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Peripheral inflammation, physical activity, and cognition in bipolar disorder

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

in

Clinical Psychology

by

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2018



The Dissertation of Sheena Isha Dev is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California San Diego

San Diego State University

2018

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## ABSTRACT OF THE DISSERTATION

Peripheral inflammation, physical activity, and cognitive performance in bipolar disorder

by

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Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2018  
San Diego State University, 2018

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**Rationale:** Bipolar disorder (BD) is associated with deficits in executive functions and processing speed, yet little is known about risk factors that contribute to the development and sustainment of these deficits. Studies have demonstrated chronic inflammation, characterized by high levels of pro-inflammatory interleukin-6 (IL-6) and C-reactive protein (CRP), and reduced physical activity in BD. Both chronic inflammation and low physical activity are linked to cognitive deficits in other clinical populations, though less is known about these associations in BD. The current dissertation project proposed to a) explore associations between cognition, inflammation and physical activity in BD; and b) examine potential lagged influences between

variable mood symptoms, a primary clinical feature of BD, and the amount of daily physical activity exhibited.

**Design:** Thirty-eight BD and 68 healthy comparison participants underwent psychiatric interview, neuropsychological assessment of executive functioning and processing speed, and a 15ml blood draw analyzed for blood serum concentration of IL-6 and CRP. For the following two weeks, participants submitted thrice-daily mood ratings on a smartphone device and wore an actigraphy watch designed to measure physical activity. Linear regression analyses determined associations between inflammation, cognition, and physical activity. Mixed effects linear regression determined the impact of mood on subsequent levels of physical activity.

**Results:** BD patients exhibited worse executive functioning and processing speed, less physical activity, and greater levels of IL-6 and CRP; higher BMI in the BD group appeared to explain group differences in inflammation and physical activity. There were no significant associations between inflammation, physical activity, and cognition in BD. Further, mood ratings did not predict subsequent levels of physical activity exhibited by BD individuals.

**Conclusion:** This study is among the first to examine relationships between inflammation, physical activity, and cognition in BD. Results suggest that inflammation and physical activity are not significant correlates of cognition in middle-aged BD individuals, and daily mood ratings do not predict next-day physical activity. Future studies are needed to better understand individual differences in cognitive performance in BD, as well as associations between inflammation and physical activity, in order to develop targeted treatment strategies aimed to reduce functional disability in this population.

## **I. Background**

Bipolar disorder (BD) is a disabling mental illness characterized by alternating manic, depressive and remitted mood states, and is estimated to affect 2.6% of the population (Kessler et al., 2005). In addition to affective dysregulation, patients typically experience poorer physical health, a higher rate of co-morbid medical diseases, and a shorter life expectancy (Laursen et al., 2013; SayuriYamagata, Brietzke, Rosenblat, Kakar, & McIntyre, 2017). A growing body of evidence has demonstrated greater prevalence of cardiovascular disease (CVD), diabetes and metabolic syndrome in this population (Crump, Sundquist, Winkleby, & Sundquist, 2013). In addition to psychiatric and medical co-morbidities, patients with BD also experience some cognitive impairment, and neuropsychological studies have highlighted a heterogeneous cognitive profile (Burdick et al., 2014). Burdick et al. (2014) identified three sub-groups comprised of cognitively intact, moderately impaired, and globally impaired patients, suggesting that some individuals with BD are more at risk to develop cognitive impairments while others remain cognitively unimpaired. However, less is known about which psychiatric or physical health factors may contribute to these differences. Although a relatively nascent area of interest, researchers investigating modifiable risk factors for cognitive impairment have identified vascular health as one potential treatment target to mitigate cognitive decline both in BD (Dev & Eyler, 2017; Gildengers et al., 2010) and in psychiatrically healthy populations (van der Flier et al., 2018). Two such predictors of vascular health, chronic inflammation and levels of physical activity (PA), have been shown to be associated with cognition in several clinical populations, but little is known about the relationships between inflammation, PA, and cognition in BD.

Among BD patients with cognitive deficits, meta-analyses have demonstrated that impairments in executive functions (EF), processing speed (PS), sustained attention, and verbal

learning persist even during euthymia (Bora, Yucel, & Pantelis, 2009; Bourne et al., 2013; Kurtz & Gerraty, 2009; Robinson & Ferrier, 2006; Torres, Boudreau, & Yatham, 2007). Among these domains, EF and PS have been relatively well studied and are of particular interest given literature demonstrating associations with vascular health and functional ability in BD. In terms of EF, BD patients perform worse on tasks of inhibitory control and mental flexibility compared to their psychiatrically healthy peers (Dev et al., 2015; Erol, Kosger, Putgul, & Ersoy, 2014). For example, Erol et al. (2014) examined 25 BD and 25 HC participants and reported that the BD group performed significantly worse on the Stroop task specifically designed to measure response inhibition. Response inhibition has also been linked to functional outcomes, and one study reported that poorer baseline response inhibition predicted lower scores on the Functioning Assessment Short Test one year later in a sample of 35 euthymic bipolar patients (Martino et al., 2009). Studies have also highlighted moderate effect sizes for PS impairment among BD patients (Bora et al., 2009; Kurtz & Gerraty, 2009). Indeed, our own group has demonstrated slower PS in euthymic BD patients compared to healthy counterparts (Dev et al., 2017). Thus, tasks of EF and PS appear to be particularly vulnerable to bipolar pathology, though more studies are needed to determine the underlying mechanism driving the development and sustainment of these cognitive deficits. Importantly, impairments in these domains are also seen among psychiatrically healthy individuals with elevated vascular risk (Frances, Sandra, & Lucy, 2016), and it is possible that there may be some overlap in the pathophysiology driving these changes in those with and without BD.

### **Vascular health in BD**

Patients with BD are more likely to develop CVD and are typically diagnosed with CVD at an earlier age than those without the disorder (Goldstein, Kemp, Soczynska, & McIntyre,



2009; Kilbourne et al., 2004; Murray, Weiner, Prabhakar, & Fiedorowicz, 2009). Further, standardized mortality rates from CVD are much higher in BD patients when compared to patients with schizophrenia (SCZ) and healthy controls (Morriss & Mohammed, 2005; Murray et al., 2009). Several indices of CVD and atherosclerosis have been previously shown to be compromised earlier in BD patients, including altered heart rate variability, pulse wave velocity, and augmentation index (Cohen et al., 2003; Henry, Minassian, Paulus, Geyer, & Perry, 2010; Lee, Kim, Hong, & Joo, 2012; Migliorini, Mendez, & Bianchi, 2011). There is also evidence of cerebrovascular risk in this population, and many neuroimaging studies have demonstrated altered levels of cerebral blood flow (Bhardwaj, Chakrabarti, Mittal, & Sharan, 2010; Culha et al., 2008; Takeuchi et al., 2011) as well as greater white matter abnormalities in bipolar brains (Barysheva, Jahanshad, Foland-Ross, Altshuler, & Thompson, 2013; Wessa et al., 2009). Among these studies, those that investigated medication effects reported none. Thus, an increased vascular burden appears to be a documented key physiological feature of the disorder.

A small body of evidence has recently highlighted the negative impact of an increased vascular burden on cognition in bipolar disorder. BD individuals with a greater number of vascular risk factors demonstrate worse performance on neuropsychological tasks of attention, memory, and verbal fluency (Schouws, Stek, Comijs, & Beekman, 2010), and the possession of vascular risk factors is associated with worse age-related performance decline on inhibitory tasks (Dev & Eyler, 2016). Similarly, greater stroke risk on the Framingham Stroke Risk Profile is associated with worse scores on the Dementia Rating Scale memory subscale among older adults with BD (Gildengers et al., 2010), and BD patients with obesity and hypertension perform worse on tasks of PS, EF, attention, and verbal learning (C. A. Depp et al., 2014). Neuroimaging findings support the relationship of cerebrovascular health with cognitive performance; studies

have shown that alterations in white matter integrity and cerebral blood flow are associated with deficits in verbal fluency and response inhibition, respectively (Bauer et al., 2015; Dev et al., 2015). Thus, it appears that altered vascular health may, in part, be responsible for some of the cognitive impairment observed in this population. Future interventions targeting vascular health could serve to mitigate both the physical and cognitive consequences of this disorder. However, the current literature has emphasized markers of accumulated vascular burden (i.e., white matter pathology, atherosclerosis, diabetes), which represent vascular pathology that has already developed from chronic vascular risk. More studies are needed to identify earlier candidate markers of vascular risk that may be used as potential treatment targets before more significant vascular disease has the opportunity develop in BD.

**Inflammation in bipolar disorder.** Chronic low-grade inflammation has been associated with increased vascular risk, and is implicated in pathways contributing to the future development of hypertension, atherosclerosis, and ischemic stroke, as well as accumulated vascular burden leading to metabolic syndrome (Hotamisligil, 2006; Legein, Temmerman, Biessen, & Lutgens, 2013; Libby, Ridker, & Hansson, 2011; Zhou, Han, Gong, Man, & Fan, 2016). Interleukin (IL) – 6 and C-reactive protein (CRP) are released into blood circulation in response to immune activation or in chronic inflammation (Brocker, Thompson, Matsumoto, Nebert, & Vasiliou, 2010; Thompson, Pepys, & Wood, 1999). Both IL-6 and CRP have been identified as emerging “nontraditional” biomarkers of vascular risk, and CRP in particular has received considerable attention for its ability to independently and reliably predict future risk of CVD and stroke (de Ferranti & Rifai, 2007; Ridker, 2016). The direct role of IL-6 and CRP in vascular health remains to be fully elucidated, though more recent work has suggested that these biomarkers may play an active role in the atherosclerotic process (de Ferranti & Rifai, 2007).

Specifically, the presence of inflammatory markers near the endothelial layer of the blood vessel triggers a complicated chain of pathophysiological reactions culminating in additional immune cell infiltration and pathological changes to the vessel wall (i.e., edema, dilation, etc.). This prolonged process ultimately leads to atherosclerosis, characterized by the build-up of plaque and weakening of the vessel wall (Ammirati, Moroni, Norata, Magnoni, & Camici, 2015).

Mounting evidence has implicated overactive inflammatory processes in bipolar disorder (Berk et al., 2011; Goldstein et al., 2009; Hamdani, Tamouza, & Leboyer, 2012). Together, these studies have described an abnormal inflammatory profile most consistently characterized by higher levels of pro-inflammatory IL-6 (Brietzke et al., 2009; Hope et al., 2009; Kim, Jung, Myint, Kim, & Park, 2007; O'Brien, Scully, Scott, & Dinan, 2006; Ortiz-Dominguez et al., 2007), CRP (De Berardis et al., 2006; De Berardis et al., 2008; Hope et al., 2011) and TNF- $\alpha$  (Brietzke & Kapczinski, 2008; Kim et al., 2007; Munkholm, Vinberg, & Vedel Kessing, 2013; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007) and decreases in anti-inflammatory IL-10 (Kapczinski et al., 2011; Kauer-Sant'Anna et al., 2009) in patients compared to age and education matched healthy controls. Notably, inflammation is observed in adolescents with BD prior to developing CVD risk (Hatch et al., 2017), indicating that CVD burden may develop subsequent to chronic inflammation. Elevations in CRP in adult BD patients are related to several vascular risk factors, including BMI, waist circumference, and the presence of metabolic syndrome (Marshe et al., 2017). Thus, those inflammatory markers, particularly IL-6 and CRP, implicated in vascular health have also been demonstrated to be dysregulated in bipolar disorder, suggesting the potential for a common pathway contributing to the pathophysiology of the disorder.

The role of inflammation in brain health and cognition has only recently begun to be explored. Among those without mental illness, elevated IL-6 and CRP are associated with cognitive impairment and linked to an increased risk of future cognitive decline and onset of dementia (Krabbe, Pedersen, & Bruunsgaard, 2004; Laurin, David Curb, Masaki, White, & Launer, 2009; Ownby, 2010). It has also been suggested that the presence of a chronic, low-level inflammatory state may explain individual variability in cognitive performance among vulnerable psychiatric populations (Hope et al., 2015; Rosenblat et al., 2015). To date, only a few research groups have investigated this relationship in BD. These studies present some preliminary evidence to suggest a link between inflammation and cognitive performance (Bauer, Pascoe, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014). One study reported that elevations in blood serum CRP was associated with worse immediate memory, language, and attention in a sample of 107 BD patients (Dickerson et al., 2013). Another linked elevations in both IL-6 and CRP to worse performance on measures of attention, PS, EF, and memory in combined samples of BD and SCZ (Misiak et al., 2018). Thus, there is some indication that higher blood serum levels of inflammatory biomarkers may be related to cognitive performance, but more studies are needed to further characterize which aspects of one's inflammatory profile most impact cognition. Given that deficits in EF and PS are consistently demonstrated in this population and are linked to functional impairment, identifying early vascular-health-related inflammatory markers associated with these domains may prove to be a useful treatment target for mitigating cognitive decline in BD and improving quality of life (see Figure 1).

