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Pro-inflammatory cytokines, mood, and sleep in interepisode bipolar disorder and insomnia: A pilot study with implications for psychosocial interventions

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Abstract

Objective—Pro-inflammatory cytokines are associated with bipolar disorder (BD), but less is known about how cytokines function during the interepisode period. This study examined cytokines, mood symptoms, and sleep in individuals with interepisode BD with complaints of insomnia. We also investigated the effects of a BD-specific modification of cognitive behavior therapy for insomnia (CBTI-BP) on cytokine levels.

Methods—The 22 adults with interepisode BD Type I and insomnia were drawn from a subset of an NIMH-funded study. Participants were randomly allocated to CBTI-BP (n = 11) or Psychoeducation (PE; n = 11). Participants completed a sleep diary, rated self-report measures of mania and depression, and provided samples assayed for interleukin (IL)-6 and tumor necrosis factor soluble receptor 2 (sTNF-R2).

Results—IL-6 was associated with mania symptoms (r_s = 0.44, p = .041) and total sleep time (r_s = −0.49, p = .026). IL-6 was related to depression symptoms at the trend level (r_s = 0.43, p = .052). sTNF-R2 was not significantly related to mood or sleep measures. From pretreatment to posttreatment, CBTI-BP compared to PE was associated with a non-significant, large effect size decrease in IL-6 (z = −1.61, p = .13, d = −0.78) and a non-significant, small-medium effect size decrease in sTNF-R2 (z = −0.79, p = .44, d = −0.38).

Conclusions—These findings provide preliminary evidence that IL-6 is related to mania symptoms and shorter TST in interepisode BD. A treatment that targets sleep in BD could potentially decrease IL-6 although replication is warranted.

Keywords

bipolar disorder; sleep; mood; inflammation; pro-inflammatory cytokines

Bipolar disorder (BD) affects nearly 4% of the population and is among the top ten leading causes of disability (1,2). Mania symptoms, depression symptoms, and sleep disturbance are hallmark features of BD (3–5). While extant research has identified a range of cognitive,

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behavioral, social, and clinical predictors of core aspects of BD, the biological correlates are not well defined.

There is evidence implicating inflammation as one putative biological mechanism across psychiatric conditions. Peripheral levels of pro-inflammatory cytokines—proteins that coordinate adaptive and innate immune response—are a common measure of systemic inflammation. Altered pro-inflammatory cytokines have been observed in major depressive disorder (6–8), schizophrenia (9), and anxiety disorders (10,11). Additionally, pro-inflammatory cytokines have been linked to poor physical health outcomes (6), neuropsychological impairment (12), and chronic pain (13); outcomes that occur at elevated rates in psychiatric conditions.

Goldstein, Kemp, Soczynska, and McIntyre (14) have proposed that inflammation may also be an important biological mechanism in BD. Their model first describes bidirectional relationships between mania or depression and inflammation. Next, these paths are mediated by sleep disturbance or chronic pain. The resulting inflammation then leads to negative mental and physical health consequences. Episodes of mania and bipolar depression have generally been associated with increased pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-related molecules (e.g., TNF-α, soluble TNF receptor 1 [sTNF-R1], and soluble TNF receptor 2 [sTNF-R2] (15–21). Previous research has also suggested that the increase in pro-inflammatory cytokines associated with mania and depression may be resolved during the interepisode period (15,22–24). However, more work is needed to determine whether subsyndromal symptoms of mania and depression may be associated with elevated pro-inflammatory cytokines during the interepisode period.

Subsyndromal symptoms during the interepisode period are common and associated with relapse to episodes of mania and depression (3,25,26). Examining the relationship between subsyndromal mood symptoms and pro-inflammatory cytokines may be useful for understanding impairment during the interepisode period. Evidence for the relationship between pro-inflammatory cytokines and symptom measures of mania and depression have been inconsistent or non-significant during acute mood episodes (15,17,18,27–31). However, the relationship between mood symptoms and pro-inflammatory cytokines has not been considered during the interepisode period. Nor has there been work examining the pathway between sleep disturbance and pro-inflammatory cytokines in BD.

