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Emotional Attention Processing among HIV-Infected Persons with Co-occurring Bipolar  
Disorder

A dissertation submitted in partial satisfaction of the  
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Carolina Posada

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2013

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2013

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ABSTRACT OF THE DISSERTATION

Emotional Attention Processing among HIV-Infected Persons with Co-occurring Bipolar Disorder

by

Carolina Posada

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2013  
San Diego State University, 2013

Professor David J. Moore, Chair  
Professor Igor Grant, Co-Chair

Rationale: Emotional attention is the attentional processing of emotionally-laden information. Despite the high prevalence of HIV infection among people with bipolar disorder (BD), relatively little is known about the neuropsychological and emotional functioning of persons with both conditions. The present dissertation project aimed to assess emotional attention among persons with HIV and BD.

Design: Thirty-nine HIV+/BD+, 27 HIV+/BD-, 29 HIV-/BD+, and 25 HIV-/BD- were administered the AGNT. Outcome variables were correct responses (CR) and Reaction time (RT). It was hypothesized that the effect of BD on AGNT performance would be worse for HIV+ individuals than for HIV- individuals. It was also hypothesized that individuals in a dysregulated mood state would demonstrate greater mood congruent attentional bias. Lastly, It was hypothesized that performance on the AGNT will be an independent predictor of engagement in risk behaviors.

Results: An ANOVA yielded significant interactions between HIV and BD for CR on the Go Happy/No-Go Sad condition, the Combined Go Happy condition, and the Combined Emotional condition. Post-hoc analyses revealed that the HIV+/BD- and the HIV-/BD+ groups performed significantly worse on the abovementioned variables than HIV-/BD- group. No significant interactions or main effects were found for RT. A mixed model ANOVA using mood state as the between subject factor and AGNT condition as the within subject factor, yielded no significant interactions but a main effect of AGNT condition such that participants with BD were more accurate at responding to sad words and faster at responding to the perceptual features of the words. A regression analysis revealed that performance on the AGNT was not a significant independent predictor of higher engagement in HIV transmission risk behaviors.

Discussion: Both HIV infection and BD independently contribute to the processing of emotional words. The less accurate processing of emotionally-laden information does not appear to be the result difficulties in processing the emotional meaning of the words. No mood congruent biases were found, but individuals with BD are more accurate at processing negative words. It appears that increased accuracy

difficulties processing positive words are associated with greater engagement in HIV-transmission sexual behaviors.

## Chapter 1: Introduction

### **Prevalence of HIV Infection and Bipolar Disorder in the General Population**

According to estimates from the 2009 UNAIDS report on the global AIDS epidemic, there were approximately 33.3 million people living with HIV worldwide at the end of 2008 (Joint United Nations Program on HIV/AIDS [UNAIDS], 2009), with over 1 million people living with HIV/AIDS in the United States (Hall et al., 2008). The worldwide lifetime prevalence of bipolar spectrum disorders is 2.4% (bipolar type-I disorder: 0.6%; bipolar type-II disorder: 0.4%; and sub-threshold bipolar disorder: 1.4%), while in the United States the prevalence is 4.4% (bipolar type-I disorder: 1.0%; bipolar type-II disorder: 1.1%; and sub-threshold bipolar disorder: 1.4%) (Merikangas et al., 2011). Importantly, both conditions remain a leading worldwide cause of disability, morbidity, and mortality from suicide (Goodwin, 2007; UNAIDS, 2009).

### **Prevalence of HIV Infection Among Individuals with Bipolar Disorder**

The prevalence of HIV infection in people with severe mental illness is generally higher than in the general population, but varies substantially (1.3-23.9%) (De Hert et al., 2011). HIV infection appears to be particularly elevated among persons with bipolar disorder (BD) (Beyer, Kuchibhatla, Gersing, & Krishnan, 2005; Cournos & McKinnon, 1997; Evans & Charney, 2003; Walkup, Crystal, & Sambamoorthi, 1999). Specific estimates of the prevalence of HIV infection among those with BD are rarely reported (Walkup et al., 1999); however, a recent study found that 2.8% of outpatients with BD were also HIV-infected (Beyer, Taylor, Gersing, & Krishnan, 2007). Several studies suggest that HIV-uninfected individuals with BD engage in more risky HIV transmission behaviors than various comparison populations (Meade & Sikkema, 2005). HIV+ persons



with BD (HIV+/BD+) are more likely to exhibit high energy, poor judgment, and impulsive risk-taking with more sexual partners than those without BD, thus, making them a group at high risk for spreading HIV infection (Angelino & Treisman, 2008). Also, the mood symptoms (depression, mania) may interfere with adherence to HIV treatment, resulting in increased morbidity and mortality (Angelino & Treisman, 2008). Despite the great public health risk that this group represents, relatively little is known about HIV+/BD+ individuals, specifically about the interplay between emotional and neuropsychological functioning.

### **HIV Infection**

The human immunodeficiency virus (HIV) is a lentivirus that compromises immune function by damaging cluster of differentiation 4+ (CD4) lymphocytes. In addition to its deleterious effects on the immune system, HIV can be highly neurovirulent. HIV crosses the blood-brain barrier (BBB) early in the course of infection (Davis et al., 1992), most likely as a consequence of the trafficking of infected cells (e.g., monocytes) across the BBB (Haase, 1986). Although HIV does not directly infect neurons, it alters neural functioning by triggering a cascade of neurotoxic molecular events, such as the upregulation of chemokines (Gonzalez-Scarano & Martin-Garcia, 2005). As many as 50% of HIV-infected individuals exhibit HIV-related neuropathologies (Budka, 2005), often taking the form of neuronal apoptosis and/or synaptodendritic injury (Ellis, Langford, & Masliah, 2007; Moore, Masliah, et al. 2006).

### **Brain Systems Affected in HIV**

HIV RNA may be present throughout the central nervous system, and HIV-associated neuropathologies are observed in many brain regions, although frontostriatal

regions appear to be specifically vulnerable. For example, following infection, the highest concentrations of HIV in the brain are found in the basal ganglia and frontal cortices (e.g., Aylward et al., 1993; Langford, Hurford, Hashimoto, Digicaylioglu, & Masliah, 2005; Wiley et al., 1999). Dendritic damage has been found particularly in the frontal cortex and basal ganglia, which has shown to be a strong correlate of the severity of HIV-associated neurocognitive impairment (Cherner et al., 2002; Ellis et al., 2007; Masliah et al., 1997; Moore, Masliah, et al. 2006). Neuroimaging studies have found cerebral volume loss (Di Sclafani et al., 1997; Patel et al., 2002; Stout et al., 1998), ventricular enlargement (Chiang et al., 2007), and reductions in caudate volume (Chiang et al., 2007; Di Sclafani et al., 1997), and corpus callosum (P. M. Thompson et al., 2006) in the brains of individuals infected with HIV. Also, thinning of primary sensory, motor, and premotor cortices have been observed (J. M. Thompson et al., 2005).

Studies using magnetic resonance spectroscopic (MRS) have found metabolic changes indicating inflammation and neuronal damage in frontal white matter (Chang et al., 2002; Paul et al., 2007; Sacktor et al., 2005), frontal gray matter (Lentz et al., 2009), and basal ganglia (Chang et al., 2002; Paul et al., 2007). Imaging studies have also found correlations between brain abnormalities and poor neuropsychological (NP) functioning in HIV infection. For example, Paul et al. (2008) used magnetic resonance imaging (MRI) to show reductions in caudate and putamen volume that were significantly correlated with measures of executive functions, verbal learning, processing speed and fine motor skills. The authors of the study also used MRS to show that metabolic changes in these two structures correlated with measures of fine motor skills. A functional MRI study showed a significant increase in parietal and frontal lobe activation during an

attention task in HIV-infected individuals as compared to HIV-uninfected individuals (Chang et al., 2001). A subsequent study by this group used MRS to show that metabolic changes in frontal white matter was correlated with poor performance on measures of executive function (Chang et al., 2002). More recently, Lepore and colleagues (2008) showed that reductions in white matter in the primary and sensory association areas correlated with cognitive deficits among individuals with AIDS. Diffusion tensor imaging (DTI) studies also have revealed significant correlations between microstructural abnormalities (i.e., increased mean diffusivity and reduced fractional anisotropy), and global cognitive impairment in the corpus callosum (Wu et al., 2006), and internal and external capsules (Gongvatana et al., 2009; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007).

Taken together, these neuropathology and neuroimaging findings provide support for the deleterious effects of HIV-infection in the brain. HIV appears to affect frontal cortices and the basal ganglia, and specifically, the white matter tracts connecting these systems. Importantly, the disruption of this fronto-striatal system appears to be associated with the cognitive deficits (e.g., executive dysfunction, slow processing speed) seen in a proportion of HIV-infected individuals.

### **Neuropsychological Functioning in HIV Infection**

Approximately 30% of asymptomatic HIV-infected patients show mild neuropsychological (NP) impairment whereas some form of NP impairment is observed in over 50% of individuals in later stage HIV disease (Heaton et al., 2010). NP impairment tends to worsen with disease severity with the greatest NP impairments typically observed among individuals with AIDS (Heaton et al., 2011; Heaton et al.,

1995). Although highly active antiretroviral therapy (HAART) has advanced the treatment of HIV-infected individuals through suppression of viral replication, improved medical status, and extended longevity (Detels et al., 1998), HIV-associated NP impairment is still common (Heaton et al., 2011; Robertson et al., 2007; Simioni et al., 2010). Although, a reduction in the incidence of HIV-associated dementia (HAD) has been widely reported (MacArthur et al., 2004; Robertson et al., 2007; Sacktor et al., 2001).

A recently published paper by Heaton and colleagues (2011) comparing rates of NP impairment before and after HAART era showed that impairment rate increased with severity of disease, and that low nadir CD4 predicted NP impairment in both eras. Interestingly, NP impairment in HIV-infected asymptomatic individuals was more common in the HAART than in pre-HAART era. Results also showed that the pattern of NP impairment was different. While in the pre-HAART era HIV-infected individuals had more impairment in motor skills, cognitive speed, and verbal fluency, in the HAART era, a high the proportion of individuals were impaired on learning (65%), executive function (53%), attention/working memory (49%), memory (48%), motor skills (33%), speed of information processing (30%), verbal fluency (25%).

Although not the most affected domain, attention deficits have been reported since early in the HIV epidemic (Grant, Wiley, & Winkelstein, 1987). Similar to other NP domains, attention deficits increase with disease severity. In a meta-analysis of NP impairments in HIV, Reger, Welsh, Razani, Martin, and Boone (2002) showed effect sizes ranging from 0.1 for asymptomatic HIV infected individuals, to 0.4 in individuals with AIDS. A recent review of the cognitive neuropsychology of HIV-associated

neurocognitive disorders by Woods, Moore, Weber, and Grant (2009), pointed out that because attention is a multidimensional construct that has been assessed through traditional tests, such as digit span and digit vigilance (Heaton et al., 1995), it may be not very specific and could considerably overlap with other cognitive functions (e.g., speed of information processing, Levine et al., 2008). However, previous studies have tried to clarify the specific mechanisms of attentional deficits in HIV, reporting impairment in the areas of divided attention (e.g., Hinkin, Castellon, & Hardy, 2000), orienting (e.g., Martin, 1995), response inhibition (e.g., Hinkin, Castellon, Hardy, Granholm, & Siegle, 1999), and sustained attention (Levine et al., 2006).