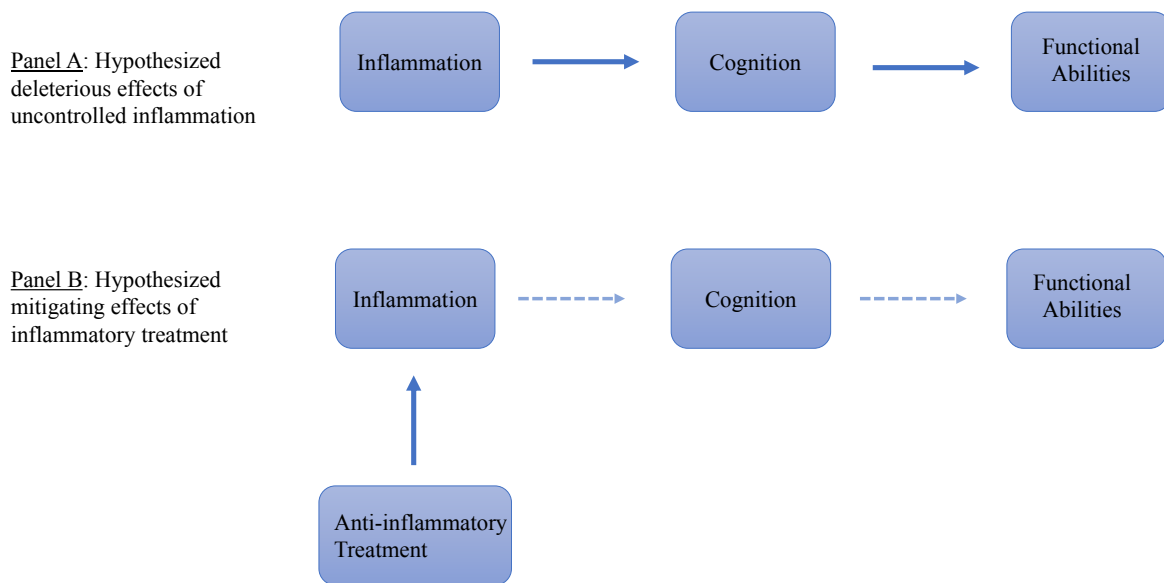


Figure 1. Schematic of proposed impact of inflammation. Panel A depicts inflammation leading to changes in cognition and functional abilities. Panel B illustrates how anti-inflammatory treatment (i.e., medication or lifestyle changes) may reduce the impact of inflammation on cognition and functional abilities.

### Physical activity

PA is directly related to many positive health outcomes (Van Citters et al., 2010), including improved vascular health (Boss et al., 2015) and cognitive performance (Buchman et al., 2012; Luque-Casado, Zabala, Morales, Mateo-March, & Sanabria, 2013). As such, programs to increase PA have become widely recommended as preventative treatments for future physical and cognitive decline, though less is known about whether PA may play a role in mitigating existing psychiatric or medical health burden. Researchers have suggested that PA increases blood flow and alters brain metabolism, ultimately contributing to maintaining intact vasculature within the brain's cerebrovascular networks (Barnes, 2015). Although the direct links between blood flow and cognition have yet to be elucidated, vascular dysfunction is associated with cognitive impairment and greater risk for future decline (de la Torre, 2012). The impact of daily PA (DPA) in BD is relatively understudied, though some early research (reviewed below) has

indicated that it may exert a positive impact on cognitive, physical and psychiatric health in this population.

Many self-report studies have indicated that BD patients spend more time engaging in sedentary behaviors compared to psychiatrically healthy samples (Melo, Daher Ede, Albuquerque, & de Bruin, 2016). The more recent advent of actigraphy and accelerometry technology has presented an ecologically valid methodology to objectively measure levels of daily activity exhibited by patients in real-world settings (Haskell, 2012). To date, only a small handful of studies have adopted this methodology to compare levels of PA in BD and healthy control (HC) groups. A recent meta-analysis reviewed 6 studies that investigated mean PA as measured by wrist-worn actigraphy watches, and concluded that BD patients engage in less PA compared to HC groups (De Crescenzo, Economou, Sharpley, Gormez, & Queded, 2017); mixed findings across studies with regard to the relationship between PA and mood were noted. Two additional actigraphy studies have since confirmed findings of lower mean PA levels over a 24 hour period and extended upon this literature to suggest that BD patients exhibit greater intra-individual variability (IIV) across time points in the afternoon during euthymia (Shou et al., 2017), and in the morning during mania (Krane-Gartiser et al., 2017). These novel studies introduce the notion that BD patients are inconsistent in the degree of PA they exhibit, and that these patterns may be related to mood state. Better understanding of factors leading to natural trends in PA can help to design specific exercise interventions aimed to encourage BD patients to reliably engage in more exercise. For example, if symptoms of mania or resolution of depression levels are accompanied with or followed by a natural increase in the degree of PA exhibited, then encouraging patients to engage in exercise during these moments may increase adherence to the

prescribed exercise regimen. Understanding IIV in PA among BD samples may also help to inform treatment development that encourages daily and consistent exercise.

Taken together, these studies suggest that BD patients exhibit differential activity levels relative to HC samples, characterized by less overall activity and greater variability over time. Unfortunately, the inpatient samples and short data collection periods used in most of these studies make it difficult to generalize these results to BD outpatients living in the community. Therefore, more studies utilizing objective measures of DPA in outpatient samples of bipolar disorder are needed to better document activity levels in this population.

**The impact of physical activity on cognition.** Engagement in higher levels of PA is associated with better performance on tests of processing speed, visuospatial processing, and executive functioning (Brown et al., 2012; Kramer & Erickson, 2007). Among studies conducted in clinical populations, higher levels of PA have been linked to the slowing of cognitive decline associated with aging, stroke, and Alzheimer's disease. Indeed, individuals exhibiting greater PA show a decreased risk for the future development of Alzheimer's disease (Buchman et al., 2012), and even low or moderate intensity exercise interventions have been shown to improve cognitive performance. A meta-analysis of 29 studies investigating changes across cognitive domains following aerobic exercise revealed modest improvements in the domains of EF and PS but not working memory (Smith et al., 2010). Thus, accumulating evidence indicates that PA exerts some positive influence on cognitive domains known to be vulnerable to BD pathology, particularly tasks of executive functioning and processing speed.

To date, only one study has explored the relationship between PA and cognition in BD. This investigation utilized a self-report assessment of PA intensity (low, moderate, or vigorous) and found that female BD patients in the vigorous PA group performed significantly better

across all cognitive domains assessed (Fellendorf et al., 2017). While this study is the first to investigate the role of PA in cognitive performance in BD, the use of self-report assessment in capturing PA limits the interpretations of these findings. Nevertheless, this study supports the need to further examine these relationships utilizing ecologically valid methodology to more accurately capture PA.

There is also a small body of research investigating associations between PA and cognition in closely related psychiatric populations. Two recent studies demonstrated that a combined regimen of both aerobic exercise and cognitive training delivered to patients diagnosed with SCZ was more effective in improving performance in EF, PS, and verbal memory compared to cognitive training protocols alone (Malchow et al., 2015; Oertel-Knochel et al., 2014). Another recent pilot study administered high velocity circuit training to 9 SCZ and 3 BD patients twice a week for 8 weeks and reported improvements across several neuropsychological tests, with the biggest effect size (Cohen's  $d = 0.92$ ) in the PS task of symbol coding (Strassnig et al., 2015). Thus, although relatively understudied within BD, there is some evidence suggesting that PA may have a positive impact on cognition in psychiatric populations. Studies characterizing the degree of PA in bipolar samples are needed in order to a) quantify the amount of activity exhibited by this population and b) determine whether the associations between PA and cognition observed in other samples is present within BD. In doing so, future exercise interventions may be targeted to improve vascular health and mitigate cognitive deficits in these patients. Taken together, studies detailing the cognitive profile of BD and the potential benefits of exercise on cognitive performance would suggest that the domains of EF and PS are most likely to benefit from such treatments (Figure 2).



**The impact of physical activity on inflammation.** Given the mounting evidence indicating both an inflammatory state in BD and the potentially negative impact of chronic inflammation on cognitive performance, identifying protective factors is an imperative early step to the development of treatment programs aimed to address cognitive impairment in this population. There has been growing interest in the impact of PA on inflammation, and the balance of studies generally suggests that acute bouts of exercise induce a pro-inflammatory state while long-term moderate exercise or PA programs produce anti-inflammatory effects (Chen, Apostolakis, & Lip, 2014; Nimmo, Leggate, Viana, & King, 2013). Of note, IL-6 and CRP have emerged as two inflammatory markers most implicated as increased in chronic inflammation and as benefitting from the anti-inflammatory effects of extended mild to moderate levels of PA. Self-reported and objectively measured levels of activity have been shown to be inversely correlated with blood serum IL-6 and CRP (Beavers, Brinkley, & Nicklas, 2010; Lavie, Church, Milani, & Earnest, 2011), and longitudinal studies have also demonstrated decreased levels of these biomarkers with regular high frequency exercise regimens (Petersen & Pedersen, 2005). It should be noted that these anti-inflammatory effects have been most consistently demonstrated in samples with vascular risk or in those with higher baseline levels of inflammation, but are inconclusive among healthy older adults (Beavers et al., 2010). Thus, BD patients fall within the category of those individuals poised to receive the most gains from this type of treatment (Figure 2), yet no studies to date have investigated the association of PA with inflammation in this psychiatric population.

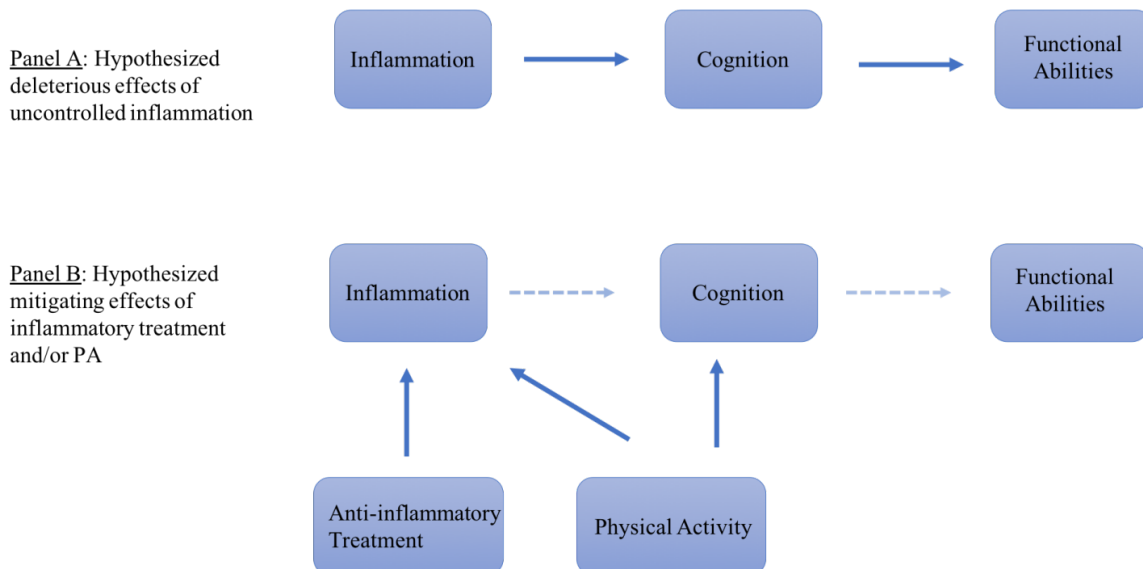


Figure 2. Schematic of proposed impact of inflammation and physical activity. Panel A depicts inflammation leading to changes in cognition and functional abilities. Panel B illustrates how anti-inflammatory treatment (i.e., medication or lifestyle changes) and/or physical activity may reduce cognitive and functional deficits.

**The relationship between physical activity and mood.** PA is associated with better mental health outcomes and has been shown to reduce depressive symptoms in psychiatrically healthy older adults, though a causal link between PA and mood has yet to be elucidated (Pemberton & Fuller Tyszkiewicz, 2016; Ten Have, de Graaf, & Monshouwer, 2011). Among patients with BD, studies have also investigated the association between varying levels of PA and mood. One recent meta-analysis investigating the clinical correlates of PA in BD reported that higher PA was related to enhanced perceptions of self-efficacy, but not mood or psychiatric symptoms (Vancampfort et al., 2013). It should be noted, however, that only one of the 11 studies reviewed in this meta-analysis utilized objective measures of PA, leaving these results susceptible to issues of validity and recall bias. Another more recent study determined the relationship between self-report frequency of exercise and mood in an outpatient sample of BD. The authors noted that less frequent exercise was associated with worse depression and quality of life and more frequent exercise was related to greater symptoms of mania (Sylvia et al., 2013).

Among those studies identified by De Crescenzo et al. (2017) that have utilized actigraphy technology, there appears to be no consistent relationship with self-reported mood symptoms. Further, none have related objectively measured PA levels to simultaneous real-time measurements of mood ratings. Only one published study has examined the clinical outcomes of exercise interventions in BD. In this pilot analysis, researchers examined changes in clinical ratings following a walking intervention in an inpatient psychiatric setting. At the conclusion of the intervention, the walking group had improved scores on the depression, anxiety and stress subscales of the Depression Anxiety Stress Scales compared to the non-walking group (Ng, Dodd, & Berk, 2007). The results of this study suggest that introducing a mild exercise intervention may stabilize mood symptoms in this population.

Thus there is some evidence, based largely on self-report studies utilizing cross sectional designs, for an association between mood symptoms and PA in bipolar disorder. However, no studies have investigated the relationship between objective real-time measurements of both PA and mood to determine a) reliable and ecologically valid quantitative measures of PA in patients and b) the temporal dynamics of the observed relationship (i.e. whether alterations in mood precede DPA or vice versa).

## II. Purpose and specific aims

Variable cognitive performance in the BD population has been well described in the literature, and new efforts to determine predictors of cognitive deficits seen in some patients are well under way. One promising avenue of research examines the potential contributions of vascular health in the development and maintenance of the executive function and processing speed impairments documented in BD. Two indicators of vascular health that have emerged as potentially early modifiable treatment targets are inflammation and physical activity. While some studies have demonstrated inter-relationships between cognition, inflammation and physical activity in other clinical populations at risk for cognitive impairment, an examination of these relationships in BD is required in order to adequately design a therapeutic intervention program targeting these factors (see Figures 1 and 2 for examples).