Sleep disturbance such as short sleep duration and insomnia have been strongly implicated in BD (3,25,32,33). Shorter sleep duration has been connected to increased IL-6 activity in other clinical samples (34,35), adolescents (36), and older men (37). However, a meta-analysis suggests that these effects may be small (38). Further, the effect of sleep deprivation on TNF-α, sTNF-R1, and sTNF-R2 activity is mixed (39–43). Chronic insomnia is related to increased IL-6 as well as a shift from nighttime to daytime IL-6 and TNF-α secretion (34,44). Total wake time (TWT) during the night, which reflects the sleep disturbance characteristic of insomnia (45), is also positively associated with IL-6 in chronic insomnia (34). Furthermore, cytokines may have a reciprocal influence on sleep disturbance, which is supported by a study that reported that higher TNF levels prior to sleep were associated with greater sleep continuity whereas lower sleep continuity was related to higher TNF

production in the morning among adults with rheumatoid arthritis (46). While these studies suggest that pro-inflammatory markers may be related to sleep disturbance in the general population and other disorders, to the best of our knowledge, no studies have examined this relationship in BD. Notably, however, it has been hypothesized that IL-6 is related to sleep disturbance in BD (14,47). Similarly, TNF-related molecules such as TNF-α, sTNF-R1, and sTNF-R2 may also be implicated given evidence for elevated activity during episodes of mania and depression as well as some evidence that sleep disturbance may be related to TNF activity (16–21,35,38,39,41–43).

The aim of this study was to examine inflammation in interepisode BD by empirically evaluating components of the Goldstein et al. (14) model of inflammation in BD. This study also tested if targeting a component of this model—sleep disturbance—can result in changes in measures of inflammation. The first aim was to test the relationship between mood symptoms and pro-inflammatory cytokines in participants with interepisode bipolar I disorder and insomnia. It was hypothesized that mania and depression symptoms would be positively associated with IL-6 and sTNF-R2. The second aim was to test the relationship between sleep disturbance and pro-inflammatory cytokines in BD. It was hypothesized that total sleep time would be negatively associated with IL-6 and sTNF-R2 and total wake time would be positively associated with IL-6 and sTNF-R2. The third aim was to test if a BD-specific modification of cognitive behavior therapy for insomnia (CBTI-BP) can affect pro-inflammatory cytokines in patients with interepisode bipolar I disorder and insomnia. It was hypothesized that CBTI-BP compared to Psychoeducation (PE) would be associated with decreased IL-6 and sTNF-R2 from pretreatment to posttreatment.

Method

Participants

The participants for the current study were drawn from a subset of those enrolled in an NIMH pilot randomized controlled trial (RCT) to determine if CBTI-BP can improve mood state, sleep, and functioning (48). Data were collected from April 2011 to March 2012. OMT collection was added to collect pilot data on inflammatory markers after 29 of the total 58 participants were enrolled, providing a sample of 29 participants for OMT collection. Two participants did not consent to OMT collection and five participants had samples that were unable to be assayed, providing a total sample of 22 participants with OMT for analysis. There were no significant differences on demographic or clinical characteristics between participants with OMT data (n = 22) compared to participants without OMT data (n = 36). Participants that provided OMT samples had significantly longer total wake time, $t(54) = 2.30$, $p = .026$. There were no other significant differences for any sleep variables between participants that did or did not provide OMT samples. Twenty-two adults with interepisode bipolar I disorder and insomnia received CBTI-BP (n = 11) or PE (n = 11). Among the randomized participants in the present sample, 3 CBTI-BP participants and 2 PE participants dropped out during treatment. Attrition rates were not significantly different between treatment groups in the present sample, $\chi^2(1, N = 22) = 0.26$, $p = .61$. Demographic characteristics of the present sample are presented in Table 1. Detailed information on study design and inclusion/exclusion criteria can be found elsewhere (see (48)). All study

procedures were approved by the University of California, Berkeley Institutional Review Board. Informed consent was obtained for all participants.

