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# Circadian preferences, oxidative stress and inflammatory cytokines in bipolar disorder: A community study

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ABSTRACT

*Objective:* To assess circadian preference among a community sample of people with bipolar disorder, major depression and without any mood disorders. Secondly, we investigated the association of circadian preference with cytokines interleukin-6 (IL-6), interleukin-10 (IL-10) and, tumor necrosis factor alpha (TNF-α) and oxidative stress assessed by thiobarbituric acid reactive substances (TBARS), uric acid and Protein Carbonyl Content (PCC).
*Method:* A cross-sectional study nested in a population-based sample. Caseness was confirmed with the Structured Clinical Interview for DSM-IV. A sample of 215 participants, in whom we measured circadian preferences, IL-6, IL-10, TNF-α, TBARS, uric acid, PCC. Biological rhythms were evaluated using the Biological Interview of Assessment in Neuropsychiatry.
*Results:* Bipolar group presented a higher alteration in biological rhythms (40.40 ± 9.78) when compared with the major depression group (36.35 ± 9.18) and control group (27.61 ± 6.89) $p < 0.001$. Subjects with bipolar disorder who were active at night and had a day/night cycle reverse showed decreased levels of IL-6 (t, 44 = 2.096; $p = 0.042$), (t, 44 = 2.213; $p = 0.032$), respectively. In the bipolar disorder group subjects who presented day/night cycle reverse had lower TBARS levels (t, 41 = 2.612; $p = 0.013$). TNF-α were decreased in subjects more active at night with bipolar disorder.
*Conclusion:* Lower serum levels of IL-6, TNF-α and TBARS were associated with evening preference in bipolar disorder group. These findings suggest that chronotype may alter the levels of interleukins and oxidative stress levels in bipolar and healthy subjects. A better understanding of the role of circadian preferences in levels of interleukins and oxidative stress are needed.

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## 1. Introduction

Chronotype is defined as a person's preferred time of the day to conduct activities (Kerkhof, 1985). Many physiological, biochemical, and psychological factors that are involved in a person's chronotype do not depend on the alternation of light and darkness (exogenous rhythms). Some studies found that subjects with bipolar disorder (BD) and major depressive disorder (MDD) tend to be more evening type. In contrast, individuals with an evening preference have been found to be more prone to depression (Merikanto et al., 2013). In a prospective study, Natale et al., 2005 postulated that subjects with an evening preference, who normally have disruptions in biological rhythms, may be predisposed to seasonal affective disorder (Natale et al., 2005).

Evidence has shown that the disruption of biological rhythms plays a direct role in the development of mood disorders (Wirz-Justice, 2006; Faria et al., 2015; Karatsoreos, 2014). Genetic studies with humans have found specific genes that make up the genesis of circadian rhythms in the manifestation of BD and depression (Mitterauer, 2000). Alterations in biological clocks at molecular level could lead to neurobiological dysfunction, which in turn may lead to a depressive state (Nechita et al., 2015). Changes in circadian rhythms have been reported in subjects during the acute episode and in the inter-episode period (Harvey, 2008; Millar et al., 2004). Besides the discussion about the causal mechanism that has been widely discussed, Bechtel (2015) highlighted that the relationship between mood disorder and biological disruption are effects of a common cause and that genes and proteins implicated in both simply have pleiotropic effects (Bechtel, 2015).

Social contacts, meals, activities, sleep-wake cycles, and biochemical pattern are characteristics of biological rhythms. Changes in these

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patterns may have an impact on mood disorders. Moreover, staying awake late at night and waking up late in the morning may result in an abnormal relationship between sleep homeostatic process and circadian rhythms (Reid and Zee, 2005).

Increasing evidence suggests that chronic mild inflammatory processes both in the periphery and the brain are involved in the pathophysiology of depression and anxiety (Berk et al., 2011). Pro-inflammatory cytokines, which include interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and anti-inflammatory cytokines, such as interleukin-10 (IL-10), are involved in this process (Gordon and Martinez, 2010). The relationship between OS mechanisms and inflammatory response are complex. Increased levels of inflammatory cytokines will promote an imbalance in redox state by increasing the levels of reactive oxygen species. Furthermore, the imbalance in redox state will increase the production of proinflammatory cytokines. Studies have shown that oxidative stress (OS), assessed by thiobarbituric acid reactive substances (TBARS), protein carbonyl content (PCC), acid uric, as well as, pro-inflammatory mechanism have a key role in the development of neurodegenerative diseases and psychiatric disorders (Ng et al., 2008; Rosenblat et al., 2015; Kapczinski et al., 2011; Magalhaes et al., 2012; Gu et al., 2015). TBARS levels are directly related to cell lipid peroxidation while antioxidant systems involve coordinated effects of antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD), and glutathione peroxidase (GPx) (Reddy et al., 1991). Despite the large number of studies showing the involvement of inflammation and oxidative stress in major depression and bipolar disorder, many authors have reported reduced levels of pro-inflammatory cytokines and oxidative stress parameters, as well as increased levels of anti-inflammatory cytokines, or no differences between them (Munkholm et al., 2013; Barbosa et al., 2014).