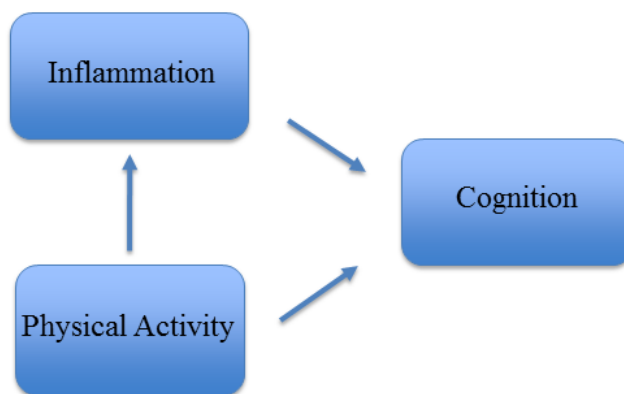


Figure 3. Proposed model describing associations between inflammation, PA, and cognition in Study 1. Note that other relationships (i.e., mood) not pictured in the model are likely, but will not be the focus of this dissertation project.

The current dissertation project is comprised of two studies in order to a) explore associations between cognition, inflammation and physical activity in bipolar disorder (Figure 3) and b) examine potential bi-directional influences between variable mood symptoms, a primary clinical feature of BD, and the amount of physical activity exhibited on a daily basis (Figure 4).

Given the lack of evidence to inform specific hypotheses, we also explored whether the relationships observed in (a) differ between BD and HC groups. Together, the results of this project will inform treatment modifications that can be utilized to positively impact vascular health, and ultimately cognition, in BD. For example, results indicating that lower inflammation is related to better cognition may encourage primary care physicians to prescribe anti-inflammatory medication prophylactically (Figure 1). A better understanding of how mood impacts PA can lead to a greater utilization of technology to monitor and regulate mood symptoms in conjunction with PA interventions.

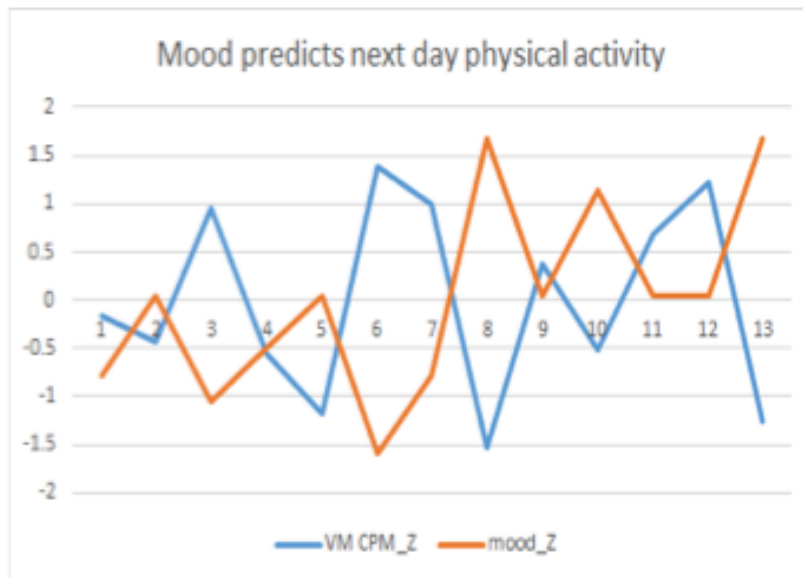


Figure 4. Example of hypothetical data supporting lagged relationship between mood and subsequent PA in Study 2. VM CPM = vector magnitude counts per minute; Z = z-score.

The proposed study is unique in that it utilizes ecological momentary assessment (EMA) methodology to capture frequent, real-time mood and activity ratings over a two-week study period. Participants were also administered neuropsychological tasks of executive functioning and processing speed, and submitted a sample of blood analyzed for peripheral levels of pro-inflammatory IL-6 and CRP.

**Study 1. Associations between cognition, inflammation and PA in bipolar disorder.**

**Specific Aim 1.** To contrast BD and HC samples on measures of cognition, inflammation and PA.

*Aim 1, Hypothesis 1.* Consistent with previous investigations, the BD group will exhibit worse performance on tasks of EF and PS, higher blood serum levels of IL-6 and CRP, and engage in less PA compared to the HC group.

*Aim 1, Hypothesis 2.* Given previous studies demonstrating greater inconsistency in PA across time in BD, it was also hypothesized that the BD group will demonstrate greater variability in levels of PA across the two-week study period compared to the HC group.

**Specific Aim 2.** To examine the relationship between cognitive performance and inflammation in BD participants.

*Aim 2, Hypothesis 1.* After controlling for relevant covariates, higher concentration of blood serum IL-6 and CRP will be associated with worse performance in executive function and processing speed.

*Exploratory aim 2.* To determine whether the relationship between inflammatory markers and cognition differs between diagnostic (BD vs. HC) groups.

**Specific Aim 3.** To examine the relationship between cognitive performance and PA in BD participants.

*Aim 3, Hypothesis 1.* After controlling for relevant covariates, greater average PA across the two week study period will be associated with better performance on tasks of executive functioning and processing speed.

*Exploratory aim 3.* To determine whether the relationship between PA and cognition differs between diagnostic (BD vs. HC) groups.

**Specific Aim 4.** To examine the relationship between inflammation and PA in BD participants.

*Aim 4, Hypothesis 1.* After controlling for relevant covariates, greater average PA across the two week study period will be associated with lower concentration of blood serum IL-6 and CRP.

*Exploratory aim 4.* To determine whether the relationship between PA and inflammatory markers differs between diagnostic (BD vs. HC) groups.

**Study 2. Lagged associations between daily mood ratings and PA in bipolar disorder.**

**Specific Aim 1.** To investigate lagged associations between daily mood ratings and subsequent PA in BD.

*Aim 1, Hypothesis 1.* Mood ratings from BD participants that indicate greater depression will be followed by decreases in levels of PA while ratings indicating greater manic symptoms will be followed by increased PA.

*Exploratory Aim 1.* To determine if there is a lagged association between initial PA and subsequent mood ratings in BD.

### **III. Methods**

#### **Participants**

Thirty-eight BD and 68 HC participants between the ages of 35 - 60 were enrolled in the proposed studies over the course of two years. All participants were proficient in the English language and capable of providing informed consent. Individuals were deemed ineligible if they endorsed a recent ( $\leq 6$  weeks) vaccination, history of neurological disorders (e.g., seizures, Parkinson's, stroke, etc.) or head trauma with loss of consciousness for  $> 15$  minutes, history of radiation or chemotherapy treatment, uncontrolled diabetes or hypertension, pregnancy, or sensory limitations expected to interfere with assessment. HC participants were also excluded if they qualified for an Axis I disorder determined by the Mini- International Neuropsychiatric Interview (MINI, (Sheehan et al., 1998)), or history of depression, BD or schizophrenia in a first-degree relative.

#### **Study Design**

Participants were recruited from an ongoing NIH-funded study, entitled Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder, under the direction of Lisa Eyler, Ph.D. at the University of California, San Diego (UCSD). As a part of this parent project, participants were scheduled for a 3-hour in-person baseline assessment during which time they underwent a psychiatric interview, neuropsychological assessment and blood draw. At the conclusion of this visit, participants were instructed on the use of their smartphone and actigraphy devices (see below), which they were required to use for two weeks following the baseline visit. A laboratory assistant collected the devices after the two-week study period was completed. Written informed consent was obtained from each participant in accordance with the UCSD Human Research Protections Program.



**Psychiatric interview.** To assess mood symptoms in the two weeks prior to study initiation, all BD participants were administered well-validated clinical instruments that have been used in studies of BD and other serious mental illnesses. Symptoms of mania in the prior two weeks were assessed using the Young Mania Rating Scale (YMRS; (Young, Biggs, Ziegler, & Meyer, 1978)), depression in the prior two weeks was measured using the Hamilton Depression Rating Scale (HAM-D; (Trajkovic et al., 2011)) and psychotic symptoms in the prior two weeks were measured with the Brief Psychiatric Rating Scale (BPRS, (Ventura et al., 1993)). Given that the use of psychotropic medication in BD has been linked to changes in cognition and brain function (Phillips, Travis, Fagiolini, & Kupfer, 2008), detailed information was collected regarding current and past medication use. A composite medication load variable was computed by assigning low (1) and high (2) medication load values for each prescription based on dosage and duration of use and summing these values across medication type to represent a unique medication load variable (Hassel et al., 2008).

**Blood draw.** A licensed phlebotomist withdrew a 15 ml blood sample from each participant at each of three visits across the two-week assessment period. For a given participant, the three blood samples were drawn at the same time of day. Samples from 38 BD and 58 HC participants were processed in the laboratory of Cristian Achim, Ph.D., in the UCSD Department of Psychiatry. Plasma aliquots from all participants were tested using a sandwich immunoassay with MSD MULTI-SPOT<sup>®</sup> Assay kits (Meso Scale Discovery, Rockville, MD). Protein targets were captured with pre-coated antibodies immobilized on independent spots in a 96-well plate. Detection antibodies were conjugated with the electrochemilluminescence (ECL) compound MSD SULFO-TAG. A voltage was applied to the plate electrode and the labeled antibodies emitted light. The intensity of the light emission was measured to quantify measures of all target

proteins present in the sample. MSD DISCOVERY WORKBENCH® analysis software generated standard curves by fitting the ECL signal from calibrators to a 4-parameter logistic model with a  $1/y^2$  weighting. Three concentration ranges of quality controls were used to evaluate assay accuracy and precision in order to ensure reliable and accurate results. Mean levels of IL-6 and CRP were calculated across the available samples (up to three samples across the two-week period) for each participant.

**Neuropsychological assessment.** All participants were administered the Symbol Coding subtest of the Brief Assessment of Cognition in Schizophrenia (BACS) battery (Keefe et al., 2004) as well as the Color Word Interference and Trail Making subtests of the Delis-Kaplan Executive Functions (D-KEFS) battery (Delis, Kaplan, & Kramer, 2001). All tests were administered by a trained psychometrist in accordance with the standardized procedures outlined in their respective manuals. Raw scores from the D-KEFS Trail Making Letter-Number switching, D-KEFS Color Word Interference Inhibition, and D-KEFS Color Word Interference Inhibition-Switch subtests were converted into standardized z-scores and averaged to derive an executive functioning (EF) composite score. Raw scores from the BACS symbol coding, D-KEFS Trail Making Letter Sequencing, and D-KEFS Trail Making Number Sequencing subtest were converted into standardized z-scores and averaged to derive a processing speed (PS) composite score.

**Ecological momentary assessment (EMA) of physical activity and mood.** Recent attention in the exercise literature has highlighted the benefits of quantifiable measurements of PA over self-report questionnaires (Haskell, 2012), yet few studies have employed objective techniques to measure patterns of PA in an outpatient BD sample. EMA technology has been gaining popularity as an effective tool to assess real-world functioning in a way that reduces

response bias and reveals temporal trends (Granholm, Loh, & Swendsen, 2008; Shiffman, Stone, & Hufford, 2008). This study takes advantage of novel EMA methodology by using both actigraphy watches and smartphone applications in order to more accurately measure mood and PA over a two-week period and to investigate time-lagged associations between daily mood and daily PA.

***Daily physical activity.*** PA was measured objectively using the ActiGraph GT3X+ (ActiGraph Inc., Pensacola, FL, USA), a tri-axial accelerometer that has previously been used among children, adolescents, and adults in the National Health and Nutrition Examination Survey (Troiano et al., 2008) and has consistently been shown to be both valid and reliable (John & Freedson, 2012; Robusto & Trost, 2012; Warren et al., 2010). Participants were asked to wear the device continuously on their non-dominant wrist, except while bathing or swimming, for 14 consecutive days. The wear location and time period are consistent with the best practices for physical activity assessment and result in high levels of acceptability and compliance among participants (Freedson, Bowles, Troiano, & Haskell, 2012; Matthews, Hagstromer, Pober, & Bowles, 2012; Troiano, McClain, Brychta, & Chen, 2014; Tudor-Locke et al., 2015). Physical activity was quantified in vector magnitude counts per minute (ActiGraph's proprietary metric), henceforth referred to as "counts." This metric incorporates intensity, frequency, and duration of acceleration and is recommended for assessing the total volume of physical activity in a 24-hour period (Bassett, Troiano, McClain, & Wolff, 2015). Raw data was reliably processed and converted to counts by an experienced team located within the UCSD Exercise and Physical Activity Resource Center. Of note, validated algorithms of metabolic equivalents (METs) are available only for hip worn actigraph devices (Hibbing, Lamunion, Kaplan, & Crouter, 2018).

Given that this study protocol incorporated wrist-worn devices only, it is not possible to categorize PA level into light, moderate, and vigorous activity based on METs.

A total PA (TPA) count was calculated to represent the average movement exhibited by each participant across the entire two-week collection period, and was utilized as both a primary predictor (Study 1, Aims 3-4) and outcome variable (Study 1, Aim 1, Hypothesis 1). A daily PA (DPA) count was calculated to represent the average movement exhibited within each day of the two-week collection period. DPA was utilized as a primary predictor in Study 2, Aim 1 of the proposed analyses.

***Daily smartphone assessment of mood.*** Daily mood rating surveys were delivered via Samsung Galaxy 3 smartphones provided to the participants by the study staff. At their baseline visit, participants were trained in the operation and maintenance of the smartphone device. Starting the following day, BD participants received text messages three times per day (i.e., morning, afternoon and evening intervals) prompting them to submit mood ratings. Specifically, they were asked to rate their mood symptoms on an 8-point scale (-4 (most ever depressed) to 0 (euthymic) to +4 (most ever manic)). These ratings were made three times daily for 14 consecutive days for a total of 42 ratings. Administration times were adjusted according to subjects' schedules. Our collaborators have previously demonstrated stable adherence with this mobile technology (Colin A. Depp et al., 2015; Granholm et al., 2008) as well as concurrent validity between mobile and clinician mood ratings (C. A. Depp, Kim, de Dios, Wang, & Ceglowski, 2012).