Treatments

CBTI-BP—Cognitive behavioral therapy for insomnia (CBT-I) was modified to increased safety and tolerability related to stimulus control and sleep restriction (48). To minimize the risk of hypomania or mania relapse resulting from sleep deprivation, time in bed was restricted to no less than 6.5 hours. CBT-I was also modified to target features of sleep in BD by incorporating components of interpersonal and social rhythm therapy, chronotherapy, and motivational interviewing. The first session focused on case formulation, goal setting, motivational interviewing, and sleep/circadian education. Subsequent sessions included behavioral modules (e.g., stimulus control, sleep restriction, and regularizing sleep-wake times) and cognitive modules (e.g., correcting unhelpful sleep-related beliefs and reducing sleep-related worry or vigilance).

PE—PE provided information about sleep, stress, diet, health, exercise, and mood in BD. PE did not facilitate or plan for behavior change.

Materials and Procedure

Structured Clinical Interview for DSM-IV (SCID)—The SCID is a semi-structured interview used to assess Axis I diagnostic criteria for the DSM-IV-TR (45). The SCID has demonstrated good reliability (49). The SCID was used to assess diagnostic criteria for BD Type I.

Duke Structured Interview for Sleep Disorders (DSISD)—The DSISD is a semi-structured interview that assesses sleep disorders defined by DSM-IV and International Classification of Sleep Disorders-2 criteria (50). The DSISD was used to assess diagnostic criteria for primary insomnia.

Young Mania Rating Scale (YMRS)—The YMRS is an 11-item measure rated on a five-point scale used to assess mania symptoms. It has been shown to have good reliability and validity (51). The YMRS was also examined with the sleep items (item #1) removed.

Quick Inventory of Depressive Symptomatology (QIDS)—The QIDS is a 16-item measure rated on a four-point scale used to assess depression symptoms (52). The measure has demonstrated good reliability and validity (52). The QIDS was also examined with the sleep items (items #1–4) removed.

Sleep diary—The sleep diary was based on the Expanded Consensus Sleep Diary for Morning, a validated self-report measure of sleep patterns (53,54). Sleep diary was recorded each morning for one week preceding the laboratory assessment. In the present study, total sleep time (TST) and total wake time (TWT) were the primary measures of sleep disturbance. TST was selected because shortened TST is linked to increased mania symptoms (33), depression symptoms (32), and pro-inflammatory cytokines (34,55,56). TWT was selected because it reflects the core insomnia diagnostic criteria (45), is associated

with negative mood in BD (25), and is related to pro-inflammatory cytokines in insomnia (34). TWT was calculated as a composite of sleep onset latency (SOL), wake after sleep onset (WASO), and early morning awakening (EMA; (25)).

Collection and measurement of cytokines—Oral Mucosal Transudate (OMT) samples were collected with OraSure devices (OraSure Technologies, Bethlehem, PA). OMT has been validated for assessing pro-inflammatory cytokines and is correlated with levels found in plasma (57). Samples were collected one week before and after the eight week treatment. All samples were collected between 3:00 and 7:00 P.M. (58). The OraSure device contains a cotton fiber pad treated with a hypertonic salt solution that enhances the transport of OMT across the gingival crevice and oral mucosa (59,60). The cotton pad is held between the right lower cheek and gum for 3 minutes. The cotton pad is then inserted into a tube containing a buffer solution to preserve the sample. Following collection, oral fluids were centrifuged at 800 g for 15 minutes and then stored at −80°C until processed. All biochemical analyses were conducted by ProNovus Bioscience, LLC (Mountain View, CA).