### **Emotional Dysregulation in HIV Infection**

In addition to cognitive difficulties, there are increasing reports that HIV patients experience higher rates of psychological dysfunction compared with seronegative individuals (Bing et al., 2001; Hinkin, Castellon, Atkinson, & Goodkin, 2001). Over the past several decades, increased rates of depression have been reported among HIV-infected individuals (Cruess et al., 2003). Major depressive disorder (MDD) is more prevalent among HIV-infected individuals than in the general population, with estimated prevalence rates varying widely from 2% to 30%, or even up to 50% of the HIV-positive patients (Dube, Benton, Cruess, & Evans, 2005; Judd et al., 2005). Patients with HIV are 2-7 times more likely to meet diagnostic criteria for current MDD than individuals in the general population (Hinkin et al., 2001). The HIV Cost and Services Utilization Study reported that 36% of the HIV+ patients met criteria for major depression and 27% for dysthymia (Bing et al., 2001). More recently, Beyer et al. (2007) reported that among individuals with unipolar depression, 1.4% were HIV infected. Notably, some of the

psychological impairments observed in HIV patients have been associated with HIV-related fronto-striatal abnormalities (Paul et al., 2005), suggesting that these difficulties are secondary to the neuropathological process of HIV, rather than arising purely as a psychological reaction to having been diagnosed with a chronic disease. Importantly, incident major depression does not appear to affect neuropsychological functioning in HIV-infected individuals (Cysique et al., 2007). In addition, secondary mania and psychosis, have been described among HIV+ patients, especially among those with advanced immunosuppression (Ellen, Judd, Mijch, & Cockram, 1999; Harris, Jeste, Gleghorn, & Sewell, 1991; Kieburtz, Zettlmaier, Ketonen, Tuite, & Caine, 1991; Lyketsos et al., 1997; Sewell et al., 1994). These conditions are thought to be associated with HIV central nervous system involvement (Mijch, Judd, Lyketsos, Ellen, & Cockram, 1999; Sewell et al., 1994) and often occur with cognitive decline (Lyketsos et al., 1997). Thus the effects of HIV in the brain are not only affecting cognition but also emotional regulation, which is consistent with some of the neuropathological and imaging studies that found greater involvement of fronto-striatal systems that also underlie emotional processing.

### **Bipolar Disorder**

BD is characterized by a recurrent and episodic course involving disturbances of mood, sleep, behavior, perception, and cognition. BD has a spectrum presentation, with major subtypes of bipolar I and bipolar II, apparently falling along a continuum of severity. According to current diagnostic categorization (DSM-IV-TR; American Psychological Association [APA], 2000), patients with bipolar I disorder have had at least one episode of mania or mixed, marked by symptoms of elated or irritable mood,

reduced need for sleep, increased goal-directed activity, rapid speech, flight of ideas, and increased energy. Additionally, in approximately 50% of bipolar I patients have a history of psychosis. Bipolar II patients have milder symptoms of mania, which, by definition, do not involve psychosis, are typically shorter in duration, and do not significantly interfere with daily functioning. Both bipolar I and bipolar II subtypes experience intermittent major depressive episodes with sad mood, suicidal ideation, and changes in appetite, sleep, and energy, often interfering significantly with psychosocial functioning (APA, 2000). The notable heterogeneity in the clinical phenotype, including multiple subtypes (bipolar I, bipolar II) and several characteristics that are present only in a subgroup of patients (i.e. psychosis, cognitive impairment), complicate the attempts to elucidate the underlying pathophysiology of the illness (Green, Cahill, & Malhi, 2007).

Although the exact etiologies of BD remain unknown, data from post-mortem, genetic, computed tomography, positron emission tomography, and magnetic resonance imaging studies provide evidence that brain abnormalities contribute to the disorder. The cause and significance of these abnormalities remain somewhat speculative, and findings are often contradictory. Recent models of BD (Green et al., 2007; Phillips, Drevets, Rauch, & Lane, 2003; Strakowski, Delbello, & Adler, 2005), however, suggest that the sometimes inconsistent and even contradictory findings involving abnormal brain anatomy, structure, and function may be understood within a framework of emotional dysregulation in circuits involving frontal cortical and limbic structures (Mahon, Burdick, & Szeszko, 2010; Mayberg, 1997).

### **Brain Systems Affected in Bipolar Disorder**

Several influential accounts have suggested that dysregulation of various nodes in the limbic system (e.g., amygdala, anterior cingulate, hippocampus), and alterations along several of the white matter tracts that connect prefrontal (e.g., orbitofrontal cortex), subcortical (e.g., ventral striatum), and medial-temporal structures (e.g., hippocampus, parahippocampal gyrus, insula) may underlie the cognitive and emotional deficits seen in BD (Bearden, Hoffman, & Cannon, 2001; Mahon et al., 2010; Phillips et al., 2003; Phillips, Ladouceur, & Drevets, 2008; Strakowski et al., 2005). Specifically, it has been postulated that emotional regulation consists of both “bottom-up” (in response to inherently perceptual properties of the stimulus) and “top-down” (in response to cognitive evaluations) processing of emotional stimuli via reciprocal connections between these structures. Therefore, alterations along these tracts are likely to play a role in the deficient emotional regulation that characterizes BD (Mahon et al., 2010; Strakowski et al., 2005). This model is consistent with findings of decreased modulatory control of the frontal cortex over the subcortical and temporal structures in BD (Altshuler et al., 2005; Foland et al., 2008; Pavuluri, O'Connor, Harral, & Sweeney, 2007).

### **Neuropsychological Functioning in Bipolar Disorder**

There is a broad consensus that patients with bipolar I and bipolar II disorders have NP impairments when compared with age matched controls of similar educational background (Bearden et al., 2001; Quraishi & Frangou, 2002). During the acute episodes of both mania and depression, patients typically manifest significant dysfunctions in most cognitive domains (Malhi et al., 2007; Martinez-Aran, Vieta, Reinares, et al., 2004; Murphy & Sahakian, 2001; Quraishi & Frangou, 2002), although patients who are in



euthymic states also experience significant cognitive deficits (Arts, Jabben, Krabbendam, & van Os, 2008; Torres, Boudreau, & Yatham, 2007). Many researchers, starting with Kraepelin, emphasized that recovery was complete between episodes. This influential legacy largely favored common assumptions that neuropsychological deficits reverted with clinical improvement suggesting that the neuropsychological deficits observed in BD are the result of “states” of mood dysregulation and not a “trait” deficit *per se*.

However, during the last decade, an increasing amount of evidence has demonstrated that many neurocognitive deficits persist into periods of clinical remission or euthymia (L. Clark & Goodwin, 2004; Martinez-Aran, Vieta, Colom, et al., 2004). For example, Bearden et al. (2006) included patients with a varying mood states from mania, to euthymia to depression. They found that bipolar patients recalled and recognize fewer words than controls in a declarative memory paradigm, independent of clinical status.

According to recent meta-analytic reviews (Kurtz & Gerraty, 2009; Robinson et al., 2006; Torres et al., 2007), neurocognitive impairments in adult euthymic BD patients cut across the domains of attention, processing speed, verbal learning/memory, and executive functions, including cognitive flexibility, inhibitory control, working memory and verbal fluency. On average, the magnitudes of the detected effects are between  $\frac{3}{4}$  to 1 standard deviation units (Robinson et al., 2006; J. M. Thompson et al., 2005). In a two-year follow-up study by (Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2008) euthymic bipolar patients showed a poorer neurocognitive performance, between  $-1$  and  $-2$  SD lower, compared to healthy controls on executive function and processing speed measures.

Contrasting with the literature on HIV, results from studies examining attention in euthymic bipolar individuals indicate that this is one of the most commonly impacted neurocognitive domains in bipolar disorder. In the meta-analytic review by Torres and colleagues (2007) reported medium effect sizes (0.60 – 0.79) were reported for studies using test of visual attention (Trails A), complex attention (Digit Symbol) and sustained attention (Continuous Performance Test, CPT) (Altshuler et al., 2004; Balanza-Martinez et al., 2005; L. Clark & Goodwin, 2004; L. Clark, Iversen, & Goodwin, 2002; Fleck, Shear, & Strakowski, 2005; Harmer, Grayson, & Goodwin, 2002; Martinez-Aran, Vieta, Colom, et al., 2004; Martinez-Aran, Vieta, Reinares et al., 2004; Strakowski, Adler, Holland, Mills, & DelBello, 2004; Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003; J. M. Thompson et al., 2005). These findings provide evidence for the assumption that NP, and in particular attention deficits are in fact a trait characteristic of BD, that may be exacerbated during states of mood dysregulation (i.e., mania, depression).

### **Emotional Cognition**

Emotional cognition is understood as an interface at which emotional and cognitive processes are integrated to generate behavior. This integration of cognition and emotion is fundamental in human behavior given that all actions and decisions occur in an emotional context (Elliott, Zahn, Deakin, & Anderson, 2011). Emotional cognition is defined as the cognitive processing of emotionally laden stimuli. Specific cognitive processes that have been studied in this field of research include attention, memory, and facial emotional recognition. Research on the interaction between emotion and cognition is particularly relevant to neurological and psychiatric disorders, given that impairments are often seen in both domains (Savage et al., 2009). This type of research “not only can

increase our understanding of the relationship between thoughts and feelings to help improve our understanding of the etiology of the specific clinical disorders, and ultimately, help generate novel and effective treatment strategies” (Savage et al., 2009, p. 206).

In the last 20 years, there has been a proliferation of studies exploring emotional processing and the interaction between emotion and cognition, facilitated by the advent of brain imaging techniques. Functional neuroimaging has revolutionized the study of all aspects of emotional function, measuring brain responses to emotional information, and thus develop brain-based models of emotional cognition (Dolan, 2002; Elliott et al., 2011). For example, existing data in healthy individuals point toward distinguishable neural systems for emotion processing and executive control. Functional neuroanatomic investigations in healthy individuals to date implicate a network of subcortical anterior limbic structures for appropriate emotion processing (Elliott et al., 2011). These structures include regions such as the amygdala, ventral striatum, subgenual (ventral) cingulate, ventromedial prefrontal cortex (VMPFC), anterior hippocampus, and anterior insula (Phillips et al., 2003).

### **Emotional Attention**

Emotional attention is defined as the attentional processing of emotionally laden information. It has been postulated that emotionally significant stimuli are processed with priority as they automatically capture attention due to their enhanced salience and more resources are allocated for their perceptual processing (M. M. Bradley et al., 2003). In healthy humans, an increased attentional capture for an enhanced orientating response to emotional stimuli has been consistently demonstrated (Algom, Chajut, & Lev, 2004;

Anderson, 2005; Mogg, Bradley, Field, & De Houwer, 2003; Ohman, Flykt, & Esteves, 2001; Pourtois, Grandjean, Sander, & Vuilleumier, 2004), while in affective disorders, a mood-congruent bias for emotional stimuli has been observed (Jongen, Smulders, Ranson, Arts, & Krabbendam, 2007; Suslow, Junghanns, & Arolt, 2001), although this finding has not been consistently reported (B. P. Bradley, Mogg, & Lee, 1997).

A widely reported finding is that patients suffering from emotional disorders exhibit greater interference for threatening words directly connected to their disorder-related concerns than for other emotional or neutral words. This interference effect is classically interpreted as reflecting an attentional bias, i.e. attention being automatically drawn to the verbal meaning of words that are emotionally relevant to the person, so that less attentional resources are available for the non-emotional relevant words (Williams, Mathews, & MacLeod, 1996). For example, it has been suggested that the bias toward negative stimuli may play a role in the etiology and maintenance of mood related disorders (D. A. Beck & Koenig, 1996; Mogg et al., 2003).

Emotional attention has been studied using modifications of traditional attention paradigms such as dot probe, Stroop, and Go/No-Go tasks. Affective Go/No-Go tasks (AGNT) are considered to be a direct measure of attentional bias, that is, the faster the response time the greater the magnitude of the emotional bias. Although stimuli for AGNT are usually words, facial expressions or symbols have also been used (Hare, Tottenham, Davidson, Glover, & Casey, 2005). AGNT has been used extensively to test emotional processing in both healthy adults and patients with affective disorders. A series of studies in BD that used AGNT with affective words as stimuli found mood-congruent response biases in both manic and depressed patients, such that manic patients made

faster responses to happy words, while depressed patients made faster responses to sad words (Elliott et al., 2004; Elliott, Rubinsztein, Sahakian, & Dolan, 2000, 2002; Murphy et al., 1999).

