Brain, Behavior, and Immunity 47 (2015) 193–200

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation

Jeremy F. Weinberger, Charles L. Raison, David B. Rye, Amy R. Montague, Bobbi J. Woolwine, Jennifer C. Felger, Ebrahim Haroon, Andrew H. Miller *

Department of Psychiatry and Behavioral Sciences, Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322, United States

ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 10 December 2014
Accepted 11 December 2014
Available online 18 December 2014

Keywords:
Cytokines
C-reactive protein
Tumor necrosis factor
Depression
Infliximab
Sleep
Polysomnography

ABSTRACT

Blockade of the inflammatory cytokine tumor necrosis factor (TNF) in depressed patients with increased inflammation has been associated with decreased depressive symptoms. Nevertheless, the impact of TNF blockade on sleep in depressed patients has not been examined. Accordingly, sleep parameters were measured using polysomnography in 36 patients with treatment resistant major depression at baseline and 2 weeks after 3 infusions (week 8) of either the TNF antagonist infliximab ($n = 19$) or placebo ($n = 17$). Markers of inflammation including c-reactive protein (CRP) and TNF and its soluble receptors were also assessed along with depression measured by the 17-item Hamilton Depression Rating Scale. No differences in sleep parameters were found as a function of infliximab treatment over time. Nevertheless, wake after sleep onset (WASO), the spontaneous arousal index and sleep period time significantly decreased, and sleep efficiency significantly increased, from baseline to week 8 in infliximab-treated patients with high (CRP > 5 mg/L) ($n = 9$) versus low inflammation (CRP $\leqslant$ 5 mg/L) ($n = 10$), controlling for changes in scores of depression. Stage 2 sleep also significantly decreased in infliximab-treated patients with high versus low inflammation. Decreases in soluble TNF receptor 1 (sTNFR1) significantly correlated with decreases in WASO and increases in sleep efficiency in infliximab-treated subjects with high inflammation. Placebo-treated subjects exhibited no sleep changes as a function of inflammation, and no correlations between inflammatory markers and sleep parameters in placebo-treated patients were found. These data suggest that inhibition of inflammation may be a viable strategy to improve sleep alterations in patients with depression and other disorders associated with increased inflammation.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Alterations in sleep are among the most common symptoms of major depression, with greater than 75 percent of depressed patients reporting significant sleep disruption (Lam, 2006; Nutt et al., 2008; Tsuno et al., 2005). Sleep disturbances in depression are associated with decreased quality of life, increased risk for suicide, and an impaired response to conventional antidepressant therapy, which occurs in up to 30% of depressed patients (Nutt et al., 2008; Rush et al., 2006). Compared to healthy controls, patients with major depression have consistently demonstrated changes in sleep architecture as measured by polysomnography including decreases in sleep efficiency, slow wave sleep, Stage 2 sleep and the latency to rapid eye movement (REM) sleep as well as increases in REM density (Thase, 2006, Benca and Peterson, 2008) (Arfken et al., 2014).

One pathophysiologic mechanism that may be involved in some of the sleep changes found in depression is inflammation (Benedict et al., 2009; Imeri and Opp, 2009; Irwin et al., 2008; Krueger, 2008; Krueger et al., 2001; Motivala et al., 2005; Opp, 2005). Markers of inflammation, including inflammatory cytokines and their receptors, acute phase proteins such as c-reactive protein (CRP), chemokines, and adhesion molecules have been found to be elevated in a significant proportion of depressed patients in multiple studies (Dowlati et al., 2010; Miller et al., 2009). Moreover, a rich literature in laboratory animals and humans has shown that inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1 induce marked alterations in sleep architecture (Imeri and Opp, 2009; Krueger, 2008; Opp, 2005). For example, in humans, administration of cytokine inducers such as endotoxin disrupts non-REM sleep in a dose dependent manner, leading to decreased slow wave (Stage 3/4) sleep at high doses (Mullington et al., 2000.) Similarly, administration of the inflammatory cytokine