All biochemical assays were conducted with IL-6 and sTNF-R2 Quantikine ELISA kits (R&D Systems, Minneapolis, MN). sTNF-R2 is the soluble receptor for TNF, which reflects TNF activity and is more stable than measuring TNF directly (61,62). Assay sensitivities were 0.11 pg/mL and 2.3 pg/mL for IL-6 and sTNF-RII, respectively. Minimum detectable dose was 0.01 pg/mL and 1.4 pg/mL for IL-6 and sTNF-RII, respectively. Intra- and inter-assay coefficients of variation (CV) for the IL-6 ELISA were 3.6% and 5.2%, respectively. Intra- and inter-assay CV for the sTNF-RII ELISA were 0.6% and 1.02%, respectively. Sensitivity and reliability values were provided by ProNovus Bioscience, LLC (Mountain View, CA). All assay kits were validated and all samples were assayed on the same lot. Each sample was tested in duplicate. The Shapiro-Wilk normality test indicated that unadjusted IL-6 ($W = .64$, $p < .001$) and sTNF-R2 ($W = .73$, $p < .001$) values were not normally distributed. Hence, values were log transformed, which resulted in values that fit a normal distribution for IL-6 ($W = .95$, $p = .270$) and sTNF-R2 ($W = .95$, $p = .312$). Histograms for unadjusted and log transformed values for IL-6 and sTNF-R2 are displayed in Figure S1, Supplemental Digital Content 1.

Medications—A pharmacotherapy tracking log was completed at pretreatment and posttreatment. Dose, time of day taken, frequency of use, missed doses, and side effects were assessed. 21 participants (95.5%) were prescribed mood stabilizers and 12 participants (54.5%) were prescribed sleep medication.

Data analysis—The first two aims were addressed with non-parametric Spearman correlations. The third aim used hierarchical linear models (HLM) with restricted maximum likelihood estimation. This statistical method can account for the relationships between repeated measurements and does not have the same missing data restrictions of traditional regression analyses. The fixed part of the model included an indicator for treatment condition (CBTI-BP and PE), time (pretreatment and posttreatment), and the interaction between treatment condition and time. The random part of the model included a random intercept for participant.

This study was a pilot study, and thus was not powered to obtain statistically significant effects at the .05 level (63,64). Reporting and interpreting results will emphasize effect sizes in addition to statistical significance (65). The correlation coefficient is a measure of effect size, and will be interpreted as 0.10 = small effect size, 0.30 = medium effect size, and 0.50 = large effect size (66,67). The treatment effect on the change in pro-inflammatory cytokines from pretreatment to posttreatment was expressed as Cohen's *d*, and will be interpreted as 0.20 = small effect size, 0.50 = medium effect size, and 0.80 = large effect size (66). Given that this was a pilot study with a small sample size, covariates were not included to reduce the possibility of overfitting models (68). All statistical analyses were conducted with R (69).

Results

Means, standard deviations, and intercorrelations for study variables are presented in Tables 1–3. Results indicated that mania symptoms were associated with IL-6 with a medium-large effect size ($r_s = 0.44$, $p = .041$) and with sTNF-R2 with a small, non-significant effect size, ($r_s = -0.10$, $p = .68$). Depression symptoms were associated with IL-6 with a trend-level, medium-large effect size ($r_s = 0.43$, $p = .052$) and sTNF-R2 with a small, non-significant effect size ($r_s = 0.22$, $p = .37$). Mania symptoms without the sleep items were associated with IL-6 with a medium effect size ($r_s = 0.45$, $p = .035$) and with sTNF-R2 with a small, non-significant effect size ($r_s = -0.19$, $p = .43$). Depression symptoms without the sleep items were associated with IL-6 with a medium effect size ($r_s = 0.43$, $p = .044$) and sTNF-R2 with a small, non-significant effect size ($r_s = 0.18$, $p = .46$).

Average TST was associated with IL-6 with a medium effect size ($r_s = -0.49$, $p = .026$) and sTNF-R2 with a small, non-significant effect size ($r_s = 0.05$, $p = .84$). Average TWT was associated with IL-6 ($r_s = -0.14$, $p = .54$) and sTNF-R2 with non-significant, small effect sizes ($r_s = -0.17$, $p = .48$).

