas activated in response to neutral images in the BPMJ group. Warm colors note increased activation to neutral images while cool colors indicate decreased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I= left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 13. Activation map of areas activated in response to marijuana images in the BPMJ group. Warm colors note increased activation to marijuana images while cool colors indicate decreased activation in response to marijuana images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I=left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 14. Activation map showing the differences in activation in response to both marijuana and neutral images in the BPMJ group. Warm colors note increased activation to marijuana images while cool colors indicate increased activation in response to neutral images. A= left insula, B= right insula, C= left amygdala, D= right amygdala, E= left anterior cingulate, F= right anterior cingulate, G= left parahippocampal gyrus, H= right parahippocampal gyrus, I= left hippocampus, J= right hippocampus, K= left caudate, L= right caudate.
Figure 15. Mean Compulsivity Index score for both pre- and post-scan.
Figure 16. Mean Purposefulness Index score for both pre- and post-scan.
Figure 17. Mean Emotionality Index score for both pre- and post-scan.
Figure 18. Mean Expectancy Index score for both pre- and post-scan.
Figure 19. Mean General Index score for both pre- and post-scan.
Figure 23. Activation map of clusters activated in response to neutral images in all groups combined. Warm colors note increased activation to neutral images while cool colors indicate decreased activation in response to neutral images. The selected regions of interest are not displayed. Instead, peak areas of activation in clusters that survived a Monte Carlo simulation are displayed. A= right lingual gyrus, B= right inferior parietal lobe and Brodman’s area 40, C= left superior temporal gyrus, D= right precuneus, E= right middle frontal gyrus and Brodman’s area 6, F= right inferior frontal gyrus and Brodman’s area 47, G= left middle frontal gyrus, H= left middle temporal gyrus, I= right insula and Brodman’s area 13.
Figure 24. Activation map of clusters activated in response to marijuana images in all groups combined. Warm colors note increased activation to marijuana images while cool colors indicate decreased activation in response to marijuana images. The selected regions of interest are not displayed. Instead, peak areas of activation in clusters that survived a Monte Carlo simulation are displayed. A= left declive, B= right precuneus, C= left postcentral gyrus and Brodman’s area 40, D= left superior parietal lobe, E= left insula F= right inferior parietal lobule, G= right superior temporal gyrus and Brodman’s area 22, H= left posterior cingulate, I= right superior parietal lobule.
Figure 25. Activation map of clusters activated in response to both neutral and marijuana images in all groups combined. Warm colors note increased activation to marijuana images while cool colors indicate increased activation in response to neutral images. The selected regions of interest are not displayed. Instead, peak areas of activation in clusters that survived a Monte Carlo simulation are displayed. A= right inferior temporal gyrus, B= left inferior temporal gyrus and Brodman’s area 37, C= left inferior parietal lobule, D= right inferior temporal gyrus, E= right cuneus and Brodman’s area 17 F= right substantia nigra, G= left posterior cingulate, H= right thalamus, I= left pyramids, J= left parahippocampal gyrus and Brodman’s area 28, K= right Brodman’s area 13
References