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Emory Clinic Building B, Suite B5100, Atlanta, GA 30322, United States. Tel.: +1 (404) 727 8260; fax: +1 (404) 778 3965.
E-mail address: amill02@emory.edu (A.H. Miller).

http://dx.doi.org/10.1016/j.bbi.2014.12.016
0889-1591/© 2014 Elsevier Inc. All rights reserved.

interferon (IFN)-alpha has been shown to increase wake after sleep onset (WASO), increase spontaneous arousals and increase sleep period time, while decreasing sleep efficiency and slow wave sleep (Raison et al., 2010). Poor sleep quality before and during IFN-alpha treatment has been found to predict the development of IFN-alpha-induced depression, which occurs in up to 30–50% of patients depending on the dose (Capuron et al., 2002; Franzen et al., 2010; Musselman et al., 2001; Prather et al., 2009). Interestingly, the pattern of sleep disruption during IFN-alpha treatment including decreased sleep continuity, sleep fragmentation and increased spontaneous arousals has also been observed in disease states associated with high inflammation such as rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus (Abad et al., 2008; Ranjbaran et al., 2007). Of note, although there are similarities between sleep changes in depression and inflammation, in contrast to findings in patients with depression, administration of IFN-alpha was associated with increased Stage 2 sleep and increased REM latency (Raison et al., 2010).

In addition to the capacity of inflammatory cytokines to disrupt sleep architecture, a number of studies have demonstrated that sleep deprivation can increase inflammatory markers both at the protein and molecular level, leading to increases of IL-6 and activation of the inflammatory signaling molecule nuclear factor kappa B (Irwin et al., 2006, 2008). These data raise the question of whether inflammation in depression is the cause or consequence of sleep alterations.

One strategy to address the relationship between sleep and inflammation in patients with depression is to block cytokines and thereby potentially reverse sleep alterations. For example, antagonism of TNF with the fusion protein etanercept reversed alterations in REM sleep in patients with alcohol dependence and insomnia (Irwin et al., 2009). Interestingly, TNF is reliably elevated in depressed patients (Dowlati et al., 2010), and TNF blockade has been shown to have antidepressant activity in inflammatory and autoimmune diseases including psoriasis and Crohn's disease (Persoons et al., 2005; Tyring et al., 2006). In addition, a recent study found that TNF blockade improved depressive symptoms in patients with treatment resistant depression (TRD), but only in patients with high baseline inflammation as reflected by a CRP > 5 mg/L (Raison et al., 2013).

In the current study, we endeavored to determine whether TNF blockade may also improve sleep parameters in TRD patients with high inflammation (CRP > 5 mg/L). Special emphasis was placed on sleep alterations previously associated with cytokine (IFN-alpha) administration including decreased sleep continuity and depth as previously described (Raison et al., 2010). Moreover, we examined whether changes in sleep as a function of infliximab were associated with changes in markers of TNF activity including plasma concentrations of TNF and its soluble receptors, soluble TNF receptor 1 and 2 (sTNFR1 and sTNFR2).