At pretreatment, there was a non-significant, small-medium effect size difference in IL-6 for CBTI-BP compared to PE ($B = 0.22$, $SE = 0.43$, $z = 0.51$, $p = .61$, $d = 0.24$). Change in IL-6 from pretreatment to posttreatment for CBTI-BP compared to PE was not significant ($B = -0.78$, $SE = 0.48$, $z = -1.61$, $p = .13$), but was associated with a large effect size ($d = -0.78$; Figure 1A). The difference in IL-6 at posttreatment for CBTI-BP compared to PE was associated with a non-significant, large effect size decrease ($B = -0.55$, $SE = 0.48$, $z = -1.17$, $p = .24$, $d = -0.88$). IL-6 increased from pretreatment to posttreatment for PE at the trend level ($B = 0.55$, $SE = 0.33$, $z = 1.67$, $p = .095$, $d = 0.88$). Change in IL-6 from pretreatment to posttreatment for CBTI-BP was associated with a non-significant, small-medium effect size ($B = -0.22$, $SE = 0.35$, $z = -0.63$, $p = .53$, $d = -0.35$).

There was a non-significant, small-medium effect size difference in sTNF-R2 at pretreatment for CBTI-BP compared to PE ($B = 0.29$, $SE = 0.45$, $z = 0.64$, $p = .52$, $d = 0.31$). Change in sTNF-R2 from pretreatment to posttreatment for CBTI-BP compared to PE was associated with a non-significant, small-medium effect size decrease ($B = -0.34$, $SE = 0.43$, $z = -0.79$, $p = .44$, $d = -0.38$; Figure 1B). There was a non-significant, small-medium effect size difference in sTNF-R2 at posttreatment for CBTI-BP compared to PE ($B = -0.15$,

SE = 0.52, *z* = −0.28, *p* = .78, *d* = −0.34). Change in sTNF-R2 from pretreatment to posttreatment for PE was not significant (*B* = 0.42, *SE* = 0.38, *z* = 1.09, *p* = .28), but was associated with a large effect size increase (*d* = 0.96). Change in sTNF-R2 from pretreatment to posttreatment for CBTI-BP was associated with a non-significant, small effect size (*B* = −0.02, *SE* = 0.40, *z* = −0.06, *p* = .95, *d* = −.06).

Discussion

The present study aimed to provide a preliminary test for sleep-related predictions derived from the Goldstein et al. (14) conceptual model of inflammation in BD. At the outset we recognize that the present study was underpowered. As such, interpretation of results will include a focus on effect sizes in addition to statistical significance at the .05 level (65).

Our first hypothesis was partially supported. IL-6 was positively correlated with mania and depression symptoms, both with and without the sleep items included. However, sTNF-R2 was associated with symptom measures of mood with small effect sizes. These results are consistent with previous research that has demonstrated that IL-6 is elevated during mania and depressive episodes (15,16,18). The present study provides preliminary evidence that even during the interepisode period, IL-6 may be related to subsyndromal mania and depression symptoms with medium-large effect sizes. This is noteworthy as previous research has suggested that the increase in pro-inflammatory cytokines associated with mania and depression may be resolved during the interepisode period (22–24).

In partial support of the second hypothesis, a negative relationship was observed between IL-6 and TST, which suggests that as TST decreased, IL-6 levels increased. However, only small effect sizes were observed between sTNF-R2 and TST. Results for IL-6 are consistent with Goldstein et al. (14), as well as empirical research that demonstrates a link between short TST and inflammation (34,55,56). This study also provides preliminary support for a theoretical paper that hypothesized that IL-6 is related to sleep disturbance in BD (47). To the best of our knowledge, this is the first study to provide evidence for this hypothesized relationship.

Small effect sizes were observed between TWT and pro-inflammatory cytokines. This finding is surprising given that other studies suggest that sleep disturbance is positively correlated with an inflammatory response (34,38,44). Given the small sample size, small effect sizes, and the cross-sectional nature of the data, it is not possible to make definite conclusions about these results. One possibility that will need to be tested in future, fully-powered studies is if the relationship between pro-inflammatory cytokines and sleep disturbance in BD is better captured by a measure of sleep duration (e.g., TST) or a measure of nocturnal wakefulness (e.g., TWT).