### **Emotional Cognition in HIV Infection**

Despite the fact that a high proportion of HIV-infected individuals exhibit cognitive deficits and emotional dysregulation (e.g., depression), and that some of the neural systems affected in HIV infection are involved in processing of emotional information (e.g., fronto-striatal systems), few studies have assessed emotional cognition in HIV. In a study of emotional attention in HIV infection, Novara et al., (2000) examined 32 HIV infected individuals using an emotional Stroop task that contained emotional words, neutral words, and HIV-related words. These words were also used in a recognition memory task 10 minutes after the administration of the emotional Stroop. Results showed that reaction times were longer for HIV-related and emotional words than for neutral ones. No differences were found between HIV-related and emotional words. The authors concluded that HIV-infected individuals showed an information-processing bias, which was independent of the semantic content of the words. Results for the incidental recognition task showed that HIV-infected individuals demonstrated a greater number of correct recognitions for HIV-related words with respect to neutral words, but not with respect to emotional words.

On a different study of emotional cognition in HIV, U. S. Clark, Cohen, Westbrook, Devlin, and Tashima (2010) examined facial emotion recognition in 50 HIV-infected participants and compared their performance to that of 50 healthy comparison individuals. Results indicate that individuals with HIV demonstrate a general impairment

in emotion recognition abilities, which is driven mostly by specific impairments in the ability to recognize fearful expressions. Furthermore, they observed a relation between emotion recognition abilities and HIV-disease factors, mainly current CD4 counts and anger recognition abilities. The authors concluded that HIV-associated neuropathological changes could be contributing to emotional processing problems among individuals with HIV.

### **Emotional Cognition in Bipolar Disorder**

Studies of emotional attention in individuals with bipolar disorder have reported heterogeneous results. The heterogeneity of these results may be due in part to the different paradigms that have been used to study emotional attention. These paradigms include emotional dot probe tasks, emotional Stroop, and AGNT. For example, a study using an emotional dot probe paradigm in mildly depressed bipolar patients found an attentional bias away from positive and depression-related words (Jongen et al., 2007). In the same study, euthymic bipolar patients showed an attentional bias towards depression-related words and away from positive words.

One of the first studies using the emotional Stroop (Bentall & Thompson, 1990) examined attentional bias in a sample of undergraduate students. Results showed that hypomanic traits were associated with an attentional bias towards depressive, but not euphoria-related words. Kerr, Scott, and Phillips (2005) have investigated the classical and emotional Stroop test and observed generally increased reaction times for all task conditions in manic, depressed and euthymic bipolar patients as well as patients with unipolar depression. In line with these findings, Malhi, Lagopoulos, Sachdev, Ivanovski, and Shnier (2005) found no differential affective interference effect on the emotional

Stroop in remitted bipolar patients as compared to healthy controls, but only significantly dampened cortical and subcortical neural responses to affective versus neutral words.

Other studies of attentional bias, using the emotional Stroop, reported that bipolar patients in either a manic or depressed state displayed greater color-naming interference for depression-related words (Lyon, Startup, & Bentall, 1999). Thus, results from studies of emotional attention using the emotional Stroop have shown that individuals with BD exhibit greater attentional bias toward emotionally-laden stimuli as compared to neutral stimuli; however, no clear mood-congruent biases have been found.

In contrast to the findings on the emotional Stroop, studies using AGNT suggested that depressed bipolar patients were biased towards negative stimuli, while manic patients were biased toward positive stimuli (Murphy et al., 1999). Subsequent neuroimaging studies with this task implicated the subgenual and rostral anterior regions of the cingulate gyrus in these emotional response biases (Elliott et al., 2000, 2002). These studies also found activation of lateral orbitofrontal cortex when inhibiting responses to no-go cues of any valence (Elliott et al., 2004; Elliott et al., 2000, 2002), although this activation was greater for sad than happy cues in patients with depression (Elliott et al., 2002) and mania (Elliott et al., 2004).

Studies of emotional cognition that focused on facial emotion recognition have found that, as compared to healthy individuals, individuals with BD have greater difficulties when recognizing the expression of facial emotion (e.g., Bora et al., 2005; Getz, Shear, & Strakowski, 2003; Lennox, Jacob, Calder, Lupson, & Bullmore, 2004; Rubinow & Post, 1992)

In summary, the review of the literature indicate that both HIV infection and BD are associated with functional and structural abnormalities in the brain circuits involved in the process of emotional stimuli (e.g., pre-frontal striatal, and limbic systems).

Although the mechanisms underlying these functional and structural abnormalities in HIV (i.e., viral infection) and BD (e.g., neurodevelopmental, neurodegenerative processes, (Goodwin, Martinez-Aran, Glahn, & Vieta, 2008) are different, individuals with both conditions may suffer a “double hit” to these brain structures which may exacerbate the cognitive and emotional deficits, and thus put HIV+/BD+ individuals at a higher risk of further cognitive deficits and mood dysregulation.

### **HIV-Transmission Risk Behaviors**

Several studies suggest that HIV-uninfected individuals with BD engage in more risky HIV transmission behaviors than various comparison populations (Hanson et al., 1992; Meade, Graff, Griffin, & Weiss, 2008). Recent evidence suggests that persons with bipolar disorder who are also substance abusing engage in a greater number of risky HIV transmission behaviors as compared to the general population, with recent manic episode, lower psychiatric severity, and greater drug severity as independent predictors of total HIV risk (Meade et al., 2008). Evidence also suggests that individuals with bipolar disorder have significantly higher baseline rates of sexual behavior than do other psychiatric populations (Raja & Azzoni, 2003), and that during manic periods may be particularly prone to engage in sexual behaviors with known intravenous drug users or HIV patients (Volavka et al., 1991). Regarding HIV, it has been reported that although learning of an HIV diagnosis tends to decrease risky sexual behavior, a subset of HIV-infected individuals continue to engage in such behavior after diagnosis (Marks, Crepaz,



Senterfitt, & Janssen, 2005). Interestingly, some researchers have proposed an influence of positive (Gonzalez et al., 2005) and negative affect in risk taking behaviors among individuals infected with HIV, such as HIV+ individuals with negative affect tend to engage more often in HIV-transmission risk behaviors than individuals in a positive affect (McKirnan, Ostrow, & Hope, 1996). Taken together, these findings indicate that, in the context of the comorbidity of HIV infection and BD, HIV+/BD+ individuals may be at a higher risk of HIV transmission. Regarding the processing of emotional information, individuals with negative affect (i.e., depression) appear to have negative cognitions about the self, about the world, and the future, thus, it is possible that they demonstrate a negative attentional bias that contributes to the exacerbation of their negative affect, and this negative affect in turn puts them at higher risk of engagement in HIV-transmission risk behaviors.

### **Preliminary Studies**

Previous studies from our group have shown that HIV+/BD+ individuals have significantly greater rates of global NP impairment, and are impaired in more NP domains than HIV+/BD-. HIV+/BD+ demonstrated greater impairment in the domains of attention, processing speed, fine motor skills, learning, and memory (Moore, Woods, et al., 2006). We decided to further examine the attention domain in these groups, specifically sustained attention given our previous findings, and the literature reports of sustained attention deficits in HIV infection and BD (Posada et al., 2012). Specifically, our study on sustained attention shows significant differences between the HIV+/BD+ individuals (n = 39) and HIV+/BD- individuals (n = 34) were found on accuracy (omission errors), reaction time (hit reaction time), and variability of the response time

(reaction time standard error) on Conner's Continuous Performance Test II CPT-II.

Interestingly, when examining performance of individuals over time in the different mood states (i.e., manic, euthymic, depressive), significant interactions between mood state and time were found indicating that individuals in a manic state had longer reaction times, more variability in their reaction times, and diminished accuracy than individuals in a depressive or euthymic mood state.

We have also examined the processing of emotionally laden stimuli in HIV+/BD+ (n = 29) individuals as compared to HIV+/BD- (n = 29) (Posada et al., 2011). Individuals were administered a modified version of emotional Stroop Test (EST) (Lyon et al., 1999), that included both traditional Stroop conditions and emotional Stroop conditions. Group comparisons were conducted for the time to complete the color-word interference for each of the conditions (sad, happy, and neutral). We also split the whole cohort by their mood state (euthymic, depressed, manic) and compared them on the same variables. The results of the study showed that the HIV+/BD+ and HIV+/BD- groups were not significantly different on the traditional Stroop task; however, HIV+/BD+ individuals had significantly longer time to complete on the neutral condition of the EST than HIV+/BD- individuals. After controlling for neuropsychological impairment, this effect was no longer significant. When examining mood state within the entire cohort, significant group (i.e., euthymic, depressed, manic) differences were found on the happy and neutral conditions, while a trend was observed for the depressed condition. In all three conditions euthymic individuals performed the fastest, while manic individuals had the longer times on the three conditions.

Regarding engagement in HIV transmission risk behaviors, our pilot data suggest increased HIV transmission risk behaviors among HIV+/BD+ persons as compared to HIV+/BD- persons. Specifically, HIV+/BD+ persons (n = 33) reported a significantly greater number of HIV transmission behaviors over the previous 6 months as compared to HIV+/BD- participants (n = 31). Furthermore, our data suggest (although not significant) that HIV+/BD+ persons in a current manic state may be engaging in more risk behaviors than those in euthymic or depressed states.

### **Summary**

Neuropathological, neuroimaging and behavioral studies have shown abnormalities in the fronto-striatal, medial-temporal and limbic systems of HIV infected individuals and also those with BD. These abnormalities appear to underlie the cognitive and emotional regulation deficits reported in HIV infection and BD. Furthermore, these deficits may predispose individuals to engage in HIV-transmission risk behaviors. Despite the high prevalence of HIV among individuals with BD, HIV+/BD+ individuals have remained a largely understudied group, with the exception of studies from our group. Results from these studies indicate that, as compared to HIV+/BD- individuals, HIV+/BD+ individuals exhibit greater general cognitive, and sustained attention deficits, demonstrate greater attentional bias towards emotionally-laden stimuli, and tend to engage in HIV transmission risk behaviors. One limitation of these studies is the lack of two comparison groups: HIV-uninfected individuals with bipolar disorder (HIV-/BD+) and healthy comparisons (HIV-/BD-). Without these two groups, it is not possible to test for interactions between HIV infection and BD, or additive effects of these two conditions.

Therefore, the present dissertation study aimed to account for this limitation by extending the examination of emotional attention to include individuals in the aforementioned groups. The study also aimed to extend the examination of emotional attention using the AGNT. Results from the present study will help clarify the independent effects of HIV infection and BD on emotional attention. It will also help clarify whether HIV+/BD+ individuals may be differentially sensitive to emotionally charged information and process it more or less effectively than neutral information. If this is the case, the ability to attend to intervention information to reduce HIV transmission risk behaviors may be strongly influenced by emotional cognition. Understanding how HIV-infected individuals with comorbid BD process information that has an emotional content, and how the processing of this information relates to risk behavior, could have important implications for the development of interventions that are directed at this specific group of people that are at high risk for HIV transmission.

### **Aims and Hypotheses**

#### **Primary Aim**

To examine performance on the AGNT among HIV+/BD+ as compared to HIV+/BD-, HIV-/BD+, and HIV-/BD- individuals.

Hypothesis 1: It is hypothesized that the effect of BD on performance on AGNT outcome variables will be worse for HIV-infected individuals than for HIV-uninfected individuals.

**Secondary Aim**

To examine, among individuals with bipolar disorder (HIV-/BD+; HIV+/BD+), the role of mood state (euthymic, depressive, hypomanic) on AGNT performance across and within mood states.

**Hypothesis 2.1.** Individuals in a dysregulated mood state (i.e., hypomania, depression) will demonstrate greater attentional bias towards mood congruent stimuli (i.e., happy, sad), as compared to individuals in a euthymic mood state.

**Hypothesis 2.2.** Individuals in a dysregulated mood state (i.e., hypomania, depression) will demonstrate greater attentional bias towards mood congruent stimuli (i.e., happy, sad), as compared to mood incongruent stimuli.

**Exploratory Aim**

To examine the association between the AGNT and self-reported measures of risk behaviors.

Hypothesis 1: Performance on the AGNT will be significantly associated with engagement in HIV-Transmission risk behaviors, and will be an independent predictor of these behaviors than traditional neuropsychological tests.