A total mood rating (TMR) score was also created by averaging all mood ratings across the entire two-week collection period. The TMR was included as covariates in regression analyses in Study 1 (Aims 1 – 4) when appropriate. A daily mood rating (DMR) was created by

averaging mood ratings within each day and was utilized as a predictor variable in the lagged analysis proposed in Study 2, Aim 1.

### **Data analysis**

Appropriate assumptions were checked prior to all testing and data transformations (e.g., square root or logarithm) were used as needed. Group differences in demographic variables were assessed, and any unexpected group differences were controlled for in subsequent analyses. All analyses were carried out using Statistical Package for Social Sciences (SPSS) 22.0. Across all relevant analyses, multiple comparisons were addressed by applying family-wise Bonferroni corrections to cognition ( $p < 0.025$ ) and inflammatory markers ( $p < 0.025$ ).

Previous studies investigating the relationship between inflammation and cognition, PA and cognition, and PA and inflammation in other samples have reported medium to large effect sizes (Oertel-Knochel et al., 2014; Smith et al., 2010; Strassnig et al., 2015). Thus, power analyses were conducted to detect medium to large effect sizes for the final sample. For independent sample t-tests, the full sample of 38 BD and 68 HC participants yields a 79% chance of detecting a medium effect size (Cohen's  $d = 0.5$ ) and a 98% chance of detecting a large effect size (Cohen's  $d = 0.8$ ). The subsample of 38 BD and 58 HC participants with IL-6 and CRP data yields a 77% chance of detecting a medium effect size (Cohen's  $d = 0.5$ ) and a 98% chance of detecting a large effect size (Cohen's  $d = 0.8$ ). For all linear regressions, a sample of 38 BD participants yields a 76% chance of detecting a medium effect size ( $f^2 = 0.15$ ) and 97% chance of detecting a large effect size ( $f^2 = 0.35$ ). Given that the within-subject linear mixed modelling proposed in Study 2 includes more data points than the regression analyses in Study 1, it is estimated that 38 BD subjects achieved adequate power to detect a medium to large effect size.

**Study 1.** Associations between cognition, inflammation and physical activity in bipolar disorder.

**Specific Aim 1, Hypothesis 1.** It was hypothesized that the BD group will exhibit worse performance on tasks of EF and PS, higher blood serum levels of IL-6 and CRP, and engage in less TPA compared to the HC group.

Independent samples T-tests were utilized to determine significant group differences in cognition (i.e., EF and PS composite scores), blood serum levels of inflammatory markers (i.e., IL-6 and CRP) and TPA.

**Specific Aim 1, Hypothesis 2:** It was hypothesized that the BD group will demonstrate greater variability in levels of PA across the two-week study period compared to the HC group.

One method commonly used to calculate intra-individual variability (IIV) is to compute the standard deviation of each individual's scores across time, known as the intra-individual standard deviation (iSD). However, this method does not account for potential trends over time or larger group means that may inflate the iSD estimate (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Wojtowicz, Berrigan, & Fisk, 2012). To account for these factors, we proposed an alternate method that utilized two linear mixed-effects (LME) regression models. The first models DPA over the two-week period:

$$\begin{pmatrix} DPA_1 \\ DPA_2 \\ \vdots \\ DPA_{14} \end{pmatrix} = \begin{pmatrix} \beta_0 \\ \beta_0 \\ \vdots \\ \beta_0 \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{1,2} \\ \vdots \\ \beta_{1,14} \end{pmatrix} \begin{pmatrix} 1 \\ 2 \\ \vdots \\ 14 \end{pmatrix} + \begin{pmatrix} \beta_2 \\ \beta_2 \\ \vdots \\ \beta_2 \end{pmatrix} \begin{pmatrix} TPA_G \\ TPA_G \\ \vdots \\ TPA_G \end{pmatrix} + \begin{pmatrix} e_1 \\ e_2 \\ \vdots \\ e_{14} \end{pmatrix} \tag{LME (1)}$$

$DPA_t = \beta_0 + \beta_{1,t} (\text{Observation}_t) + \beta_2 (TPA_G) + e_t$

DPA<sub>t</sub> was the outcome variable that represents the average DPA for one individual at time-point  $t$  (days 1-14), Observation<sub>t</sub> was the explanatory variable that represents the day of collection, and TPA<sub>G</sub> is the group indicator. Subject-specific random intercepts and slopes represented each participant's unique level of DPA at the beginning of the collection period ( $\beta_0$ ) and varying trajectories of change in DPA over time ( $\beta_1$ ). The diagnostic group mean (TPA<sub>G</sub>) was also included in the model as a fixed effect. By conducting this model for each individual within each group, contributions from previous time points were partialled from each individual's DPA measurement to remove systematic variation due to time-point, including linear, quadratic, cubic, and fourth polynomial trends. Further, considering the linear relationship between mean and standard deviation (Atkinson & Nevill, 1998), the addition of the group mean PA reduced the impact of expected group differences in PA on the individual variability.

The variability of each individual's PA (IIV), after considering time trends and group means, was represented by,  $s_{it}^2$ , the squared difference between the residuals of LME (1) and the mean PA; this value was then log-transformed to ensure positive values (Watts, Walters, Hoffman, & Templin, 2016). Therefore, group differences in IIV were determined by LME (2), in which  $\log(s_{it}^2)$  was the outcome variable representing IIV, and Group was the explanatory variable to indicate diagnostic group membership. Subject specific random intercepts represented each HC participant's (Group = 0) unique level of IIV, and the diagnostic group was included as the main effect.

$$\log(s_{it}^2) = \beta_0 + \beta_2(\text{Group}) + e_i \quad \text{LME (2)}$$

***Specific Aim 2, Hypothesis 1.*** It was hypothesized that a higher concentration of blood serum IL-6 and CRP would be associated with worse performance in EF and PS.

A series of four linear regressions were performed to assess the relationship between inflammatory markers and cognitive performance in the BD sample. EF and PS composite scores were investigated as outcome variables in the models, while blood serum concentration levels of IL-6 and CRP were utilized as the primary predictor variables. Potential covariates found to be significantly correlated with either PS or EF were included in the model.

***Exploratory Aim 2.*** Among the whole sample, group (BD vs HC) and group-by-biomarker interaction terms were added to the above models in order to identify potential diagnostic group differences in the associations between cognitive performance and blood serum levels of inflammatory markers.

***Specific Aim 3, Hypothesis 1.*** It was hypothesized that greater TPA would be associated with better performance on tasks of EF and PS.

A series of two linear regressions were performed to assess the relationship between TPA and cognitive performance in the BD sample. EF and PS composite scores were investigated as outcome variables in the regression models, while TPA was utilized as the primary predictor variable. Potential covariates found to be significantly correlated with either PS or EF were included in the models.

***Exploratory Aim 3.*** Among the whole sample, group (BD vs HC) and group-by-TPA interaction terms were added to the above models in order to identify potential diagnostic group differences in the associations between cognitive performance and TPA.

***Specific Aim 4, Hypothesis 1.*** It was hypothesized that greater TPA would be associated with lower concentrations of blood serum IL-6 and CRP.



A series of two linear regressions were performed to assess the relationship between TPA and blood serum inflammatory biomarkers in the BD sample. Blood serum concentration levels of IL-6 and CRP were investigated as outcome variables in the regression models, while TPA was utilized as the primary predictor variable. Potential covariates found to be significantly correlated with either IL-6 or CRP were included in the models.

**Exploratory Aim 4.** Among the whole sample, group (BD vs HC) and group-by-TPA interaction terms were added to the above models in order to identify potential group differences in the associations between TPA and blood serum levels of inflammatory markers.

**Study 2.** Lagged associations between mood ratings and PA in bipolar disorder.

**Specific Aim 1, Hypothesis 1.** It was hypothesized that mood ratings made by BD participants who indicated greater depression would be followed by decreases in levels of PA while ratings indicating greater mania would be followed by increases in levels of activity.

Linear mixed models were used to evaluate the effect of present mood ( $MR_t$ ) on subsequent averaged DPA ( $DPA_{t+1}$ ), while adjusting for subsequent MR ( $MR_{t+1}$ ) in the BD sample only.  $DPA_{t+1}$  was included as the outcome variable of interest. Subject-specific random intercepts and slopes represented each participant's unique level of  $DPA_{t+1}$  exhibited at the beginning of the collection period (intercept) and the varying trajectories of change in  $DPA_{t+1}$  over time (slope).  $MR_t$  was included in the model as the fixed main effect and  $MR_{t+1}$  was included as a covariate.

**Exploratory Aim 1.** Linear mixed models were used to evaluate the effect of present DPA ( $DPA_t$ ) on subsequent  $MR_{t+1}$ , while adjusting for subsequent  $DPA_{t+1}$  in the BD sample only.  $MR_{t+1}$  was included as the outcome variable of interest. Subject-specific random intercepts and slopes represented each participant's unique level of  $MR_{t+1}$  exhibited at the beginning of the

collection period (intercept) and the varying trajectories of change in  $MR_{t+1}$  over time (slope).  $DPA_t$  was included in model as the fixed main effect and  $DPA_{t+1}$  was included as a covariate.

## IV. Results

### Overall Adherence to EMA methodology

In order to demonstrate the feasibility of utilizing novel EMA devices among HC and BD samples, adherence rates for smartphone surveys (BD group only) and actigraphy (both BD and HC) watches were calculated. Among the HC group ( $n = 68$ ), individuals wore the actigraphy watch for an average of 12.00 (range: 4-17) days and the average adherence rate (number of days worn/total number of days possible = 0.86,  $SD = 0.19$ ) was not associated with total PA  $r(67) = 0.05, p = 0.68$ ) across the study period. In the BD sample ( $N = 38$ ), individuals submitted an average of 12.64 (range: 3 – 14) days of mood ratings and wore the actigraphy watch for an average of 12.42 (range: 8-14) days. The average adherence rates for surveys (number of days submitted/total number of days possible = 90.3,  $SD = 0.16$ ) and watch data (number of days worn/total number of days possible = 0.89,  $SD = 0.13$ ) was not associated with total mood ratings ( $r(37) = -0.14, p = 0.42$ ) or total PA  $r(67) = 0.07, p = 0.67$ ) across the study period, respectively.

### Study 1. Associations between cognition, inflammation, and PA in bipolar disorder

The final full sample consisted of 38 BD and 68 HC participants. All analyses utilizing inflammatory biomarkers IL-6 and CRP were conducted using the subsample of 38 BD and 58 HC for which blood samples were analyzed. Variables that violated assumptions of normality (IL-6, CRP, current medication load, and lifetime medication load) were appropriately transformed (IL-6 and CRP) or subjected to nonparametric statistical tests (current and lifetime medication load; spearman's rho). Histograms demonstrating distributions of each primary outcome variable used in all subsequent analyses are displayed in Figure 5.

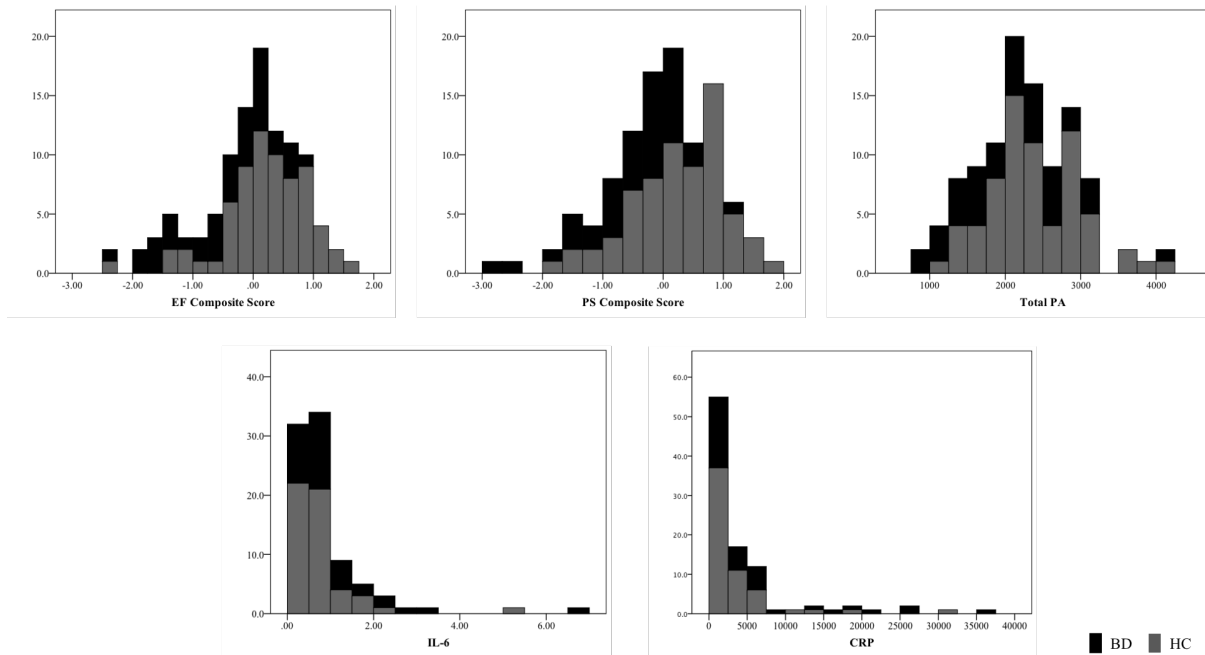


Figure 5. Histograms of primary outcome variables in the full sample. EF = executive functioning; PS = processing speed; PA = physical activity; IL-6 = interleukin-6; CRP = c-reactive protein; BD = bipolar disorder; HC.= healthy controls.