2. Methods

2.1. Sample

Subjects included in this study were participants in a previously published single-site, parallel-group, randomized, double-blind trial of infliximab versus placebo for antidepressant non-responders with a diagnosis of major depression according to the *DSM-IV* criteria as assessed by the Structured Clinical Interview for *DSM-IV* (SCID) (First MB, 1997; Raison et al., 2013). Subjects were recruited from television, radio, newspaper and internet advertisements and were men and women between the ages of 25 and 60 years. All subjects were on a stable antidepressant regimen or off all antidepressant therapy for at least 4 weeks prior to baseline. No changes in antidepressant treatment were allowed during the study. All participants were required to have experienced moderate treatment resistance in the current depressive episode, as determined by a score of 2 or higher on the Massachusetts General Hospital Staging method for treatment resistance (Petersen et al., 2005), and to exhibit moderate severity of depression as determined by a score of 14 or higher using the Quick Inventory of Depressive Symptomatology, Self-Report (Trivedi et al., 2004) at screening and a score of $\geqslant$20 on the 17-item Hamilton Depression Rating Scale (HAM-D)-17 at randomization (Hamilton, 1960). Exclusion criteria included the presence of any autoimmune disorder (confirmed by laboratory testing); a history of tuberculosis (confirmed by chest X-ray, tuberculin skin testing, and blood testing) or being at high risk for tuberculosis exposure; the presence of hepatitis B or C or human immunodeficiency virus infection (confirmed by laboratory testing); evidence of active fungal infection; a history of recurrent viral or bacterial infections; a history of cancer, excluding basal cell or squamous cell carcinoma of the skin (fully excised with no recurrence); the presence of an unstable cardiovascular, endocrinologic, hematologic, hepatic, renal, or neurologic disease (determined by physical examination and laboratory testing); a history of schizophrenia (determined by SCID); active psychotic symptoms of any type; substance abuse and/or dependence within the past 6 months (determined by SCID); active suicidal ideation determined by a score of 3 or higher on item #3 of the HAM-D-17 (Hamilton, 1960); and/or a score of less than 28 on the Mini-Mental State Examination, indicating more than mild cognitive impairment (Folstein et al., 1975).

Subjects were also excluded if they had more than moderate sleep apnea or periodic limb movement disorder (PLMD) at baseline as evidenced by an apnea-hypopnea (AH) index greater than 30 or a PLM index greater than 50. All participants provided written informed consent, and all procedures were approved *a priori* by the Institutional Review Board of Emory University, Atlanta, Georgia. The study was registered at clinicaltrials.gov (NCT00463580) in April 2007, and the CONSORT diagram has been previously published (Raison et al., 2013).

2.2. Study procedures

Participants were enrolled between December 2008 and March 2011. To achieve similar representation of baseline inflammatory status in each group, group assignment, determined at screening, was stratified based on a CRP > 2 mg/L or $\leqslant$2 mg/L. A CRP concentration of 2 mg/L was chosen because it is the central value in the "medium" relative risk category of inflammation (1–3 mg/L) recommended by the American Heart Association and the Centers for Disease Control and Prevention (Pearson et al., 2003). Group assignment was also stratified by sex. Following screening for inclusion and exclusion criteria, all participants reported to the infusion center in the Emory Division of Digestive Diseases on 3 separate occasions (baseline, 2 weeks, and 6 weeks) to receive an infusion of either infliximab (5 mg/kg) or placebo over 120 min through an indwelling catheter. The baseline visit was scheduled no later than 1 month after screening. The dosing protocol and scheduling of infliximab infusions were matched to the standard induction regimen for treatment of inflammatory bowel disease (Rutgeerts et al., 2004). Independent pharmacists dispensed infliximab or placebo in a 250-mL saline bag according to a computer-generated randomization list, blocked in units of 4, provided by a study statistician. The placebo was matched to infliximab on the basis of color and consistency when dissolved in saline. Infliximab and placebo were provided free of charge by Centocor OrthoBiotech Services (Horsham, Pennsylvania).

Aside from the infusions, all study procedures took place in the Emory University Hospital Clinical Research Network (CRN).