## Chapter 2: Methods

### **Participants**

We screened 150 participants, enrolled 133 participants, and 125 participants completed the study evaluation. Of the 125 participants, we excluded 5 individuals due to outlier performance on the AGNT (i.e., 3 SD below the group). We examined the performance of 39 HIV-infected individuals with comorbid bipolar disorder (HIV+/BD+), 27 HIV-infected individuals without bipolar disorder (HIV+/BD-), 29 HIV-seronegative individuals with bipolar disorder (HIV-/BD+), and 25 healthy comparisons participants (HIV-/BD-) on the AGNT. Individuals in the HIV+/BD- and HIV-/BD- groups were recruited from among those subjects seen through the various longitudinal studies at the HNRP. The HIV+/BD+ group was recruited exclusively from David Moore's (PI) intervention study ("Electronic Reminders to Improve Adherence among HIV+ Persons, iTAB"). The HIV-/BD+ group was recruited from ongoing bipolar studies at UCSD (e.g., "Structural and Functional Brain Aging in Bipolar Disorder", Lisa Eyler, PI; "Development of a Personalized Real-Time Intervention for Bipolar Disorder", Colin Depp, PI; and "Inhibitory Deficits in Mania" William Perry, PI). For the HIV+/BD+, HIV+/BD-, and HIV-/BD- groups, we utilized data from neuropsychological testing and psychiatric evaluations collected as part of other HNRP studies (e.g., HIV Neurobehavioral Research Center, HNRC; Translational Methamphetamine AIDS Research Center, TMARC, California NeuroAIDS Tissue Network). The HIV-/BD+ group underwent a brief NP examination that included tests for seven cognitive domains, an HIV antibody test to confirm HIV-seronegativity; and clinical psychiatric interview, the Composite International Diagnostic Interview (CIDI, World Health Organization,

1997) to confirm bipolar disorder diagnosis, as well as to assess for substance use history. For the HIV+/BD+ group, confirmation of bipolar diagnosis was done as part of David Moore's iTAB study visit. For all groups, current mood state for severity of manic symptoms was assessed using the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978). The Beck Depression Inventory-II (BDI-II, A. T. Beck, Steer, Ball, & Ranieri, 1996) was used to assess for depressive symptoms. The study protocol was executed in accordance with the standards approved by the University of California, San Diego Human Research Protections Program.

Participants in the HIV+/BD+ and HIV-/BD+ groups were classified into 3 mood state groups (i.e., euthymic, depressed, and hypomanic) depending on their scores on the YMRS and BDI-II. YMRS cut off score for mild manic symptoms has been reported as 12 (Young et al. 1978); however, when using this cut off, only 6 participants met criteria for mania. In order to increase our hypomanic group size we examined the distribution of the data and decided to use a 75 quartile split that yielded 9 as the YMRS cutoff score (Table 1). Participants with scores of 9 or higher on the YMRS were classified as hypomanic or manic; participants with a score of 13 or higher on the BDI-II were classified as depressed; participants with scores lower than those two cut offs for YMRS and BDI-II were classified as euthymic; participants with scores higher than the cutoffs for both YMRS and BDI-II were considered to be on a mixed state and classified under the hypomania group. There were 28 individuals in the depressed group, 27 individuals in the euthymic group, and 13 individuals in the hypomanic group (6 individuals in a mixed episode). How many mixed?

**Table 1.** Proportion of Individuals Classified into Mood Groups

Cut off score	Hypomanic	Depressed	Euthymic
BDI-II > 11, YMRS > 12.	10% (7)	50% (34)	40% (27)
BDI-II > 11, YMRS > 9	19% (13)	41% (28)	40% (27)

Note: BDI-II= Beck Depression Inventory-II. YMRS= Young Mania Rating Scale.

### **Inclusion Criteria**

- English as first language
- Ability to provide informed consent
- 18 years or older at the time of enrollment
- HIV-infected (HIV+/BD+; HIV+/BD-)
- Lifetime or current diagnosis of Bipolar Disorder I or II (HIV+/BD+; HIV-/BD+)

### **Exclusion Criteria**

Exclusion criteria included any conditions that may confound interpretation of findings.

- Neurologic: head injury with loss of consciousness for greater than 1 hour (or resulting in neurologic complications), penetrating skull wounds, brain surgery, active seizure disorder, or other CNS disorders that might affect neuropsychological functioning (e.g., meningitis, stroke, heavy metal poisoning, Parkinson's disease).
- Psychiatric: schizophrenia or schizoaffective disorder.



- Substance abuse: current intoxication as determined by on-site urine toxicology for illicit or prescribed substances, breathalyzer test, and clinical assessment.

## **Measures**

### **Beck Depression Inventory-II**

The BDI-II (A. T. Beck et al., 1996) consists of 21 items to assess the intensity of depression in clinical and normal patients. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression. The BDI-II was used to assess severity of depressive symptoms. A cutoff score of 13 (A. T. Beck et al., 1996) was used to classified participants into depressed or non-depressed.

### **Risk Assessment Battery**

This questionnaire includes two subscales evaluating sex- and drug-related risk behaviors for the 6 months prior to the assessment (Navaline et al., 1994). The 15-item drug-risk subscale generates scores ranging from 0 to 22, and the 9-item sex-risk subscale generates scores ranging from 0 to 18. Higher scores indicate greater overall risk of HIV transmission. Total RAB scores range from 0 to 40. The RAB was used to assess risk behaviors for the 6 months prior to the assessment.

### **Composite International Diagnostic Interview**

The CIDI (World Health Organization, 1997) is a computer-assisted interview and is designed to map onto DSM-IV diagnoses. The CIDI was used to determine current and lifetime psychiatric and substance-related disorders. The CIDI was used to confirm BD diagnosis (BD I, BD II) and substance use disorders.

### **Young Mania Rating Scale**

This interview provides the clinician with behavioral anchors on which to rate the participant, and is widely considered to be the gold standard for the assessment of manic symptoms (Young et al., 1978). Scores range from 0 to 60. The continuous YMRS total score was used to determine the severity of mania symptoms. A cutoff score of 9 was used to classified participants individuals as hypomanic, manic or mixed.

### **Neuropsychological Battery**

A comprehensive neuropsychological battery that met the standard of practice for neuropsychological research in HIV (Butters et al., 1990) was administered to all participants HIV. The approximately 3 hours battery included measures divided into seven domains in the following manner.

**Verbal fluency.** Controlled Oral Word Association Test (COWAT-FAS) semantic verbal fluency (animals; Gladsjo et al., 1999).

**Attention/working memory.** Letter Number Sequencing from the Wechsler Adult Intelligence Scale-III (WAIS-III; Heaton, Taylor & Manly, 2002; Psychological Corporation, 1997).

**Learning.** Hopkins Verbal Learning Test-Revised (HVLN-R; Benedict, Schretlen, Groninger, & Brandt, 1998) Total Trial 1-3 Recall, Brief Visuospatial Memory Test-Revised (BVMN-R; Benedict, 1997) Total Trial 1-3 Recall.

**Memory.** HVLN-R Delayed Recall (Benedict et al., 1998), BVMN-R Delayed Recall (Benedict, 1997).

**Speed of information processing.** Trail Making Test Part A (TMT-A, Heaton, Grant, & Matthews, 1991), WAIS-III Digit Symbol and Symbol Search (Heaton et al., 2002; Psychological Corporation, 1997).

**Executive functions.** Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000); Trail Making Test Part B (TMT-B; Heaton et al., 1991).

**Motor.** Grooved Pegboard Dominant and Non-dominant hand (Heaton et al., 1991; Kløve, 1963).

Raw scores from the measures listed above were converted to demographically-corrected T-scores whenever possible, using the best available normative data, in an effort to minimize the effect of demographic characteristics, such as age, education, sex, and ethnicity, on neuropsychological test performance. An average T-score variable was created as a summary score for the whole NP battery.

A similar AGNT task as described in Elliott et al. (2000) was used in this study. In this task, participants are required to respond to a target word and withhold a response when they are presented with non-target words. There are two types of target words: happy and sad, and 3 types of distractor words: happy, sad, and neutral. There are different experimental combinations containing sad, happy, and neutral words, as well as control conditions where participants must respond to neutral words presented in lowercase and uppercase font. Words were presented on a computer screen. Participants were shown a sequence of words and they were instructed to only respond with a button press to words from one of these conditions. For example, they must press the button

(Go) when presented with happy words, but must not press the button (No-Go) when presented with sad words. There are 6 different conditions in total:

1. Go Happy/No-Go Sad
2. Go Happy/ No-Go Neutral
3. Go Sad/No-Go Happy
4. Go Sad/No-Go Neutral
5. Go UPPER/No-Go lower
6. Go lower/No-Go UPPER

These 6 conditions plus 2 rest conditions equal a single block of the experiment. Each condition consists of: instructions for 3s, countdown for 3s, and the presentation of 20 words for 24s (10 from one condition, 10 from another). Each word is presented for 300ms and a 900ms response time is given. Each condition is therefore 30 seconds long in total. The experiment is presented in 4 blocks, each containing all 6 conditions as well as 2 rest conditions. Each condition is therefore seen 4 times in total across the entire experiment. One block is equal to 6 conditions (180s) plus 2 rest conditions (60s), and is therefore 240 seconds long. The entire experiment is therefore 960 seconds long (16 minutes). The order of trials in each block was pseudo-randomized (Table 2). For each of these 6 conditions, 2 outcome measures were obtained:

- Reaction Time (RT): time to respond to targets in milliseconds
- Correct Responses (CR): response to targets

New variables were created that summarized across conditions for Correct Responses:

- Combined Go Happy: Go Happy/No-Go Sad plus Go Happy/ No-Go Neutral
- Combined Go Sad: Go Sad/No-Go Happy plus Go Sad/No-Go Neutral

**Table 2.** AGNT Block Trials

<b>Block 1</b>	<b>Block 2</b>	<b>Block 3</b>	<b>Block 4</b>
Go Happy, No Sad	Go Sad, No Neutral	Go Happy, No Neutral	Go Sad, No Happy
Go UPPER, No Lower	<i>Rest</i>	Go UPPER, No Lower	<i>Rest</i>
Go Sad, No Neutral	Go Happy, No Sad	Go Sad, No Happy	Go Happy, No Neutral
<i>Rest</i>	Go Lower, No UPPER	<i>Rest</i>	Go Lower, No UPPER
Go Happy, No Neutral	Go Sad, No Happy	Go Happy, No Sad	Go Sad, No Neutral
<i>Rest</i>	Go UPPER, No Lower	<i>Rest</i>	Go UPPER, No Lower
Go Sad, No Happy	Go Happy, No Neutral	Go Sad, No Neutral	Go Happy, No Sad
Go Lower, No UPPER	<i>Rest</i>	Go Lower, No UPPER	<i>Rest</i>
Total target words: 60	Total target words: 60	Total target words: 60	Total target words: 60
Total distractor words: 60	Total distractor words: 60	Total distractor words: 60	Total distractor words: 60

- Combined Control: Go UPPER/No-Go lower plus Go lower/No-Go UPPER
- Combined Emotional: Combined Go Happy plus Combined Go Sad
- Omission Errors Go Happy: no response to targets (combined happy words)
- Omission Errors Go Sad: no response to targets (combined sad words)
- Commission Errors No-Go Happy: response to distractors (combined happy words)
- Commission Errors No-Go Sad: response to distractors (combined sad words)

New variables were created that summarized across conditions for Reaction Time:

- Happy processing: Combined Go Happy (RT) minus Combined Control (RT)
- Sad processing: Combined Go Sad (RT) minus Combined Control (RT)

Worse performance in this task was defined as less correct responses, longer RTs, higher number of omission errors, and higher number of commission errors. Attentional bias in this task was defined as the time to respond to targets (only accurate responses): the faster the response (i.e., shorter RTs), the greater the magnitude of the attentional bias.

### **Procedures**

After providing informed consent to participate, all participants were asked to complete an alcohol breathalyzer and to provide urine for toxicology testing. One participant (HIV+/BD-) tested positive for substances (i.e., methamphetamine). He was rescheduled and completed the study at a later time.