**Clinical and demographic characteristics.** Groups in the full sample did not significantly differ in age ( $t(104) = 1.063, p = 0.29$ ), gender ( $\chi^2(1) = 0.37, p = 0.52$ ), or estimated pre-morbid IQ ( $t(104) = -0.44, p = 0.5$ ). The HC group was significantly more educated ( $t(104) = -2.21, p = 0.03$ ) and were observed to have lower BMI ( $t(104) = 2.37, p = 0.02$ ), systolic blood pressure ( $t(104) = 2.08, p = 0.04$ ), and stroke risk ( $t(104) = 2.45, p = 0.02$ ) compared to BD patients (See Table 1). Reported group differences remained in the subsample of participants with analyzed blood samples (data not shown). It should be noted that although the HC group obtained significantly more formal education, the difference is minimal ( $< 1$  year) and both groups were relatively well educated (at least some college level courses). This is inconsistent with census studies reporting lower educational attainment in bipolar samples (Mojtabai et al., 2015). Further, relative to published normative samples, both groups performed within normal limits on all cognitive tasks (BD mean scaled scores range: 9-11; HC mean scaled scores range: 11-12), indicating that none of the participants were clinically impaired with respect to either EF

or PS. Therefore, the following analyses should be interpreted in the context of a sample that is relatively well-educated and generally cognitively intact.

Table 1. Demographic characteristics of BD and HC participants.

	BD <i>M (SD)</i>	HC <i>M (SD)</i>	<i>p</i>
Age	50.09 (7.74)	48.42 (7.77)	0.29
Gender [% Female]	60.5	54.4	0.68
Education	14.34 (2.20)	15.29 (2.09)	0.03*
Pre-morbid IQ	115.23 (8.07)	115.91 (6.90)	0.70
BMI	31.30 (6.16)	28.42 (5.67)	0.02*
Systolic BP	126.89 (11.97)	122.22 (10.54)	0.04*
Diastolic BP	81.41 (8.52)	78.70 (9.58)	0.15
Stroke Risk	5.16 (3.56)	3.24 (2.28)	0.001**

Note: BD = bipolar disorder; HC = healthy comparison; M = mean; SD = standard deviation; IQ = intelligence quotient; BMI = body mass index; BP = blood pressure. \* $p < .05$ ; \*\* $p \leq 0.001$

The BD sample consisted of 4 individuals without current elevated mood symptoms, 18 with significantly elevated symptoms of depression (HAM-D  $\geq 7$ ; (Trajkovic et al., 2011)), 1 with significantly elevated symptoms of mania (YMRS  $\geq 6$ ; (Young et al., 1978)), and 15 with significantly elevated symptoms of both depression and mania. On average, BD participants reported clinically significant levels of depression, mild symptoms of mania, and mild levels of psychiatric distress (BPRS; (Leucht et al., 2005)) at baseline. Over the course of the two week data collection period, the BD group reported mildly depressed mood (mean: -0.23; range: -1.82 to 0.93). See Table 2 and Figure 6 for clinical characteristics in the BD sample.

Table 2. Clinical characteristics of BD sample [Mean (range)]

HAM-D	18.58 (2 – 43)
YMRS	6.65 (0 – 19)
BPRS	40.13 (25 – 63)
Total MR	-0.23 (-1.82 – 0.93)
Current medication load	3.26 (0 – 7)
Lifetime medication load	1111.04 (0 – 6570)
Duration of Illness	33.14 (14.60 – 50.67)
Lifetime # of Manic Episodes	26.71 (1 – 240)
Lifetime # of Depressed Episodes	48.97 (1 – 240)
Lifetime # of Mixed Episodes	29.93 (1 – 110)
Lifetime # of Suicide attempts	2.10 (0 – 9)

Note: HAM-D = Hamilton depression scale; YMRS = Young mania Rating scale; BPRS = Brief psychiatric rating scale; MR = cell phone-based mood ratings.

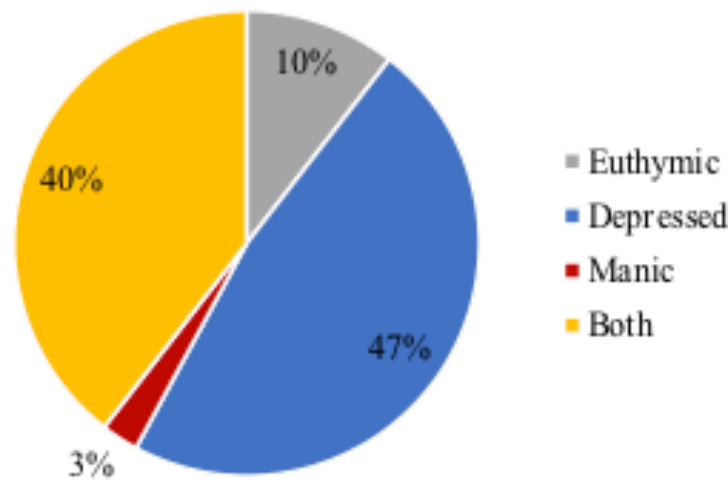


Figure 6. Mood states of BD participants at baseline visit

**Group differences in inflammation, PA, and cognition.** BD participants performed worse on tasks of EF ( $t(104) = -4.62, p < 0.000$ ) and PS ( $t(104) = -4.66, p < 0.000$ ), exhibited higher levels of IL-6 ( $t(94) = 2.83, p = 0.01$ ) and CRP ( $t(94) = 2.40; 0.02$ ), and engaged in less PA ( $t(104) = -2.23, p = 0.03$ ) across the two week period (Aim 1 Hypothesis 1). Group

differences in cognition (EF and PS) and inflammatory biomarkers (IL-6 and CRP) remained statistically significant following family-wise Bonferroni corrections ( $p < 0.025$ ). See Table 3 and Figure 7. After accounting for group differences in BMI and stroke risk, diagnostic group differences in inflammatory biomarkers (IL-6:  $\beta = -0.15$ ,  $t = -1.68$ ,  $p = 0.10$ ; CRP:  $\beta = -0.08$ ,  $t = -0.98$ ,  $p = 0.33$ ) and physical activity ( $\beta = 0.14$ ,  $t = 1.43$ ,  $p = 0.16$ ) did not remain significant, indicating that accumulated vascular burden may be more significantly driving these differences relative to psychiatric diagnosis.

Table 3. Group differences in cognition, inflammation, and physical activity.

	BD <i>M (SD)</i>	HC <i>M (SD)</i>	<i>t</i>	<i>p</i>	Cohen's <i>d</i>
EF Composite	-0.47 (0.82)	0.23 (0.71)	-4.63	0.000**	0.92
PS Composite	-0.49 (0.82)	0.27 (0.79)	-4.66	0.000**	0.94
IL-6	-0.15(0.68)	-0.53 (0.62)	2.83	0.01*	0.58
CRP	8.00 (1.34)	7.35 (1.26)	2.34	0.02*	0.50
Total PA	2084.99 (709.67)	2379 (620.37)	-2.23	0.03*	0.44

Note: EF = executive functioning; PS = processing speed; BD = bipolar disorder; HC =healthy comparison; IL-6 = interleukin-6; CRP = c-reactive protein; PA= physical activity. \* $p < .05$ ; \*\* $p < 0.001$ .

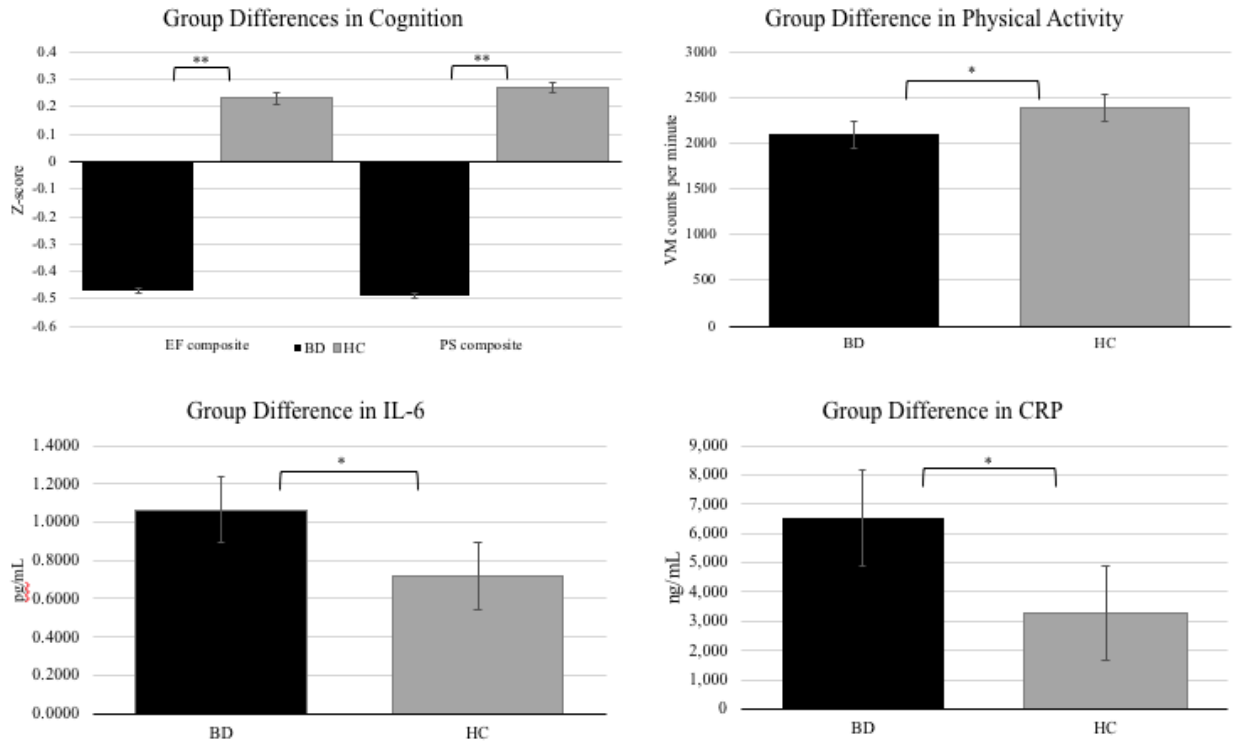


Figure 7. Group differences in cognition, physical activity, and inflammatory biomarkers. EF = executive functioning; PS = processing speed; BD = bipolar disorder; HC = healthy comparison; VM = vector magnitude; IL-6 = interleukin-6; CRP = C-reactive protein; pg/mL = picogram per milliliter; ng/ml = nanogram per milliliter. \* $p < .05$  \*\* $p < 0.001$

**Intra-individual variability of PA.** Figure 8 displays DPA exhibited by each individual and the mean DPA exhibited within each group. After accounting for polynomial trends, no group differences were observed in the IIV of PA across the data collection period (Aim 1, Hypothesis 2), indicating that BD and HC participants were equally consistent in the amount of PA they engaged in across days (Table 4).



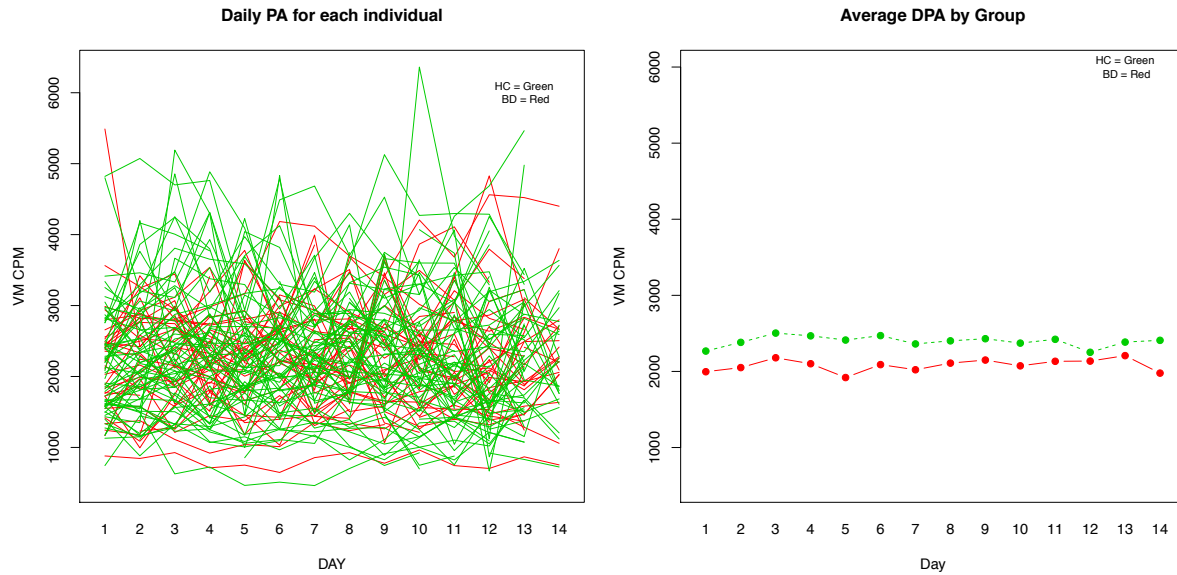


Figure 8. Physical activity across the 14 day data collection period. PA = physical activity; VM CPM = vector magnitude counts per minute; HC = healthy control; BD = bipolar disorder.

Table 4. Group means and differences in IIV.