Clinical assessments of depression using the HAM-D-17 (Hamilton, 1960) occurred weekly during the first 4 weeks of the study and then every 2 weeks until the end of the study. At baseline and 2 weeks after the final infusion (8 weeks), subjects were admitted to the CRN hospital unit and underwent 2 nights of polysomnography following standard procedures as previously described and described below (Raison et al., 2010). Each night, lights out occurred no later than 11:00 pm, and each morning, subjects were awakened at 7:15 am. Subjects were not required to attempt to go to sleep after lights out. The first night of each inpatient visit was used for accommodation to the CRN environment and at baseline was used to screen for sleep disorders. During each CRN admission, blood was withdrawn from an indwelling catheter into EDTA-coated tubes between 8 am and 10 am for assessment of plasma TNF, sTNFR1 and sTNFR2. Following sampling, blood was immediately centrifuged at $1000\times g$ for 10 min at 4 °C. Plasma was removed and frozen at −80 °C until assay. Urine drug screens were conducted at each CRN visit to rule out substance abuse. The subject sample described in this report represent a subset of subjects whose depression scores (HAM-D-17) and peripheral blood gene expression across treatment have been reported on previously (Mehta et al., 2013; Raison et al., 2013).

2.3. Sleep assessment

Subjects were connected to the PSG recorder at approximately 8:30 pm on each evening of sleep assessment. Sleep was recorded and analyzed using an Embla A10 device using compatible SomnologicaScience software (Embla Systems; Broomfield, CO). PSG assessment included placement of electrodes for electroencephalography, electrooculography, and submental electromyography. A standard sleep montage of electroencephalography (EEG) (C3/A2-C4/A1) and (O2/C3-O1/C4), monopolar left and right electrooculography (EOG) referenced to the opposite mastoid, and surface mentalis electromyography (EMG) was used. In addition, ECG (modified lead II), respiratory airflow, snoring sounds, respiratory effort (rib cage and abdomen), and anterior tibialis surface EMG were recorded unilaterally.

2.3.1. Sleep scoring

All digital records from polysomnography (PSG) were manually scored by a single registered PSG technologist without knowledge of group assignment or clinical status. Records were reviewed by an American Board of Sleep Medicine specialist to further ensure scoring accuracy, particularly in the determination of sleep onset and the quality and quantity of REM sleep.

Sleep stages were manually scored following standard criteria (Rechtschaffen, 1968). Nocturnal PSG sleep measures calculated included: sleep period time (total minutes from sleep onset until awakening), total sleep time (total minutes in any stage of sleep); sleep efficiency (total sleep time/sleep period time × 100); wake after sleep onset (WASO) [amount of wake time in minutes during the sleep period time characterized by relatively low voltage, mixed frequency EEG activity scored according to standard criteria (Rechtschaffen, 1968)]; time spent (minutes) in Stages 1, 2, and 3/4 (referred to as slow wave sleep; SWS), rapid-eye-movement (REM) sleep [the total minutes characterized by rapid eye movements, muscle atonia, and desynchronized EEG activity as measured by PSG and scored according to standard criteria (Rechtschaffen, 1968)]; and REM latency [latency in minutes to the first epoch of REM sleep, which was the time between the first epoch of any stage of sleep and the first epoch of REM (defined by not less than 3 consecutive minutes of REM sleep with intervening wake time excluded)]. Sleep onset was defined as the first minute of Stage 2 or REM sleep followed by at least 8 min of sleep in the next 9 min until final awakening. The spontaneous arousal index (changes in EEG frequency lasting at least 3 s divided by the number of hours of total sleep time) was also measured according to American Academy of Sleep Medicine Guidelines (1992).

2.5. Assessment of inflammatory markers

Plasma concentrations of TNF, sTNFR1 and sTNFR2 were determined using sandwich ELISA (R & D Systems, Minneapolis, MN). All samples were assayed in duplicate. Quality control plasma of both low and high cytokine or cytokine receptor concentrations was included with every assay. The mean inter- and intra-assay coefficients of variation were reliably 10% or less for the ELISAs. CRP was measured by the immunoturbidimetric method using the Beckman AU 480 chemistry analyzer and the Ultra WR CRP reagent kit (Sekisui Diagnostics, Framingham, MA). Inter- and intra-assay coefficients of variation were reliably less than 3% for CRP determinations. No values for any of the inflammatory markers were below the limits of detection of the assays.