Participants in the HIV-/BD+ group were recruited from ongoing bipolar studies at UCSD (e.g., "Structural and Functional Brain Aging in Bipolar Disorder," "Inhibitory Deficits in Mania," "Development of a Personalized Real-Time Intervention for Bipolar Disorder"). Because these participants were new to the HNRC, individuals in the HIV-/BD+ group were asked to undergo a finger stick procedure to obtain a drop of blood. This blood was used to test for infectious diseases and to confirm HIV serostatus. Additional assessment for this group included self-report questionnaires, and a psychodiagnostic interview to assess for mood and substance use disorder (e.g., CIDI, YMRS).

Individuals in the HIV+/BD-, and HIV-/BD- groups were recruited from other HIV Neurobehavioral Research Program (HNRP) studies (e.g., HIV Neurobehavioral Research Center, HNRC; Translational Methamphetamine AIDS Research Center, TMARC,) and had completed these additional assessments (HIV antibody testing, and

clinical interviews). Authorization for data sharing with other HNRP IRB-approved research projects was obtained in the original consents signed by participants upon enrollment into these studies.

Individuals in the HIV+/BD+ group completed all the assessments (i.e., HIV antibody testing, neuromedical examinations, neuropsychological testing, psychiatric evaluations, and AGNT) as part of their participation in the study “Electronic Reminders to Improve Adherence among HIV+ Persons, iTAB”. Data collected by the iTAB study was combined with data collected in the present study for analysis. Authorization to share data was obtained when participants were enrolled in the study.

## Chapter 3: Data Analytic Plan

### **Statistical Analysis**

All outcome variables were examined for normality and homogeneity of variance as needed (Shapiro–Wilk test, Levene’s Test). Transformations were made or a nonparametric procedure was utilized as needed. Due to multiple statistical comparisons, statistical significance was defined as  $p < 0.01$ .

### **Primary Aim, Hypothesis 1**

HIV+/BD+, HIV+/BD-, HIV-/BD+, and HIV-/BD-, were compared on all the outcome measures of the AGNT. A two-way analysis of variance (ANOVA) was conducted to test for an interaction between HIV infection and bipolar disorder on performance on all the outcome measures. Statistically significant interactions were followed by planned post-hoc analyses using Tukey HSD tests in order to examine the nature of the interactions.

### **Secondary Aim, Hypotheses 2.1 and 2.2**

We conducted a mixed model analysis of variance (ANOVA) with mood state (i.e., euthymic, depressed, and hypomanic) as the between group factor, and condition (i.e., Combined Go Happy, Combined Go Sad, Combined Control) as the within subjects factor. This analysis allowed us to examine an individual’s performance on a specific condition of the AGNT (i.e., Combined Go Happy) as compared to his or her own performance on another condition (i.e., Combined Go Sad). It also allowed us to examine the performance of individuals on a specific mood state (i.e., hypomanic) as compared to individuals on a different mood state (i.e., depressed, euthymic).



### **Exploratory Aim, Hypothesis 1**

We conducted regression analyses to assess the ability of the both AGNT and traditional NP measures to predict engagement in HIV-transmission risk behaviors

#### **Independent Variables**

- Diagnostic groups with four levels: HIV+/BD+, HIV+/BD-, HIV-/BD+, and HIV-/BD-
- Mood states groups (within the HIV+/BD+ and HIV-/BD+ groups): euthymic, depressed, hypomanic

#### **Dependent Variables (Outcome Measures)**

##### **Affective go/no-go task individual variables.**

- Go Happy/No-Go Sad (RT; CR)
- Go Happy/ No-Go Neutral (RT; CR)
- Go Sad/No-Go Happy (RT; CR)
- Go Sad/No-Go Neutral (RT)

##### **Affective go/no-go task combined variables.**

- Combined Go Happy: Go Happy/No-Go Sad plus Go Happy/ No-Go Neutral
- Combined Go Sad: Go Sad/No-Go Happy plus Go Sad/No-Go Neutral
- Combined Control: Go UPPER/No-Go lower plus Go lower/No-Go UPPER
- Combined Emotional: Combined Go Happy plus Combined Go Sad
- Omission Errors Go Happy: no response to targets (combined happy words)
- Omission Errors Go Sad: no response to targets (combined sad words)

- Commission Errors No-Go Happy: response to distractors (combined happy words)
- Commission Errors No-Go Sad: response to distractors (combined sad words)

**Neuropsychological battery.**

- Neuropsychological Battery average T-Score

**RAB.**

- Total score
- Sex: Sex related risk behaviors subscale score
- Drug: Drug related risk behaviors subscale score

## Chapter 4: Results

### **Demographics and Disease Characteristics**

The demographic and clinical characteristics of the study participants are presented in Tables 3 and 4. The study groups were comparable on age and ethnicity. The cohort was predominantly middle-aged Caucasians. Groups were significantly different with regard to gender, with the HIV-/BD+ being predominantly female, while the other three groups were predominantly male. Groups also significantly differed with regards to years of education; on average, the HIV-/BD- completed 3 years of college, HIV-/BD+ 2 years of college, and the HIV+/BD+ and HIV+/BD- groups completed one year of college. Regarding neuropsychological functioning, a significant main effect of BD was found such that the HIV-/BD+ and the HIV+/BD+ groups had a significantly lower average T-scores. Similarly, as expected, the BD groups had a significantly higher proportion of individuals that met criteria for a major depressive episode in their lifetime and a higher number of psychiatric hospitalizations as compared to the non-BD groups. Manic symptoms, as assessed by the YMRS, were mild on average, but significantly higher for the BD groups as compared to the BD- groups, as would be expected. BDI-II scores were minimal for the HIV-/BD- group and HIV+/BD- groups, and mild for the HIV+/BD+ and the HIV-/BD+ groups. Significant differences were also found for alcohol, cocaine, opioid, and methamphetamine lifetime use disorders (abuse and/or dependence), where the HIV-/BD- group had a significantly lower proportion of individuals meeting lifetime criteria for substance use disorder than the other three groups. Regarding current substance use disorders (within the last month), two individuals met criteria for alcohol use disorder (1 HIV+/BD+; 1 HIV-/BD-), two

**Table 3.** Demographic and HIV Disease Characteristics of the Groups

<b>Variable, Mean (SD)</b>	<b>HIV+/BD+</b> <b>(n = 39)</b> <b>a</b>	<b>HIV+/BD-</b> <b>(n = 27)</b> <b>b</b>	<b>HIV-/BD+</b> <b>(n = 29)</b> <b>c</b>	<b>HIV-/BD-</b> <b>(n = 26)</b> <b>d</b>	<b>P values</b> <b>Pairwise</b> <b>comparisons</b>
<b>Descriptive Mean</b> <b>(SD)</b>					
Age	47.7 (11.1)	51.8 (10.9)	45.4 (14.2)	45.6 (15.1)	p = 0.5
Education	13.1 (2.2)	13.0 (5.3)	14.2 (2.2)	15.0 (2.6)	p = 0.02 a,b < d
Gender % male	87	75	43	67	p < 0.01
Ethnicity % white	59	46	74	75	p = 0.2
Average NP T-Score	45.2 (7.5)	51.5 (7.3)	44.6 (6.0)	51.9 (4.7)	p < 0.01 a, c < b, d
NP % Impaired	32 (12)	12 (3)	38 (11)	10 (2)	p < 0.01
% HCV infected	36 (12)	9 (2)	4 (2)	27 (4)	p = 0.08
<b>HIV Disease Mean</b> <b>(SD)</b>					
CD4 Count	681.0 (299.5)	648.1 (296.8)	N/A	N/A	p = 0.9
CD4 Nadir Count	244.6 (198.3)	208.7 (210.3)	N/A	N/A	p = 0.3
HIV RNA plasma (log copies/ml)	1.9 (0.8)	1.9 (0.8)	N/A	N/A	p = 0.6
% AIDS (#)	61 (25)	48 (14)	N/A	N/A	p = 0.3
% ARVs (#)	97.5 (39)	92.3 (24)	N/A	N/A	p = 0.4

*Note:* NP = Neuropsychological; HCV = Hepatitis C virus; ARV = Antiretrovirals

**Table 4.** Psychiatric Characteristics of the Groups

<b>Variable, Mean (SD)</b>	<b>HIV+/BD+</b> <b>(n = 39)</b> <b>a</b>	<b>HIV+/BD-</b> <b>(n = 27)</b> <b>b</b>	<b>HIV-/BD+</b> <b>(n = 29)</b> <b>c</b>	<b>HIV-/BD-</b> <b>(n = 26)</b> <b>d</b>	<b>P values</b> <b>Pairwise</b> <b>comparisons</b>
<b>Descriptive Mean (SD)</b>					
<b>Psychiatric</b>					
Number Psychiatric Medications	2.9 (1.6)	2.2 (1.6)	2.5 (1.7)	0.8 (1.5)	p < 0.01 d < b < c, a
Number Psychiatric Hospitalizations	4.5 (7.6)	0.1 (0.4)	5.5 (9.1)	0.1 (0.2)	p < 0.01 d, b < a, c
YMRS	4.9 (4.6)	1.3 (1.6)	5.1 (4.7)	0.7 (1.0)	p < 0.01 d, b < a, c
BDI-II Total	15.1 (11.1)	8.3 (8.0)	14.2 (12.0)	3.4 (6.0)	p < 0.01 d < b < c, a
Age 1 <sup>st</sup> depressive episode	19 (1.9)	25.0 (2.8)	22.0 (2.1)	34.0 (3.9)	p = 0.3
Age 1 <sup>st</sup> manic episode	26 (1.6)	N/A	24.0 (1.8)	N/A	p = 0.6
<b>Substance Lifetime Abuse/Dependence</b>					
% Alcohol (#)	51 (21)	27 (7)	46 (12)	19 (5)	p = 0.03
% Marijuana (#)	22 (19)	8 (2)	19 (5)	7 (2)	p = 0.6
% Cocaine (#)	34 (14)	12 (3)	27 (7)	4 (1)	p = 0.01
% Opioid (#)	12 (5)	4 (1)	4 (1)	4 (1)	p = 0.3
% Methamphetamine (#)	44 (18)	23 (6)	15 (4)	11 (3)	p = 0.01
% Any substance (#)	83 (34)	50 (13)	58 (15)	27 (8)	p = 0.01

*Note:* YMRS= Young Mania Rating Scale; BDI-II= Beck Depression Inventory-II.

individuals met criteria for cannabis use disorder (1 HIV+/BD-; 1 HIV+/BD-), and one individual met criteria for methamphetamine use disorder (HIV+/BD-). With regard to HIV disease characteristics, no significant differences were found between the two HIV+ groups. Participants in these groups had, on average, normal current CD4 counts and low HIV viral load, which is indicative of well-controlled HIV disease (see Tables 3 and 4).

### **Individual AGNT Conditions**

A two-way ANOVA yielded a significant interaction between HIV and BD on Go Happy/No-Go Sad (CR,  $F_{3, 116} = 3.56, p < 0.01$ ) and Go Sad/No-Go Happy (CR,  $F_{3, 116} = 3.36, p = 0.01$ ). A main effect of HIV approached significance for Go Sad/No-Go Happy (CR;  $F_{3, 116} = 3.36, p = 0.04$ ), Go Sad/No-Go Happy (RT;  $F_{3, 116} = 1.83, p = 0.03$ ), Go Sad/No-Go Neutral (CR;  $F_{3, 116} = 2.61, p = 0.03$ ), and Go Sad/No-Go Neutral (RT;  $F_{3, 116} = 1.97, p = 0.02$ ). However, after controlling for gender, education, and substance use diagnosis, only the significant interaction for Go Happy/No-Go Sad (CR,  $F_{6, 107} = 2.03, p < 0.01$ ) remained. Planned follow-up analyses showed that the HIV+/BD- and the HIV-/BD+ were significantly different from the HIV-/BD-. The HIV+/BD+ did not significantly differ from any other group (see Table 5, Figure 1).