	HC	BD	
IIV ( $\log(s_{it}^2)$ )	10.71	10.00	
	$\beta$	t	p-value
Intercept	10.96	82.73	0.000**
Group	-0.29	-1.30	0.20

Note: IIV= intra-individual variability; HC = healthy control; BD = bipolar disorder;  $\beta$  = standardized coefficient; t = t-statistic. \*\* $p < 0.001$

**Relevant associations with inflammation, PA, and cognition.** Group-wise exploratory correlational analyses were conducted in order to identify appropriate covariates for remaining regression analyses. Among the BD group, older age was associated with worse EF performance ( $r(36) = -0.42, p = 0.01$ ) and higher stroke risk was associated with worse PS performance ( $r(36) = -0.36, p = 0.03$ ). Higher levels of pro-inflammatory IL-6 and CRP in the BD group was associated with greater BMI ( $r(37) = 0.59, p < 0.000$  and  $r(37) = 0.58, p < 0.000$ , respectively) and systolic blood pressure (SBP;  $r(37) = 0.43, p = 0.01$  and  $r(37) = 0.36, p = 0.03$ , respectively). Greater psychiatric distress as reported on the BPRS predicted higher levels of CRP ( $r(37) =$

0.37,  $p = 0.02$ ); no other mood symptoms assessed at the baseline visit (YMRS, HAM-D, etc.), average survey mood ratings, or medication load variables were associated with cognition, physical activity, or inflammatory biomarkers in the BD group. Further, these outcome variables did not significantly differ with respect to mood group (i.e., euthymic, manic, depressed, mixed; data not shown, all  $p$ 's  $> 0.05$ ).

Among the HC group, greater education was associated with better performance on tasks of both EF ( $r(67) = 0.30, p = 0.01$ ) and PS ( $r(67) = 0.25, p = 0.04$ ). Worse EF performance was associated with higher SBP ( $r(67) = -0.27, p = 0.03$ ), BMI ( $r(67) = -0.25, p = 0.04$ ), and stroke risk ( $r(67) = -0.31, p = 0.01$ ), while slower PS was related to older age ( $r(67) = -0.30, p = 0.01$ ). Finally, higher BMI in the HC group was associated with greater levels of pro-inflammatory IL-6 ( $r(57) = 0.57, p < 0.000$ ) and CRP ( $r(57) = 0.65, p < 0.000$ ). There were no significant associations between relevant demographic characteristics and total PA in either BD or HC participants (all  $p$ 's  $< 0.05$ ).

For all *a priori* aims, variables that were significantly associated with the primary outcome variables of inflammation, PA, and cognition were included as covariates in appropriate models. Covariates were also identified for exploratory analyses investigating diagnostic group differences in these associations. In these models, covariates were deemed appropriate for model inclusion if they exhibited significant a) group differences between BD and HC groups (see Table 1), and b) relationships to the outcome variables of interest (i.e., inflammation, PA, or cognition).

**Inflammation and cognition.** Among the BD participants, age and stroke risk were included in models investigating associations between inflammatory biomarkers and EF and PS,

respectively (Specific Aim 2 Hypothesis 1). These analyses revealed that blood-serum levels of IL-6 did not predict performance on tasks of EF or PS in the BD group (see Table 5).

Table 5. Associations between IL-6 and cognition in BD

	$\beta$	t	p-value
<b>Executive Functioning</b>			
Age	-0.40	-2.51	0.02*
IL-6	-0.09	-0.58	0.56
<b>Processing Speed</b>			
Stroke risk	-0.39	-2.50	0.02*
IL-6	0.18	1.14	0.26

Note: BD = bipolar disorder; IL-6 = interleukin-6;  $\beta$  = standardized coefficient; t = t-statistic. \*p < 0.05.

Similarly, blood-serum levels of CRP also did not predict performance on tasks of EF or PS in the BD group (See Table 6). All associations remained non-significant when covariates were removed from the model (data not shown; all *p*'s < 0.5).

Table 6. Associations between CRP and cognition in BD

	$\beta$	t	p-value
<b>Executive Functioning</b>			
Age	-0.50	-3.02	0.005*
CRP	0.22	1.43	0.16
<b>Processing Speed</b>			
Stroke risk	-0.38	-2.34	0.03*
CRP	0.07	0.44	0.66

Note: BD = bipolar disorder; CRP = c-reactive protein;  $\beta$  = standardized coefficient; t = t-statistic. \*p < 0.05.

Exploratory regression analyses with group-by-biomarker interaction terms were conducted to examine potential group differences in the relationship between inflammatory biomarkers and cognition. After accounting for education, SBP, BMI, and stroke risk, there were no significant group-by-biomarker interactions on EF. After accounting for education, SBP, and stroke risk, there was a significant group-by-IL-6 interaction on PS (Table 7). There was no observed group-by-CRP interaction on PS. Notably, all interactions, including that of group-by-

IL-6, were non-significant when covariates were removed from the model (data not shown; all  $p$ 's < 0.5).

Table 7. Exploratory analyses investigating group-by-biomarker interactions on cognition.

<b>CRP</b>			
	$\beta$	t	<i>p</i> -value
<b>Executive Functioning</b>			
Education	0.19	2.01	0.05*
SBP	-0.16	-1.27	0.21
BMI	-0.08	-0.64	0.52
Stroke Risk	-0.15	-1.31	0.19
Group	1.09	1.89	0.06
CRP	0.12	0.98	0.33
Group-by-CRP	-0.82	-1.42	0.15
<b>Processing Speed</b>			
Education	0.19	2.00	0.05*
SBP	-0.03	-0.27	0.79
Stroke Risk	-0.27	-2.49	0.02*
Group	0.75	1.34	0.19
CRP	-0.01	-0.12	0.91
Group-by-CRP	-0.45	-0.81	0.42
<b>IL-6</b>			
	$\beta$	t	<i>p</i> -value
<b>Executive Functioning</b>			
Education	0.22	2.80	0.03*
SBP	-0.16	-1.30	0.20
BMI	0.07	0.55	0.59
Stroke Risk	-0.16	-1.00	0.32
Group	0.234	2.07	0.04*
IL-6	-0.16	-1.30	0.20
Group-by-IL-6	-0.03	-0.29	0.77
<b>Processing Speed</b>			
Education	0.19	2.06	0.04*
SBP	-0.06	-0.56	0.58
Stroke Risk	-0.06	-0.56	0.02*
Group	0.20	1.87	0.07
Total IL-6	-0.02	-0.02	0.85
Group-by-IL-6	-0.21	-2.08	0.04*

Note: CRP = C-reactive protein; IL-6 = interleukin-6; SBP = systolic blood pressure; BMI = body mass index.  $\beta$  = standardized coefficient; t = t-statistic; \*  $p < 0.05$

Further exploratory analyses were conducted to better understand the nature of the group-by-IL-6 interaction on processing speed identified in exploratory aim 2. Surprisingly, the interaction term was not significant when no covariates were included in the model ( $\beta = -0.14$ ,  $t = -1.40$ ,  $p = 0.20$ ), and an examination of collinearity in the full model revealed that this assumption was not violated in this model (variance inflation factors (VIFs)  $< 2$ ; (Myers, 1990)). Three additional models that incorporated each of the identified covariates (i.e., education, SBP, and stroke risk) were then explored one at a time. Of these, only the model that included SBP generated a significant interaction term ( $\beta = -0.23$ ,  $t = -2.10$ ,  $p = 0.04$ ). After partialling out contributions of SBP on IL-6 (IL-6<sub>adj</sub>), a regression model that included the main effects of group, IL-6<sub>adj</sub>, and a Group-by- IL-6<sub>adj</sub> interaction term revealed a marginally significant interaction ( $\beta = -0.17$ ,  $t = -1.81$ ,  $p = 0.07$ ). Although associations were opposite in direction in the two groups, the correlations between IL-6<sub>adj</sub> and PS were not significant in either group (BD:  $r(37) = 0.20$ ,  $p = 0.24$ ; HC:  $r(57) = -0.18$ ,  $p = 0.18$ ). This is consistent to the absence of significant correlations between non-adjusted IL-6 and PS in both groups (reported previously). Thus, there is not strong and consistent evidence for a differential relationship of IL-6 to PS in the two diagnostic groups.

**PA and cognition.** Controlling for age and stroke risk respectively (as reported above), average PA across the two week data collection period was not significantly associated with either EF or PS performance in BD participants (Specific Aim 3, Hypothesis 1; See Table 8). These associations remained non-significant when covariates were removed from the model (data not shown; all  $p$ 's  $< 0.5$ ).

Table 8. Associations between PA and cognition in BD.

	$\beta$	t	p-value
<b>Executive Functioning</b>			
Age	-0.39	-2.57	0.02*
Total PA	0.15	0.96	0.35
<b>Processing Speed</b>			
Framingham Stroke Risk	-0.35	-2.19	0.04*
Total PA	0.04	0.22	0.83

Note: PA = physical activity; BD = bipolar disorder;  $\beta$  = standardized coefficient; t = t-statistic; \* $p < 0.05$ .

Exploratory regression analyses with group-by-PA interaction terms were conducted to examine potential group differences in the relationship between PA and cognition (Exploratory Aim 3). After accounting for education, SBP, BMI, and stroke risk, there was no significant group-by-PA interaction on EF. Similarly, after accounting for education, SBP, and stroke risk, there was no significant group-by-PA interaction on PS (See Table 9). These interactions remained non-significant when covariates were removed from the model (data not shown; all  $p$ 's  $< 0.5$ ).

Table 9. Group-by-PA interactions on cognition.

	$\beta$	t	p-value
<b>Executive Functioning</b>			
Education	0.31	2.15	0.78
SBP	-0.22	-1.81	0.07
BMI	-0.07	-0.65	0.52
Stroke Risk	-0.02	-0.16	0.88
Diagnostic Group	0.54	1.79	0.08
Total PA	0.14	1.46	0.15
Group-by-PA	-0.27	-0.90	0.37
<b>Processing Speed</b>			
Education	0.20	2.08	0.04*
SBP	-0.16	-1.58	0.12
Stroke Risk	-0.15	-1.51	0.14
Diagnostic Group	0.49	1.60	0.11
Total PA	0.01	0.15	0.88
Group-by-PA	-0.17	-0.55	0.59

Note: PA = physical activity;  $\beta$  = standardized coefficient; t = t-statistic; SBP = systolic blood pressure; BMI = body mass index. \* $p < 0.05$ .

**PA and Inflammation.** Among the BD group, regression models investigating associations between PA and IL-6 included both SBP and BMI as covariates, while models relating PA and CRP included SBP, BMI and BPRS scores (Specific Aim 4, Hypothesis 1). Total PA was not associated with pro-inflammatory IL-6 or CRP in BD participants (See Table 10). These associations remained non-significant when covariates were removed from the model (data not shown; all  $p$ 's < 0.5).

Table 10. Associations between total physical activity and inflammatory markers in BD.

	$\beta$	T	$p$ -value
<b>IL-6</b>			
SBP	0.19	1.15	0.26
BMI	0.50	3.10	0.004*
Total PA	-0.01	-0.04	0.97
<b>CRP</b>			
SBP	0.13	0.81	0.43
BMI	0.43	2.52	0.02
BPRS	0.27	1.52	0.14
Total PA	0.02	0.11	0.92

Note: BD = bipolar disorder; IL-6 = interleukin-6; CRP = c-reactive protein; SBP = systolic blood pressure; BMI = body mass index; PA = physical activity;  $\beta$  = standardized coefficient; t = t-statistic.  
\*  $p < 0.05$ .

Exploratory regression analyses with group-by-PA interaction terms were conducted to examine potential diagnostic group differences in the relationship between PA and inflammatory biomarkers (Exploratory Aim 4). After accounting for SBP and BMI, there were no significant group-by-PA interactions on either IL-6 or CRP (See Table 11). These interactions remained non-significant when covariates were removed from the model (data not shown; all  $p$ 's < 0.5).

Table 11. Group-by-PA interactions on inflammatory biomarkers.

		$\beta$	t	p-value
<b>IL-6</b>				
	SBP	-0.66	7.58	0.000**
	BMI	0.09	1.03	0.31
	Group	0.23	1.01	0.32
	Total PA	0.22	3.04	0.003*
	Group-by-PA	-0.16	-0.70	0.49
<b>CRP</b>				
	SBP	-0.69	-6.99	0.000**
	BMI	0.14	1.36	0.18
	Group	-0.26	-0.99	0.33
	Total PA	-0.25	-3.06	0.003*
	Group-by-PA	0.15	0.57	0.57

Note: PA = physical activity;  $\beta$  = standardized coefficient; t = t-statistic; SBP = systolic blood pressure; BMI = body mass index; IL-6 = interleukin-6; CRP = C-reactive protein. \*  $p < 0.05$ .

Further exploratory analyses revealed that the main effects of total PA in the whole sample displayed in Table 10 did not remain significant (IL-6:  $\beta = -0.15$ ,  $p = 0.09$ ; CRP:  $\beta = -0.06$ ,  $p = 0.5$ ) when interaction terms are removed from the models. Assumptions of collinearity were checked, and VIF for the Group (VIF = 11.88) and Group-by-PA (VIF = 11.82) terms in both models exceeded acceptable cut-offs ( $>10$ ; (Myers, 1990)). This suggests that assumptions of collinearity were violated in these models; therefore, the significant main effects observed in the whole model will not be interpreted (Field, 2013).

## Study 2. Lagged associations between daily mood ratings and PA in bipolar disorder

In order to ensure adequate power for the time lagged analysis, participants whose combined and consecutive (i.e., 24 hour lag) smartphone and actigraphy watch adherence were below 60% ( $< 8$  consecutive days;  $n = 7$ ) were excluded from the analysis. Therefore, the final sample of 31 BD participants submitted an average of 13.12 days (range: 11-14) of mood ratings and wore the actigraphy watch for 12.48 (range: 8-14) days. The average adherence rates for surveys (number of days submitted/total number of days possible = 0.94, SD = 0.07) and watch



data (number of days worn/total number of days possible = 0.89, SD = 0.22) was not associated with total mood ratings ( $r(30) = 0.03, p = 0.88$ ) or total PA ( $r(30) = 0.10, p = 0.58$ ) across the study period, respectively.