The third aim was to test if CBTI-BP can affect pro-inflammatory cytokines in patients with interepisode bipolar I disorder and insomnia. These findings provide preliminary evidence that CBTI-BP may reduce IL-6 in patients with interepisode bipolar I disorder and insomnia. The change in IL-6 from pretreatment to posttreatment for CBTI-BP compared to PE was associated with a large effect size decrease. An inspection of the mean values indicated that

patients who received CBTI-BP had lower IL-6 from pretreatment to posttreatment compared with patients who received PE. The group difference effect size was large, although the difference did not reach statistical significance. Results for sTNF-R2 were in the same direction as IL-6, but with small effect sizes. Taken together, a nonpharmacological intervention that improves sleep (e.g., CBTI-BP) may be a promising intervention to target pro-inflammatory cytokines in BD.

The within group change in pro-inflammatory cytokines is also notable. The small-medium effect size decrease in IL-6 in the CBTI-BP condition should be evaluated in comparison to the PE group, which was associated with a large effect size increase in IL-6. Similar results were observed with sTNF-R2, but with smaller effect sizes. It is possible that for participants in the PE condition, sleep disturbance, as well as other factors related to inflammation such as return to mood episode, were not addressed to the same degree as CBTI-BP. Indeed, CBTI-BP compared to PE was associated with reduced risk of mood episode relapse and improved sleep (48). In a fully powered study it will be important to determine what factors mediate changes in pro-inflammatory cytokines as a result of treatment.

Several limitations are important to consider. First, the interpretability and generalizability of these findings are limited by the small sample size. Second, this study included adults with both insomnia and BD. While insomnia occurs in 50% of interepisode BD patients (3), findings from this sample may not generalize to all patients with BD. Third, due to recommendations for small sample sizes and risk of overfitting statistical models (68), we did not control for variables known to influence pro-inflammatory cytokines such as age, sex, socioeconomic status, race and ethnicity, or body mass index (70). In a fully powered study, it may be informative to evaluate the influence of these factors. Fourth, 95.5% of participants were prescribed mood stabilizers. Although this may bias the results, we suggest that the present study is notable because effects were observed despite most participants taking medication known to reduce inflammation (71). Last, sTNF-R2 was related to study variables with small effect sizes. Although there is evidence that sTNF-R2 is related to BD (16), it is possible that this elevation is characteristic of acute illness phase rather than the interepisode period. Future studies will be necessary to further define the role of sTNF-R2 with respect to sleep and mood during the interepisode period.

In sum, this study provides preliminary evidence that IL-6 may be related to mood symptoms and sleep duration in participants with interepisode bipolar I disorder and insomnia. Furthermore, targeting sleep disturbance with CBTI-BP may result in changes in IL-6. Although the results of this study are encouraging, replication and further investigation in larger samples is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

BD	Bipolar disorder
IL-6	interleukin-6
sTNF-R2	tumor necrosis factor soluble receptor 2
OMT	oral mucosal transudate
TWT	total wake time
TST	total sleep time
SOL	sleep onset latency
WASO	wake after sleep onset
EMA	early morning awakening
RCT	randomized controlled trial
CBTI-BP	cognitive behavior therapy for insomnia modified for bipolar disorder
PE	psychoeducation
SCID	structured clinical interview for DSM-IV
YMRS	Young Mania Rating Scale
QIDS	Quick Inventory of Depressive Symptomatology