### **Combined AGNT Conditions**

A two-way ANOVA yielded a significant interaction between HIV and BD on the following conditions: Combined Go Happy (CR,  $F_{3, 116} = 3.13, p < 0.01$ ), Combined Go Sad (CR;  $F_{3, 116} = 3.56, p = 0.01$ ) and Combined Emotional (CR,  $F_{3, 116} = 3.65, p < 0.01$ ) conditions. Also, a significant main effect of HIV was found for the Combined Control condition (RT;  $F_{3, 116} = 4.44, p < 0.01$ ). A main effect of HIV approached significance for the Combined Go Happy (RT;  $F_{3, 116} = 2.11, p = 0.02$ ) and the Combined Go Sad (CR;

Table 5. AGNT Individual Variables

Vrb, Mean (SD)	HIV+/BD+ (n = 39) a	HIV+/BD- (n = 27) b	HIV-/BD+ (n = 29) c	HIV-/BD- (n = 26) d	HIV effect	BD effect	Interaction effect	Covariates
Go Happy/No-Go Sad (CR) what are the CR values?	32.1 (5.6)	29.5 (7.7)	31.1 (5.4)	34.6 (3.5)	p = 0.4	p = 0.9	p = 0.01 b, c < d	
Go Happy/No-Go Neutral (CR)	30.6 (6.7)	28.0 (8.8)	28.0 (5.7)	30.3 (4.9)	p = 0.6	p = 0.6	p = 0.2	
Go Sad/No-Go Happy (CR)	33.6 (6.2)	31.4 (8.0)	33 (6.1)	36.7 (3.2)	p = 0.3	p = 1.0	p = 0.04	Education*
Go Sad/No-Go Neutral (CR)	34 (8.8)	32 (6.4)	34 (4.6)	36 (3.3)	p = 0.2	p = 0.7	p = 0.1	

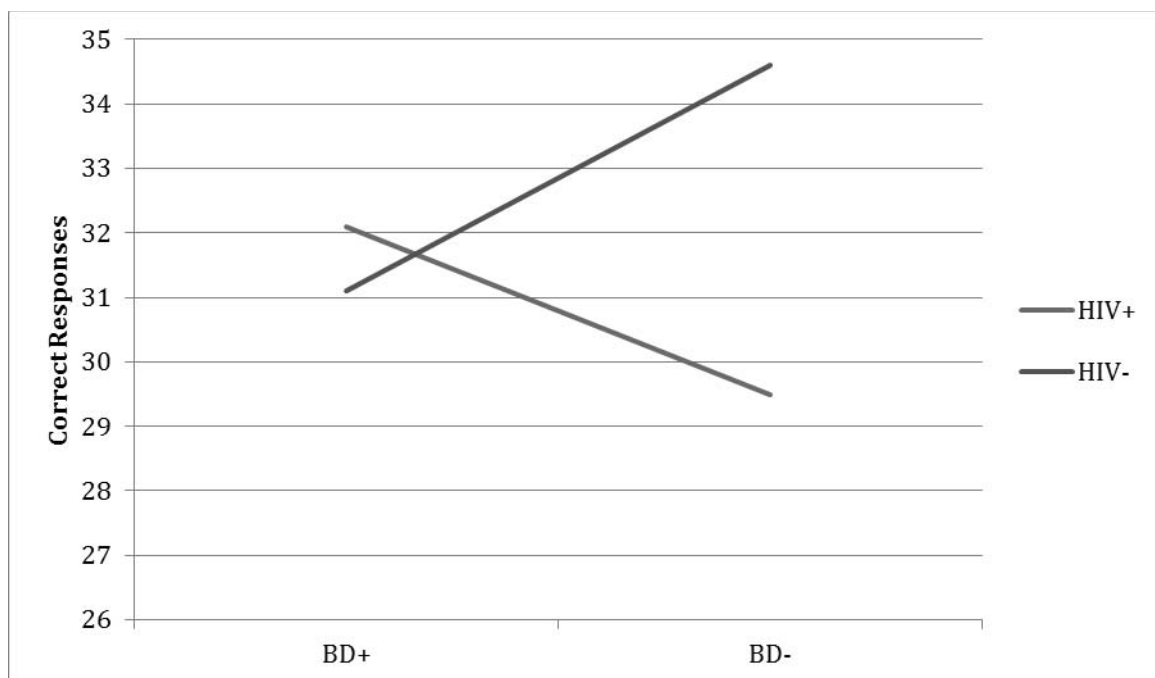
(table continues)

**Table 5.** AGNT Individual Variables, Continued

Go Happy/No-Go Sad (RT)	273.7 (67.5)	276.5 (55.3)	257.3 (78.0)	250.7 (55.6)	p = 0.1	p = 0.7	p = 1.0	
Go Happy/No-Go Neutral (RT)	287.3 (64.8)	288.2 (73.3)	269.0 (83.1)	269.0 (77.7)	p = 0.2	p = 0.8	p = 0.7	
Go Sad/No-Go Happy (RT)	289.2 (68.6)	286.1 (6.4)	266.3 (80.7)	254.7 (63.5)	p = 0.2	p = 0.4	p = 0.9	
Go Sad/No-Go Neutral (RT)	291.4 (72.8)	303.2 (84)	268.6 (77)	262.8 (73.0)	p = 0.06	p = 1.0	p = 1.0	

*Note:* Vrb = variable; SD = standard deviation; CR = Correct Responses; RT = reaction time





**Figure 1.** Significant interaction between HIV and bipolar disorder on the go happy/no-go sad condition (CR) of the AGNT.

$F_{3, 116} = 3.56, p = 0.02$ ). However, after controlling for gender, education, and substance use diagnosis, only the significant interaction for Combined Go Happy (CR;  $F_{6, 107} = 1.87, p < 0.01$ ) and Combined Emotional ( $F_{6, 107} = 2.53, p < 0.01$ ) remained significant at the  $p < 0.01$ . A main effect of HIV was still approaching significance for Combined Go Happy (RT;  $F_{6, 107} = 1.22, p = 0.06$ ) and the Combined Go Sad (CR;  $F_{6, 107} = 2.56, p = 0.06$ ). Of note, education approached significance for Combined Go Sad (CR;  $F_{6, 107} = 2.99, p = 0.02$ ) (see Table 6, Figure 2). No significant interactions or main effects were found for Happy Processing or Sad Processing (see Table 7).

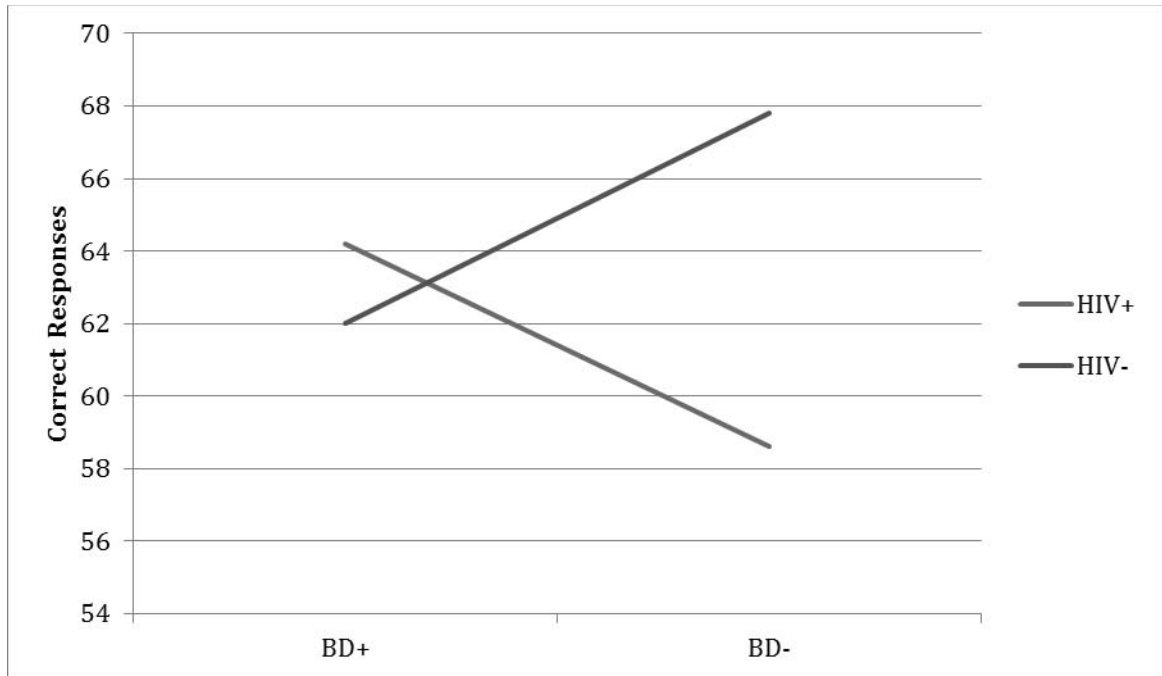
### Omission and Commission Errors

A two-way ANOVA revealed an interaction effect approaching significance for the Omission Errors Go Happy ( $F_{6, 107} = 3.0, p = 0.05$ ) and Omission Errors Go Sad ( $F_{6, 107} = 1.87, p = 0.02$ ) conditions, such that the HIV+/BD- group had significantly greater

**Table 6.** AGNT Combined Variables

Vrb, Mean (SD)	HIV+/BD+ (n = 39) a	HIV+/BD- (n = 27) b	HIV-/BD+ (n = 29) c	HIV-/BD- (n = 25) d	HIV effect	BD effect	Interaction effect	Covariates
Combined Go Happy (CR)	64.2 (11.0)	58.6 (15.6)	62.0 (10.4)	67.8 (5.6)	p = 0.4	p = 0.9	p = 0.01 b, c < d	
Combined Go Sad (CR)	67.6 (11.2)	63.5 (13.0)	67.0 (9.6)	72.8 (5.8)	p = 0.2	p = 0.8	p = 0.05 a, b, c < d	Education*
Combined Control (CR)	29.3 (9.2)	29.8 (9.9)	32.5 (7.9)	33.4 (5.7)	p = 0.2	p = 0.9	p = 0.9	
Combined Emotional	131.8 (20.8)	121.7 (27.3)	129.0 (18.8)	141.6 (8.5)	p = 0.3	p = 0.9	p = 0.01 b, c < d	
Combined Go Happy (RT)	298.8 (129.2)	332.5 (146)	259.7 (85.0)	276.7 (103)	p = 0.06	p = 0.3	p = 1.0	
Combined Go Sad (RT)	281.4 (110.1)	288.5 (104)	289.9 (97)	273.0 (133)	p = 0.7	p = 0.7	p = 0.7	
Combined Control (RT)	159.1 (64)	159.6 (57.4)	145.6 (43.9)	120.0 (47.0)	p = 0.06	p = 0.1	p = 0.4	

Note: Vrb = variable; SD = standard deviation; CR = Correct Responses; RT = reaction time; \*p < 0.05



**Figure 2.** Significant interaction between HIV and bipolar disorder on the combined go happy condition (CR) of the AGNT.

**Table 7.** AGNT RT Variables Combined across all Conditions

Vrb, Mean (SD)	HIV+/BD+ (n = 39)	HIV+/BD- (n = 27)	HIV-/BD+ (n = 29)	HIV-/BD- (n = 26)	P values
Happy Processing	136.9 (114.4)	169.1 (144.5)	119.2 (80.4)	163.5 (89.3)	p = 0.4
Sad Processing	119.5 (113.2)	131.6 (82.7)	149.4 (75.0)	154.6 (120.4)	p = 0.7

Note: Vrb = variable; SD = standard deviation

number of errors than the HIV-/BD- group. In terms of Commission Errors, an interaction effect approached significance for the Commission Errors No-Go Sad condition (i.e., individuals responded to sad words when they were not supposed to;  $F_{6, 107} = 2.90, p = 0.05$ ), such that the HIV-/BD+ had a significantly greater number of Commission Errors than the HIV-/BD- group. Also, a significant main effect of gender was found for this group such that males had significantly more Commission Errors than females (see Table 8).