Anti-inflammatory agents have become of great interest in the novel treatment of MDD. A recent study found that infliximab reduced the depression-like behavior in rats exposed to chronic mild stress (CMS) compared with vehicle-injected in stressed and non-stressed rats (Karson et al., 2013). Similarly, a meta-analysis with 6262 subjects showed that the use of nonsteroidal anti-inflammatory drugs was associated with better antidepressant effects. The treatment, in particular celecoxib, decreased the depressive symptoms without increased risks of adverse effects, with or without concomitant antidepressant medication (Kohler et al., 2014).

Researchers have found that in post-mortem frontal cortex of BD patients there were moderately increased plasma levels of pro-inflammatory cytokines, such as IL-6 (Maes et al., 1995; Ortiz-Dominguez et al., 2007; Rao et al., 2007). There is also some evidence suggesting oxidative disturbances in serum MDA levels measured as thiobarbituric acid reactive substances (TBARS) in psychiatric disorders, such as bipolar mood disorder and major depression (Tuncel et al., 2015; Ng et al., 2008).

There are some evidence that circadian disruption adversely affects immune function (Adams et al., 2013; Lange et al., 2010; Toth, 1995). In a randomized double-blind placebo-controlled study with depressive patients, Cho et al. found higher levels of IL-6 and TNF-α in women who had sleep disturbance when compared to those without sleep disturbance (Cho et al., 2008). Cytokines are known to have a circadian pattern and it is established that pro-inflammatory and anti-inflammatory processes present a circadian regulation. The relationship between circadian rhythms and inflammation is an important step in understanding the effects of chronic stress (Scheff et al., 2010).

In addition, TNF-α is considered a key sleep regulatory substance (Bryant and Curtis, 2013). The redox balance is influenced by inflammatory cytokines and reactive oxygen species promote production of proinflammatory cytokines (Filippin et al., 2008; Trachootham et al., 2008). However, there is a lack of studies on circadian preference aiming at immune response and OS in patients with mood disorder.

### 1.1. Aims of the study

The present study aimed to assess circadian preference among a sample of individuals with BD, major depression, compared to a control group. Secondly, we investigated the association of circadian preference with interleukin-6, interleukin-10, tumor necrosis factor, thiobarbituric acid reactive substances, uric acid, protein carbonyl content (PCC) within groups. As far as we know, the present study is the first to verify the immune response and oxidative stress and circadian preferences in individuals with depression and bipolar disorder.

## 2. Methods

This was a cross-sectional study nested in a population-based study with drug-naïve young adults aged 18–24 years. The main purpose was to assess the prevalence of mood disorder in the population. The study sample consisted of 1.560 participants, living in an urban area of the city of Pelotas, southern Brazil. Sample selection was performed by clusters, in the period ranging from August 2007 to December 2008, in a population of 39,667 people in the age range according to the current census of 448 sectors in the city of Pelotas (IBGE, 2008). In order to ensure the necessary sample inclusion, 89 census-based sectors were systematically drawn. After being identified, the subjects were informed about the experiment and provided their free and informed consent. Those who accepted the invitation answered a questionnaire regarding socio-demographic data, and participated in a structured diagnostic interview. The study was approved by the Ethics Committee of the Catholic University of Pelotas (UCPel).

After an initial psychopathology screen, all participants underwent the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). There was an attempt to recruit every person with a past or current history of manic or hypomanic episode – the target sample – from the population-based study. Additionally, two groups of control subjects were recruited from the population-based study: people without any history of affective disorder were randomly selected and matched to cases on age and sex, and socio-economic situation— (healthy controls); and people with a current depression but no history of (hypo) mania (active control group). Of these, we were able to obtain data on 214 subjects (83% of the originally intended sample) (Jansen et al., 2011; Magalhães et al., 2012) (Fig. 1). The Structured Clinical Interview for DSM-IV (SCID) was used to improve diagnosis reliability (IBGE, 2008). Some subjects were reclassified after this interview, which was used as the group defining criterion for the present study. The SCID-interviews were conducted by trained psychologists.

Chronotype was assessed using the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009, 2010). It is an 18-item interviewer-administered instrument used to investigate the main areas related to circadian rhythm disturbance (sleep, social rhythm, activities, and eating pattern) in bipolar disorder. Higher scores indicate greater biological rhythm alterations. Three more questions are used to assess chronotype (morningness-eveningness preferences): "Do you tend to be more energized for work and interpersonal relationships at night?"(Active at night), "Do you feel more productive in the morning?" (Less productive in the morning) and "Do you have your day/night cycle reversed?" (Day/night cycle reverse). The responses range from never (0), seldom (1), often (2) to always (3). The validity and reliability studies of the Portuguese BRIAN version include information about its factor analysis (Giglio et al., 2009). The severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967), and the severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS) (Vilela et al., 2005).

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