**Associations between daily mood ratings and PA in BD.** Results of *a priori* and exploratory analyses are presented in Table 12. Present day mood rating was marginally associated with levels of present day PA exhibited by the BD group (Model A.1:  $F(1,315.3) = 3.34, \beta = 76.36, t = 1.83, p = 0.07$ ). Unsurprisingly, higher present day mood predicted an increase in mood ratings submitted the following day (Model A.2:  $F(1, 324.8) = 26.36, \beta = 0.28, t = 5.13, p < 0.000$ ). Contrary to our hypothesis, present day mood ratings did not predict next day levels of PA (Model A.3:  $F(1,313,79) = 3.61, \beta = -31.98, t = -0.73, p = 0.47$ ) after accounting for next day mood (Specific Aim 1). Our exploratory analysis investigating the converse relationship was also found to be non-significant; present day PA did not predict next day mood rating (Model B:  $F(1,312.63) = 1.38, \beta = 8.02e^{-5}, t = 1.18, p = .24$ ). See Figure 9.

Table 12. Lagged associations between mood and PA.

	<b>Coefficient</b>	<b>St. Error</b>	<b>t</b>	<b>p-value</b>
<b>A. Effects of present day mood</b>				
A.1 Present day PA	76.36	41.79	1.83	0.07
A.2 Next day mood	0.28	0.05	5.13	0.000**
A.3 Next day PA±	-31.98	43.83	-0.73	0.47
<b>B. Exploratory Effects of present day PA</b>				
B.3 Next day mood	$8.02e^{-5}$	$6.83e^{-5}$	1.18	0.24

Note: St. Error = standard error; t = t-statistic; PA = physical activity. ± Statistics for next day mood covariate in model A.3 not shown. \*\* $p < 0.001$

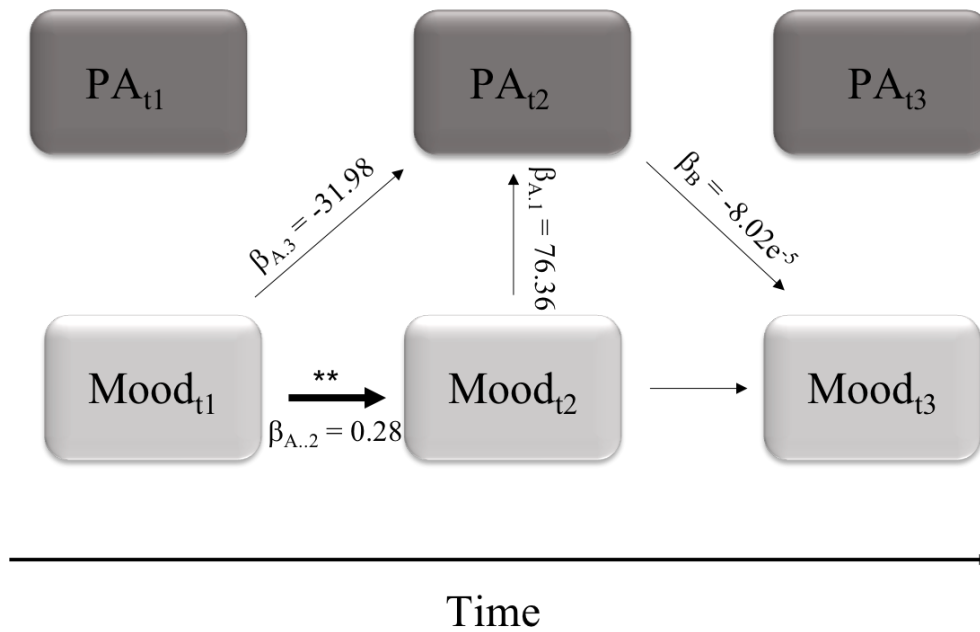


Figure 9. Visual representation of lagged associations between mood and PA. t = time point; PA = physical activity;  $\beta$  = standardized coefficient; A = *a priori* models; B = exploratory models. \*\*  $p < 0.000$

## V. Discussion

The present dissertation project was designed to investigate the relationships between peripheral inflammation, PA, and cognitive performance in bipolar disorder. Further, to disentangle predictors of hypothesized daily variability in PA, a second study was designed to utilize novel EMA technology to examine daily lagged associations between mood ratings and degree of PA exhibited by BD participants. Relative to HC, BD participants in our sample exhibited worse performance on tasks of EF and PS, higher blood serum levels of pro-inflammatory IL-6 and CRP, and less PA over a two week period. Notably, higher BMI and stroke risk in the BD group appears to account for group differences in inflammatory biomarkers and PA. There were no observed significant relationships between inflammatory biomarkers (IL-6 and CRP), PA, and cognitive performance (EF and PS) in this sample of 38 BD participants. Baseline mood symptoms and mood state and average mood ratings across the two-week assessment period did not correlate with inflammatory levels, PA, or cognitive performance. Further, daily lagged analyses revealed that present day mood was not related to next day PA; the converse was also not significant.

Our analyses revealed significant group differences in the expected directions; BD patients were found to display greater blood-serum inflammation, engage in less PA, and perform worse on cognitive tasks of EF and PS compared to the HC group. These results are consistent with a host of previous investigations demonstrating these group differences (Bora et al., 2009; Krane-Gartiser, Henriksen, Morken, Vaaler, & Fasmer, 2014; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013). However, group differences in PA and inflammatory biomarkers did not remain significant after accounting for BMI. This finding can be interpreted in the context of literature demonstrating the impact of BMI on outcomes in BD. For example, recent studies have

elucidated that BMI, and not mood symptoms (Bond et al., 2016) or PA (Rawson et al., 2003), more significantly contributed to elevations in inflammation in BD and HC samples, respectively. Higher BMI in BD is also associated with worse cognitive performance (Colin A. Depp et al., 2015; C. A. Depp et al., 2014; McIntyre et al., 2017; Mora et al., 2017), alterations in brain structure (Islam, Metcalfe, MacIntosh, Korczak, & Goldstein, 2018), greater risk of CVD, and higher mortality rates (Osby, Brandt, Correia, Ekbom, & Sparen, 2001). Therefore, it is possible that BMI is a marker that confers greater risk on functional outcomes in BD, and may prove to be a more useful objective in developing treatments targeted to reduce disability in chronic middle aged patients. For example, more comprehensive treatment regimens aimed at weight loss may correspondingly address concerns regarding daily PA as well as alleviate systemic inflammation. Notably, it has also been suggested that central obesity (i.e., waist-to-hip ratio or waist circumference), and not BMI, is a more accurate obesity predictor of CVD and mortality risk (Hamer, O'Donovan, Stensel, & Stamatakis, 2017; Sahakyan et al., 2015). When this measure replaced BMI in the model, group differences in inflammation and PA remained significant, indicating that this alternate method of quantifying obesity has a unique relationship with these outcomes. Finally, given that the relationship between BMI and inflammation and PA in BD is likely bidirectional, more complex statistical models are required in order to better understand causality. Nevertheless, future studies designed to disentangle the relative contributions of both BMI and central obesity to poor health outcomes in BD is warranted.

### **Predictors of cognition in BD**

Although BD participants performed worse on tasks of EF and PS, neither inflammation nor PA measured during a two-week period following testing were significantly related to cognitive performance in the BD group. These findings suggest that the identified markers may

not underlie cognitive difficulties in this population. It should be noted that the BD sample was relatively well educated and their cognitive performance was normatively unimpaired, thus it is possible that our sample is analogous to the generally cognitively intact patient sub-group identified by Burdick et al. (2014) in their BD sample. Therefore, the lack of cognitive variability among BD participants in our sample may have contributed to the absence of significant associations with the hypothesized predictors (i.e., inflammation and PA). Future studies should focus on a BD sample with higher inter-individual variability in cognitive performance in order to elucidate which markers predict performances that fall within the impaired range. It is also unknown whether the PA and inflammation levels that were measured during the two-week burst are representative of the general levels of activity and pro-inflammatory profiles of the participants. It may be that the cumulative effects of PA and inflammation, but not acute measures of these, are more important to determining cognitive performance levels. Alternatively, there could be acute effects of PA and inflammation levels on cognition in BD but only if PA and inflammation are measured in the weeks *prior* to cognitive testing. Future analyses of cognitive performance data collected at the end of the two-week burst might reveal such associations. Finally, the potential influence of PA and inflammation may be stronger on *change* in cognition over time rather than cognitive performance at a given time-point. Longitudinal data from the ongoing study could be examined in future analyses to see whether PA or inflammation predict cognitive declines in BD.

These results may also suggest that this relatively high functioning sample of middle-aged participants has not accumulated enough pathophysiological burden to impact cognitive functioning. Even if our measures of inflammation and PA were representative of the general state of these participants, it is possible that the cumulative effect of systemic inflammation and

sedentary behaviors does not produce a measurable change in cognition until later in life. This hypothesis is supported by theories of accelerated aging and neuro-progression in BD, which assert that a lifelong cumulation of disease markers leads to an accelerated trajectory of cognitive aging (Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015; Post, Fleming, & Kapczinski, 2012). Therefore, longitudinal studies are required to follow the present cohort to detect whether the hypothesized relationships emerge later in life.

It is also possible that other domains of cognitive functioning are more sensitive to the hypothesized effects of inflammation and PA. For example, episodic memory is another cognitive domain that has been shown to be vulnerable in BD populations (Bora et al., 2009), though it is not as strongly linked to vascular risk. Exercise studies have documented improvements in memory following exercise regimens (Smith et al., 2010), and animal models have demonstrated an increase in hippocampal brain derived neurotrophic factor (BDNF), thought to be associated with neurogenesis, in response to aerobic activity (Neeper, Gomez-Pinilla, Choi, & Cotman, 1995). Although the present study did not directly measure the intensity or type of activity, it is possible that daily PA levels have a more direct impact on memory performance relative to EF or PS. Future analyses will focus on better understanding the relationships between PA and other cognitive domains.

Studies have established relationships between blood-based peripheral inflammatory markers and measures of brain structure and function in patients with major depressive disorder, Alzheimer's disease, and mild cognitive impairment (Frodl & Amico, 2014). Nevertheless, it is possible that blood-based levels of inflammation do not accurately capture the degree of inflammation migrating across the blood brain barrier, particularly in patient populations such as BD that are characterized by a rather low grade chronic inflammatory profile. The utilization of

more direct measures of neuro-inflammation is critical to better understand the degree of inflammation required to impact cognition. For example, quantitative magnetization transfer imaging is one MRI technique that has demonstrated its ability to detect inflammation induced changes to white matter microstructure during an artificially produced inflammatory state (Harrison et al., 2015). More evidence is required to determine how these measures may be used to identify individuals at inflammatory risk for cognitive impairment. While these techniques may offer a more accurate picture of the burden of inflammation on the brain, their costly and time consuming nature render them less feasible in clinical settings. Future studies should focus on combining levels of blood serum inflammatory biomarkers and novel neuroimaging techniques to understand mechanisms driving cognitive change as well as to develop a clinically feasible tool to address these concerns in a health care setting.

### **Understanding physical activity in BD**

As hypothesized, our BD sample engaged in less TPA over the two week collection period. However, TPA was not associated with cognition and inflammation, nor did the BD sample demonstrate greater variability in PA across days. This is inconsistent with previous studies (cited above) demonstrating improved cognition and reduced inflammation with greater exercise or PA. There are several alternate explanations that may have contributed to the lack of significance among these associations. The PA metric measured by our wrist worn devices, the vector magnitude counts per minute, is a measure of total volume of activity exhibited in all three axes. Unfortunately, this metric renders us unable to form conclusions regarding the categorical type (i.e., walking vs. running) and the intensity (i.e., light, moderate, vigorous) of PA each individual exhibits, and it is possible that the device is more accurately measuring random daily movement and not exercise activity. It could be argued that BD participants with

greater manic symptoms registered higher PA as a result of increased goal directed activity and not exercise or walking behaviors, and therefore our measure of activity did not exert the expected effects on inflammation and cognition. However, this hypothesis is not supported by the present sample as neither total smartphone mood nor baseline mood ratings (i.e., YMRS, HAM-D) were associated with total PA. While this type of daily movement is helpful to observe in the context of understanding differences in the daily habits of BD and HC groups, this construct is less informative in investigating cardiovascular health and its impact on cognition and inflammation. It is possible that the hypothesized relationships with inflammation and cognition are only seen in the presence of more intense levels of PA. Indeed, aerobic fitness has been shown to exert a positive impact on cognition in depression (Oertel-Knochel et al., 2014), and a recent study has also demonstrated that CRP may moderate this relationship in younger adults (Hwang, Castelli, & Gonzalez-Lima, 2017). Therefore, future investigations aimed to examine the impact of physical activity on inflammation and cognition should focus on quantifying the degree of activity by introducing hip-worn devices to calculate the metabolic equivalent of task, or introducing exercise regimens in randomized controlled trials.

To explore this more completely, we utilized additional data available to us in which BD and HC participants were asked to report whether they exercised and, if applicable, rate the intensity of exercise (i.e., mild, moderate, or vigorous; data not shown) on daily smartphone surveys delivered to them each evening of the data collection period. Among those days in which participants reported engaging in exercise, there were no group differences in the intensity of exercise reported, the average intensity over the two week period was not associated with TPA, nor were there group differences in TPA when each of the intensity ratings were treated as grouping variables. Intensity ratings were also found to be unrelated to inflammation and



cognition. Similar analyses were carried out at the daily level and also yielded no significant associations between daily self-reported intensity of exercise and daily PA captured by the actigraphy device. The lack of significant associations in these exploratory analyses may be explained in several ways. First, it is possible that the smart phone surveys of exercise intensity and actigraphy measurement of PA represent two related, yet distinct, constructs. Indeed, PA measured by actigraphy encompasses all movement exhibited while questions regarding intensity of exercise are exclusive to periods subjectively identified as exercise. Alternatively, it is also possible that individuals are inaccurate in reporting their level of exercise. Future analyses could use individually-tailored analyses of the actigraphy count data to identify “bouts” of high activity that might correspond to exercise epochs. The length and frequency of such bouts could then be examined for group differences and for associations with inflammation and cognitive performance.