2.6. Statistical analysis

T tests and Chi Square analyses (or Fisher Exact tests where indicated) were used to compare sociodemographic and clinical variables between treatment groups at baseline. To evaluate the effects of treatment on sleep variables as a function of time, repeated measures analysis of covariance was employed. Age, sex, body mass index (BMI), race, psychotropic medications (yes versus no) were included as covariates in these analyses. To control for changes in depressive symptoms over time, changes in HAM-D-17 scores from baseline to week 8 (baseline-week 8) were also entered into the model. In the case of significant main effects of group or time or a group by time interaction, post hoc comparisons between specific means were conducted using Tukey tests. The same statistical strategy was also used to evaluate the effect of baseline inflammatory status as determined by a baseline CRP> or ⩽5 mg/L on sleep parameters as a function of time. A CRP cut-off off 5 mg/L was chosen for high inflammation in these analyses based on a previous study by our group demonstrating that at CRP concentrations of 5 mg/L, infliximab begins to differentiate from placebo in terms of effects on depressive symptoms (Raison et al., 2013). Each treatment group was analyzed separately in these analyses to obviate limitations in the interpretation of 3-way interactions among treatment, time and inflammatory status. For sleep parameters for which there was a significant main effect of inflammatory status or time or their interaction, general linear equations were employed to examine the relationship between the change in sleep parameter over time and change in the inflammatory measures. Because CRP was used as the stratification variable and TNF exhibited marked increases at week 8 (due to infliximab interference with the TNF assay – see below), only plasma sTNFR1 and sTNFR2 concentrations were included in these analyses. Age, sex, BMI, race, psychotropic medications (yes versus no) and change in depressive symptom score (from baseline to week 8) were also included in the models. All tests of significance were two-tailed with an alpha level of 0.05. Data was analyzed using SPSS, Version 21. Power calculations were performed using G*Power (Faul et al., 2007).

3. Results

3.1. Sample characteristics

Thirty-six of the 60 patients who were originally enrolled in the study had complete polysomnography data at baseline and week 8 and did not exhibit evidence of significant sleep apnea or PLMD.

Baseline sociodemographic characteristics and clinical data for these subjects are indicated in Table 1. Age, gender, race, BMI, baseline HAM-D-17 and psychotropic medication use were similar between the groups. Consistent with the stratification procedure, baseline CRP also did not significantly differ between groups. No significant differences were found between the patients included in the sleep study ($n = 36$) and those who were excluded ($n = 24$) (data not shown).

3.2. Sleep measures

3.2.1. Baseline sleep

Table 2 shows baseline sleep parameters in study participants. There were no significant differences among the sleep measures by treatment group at baseline. To assess whether baseline inflammation level was associated with sleep parameters, as previously described, patients were stratified by high and low inflammation based on a CRP > 5 mg/L versus a CRP $\leqslant$ 5 mg/L, and sleep parameters compared. As previously reported in IFN-alpha-treated patients, sleep period time was significantly greater in patients with high versus low inflammation (487.9 SD 50.7 versus 444.1 SD 67.3, respectively, $t = -2.09$, $p = 0.045$) (Raison et al., 2010). Also similar to IFN-alpha-treated patients, REM latency from sleep onset was increased in patients with high versus low inflammation but only at a trend level of significance (170.3 SD 108.8 versus 104.6 SD 64.3, respectively, $t = -2.04$, $p = 0.055$) (Raison et al., 2010). No other significant differences between patients with high and low inflammation were found, and no significant correlations were found between baseline inflammatory markers (sTNFR1 and 2) and any of the baseline sleep parameters.