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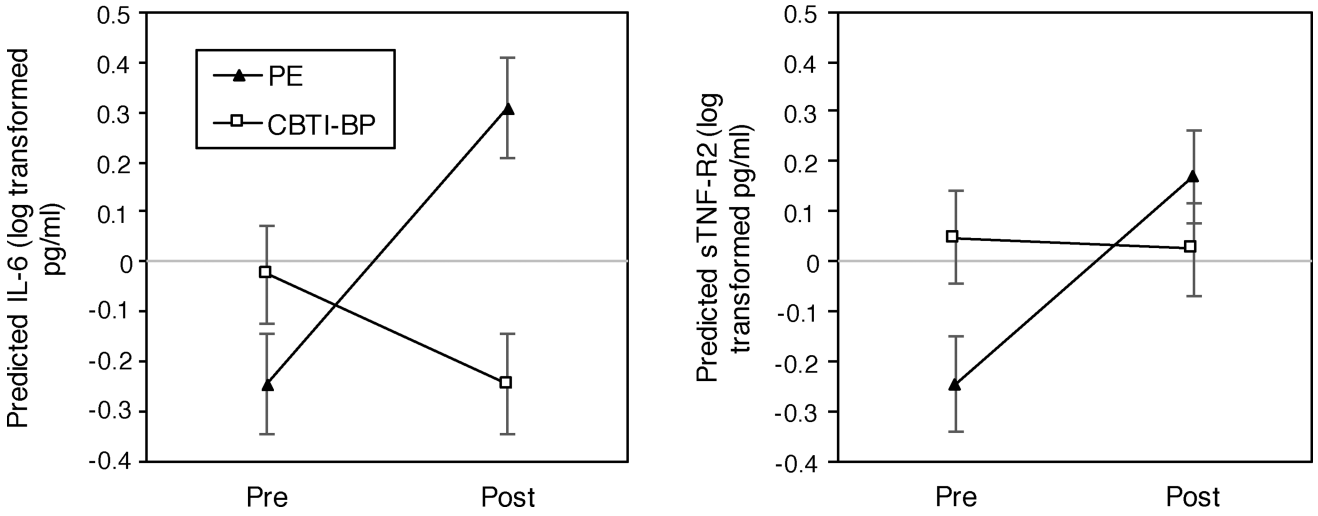

Figure 1.

Graphs of fitted values derived from hierarchical linear models of pretreatment to posttreatment change in log transformed IL-6 and sTNF-R2 for CBTI-BP compared to PE. A) Predicted IL-6 by time period and treatment group. B) Predicted sTNF-R2 by time period and treatment group.

Note. CBTI-BP sample size: pretreatment (n = 11) and posttreatment (n = 8). PE sample size: pretreatment (n = 11) and posttreatment (n = 9). Error bars refer to the standard error of the predicted means.

Table 1

Pretreatment demographic and clinical characteristics for CBTI-BP and PE.

	CBTI-BP (n = 11)		PE (n = 11)			
	M or N	**% or SD**	**M or N**	**% or SD**	***t* or χ^2**	***p***
Age	37.4	14.3	35.4	9.1	0.39	.70
Female	7	63.6%	Female	5	45.5%	.39
Ethnicity (1 declined to answer)					3.20	.07
Hispanic or Latino	2	18.2%	0	0.0%		
Not Hispanic or Latino	8	72.7%	11	100.0%		
Race					6.52	.48
American Indian/Alaska Native	0	0.0%	0	0.0%		
Asian	1	9.1%	4	36.4%		
African American	1	9.1%	2	18.2%		
White	6	54.6%	5	45.5%		
Bi-racial/Multi-racial	2	18.2%	0	0.0%		
Marital Status (1 declined to answer)					3.45	.63
Single	7	63.6%	7	63.6%		
Married/Partnered	2	18.2%	2	18.2%		
Divorced/Separated/Widow	2	18.2%	2	18.2%		
Employed (1 declined to answer)					2.79	.42
Full-time	2	18.2%	0	0.0%		
Part-time	2	18.2%	2	18.2%		
Unemployed	7	63.6%	8	72.7%		
Income (2 declined to answer)					6.49	.26
<$20,000	4	36.4%	6	54.6%		
$20,000–$35,000	0	0.0%	1	9.1%		
$35,000–$50,000	2	18.2%	3	27.3%		
$50,000–$60,000	2	18.2%	1	9.1%		
>$60,000	1	9.1%	0	0.0%		
Bipolar disorder onset	22.6	11.5	25.6	11.5	0.61	.55
Bipolar disorder duration	14.8	13.6	9.8	5.9	−1.11	.28