### **Mood States**

The HIV+/BD+ and the HIV-/BD+ groups were divided into three mood state groups: euthymic, depressed, and manic/hypomanic. A mixed model ANOVA was conducted in order to test for differences between groups and within subjects across the combined AGNT conditions (i.e., Combined Go Happy, Combined Go Sad, Combined Control) for both CR and RT. We also tested for interactions between mood state and condition. Results showed no interactions effects for either CR or RT. A significant main effect of condition was observed for both CR ( $F_{2, 134} = 7.05, p < 0.01$ ), and RT ( $F_{2, 134} = 64.51, p < 0.01$ ) where individuals across all mood states had more correct responses for the Combined Go Sad than for the Combined Go Happy or the Combined Control conditions. In the case of RT, individuals across groups tended to have faster RTs on the Combined Control condition than on the Combined Go Sad or Combined Go Happy conditions. A follow-up analysis comparing the Combined Happy to the Combined Sad for RTs showed no significant effects of mood state. Table 9 shows the mean and standard deviations for the combined variables for the three mood state groups.

**Table 8.** Omission and Commission Errors across Groups

<b>Vrb, Mean (SD)</b>	<b>HIV+/BD+</b> (n = 39) <b>a</b>	<b>HIV+/BD-</b> (n = 27) <b>b</b>	<b>HIV-/BD+</b> (n = 29) <b>c</b>	<b>HIV-/BD-</b> (n = 25) <b>d</b>	<b>HIV</b> effect	<b>BD</b> effect	<b>Interaction</b> effect	<b>Covariates</b>
Omission Errors Happy	15.8 (10.9)	21.4 (15.3)	18.0 (10.4)	11.8 (5.5)	p = 0.4	p = 0.9	p = 0.02 b > d	
Omission Errors Sad	12.4 (11.5)	16.9 (12.9)	13.0 (9.6)	6.5 (4.6)	p = 0.2	p = 0.8	p = 0.05 b > d	Education*
Commission Errors Happy	7.1 (5.5)	7.4 (6.6)	5.1 (4.5)	3.3 (2.5)	p = 0.1	p = 0.6	p = 0.4	
Commission Errors Sad	5.1 (3.8)	6.2 (5.3)	5.1 (3.3)	3.0 (2.4)	p = 0.7	p = 0.3	p = 0.05 c > d	Education* Gender** male > female

*Note:* Vrb = variable; SD = standard deviation; \*p < 0.05, \*\*p < 0.01

**Table 9.** AGNT Variables across Mood States

<b>Vrb, Mean (SD)</b>	<b>Depressed (n = 28)</b>	<b>Euthymic (n =27)</b>	<b>Manic (n = 13)</b>	<b>P value</b>
Combined Go Happy (CR)	64.9 (11.2)	64.8 (8.9)	56.4 (10.8)	p = 0.03
Combined Go Sad (CR)	67.8 (12.2)	68.8 (8.2)	63.6 (10.5)	p = 0.2
Combined Control (CR)	64.0 (13.6)	65.8 (11.9)	55.2 (16.9)	p = 0.1
Combined Emotional (CR)	120.0 (19.8)	133.1 (18.3)	130.8 (3.3)	p = 0.04
Combined Go Happy (RT)	288.7 (131.5)	284.8 (96.0)	262.3 (14.9)	p = 0.9
Combined Go Sad (RT)	277.9 (101.1)	286.5 (96.8)	297.3 (132.1)	p = 0.9
Combined Control (RT)	147.1 (65.6)	151.3 (58.0)	167.9 (45.0)	p = 0.2

*Note:* Vrb = variable; SD = standard deviation; CR=Correct Responses; RT = reaction time

Post hoc correlational analyses between the BDI-II, YMRS and the correct responses for the Combined Go Happy, the Combined Go Sad and the Combined Emotional conditions revealed no significant correlations among the HIV+/BD- and the HIV-/BD+ groups. However, a correlation between BDI-II and the Commission Errors Sad condition approached significance ( $\rho = -0.45, p = 0.02$ ).

### **HIV-Transmission Risk Behaviors**

In terms of HIV-transmission risk behaviors, individuals in the four groups self reported a low rate of engagement in Drug Risk Behaviors; only 6 individuals (4 HIV+/BD+ and 2 HIV+/BD-) reported using drugs in the last 6 months. In terms of Sexual Risk Behaviors, groups were not significantly different in the number of sexual risk behaviors they engaged in (see Table 10). A significant negative correlation between Go Happy/No-Go Sad (CR) and Total Risk Behaviors was found among the HIV-/BD+ group only ( $\rho = -0.44, p = 0.01$ ). Among the HIV+/BD+, a correlation between the

**Table 10.** Risky Behaviors across the Groups

<b>Vrb, Mean (SD)</b>	<b>HIV+/BD+</b> <b>(n = 39)</b>	<b>HIV+/BD-</b> <b>(n = 27)</b>	<b>HIV-/BD+</b> <b>(n = 29)</b>	<b>HIV-/BD-</b> <b>(n = 26)</b>	<b>P value</b>
Drug	0.4 (1.9)	0	0.1 (0.3)	0	p = 0.1
Sex	3.6 (3.8)	2.0 (2.7)	2.1 (2.3)	2.9 (2.2)	p = 0.3
Total	4.0 (4.9)	2.2 (2.6)	2.2 (2.3)	2.9 (2.2)	p = 0.2

*Note:* Vrb = variable; SD = standard deviation

Combined Go Happy (CR) and risk drug behaviors approached significance ( $\rho = -0.37, p = 0.03$ ). No significant correlations were found between mood scales (i.e., BDI-II, YMRS) and self-reported engagement in HIV-transmission risk behaviors.

In an attempt to identify the relative contributions of neuropsychological functioning and emotional attention to the engagement on HIV-transmission risk behaviors, we conducted a regression analysis that included NP average T-scores and the Combined Emotional condition of the AGNT. Results showed that although neither NP nor the Combined Emotional condition were significant: NP ( $F_{2,18} = 3.5, p = 0.04$ ); Combined Emotional condition ( $F_{2,18} = 3.5, p = 0.08$ ).

## Chapter 5: Discussion

The present study sought to examine the performance of a group of HIV-infected individuals with bipolar disorder as compared to individuals with only HIV infection, individuals with only bipolar disorder, and healthy comparison persons on an Affective Go/No-Go Task. Results from this study showed significant interactions between HIV infection and BD on certain specific emotional conditions (i.e., Go Happy/No-Go Sad, Combined Go Happy, Combined Emotional) such that HIV+/BD- individuals and HIV-/BD+ individuals were significantly less accurate on these conditions compared to healthy comparison participants. Individuals dually affected with HIV infection and BD (HIV+/BD+) performed similarly to the HIV+/BD- and HIV-/BD+ individuals and they did not significantly differ from the healthy comparison group.

Contrary to our hypothesis, the dually affected group did not demonstrate a “double hit” effect of HIV and BD on the processing of emotionally-laden information. These results are surprising given that both HIV infection and BD are associated with functional and structural abnormalities in the brain circuits involved in the processing of emotional stimuli (e.g., pre-frontal striatal and limbic systems). Several possibilities may explain these results: First, it may be that one of the illnesses somehow “neutralizes” the other, thus a double hit is prevented. Results from our study suggest that, although not significantly, the BD only group was more accurate than the HIV only group on the Combined Go Happy and Combined Go Sad conditions. Thus, BD, to some extent, may be facilitating the processing of emotional information in the dually affected group. The facilitation of this processing may be mediated by an overactive limbic system, specifically an overactive amygdala (Cerullo, Adler, Delbello, & Strakowski 2009; Chen,



Suckling, Lennox, Ooi, & Bullmore, 2011; Wessa & Linke, 2009). A proposed model of the cognitive control of emotion focuses on interacting bottom-up and top-down systems. The bottom-up system is responsible for emotional appraisal and centers on the amygdala and striatum. Meanwhile, the top-down system exerts cognitive or regulatory control and depends on prefrontal structures (Ochsner & Gross, 2005). Therefore, if striatal circuits are affected in HIV, these individuals may have more problems processing the emotionally-laden stimuli, but among individuals with both illnesses, an overactive amygdala, such as the one in BD, may compensate for these deficits.

Second, it is possible that unknown factors that are inherent to the fact of having both illnesses, somehow prevents these individuals from taking a “double hit” to the specific brain regions responsible for emotional processing. For example, it may be possible that the different medications used to treat both HIV (i.e., antiretrovirals) and BD (i.e., psychotropics) may interplay and have an effect that facilitates the attentional processing of emotionally-laden stimuli.

Third, it is also possible that because these individuals have increased demands in managing both illnesses, they have developed cognitive strategies and/or recruited neural systems that prevent them from developing further deficits. Furthermore, because they have to medically treat both illnesses, individuals with HIV and comorbid BD may receive better health care, which in turn, may translate into less severity of each condition (although this is probably only true for the dually affected persons who find their way into a research study). This hypothesis is supported by the results of our study in terms of disease characteristics that show rather healthy groups with regards to HIV disease and mood symptoms. Related to this, it could also be that having both conditions made

individuals more aware of their mortality risks, and thus, they take better care of themselves (i.e., better medication adherence, healthier diets, more exercise), which in turn may translate into better brain functioning. Last, there is the possibility that unknown factors, which were not measured in the current study, may account for the lack of “double hit” in this group of HIV+/BD+ individuals.

Lastly, the lack of a “double hit” finding may be the result of Type II error. As a way to avoid the risk of Type I error, we choose a conservative significance level ( $p < 0.01$ ), which could have resulted in failure to reject the null hypothesis (i.e., no significant differences between the groups on AGNT variables). Furthermore, the study had enough power to detect medium effect sizes, and indeed the effect size between HIV+/BD+ and HIV-/BD- on Combined Emotional was medium (i.e., 0.7), therefore, it is possible that there exists a “double hit” effect, but the conservative design of the study prevented us from finding it.

In terms of accuracy, worse performance on the AGNT was expected for both the HIV-/BD+ and the HIV+/BD- groups as compared to the HIV-/BD- group. It has been reported in the literature that, in general, individuals with BD have difficulties processing the emotional meaning of words. Although, the most highlighted finding from previous studies is a mood congruent bias (Elliot et al., 2001, 2004; Murphy et al., 1999), some of the studies have reported worse accuracy of bipolar individuals in different mood states for emotionally-laden words (Murphy et al., 1999). Regarding HIV, less is known about the attentional processing of emotional information among HIV-infected individuals with the exception of two recent studies of HIV-infected individuals that examined facial emotion recognition. U. S. Clark et al., (2010) showed that individuals with HIV

demonstrate a general impairment in emotion recognition abilities, which is driven mostly by specific impairments in the ability to recognize fearful expressions. Lane, Moore, Batchelor, Brew, and Cysique (2012) also examined facial emotion recognition and demonstrated mild deficits in processing of emotional facial expression among HIV individuals. Thus, although emotional attentional processing has not been extensively studied, the results of the present study are, to a certain point, consistent with previous studies that showed deficits in emotional processing among individuals with BD, as well as HIV-infected individuals.

In terms of reaction time, although not statistically significant, it appears that HIV infection has a slightly stronger effect on performance on the AGNT as compared to the other 3 groups. Individuals with HIV were slower at processing both happy words as well as the perceptual features of the words. These findings are in line with several studies that have consistently showed slower reaction times to neutral stimuli in HIV infection when compared to HIV-negative individuals (e.g., Ettenhofer et al., 2010; Hardy & Hinkin, 2002; Heaton et al., 1995; Karlsen, Reinvang, & Froland, 1992). The proposed etiology for slow reaction times in this population appears to be the result of frontal-subcortical dysfunction associated with the progression of illness (Cysique, Maruff, & Brew, 2006).

Importantly, this is the first study to examine emotional attention using the AGNT in this particular population of HIV infected individuals with comorbid bipolar disorder. To our knowledge only one previous study has assessed the attentional processing of emotionally-laden information in this group. This study, from our group (Posada et al., 2011), used the Emotional Stroop and found no differences between a HIV+/BD+ group and a HIV+/BD- group in the time the individuals took to complete the Color-Word

interference card for either the emotional conditions (happy and sad) or the neutral condition. Results from the current study are somewhat consistent with the results from this previous study in that there are no significant differences in the time individuals, across the groups, take to process either emotional or neutral information. However, it is important to recognize that although both tasks measure attention, different constructs are assessed by these two tasks. The emotional stroop assesses the ability to inhibit emotionally-laden stimuli and the interference effect that occurs in naming the print color of an emotionally-laden word; longer times naming the colors indicate a greater interference effect. In the AGNT, attention is automatically captured by the emotional salience of the words, thus shorter reaction times indicate greater attentional bias. Thus, the present study contributes to the understanding of emotional attention among HIV infected individuals with comorbid bipolar disorder by showing how both HIV and BD have an independent effect on the accuracy of processing of information that is emotionally-laden, as well as, providing evidence of a negative attentional bias among individuals with BD independent of their mood state. .