3.3. Sleep parameters over time as a function of treatment group and inflammation status

The effects of treatment, time, and inflammation status on sleep architecture were explored. No significant main effects of treatment or treatment by time interactions for any of the sleep parameters were found. We next explored the impact of inflammation status (CRP > 5 m/L versus CRP $\leqslant$ 5 mg/L) on sleep parameters in infliximab-treated and placebo-treated patients analyzed separately. In infliximab-treated patients, a significant inflammation by time interaction was found for sleep period time ($F[1,11] = 5.61$, p = 0.037), WASO ($F[1,11] = 6.79$, $p = 0.024$), sleep efficiency ($F[1,11] = 4.83$, $p = 0.05$), spontaneous arousal index

Table 1
Sociodemographic and clinical characteristics of the study sample.

Characteristic	All ($n = 36$)	Infliximab ($n = 19$)	Placebo ($n = 17$)	P value
Age (mean, SD), y	43.4 (9.1)	41.1 (8.0)	46.0 (9.8)	.11
Gender, No. (%)				.40
Female	25 (69.4)	12 (63.2)	13 (76.5)	
Male	11 (30.1)	7 (36.8)	4 (23.5)	
Ethnicity, No. (%)				.55
White	28 (77.8)	14 (73.7)	14 (82.4)	
Black	8 (22.2)	5 (26.3)	3 (17.6)	
Other				
BMI, mean (SD)	30.8 (7.9)	29.8 (7.0)	32.0 (8.9)	.42
Baseline CRP, mean (SD), mg/L	6.0 (9.5)	6.8 (10.4)	5.2 (8.5)	.61
Baseline TNFR1, mean (SD), ng/ml	1.1 (0.3)	1.1 (0.2)	1.2 (0.3)	.33
Baseline TNFR2, mean (SD), ng/ml	2.5 (0.6)	2.3 (0.5)	2.6 (0.6)	.61
Baseline HAM-D-17 score, mean (SD)	24.3 (4.1)	24.0 (4.1)	24.7 (4.1)	.56
Baseline psychotropic use, No. (%)	25 (69.4)	12 (63.2)	13 (76.4)	.40
Antidepressants	22 (61.1)	10 (52.6)	12 (70.6)	.32
Mood Stabilizers	4 (11.1)	2 (10.5)	2 (11.8)	1.0
Antipsychotics	6 (16.7)	4 (21.1)	2 (11.8)	.66
Sedative/hypnotics	0 (0)	0 (0)	0 (0)	1.0

BMI – body mass index; CRP – c-reactive protein; HAM-D-17 – 17 item Hamilton Depression Rating Scale; No. – number; SD – standard deviation.

Table 2
Mean (±SD) sleep parameters in infliximab-treated and control subjects.