	CBTI-BP (n = 11)		PE (n = 11)			
	M or N	% or SD	M or N	% or SD	*t* or χ^2	*p*
Mood medication	11	100.0%	10	91.1%	1.05	.31
Sleep medication	7	63.6%	5	45.5%	0.73	.39

Table 2

Pro-inflammatory cytokines, mood, and sleep at pretreatment and posttreatment for CBTI-BP and PE.

	CBTI-BP				PE					
	Pretreatment (n=11)		Posttreatment (n=8)		Pretreatment (n=11)		Posttreatment (n=9)			
	M or N	% or SD	M or N	% or SD	M or N	% or SD	M or N	% or SD	*t*	*p*
Cytokines										
IL-6[a] (pg/ml)	0.85	0.73	0.69	0.46	0.77	1.27	2.48	5.25	−1.46	.16
IL-6[b] (pg/ml)	−0.58	1.03	−0.59	0.75	−0.81	0.89	−0.24	1.37	−1.61	.13
sTNF-R2[a] (pg/ml)	67.40	70.66	60.97	53.12	42.99	38.02	55.57	45.36	−0.81	.43
sTNF-R2[b] (pg/ml)	3.72	1.04	3.79	0.87	3.54	0.65	3.82	0.62	−0.79	.44
Mood										
YMRS	3.14	2.72	3.50	3.38	3.38	3.95	4.50	3.46	0.53	.60
YMRS[c]	3.39	2.41	3.25	2.96	3.14	2.84	4.00	3.15	−0.01	.99
QIDS	9.91	6.39	8.25	7.21	9.50	4.58	5.67	3.39	0.59	.56
QIDS[c]	7.09	6.32	6.25	6.43	7.18	4.49	3.67	3.46	0.82	.42
Sleep										
Time in Bed	503.93	86.51	480.89	78.51	574.82	86.47	588.57	127.04	−1.31	.21
Total Sleep Time	396.01	82.86	409.14	100.72	441.53	87.33	491.01	94.96	−1.04	.31
Total Wake Time	104.97	34.89	73.06	28.63	135.94	41.51	97.56	73.10	0.18	.86
Sleep Onset Latency	36.85	21.22	23.82	9.88	54.25	38.11	54.46	86.25	−0.75	.46
Wake After Sleep Onset	26.98	18.48	29.18	25.87	19.45	9.24	6.83	7.03	1.49	.16
Early Morning Awakening	28.98	34.13	22.46	20.92	25.55	25.42	17.68	37.25	−0.19	.86
Sleep Efficiency	79.71	6.64	83.60	8.35	75.89	7.18	84.13	8.32	−0.93	.37

Note.

[a] Log transformed.

[b] Unadjusted.

[c] Sleep items removed. The *t* statistic and *p* value refer to the interaction between condition (CBTI-BP and PE) and time (pretreatment and posttreatment).

Table 3

Spearman correlations between pro-inflammatory cytokines, mood, and sleep at pretreatment.

	1	2	3	4	5	6	7	8
1. IL-6	-							
2. sTNF-R2	0.08	-						
3. YMRS	0.44*	−0.10	-					
4. YMRS[a]	0.45†	0.22	0.16	-				
5. QIDS	0.45*	−0.19	0.89***	0.32	-			
6. QIDS[a]	0.43*	0.18	0.22	1.00***	0.39†	-		
7. TST	−0.49*	0.05	−0.35	−0.21	−0.53*	−0.25	-	
8. TWT	−0.14	−0.17	−0.05	−0.02	0.07	0.05	0.01	-

Note.

[a]Sleep items removed.

*** $p < .001$;

* $p < .05$;

† $p < .10$.