Understanding IIV of PA is a relatively novel concept among the actigraphy and exercise literature. Previous research groups investigating IIV have defined this construct by calculating iSD, dividing the iSD by the mean (coefficient of variance), or by employing linear mixed models to statistically account for linear trends and group differences in means. We took the latter approach, adopted from Watts et al. (2016), to calculate IIV of PA in our sample of BD participants and found that there were no group differences in the day to day variability of PA exhibited. This finding is inconsistent with the two previous studies that have demonstrated greater variability in PA across time in BD (Krane-Gartiser et al., 2017; Shou et al., 2017). While it is possible that significant group differences in these studies can be explained by differences in methodology, it should be noted that the present sample also did not yield significant group differences in the iSD of PA (data not shown) across days of the study. Notably, while the

current investigation utilized a 24 hour period (1 day) as the smallest unit of time, these previous studies instead chose to break one day into multiple components (e.g., morning, afternoon, evening). It is therefore possible that heightened variability is only observed when time points are broken into units finer than 24 hour periods.

To the best of our knowledge, this was the first study to investigate the lagged associations between mood and PA in a sample of BD patients. Unfortunately, our hypothesis that mood would influence PA exhibited the following day was not supported by the data. A majority of the BD participants reported simultaneous elevations in both manic and depressed symptoms ( $n=15$ ) at baseline, and the overall sample exhibited a relative small range of daily mood ratings (range:  $-1.82 - 0.93$ ). Therefore, individuals in the current sample may not have experienced sufficient polarity or variability in mood that is required to induce a measurable change in PA. It is also possible that the proposed lagged associations exist on a smaller time interval (i.e., hourly) and these relationships remained undetected in our analysis conducted on the time scale of 24 hours. Group differences in IIV (Krane-Gartiser et al., 2017; Shou et al., 2017) demonstrated by studies that divided one day into three time points (i.e., morning, afternoon and evening) suggests that this strategy may also yield interesting results with regard to lagged analyses. Future studies should focus on obtaining data that represents a wider range of mood symptoms or alternate measurement of mood (i.e., positive and negative affect), and attempt to break the lagged time scale into smaller units. In addition, it might be fruitful to examine the time lagged association between atypicality of mood and atypicality of PA levels. The deviation of each day's measurement of mood or PA from that participant's estimated trajectory over the two-week period may indicate unusually extreme moods or levels of PA, and these may be more predictive of each other than the absolute levels of either.

## **Differential associations between inflammation, PA, and cognition in bipolar and healthy control samples**

Given established relationships between inflammation, PA, and cognition in psychiatrically healthy samples, it is critical to not only examine whether these relationships exist among BD patients but also to explore whether the observed relationships differ between groups. Significant group interactions might suggest that the underlying pathophysiology of BD alters the relationships between inflammation, PA, and cognition in a manner that may prove useful in designing targeting treatments. To this end, we included the full sample of BD and HC participants to explore group interactions among all *a priori* models. Results suggest that neither group shows strong relationships between inflammation, PA and cognition. This may be explained by the fact that our BD group appears to be relatively high functioning and only mildly symptomatic, and therefore is likely more similar to the HC group than expected. The lack of relationships in either group was unexpected given the prior literature, but can be explained by many of the same methodological considerations reviewed above, including chosen cognitive domains, and methods for assessing PA. HC participants were also excluded for medical or neurological comorbidities that can lead to over-active inflammatory processes or cognitive impairment, which may have resulted in a sample that did not possess adequate variability to detect these associations.

## **Unique methodology to investigate outcomes in BD**

The study of bipolar disorder presents numerous challenges for investigators interested in understanding underlying mechanisms driving poor functional outcomes. This challenge is a result of many factors, including but not limited to the cyclical and alternating course of the disease, numerous comorbidities, treatment resistance in individual patients, and disparities in

access to healthcare in academic medical settings. This dissertation project is unique in that it conceptualizes these challenges as a fundamental feature of the disease, and employs several novel techniques aimed to either quantify their impact or to promote greater access in the context of potentially chaotic lifestyles. These methodologies warrant further discussion.

**EMA assessment.** EMA technology as a feasible platform presents an exciting new avenue to measure ecologically valid data to better understand functional disturbance experienced by BD patients. Severity and chronicity of illness as well as cognitive functioning are associated with worse functional outcomes, and have been specifically reported to predict reduced social and occupational engagement (Gitlin & Miklowitz, 2017). However, many of the currently used symptom inventories administered in research and clinical settings are subject to recall and state-dependent biases (Artino, Phillips, Utrankar, Ta, & Durning, 2018). Further, chaotic lifestyles associated with polarized mood can make it unreasonable to expect some BD patients to return to clinical settings regularly. EMA offers an alternative approach to measure these dynamic constructs in real world settings. Additionally, this technology can be utilized as a platform to deliver tailored treatments (C. A. Depp, Moore, Perivoliotis, & Granholm, 2016) as well as assess cognitive functioning (Moore, Swendsen, & Depp, 2017). Therefore, it is critical to establish acceptable adherence and feasibility of this methodology.

The results of this study lend support to the feasibility of utilizing EMA technology to measure both mood and PA in BD samples. Of our total BD sample, 81% (n = 31) passed minimal criteria of 60% consecutive day adherence to both smartphone mood ratings and actigraphy watches. Of this subsample, average adherence rates for both smartphone and watch platforms exceeded 85%. These rates are comparable to other reports of greater than 80% adherence in populations with severe mental illness (i.e., BD and schizophrenia), though study

aims (e.g., assessment vs. treatment delivery) and EMA platform (e.g., smartphone surveys vs. text messages) differ across these studies (C. A. Depp, Moore, Perivoliotis, et al., 2016). Our own collaborators have also published acceptable adherence rates of 68% in BD (C. A. Depp, Moore, Dev, et al., 2016) and 86% in older adults with HIV (Moore, Kaufmann, et al., 2017) who were delivered smartphone assessments. Of the small handful of studies that have utilized actigraphy watches among BD patients, most have done so among inpatient samples where watch adherence was likely closely monitored by medical professionals. To date, only two other research groups employed this technology in outpatient BD samples and only one reported adherence rates, which noted an average daily adherence also exceeding 80% (Shou et al., 2017). Therefore, previous investigations, combined with the current study, suggest smartphone surveys and actigraphy watches are feasible not only in control participants, but also in older adults and those with affective disturbance. Future studies should utilize this technology to assess mood, cognitive, and functional status in patients as well as to deliver individualized treatment protocols.

**Intra-individual variability.** Even within a clinically defined mood state (i.e. manic, depressed, mixed), symptoms of BD can manifest in a number of combinations that lead to varied behavioral changes across days. For example, it is conceivable that an individual experiencing a mixed state alternates between sedentary behaviors, extreme bouts of activity, or substance use within a matter of days. Therefore, understanding variability in behaviors across time within individuals may be not only an important descriptive feature of the disorder but also an important contributing factor to pathophysiological changes and/or functional disability in this population. Our investigation of IIV in PA did not yield significant results, the potential reasons for which have already been discussed, but nevertheless demonstrate one method that can be

utilized to model variability in BD. The strength of this approach lies in its ability to account for group differences in mean levels of PA as well varying systematic trends in PA across time in each participant. Although not a focus of this project, this method also allows investigators to build more complex models to better understand the impact of IIV in BD. For example, future studies should explore whether IIV of PA, and not total PA, is significantly associated with inflammation or cognition. Alternatively, these models can be applied to investigate IIV of other constructs, including both inflammation and cognition, across time.

**Lagged associations.** Given that mood polarity and variability is a cardinal feature of BD, it is also critical to understand how changes in mood across time might impact other behavioral, physiological, and cognitive characteristics of the disorder. Towards this end, we employed a lagged analysis to determine how daily changes in mood impacts subsequent daily levels of PA. Although our results were nonsignificant, other studies have used this approach in BD to investigate lagged associations of daily rated positive and negative affect on next day levels of impulsivity (C. A. Depp, Moore, Dev, et al., 2016) and sleep (Kaufmann, Gershon, Eyler, & Depp, 2016) with success. As with IIV, this method allows investigators to better understand temporal correlates of varying mood and affect. Future studies should investigate how changes in daily levels of mood impact inflammation or cognitive domains known to be sensitive to mood (i.e., processing speed).

### **Study limitations**

The present dissertation project has a number of limitations that should be considered. The cross sectional nature of this study limits our ability to investigate causal links between inflammation, PA, and cognition, or to understand how these relationships may alter with respect to age. Additionally, we were unable to recruit the proposed sample size of 55 BD subjects,

which limits our power to detect the hypothesized associations. Nevertheless, effect sizes for all independent samples t-tests and multiple regression analyses ranged from medium to large (Cohen's  $d$  range: 0.44 – 0.92;  $f^2$  range: 0.39 – 0.67). The smaller sample size also restricts our ability to explore mediating effects, though these data do support further investigation of obesity as potential a mediating factor among the proposed relationships. Our reduced sample size is primarily explained by the high numbers of patients who were excluded at their screening visit. These exclusions were due to unforeseen co-morbidities among BD participants that posed potential confounding relationships to the parent project's study aims. Figure 9 displays an example of the number of dropped participants in year one of the study.

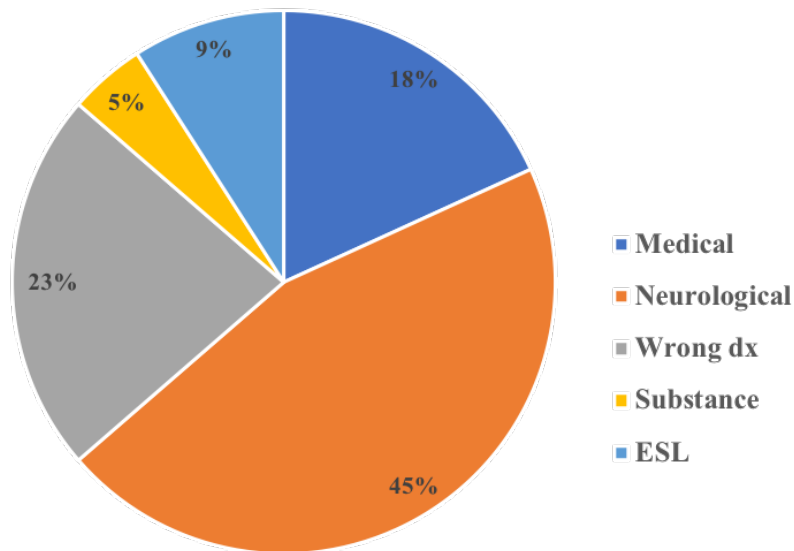


Figure 10. Year 1 reasons for excluding bipolar patients (n=22). ESL = English as a second language; dx = diagnosis.

Methods proposed to assess inflammation may have also limited our ability to detect relationships in the present sample. There are several alternative peripheral biomarkers that are implicated in inflammation or vascular risk, including intercellular adhesion molecule (I-CAM), vascular cell adhesion molecule (V-CAM), vascular endothelial growth factor (VEGF), and TNF- $\alpha$ , that are also worth considering in the context of the hypothesized relationships. These

biomarkers were not included in our *a priori* hypotheses due to the lack of literature demonstrating elevations of these specific biomarkers in BD and/or their associations with cognition or PA in other populations. Nevertheless, exploratory models were conducted to determine whether these alternate biomarkers emerge as important predictors of cognition or PA. The results of these analyses (data not shown) were likewise nonsignificant, indicating that our choice of biomarkers did not limit findings in the current sample. An alternative approach to investigating relationships with biomarkers includes combining all biomarker data to create a latent, or composite, variable that represents a robust inflammatory index score. For example, we have previously created a vascular endothelial index (VEI), comprising of I-CAM, V-CAM, VEGF, and found that a higher VEI was related to performance on tasks of executive functions in HC but not SZ groups (Nguyen et al., 2017). Although it is outside the scope of this project to perform factor analyses to create a data driven inflammatory index, we created exploratory composite scores by averaging biomarkers with strong correlational (IL-6 and CRP;  $r(95) = 0.63$ ,  $p < 0.000$ ) or theoretical (I-CAM, V-CAM, and VEGF) relationships, and found no significant relationships between these composite scores and cognition or PA. Finally, high sensitivity CRP (hsCRP) is another measure of CRP that has demonstrated clinical utility in detecting an individual's future risk to develop cardiovascular conditions (Ridker, 2004). While this unit of measurement was not utilized in the current project, future analyses would benefit from incorporating hsCRP to determine if the hypothesized relationships exist.

## **Conclusions**

Despite the abovementioned limitations, this study is among the first to investigate a) relationships between inflammation, PA, and cognition; and b) lagged associations between daily mood ratings and next day levels of PA. The present data replicated previous studies



demonstrating greater blood serum levels of IL-6 and CRP, lower levels of PA, and worse performance on tasks of EF and PS in BD participants compared to HC. However, our hypotheses regarding associations between inflammation, PA, and cognition were not supported, suggesting that IL-6, CRP, and PA measured during a two-week period may not contribute to cognitive performance deficits in BD. Further, PA in the BD group was relatively stable across time and was not influenced by daily changes in mood, suggesting that PA in this population occurs relatively independent of mood. Further studies are needed to examine predictors of cognition in BD and associations with inflammation and PA.

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