Interestingly, no significant differences were found between groups on the control condition, which represents a traditional Go/No-Go paradigm without an emotional component; that is, individuals are asked to respond to an emotionally neutral target (i.e., UPPER case letters) and withhold a respond to an emotionally neutral distractor (i.e., lower case letters). As described above, attentional deficits have been described in both HIV infection and bipolar disorder independently when compared to healthy comparisons. Attention in these groups has been assessed using different types of tasks including sustained attention, selective attention, divided attention, and response

inhibition among others. What is common to all these tests is that they utilized neutral stimuli. The AGNT examined attentional processing of emotionally-laden information by comparing emotional conditions to a control condition that does not require the processing of the meaning of the words, therefore, placing less attentional demands. In the present study results showed that differences between the groups were found only on the emotional condition but not on the control condition, indicating that AGNT is capturing attentional processes that are not captured by more traditional attentional tasks that use neutral stimuli. These results provide further evidence that accuracy deficits in the AGNT are the result of deficits in processing information that is emotionally laden and not the result of general attention deficits. In fact, a small correlation that approached significance was found between Combined Emotional and the T-score for Speed of Information Processing domain ( $\rho = 0.23, p = 0.02$ ), but not between Combined Emotional and the T-score for the Attention domain ( $\rho = 0.11, p = 0.2$ ).

In an attempt to identify the type of errors that were decreasing accuracy on the AGNT, we examined Omission and Commission errors across the groups. Results showed interactions that approached significance between HIV and BD on the Omission Errors Go Happy, and the Omission Errors Go Sad conditions, such that HIV+/BD- individuals made a significantly larger number of Omission Errors as compared to healthy comparisons. For Commission Errors, an interaction approached significance on the Commission Errors Go Sad such that the HIV-/BD+ group made more errors than the healthy comparison participants. These results indicate that the accuracy deficits found may be the results of decreased target detection rather than impulsivity (i.e., inability to inhibit a response). These target detection deficits could be the result of inattention,

and/or inability to recognize the emotion of the word, as previous studies of emotion recognition have found emotion recognition deficits among HIV infected individuals (U. S. Clark et al., 2010, Lane et al., 2012). Previous studies of sustained attention have shown target detection deficits in BD (L. Clark & Sahakian, 2005; see L. Clark & Goodwin, 2004 for a review) but not in HIV (Damos, John, Parker, & Levine, 1997; Karlsen et al., 1992). Previous findings from our group showed differences on Omission rather than Commission errors (Posada et al., 2012) between a group of HIV+/BD+ and a group of HIV+/BD-. However, the previous study of sustained attention showed that the HIV+/BD+ group was less accurate and made more Omission errors than the HIV+/BD- group, which is the opposite of the current study findings. The contrasting results between the two studies may be due to the type of stimuli used (i.e., neutral vs. emotional). However, further examination of sustained attention among HIV+/BD+ individuals using both type of stimuli is necessary to support this hypothesis.

The present study also aimed to examine mood congruent attentional bias among individuals with bipolar disorder independent of their HIV status (i.e., HIV-/BD+, HIV+/BD+). Contrary to our hypotheses, no mood congruent biases were found in the depressive, hypomanic and euthymic groups. Results showed that, regardless of mood state, individuals are faster at processing the perceptual features of neutral words than at processing positive or negative meanings of the words. These results are not surprising given that attention is automatically captured by the perceptual features of the words (i.e., UPPER CASE vs. lower case words), there is no reading or processing of the meaning of the words. However, when reaction times for Combined Go Happy and Combined Go Sad conditions were compared, no differences were found either. These findings are

inconsistent with several reports of mood congruent bias shown on the AGNT among persons living with bipolar disorder. These previous studies suggested that depressed bipolar patients were biased towards negative stimuli, while manic patients were biased toward positive stimuli (Elliot et al., 2000, 2002; Garcia-Blanco, Perea, & Livianos, 2013; Murphy & Sahakian, 2001; Murphy et al., 1999). However, many of these studies have been done in individuals on inpatient units that are in exacerbated mood states (i.e., moderate to severe depression and mania). It is possible that the failure to detect mood congruent bias in the present study is the result individuals with bipolar disorder not being in an exacerbated mood state. As described above, both the BDI-II and YMRS average scores were in the mild end of the spectrum. Thus, the severity of the mood symptoms may not have been enough to enable the individuals' attention to be automatically drawn towards stimuli congruent with their current mood state.

Alternatively, it is possible that our group of individuals with bipolar disorder does not demonstrate a mood congruent attentional bias. One study of bipolar disorder individuals in a depressive state failed to find mood congruent bias (Rubinsztein, Michael, Underwood, Tempest, & Sahakian, 2006); similarly, studies of emotional attention using the emotional Stroop test have shown that individuals with BD exhibit greater attentional bias toward emotionally-laden stimuli as compared to neutral stimuli; however, no clear mood-congruent biases have been found (Lyon et al., 1999; Malhi et al., 2005).

Although attentional bias are measure in terms of reaction times (i.e., faster RTs, greater attentional bias), we decided to also examine accuracy among the BD+ groups to understand if mood state facilitates accuracy. Results from the study showed that mood state did not have a significant effect on accuracy; however, individuals in the

HIV+/BD+ and HIV-/BD+ were more accurate at responding to negative (i.e., sad) information than positive (i.e., happy) information, or the features of the words (i.e., UPPPER vs lower case). This is surprising given the fact that the control condition imposed less demands on attention because it did not require the processing of the meaning of the words. It is possible the negative information is more salient and thus automatically processed. Previous studies have shown attentional bias towards negative information but only in depressed individuals (in both unipolar and bipolar depression), and attentional bias towards positive information among euthymic individuals and bipolar individuals in a manic mood state. In the present study, no significant correlations between the AGNT condition and symptoms of depression or mania were found. Therefore, the negative attentional bias is not necessarily mood congruent. However, all the BD individuals in the current study have experienced at least one depressive episode in their lives. Depression has long been associated with a pattern of cognition biased toward negative information, with depressed individuals showing a tendency to attend to, and remember negative stimuli more than do controls (Leppanen, 2006). Furthermore, negative biases have been hypothesized to have a role in the etiology and maintenance of depression (A. T. Beck, Rush, Shaw, & Emery, 1979). Therefore, it is possible that negative attentional bias is not state dependent but a trait that may predispose individuals to further depressive episodes.

Regarding engagement in risk behaviors, in general, individuals in the study did not engage in many risk behaviors during the six months previous to the evaluation. This may be the result of a selection bias given that some of the studies from which the individuals were recruited had stricter exclusion criteria regarding substance use, which



also explains the low rate of drug related risk behaviors. Also, individuals who voluntarily participate in research may be more stable, less symptomatic, and therefore not likely to engage in many risk behaviors. However, other demographic factors such as age (i.e., being an older cohort) may have contributed to the lower engagement in risk behaviors. Additionally, the fact that half the cohort already has HIV may make these individuals engage in fewer risk behaviors as studies have shown that after diagnoses, HIV+ individuals tend to engage in less HIV-transmission risk behaviors (Gonzalez et al., 2005).

Although not significant, there was a trend showing that the HIV+/BD+ group engaged in more sex risk behaviors than the other three groups. Associations between processing of emotional words and engagement in risk behaviors were found for the HIV-/BD+ group and the HIV+/BD+ group such that worse accuracy when processing positive words is associated with greater engagement sex risk behaviors. No associations were found between severity of mood symptoms and engagement in HIV-transmission risk behaviors. These results are consistent with results from previous studies from our group that suggest increased HIV transmission risk behaviors among HIV+/BD+ persons when compared to HIV+/BD- persons. However, our previous study suggested that HIV+/BD+ individuals in a hypomanic state engage in more sex risk behaviors. Also, previous studies have shown that BD individuals in a manic state tend to engage in greater number of risky HIV transmission behaviors when compared to the general population (Meade et al., 2008). Results from the current study are puzzling given the fact that we found no associations between mania symptoms and risk behaviors. Given the fact that studies have shown mood-congruent attentional bias among BD individuals

in a manic state, it would be expected that greater engagement in HIV-transmission risk behaviors would be associated with better processing of positively-laden information in this population, but our results show the opposite pattern. However, it may be that these behaviors are not necessarily related and further research with individuals that engage in more risky behaviors is necessary to draw conclusions. Regarding neuropsychological functioning, it appears that it is a better, although not significantly independent, predictor of engagement in HIV-transmission risk behaviors as compared to performance on the AGNT. These results are consistent with previous studies that showed that cognitive dysfunction, specifically executive dysfunction is associated with risk taking behaviors (Anand, Springer, Copenhaver, & Altice, 2010).

Several limitations of the present study must also be acknowledged. The sample size of the present study is relatively small and the groups were not well matched in terms of demographic factors; especially education. Some significant interaction and main effects did not hold after controlling for education. It is possible that some of the words used in the experiment were difficult to interpret for individuals with low levels of education. However, identifying and engaging HIV-infected people with co-occurring severe mental illness in research is difficult and, taking this into account, our sample of prospectively assessed HIV+/BD+ is actually one of the largest of its kind. More importantly, this is the first study that examines emotional attention in HIV and bipolar disorder. Another limitation of the present study is the lack of a Go-Neutral condition to compare processing of emotional meaning to processing of emotion-neutral semantic meaning, therefore, we cannot conclusively say that individuals in this study processes

emotionally-laden information either more or less efficiently than they process neutral information.

Future studies that aim to better understand emotional attention in HIV and bipolar disorder should include demographically matched groups as well as individuals with greater severity of mood symptoms (i.e., depression and mania). Also, future studies using the AGNT should include a Go-Neutral condition that allows to better determine whether the processing of emotionally-laden information is more or less efficient than the processing of emotion-neutral information in this specific population. Importantly, functional imaging studies could shed light on the specific fronto-striatal and limbic systems underlying the processing of emotionally-laden information in persons with HIV and bipolar disorder. These studies would be key in order to understand the interplay between limbic and prefrontal systems, and confirm or disprove the hypothesis that an overactive limbic system facilitates the processing of emotional information among HIV-infected individuals with a comorbid bipolar disorder.

Finally, interventions aimed at preventing HIV-transmission risk behaviors should take into consideration the processing of emotionally-laden information in individuals with HIV and bipolar disorder. Results from the current study indicate that individuals with these illnesses process negative information more accurately than positive information. Thus, interventions should highlight the consequences of engagement in HIV-transmission risk behavior using negatively-laden words. That is, presenting this information in a “loss-frame,” highlighting the costs of engagement in risk behaviors rather than highlighting the benefits of not engaging in risk behaviors (i.e., “gain-frame”). However, when dealing with individuals in a manic state, it may be more effective to use

positively-laden language as the literature has shown their attention is better captured by positively laden words. Health care professionals interacting with this population should be aware that cognitive impairment may put them at higher risk of engagement in HIV transmission risk behaviors.

Overall, our findings complement and expand upon the results of previous studies by highlighting the independent effects of HIV infection and bipolar on the processing of emotionally-laden information, and the fact that having both illnesses does not disproportionately affect the processing of this type of information. The less accurate processing of emotionally-laden information does not appear to be the result of attention or processing speed deficits but the result of difficulties processing the emotional meaning of the words. In this sense, the AGNT captures information processing deficits that go beyond what is captured by attention tasks that use neutral stimuli. Lastly, it appears that increased difficulties processing positive words may lead to greater engagement in sex risk behaviors; however, global cognitive functioning, as measured by traditional neuropsychological tests, appeared to be a better predictor of engagement in HIV-transmission risk behaviors than emotional attention.

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