	All			Infliximab			Placebo	
	Baseline $N = 36$	Week 8 $N = 36$	Delta $N = 36$	Baseline $N = 19$	Week 8 $N = 19$	Delta $N = 19$	Baseline $N = 17$	Week 8 $N = 17$	Delta $N = 17$
Sleep period time (min)	461.2 (64.3)	459.2 (66.8)	−2.0 (90.5)	475.3 (51.7)	455.9 (66.0)	−19.3 (81.1)	445.4 (74.5)	462.9 (69.6)	−17.5 (98.7)
Total sleep time (min)	408.2 (68.8)	417.1 (71.8)	8.9 (78.6)	424.6 (57.6)	417.6 (75.1)	−7.1 (71.2)	390.0 (77.1)	416.6 (70.3)	26.8 (84.6)
Wake after sleep onset (min)	52.9 (39.9)	42.1 (36.8)	−10.9 (45.4)	50.6 (27.8)	38.3 (34.5)	−12.2 (37.7)	55.5 (-51.1)	46.2 (39.8)	−9.3 (53.9)
Total sleep efficiency	88.6 (8.7)	90.9 (7.7)	2.3 (9.3)	89.2 (6.7)	91.5 (7.7)	2.3 (7.2)	87.9 (10.7)	90.2 (7.9)	2.3 (11.4)
REM latency (min)	130.2 (89.1)	123.0 (86.1)	−7.2 (79.9)	113.7 (79.8)	92.8 (46.6)	−20.9 (77.9)	148.6 (97.5)	156.7 (107.1)	8.2 (81.5)
Sleep stages									
Stage 1 (min)	2.4 (2.1)	1.9 (2.4)	−0.5 (2.5)	2.6 (2.2)	1.9 (2.3)	−0.8 (2.7)	2.1 (2.0)	1.9 (2.7)	−0.2 (2.3)
Stage 2 (min)	222.0 (63.8)	228.8 (63.1)	6.9 (71.2)	226.9 (59.1)	221.9 (53.1)	−5.0 (68.9)	216.5 (70.1)	236.6 73.7)	20.1 (73.3)
Stage 3/4 (min)	97.1 (41.1)	87.6 (28.7)	−9.5 (36.6)	102.6 (48.1)	83.8 (26.8)	−18.8 (37.7)	91.0 (31.8)	91.8 (30.9)	0.8 (33.3)
REM (min)	86.7 (43.9)	98.9 (39.0)	12.2 (44.7)	92.6 (45.3)	110.2 (37.8)	17.6 (41.8)	80.2 (42.6)	86.3 (37.5)	6.1 (48.4)
Spontaneous arousal index	21.0 (7.9)	19.7 (9.0)	−1.3 (7.2)	19.6 (6.4)	18.8 (6.6)	−.83 (6.5)	22.6 (9.2)	20.8 (11.2)	−1.8 (8.2)
AH index	4.0 (7.3)	4.4 (8.2)	0.4 (4.5)	2.7 (6.1)	3.2 (7.6)	0.6 (2.9)	5.4 (8.4)	5.6 (8.9)	0.2 (5.9)

Min – minutes; REM – rapid eye movement; AH – apnea-hypopnea; SD – standard deviation.

Table 3
Mean (±SD) sleep parameters in infliximab-treated subjects stratified by CRP.

	CRP > 5 mg/L			CRP ⩽ 5 mg/L		
	Baseline $N = 9$	Week 8 $N = 9$	Delta $N = 9$	Baseline $N = 10$	Week 8 $N = 10$	Delta $N = 10$
Sleep period time (min)[a]	506.2 (37.2)	440.0 (70.3)	−66.2 (75.0)	447.4 (48.0)	470.2 (62.0)	22.8 (63.2)
Total sleep time (min)	454.1 (31.9)	416.6 (71.1)	−37.5 (77.6)	398.1 (64.0)	418.4 (82.3)	20.3 (55.2)
Wake after sleep onset (min)[a]	52.1 (22.3)[b]	23.4 (12.9)[c]	−28.6 (28.2)	49.3 (33.1)	51.8 (42.5)	2.5 (40.2)
Total sleep efficiency (%)[a]	89.8 (4.2)	94.5 (3.5)	4.7 (6.3)	88.6 (8.5)	88.7 (9.5)	0.0 (7.6)
REM latency (min)	142.0 (97.9)	107.6 (60.9)	−34.4 (108.8)	88.2 (53.5)	79.6 (25.3)	−8.6 (35.8)
Sleep stages						
Stage 1 (min)	1.4 (1.6)	0.5 (0.8)	−0.9 (1.8)	3.7 (2.3)	3.1 (2.5)	−0.6 (3.4)
Stage 2 (min)[a]	253.3 (46.7)[b]	210.0 (52.2)	−43.2 (69.4)	203.1 (61.0)	232.5 (54.2)	29.4 (49.6)
Stage 3/4 (min)	119.7 (53.8)	94.6 (24.7)	−25.2 (51.7)	87.2 (38.8)	74.1 (26.1)	−13.1 (20.0)
REM (min)	80.0 (39.5)	111.6 (35.6)	31.9 (35.4)	104.2 (49.0)	108.9 (41.5)	4.8 (44.6)
Spontaneous arousal index[a]	21.2 (3.4)	18.3 (5.6)	−2.9 (6.7)	18.3 (8.1)	19.3 (7.6)	1.0 (6.0)

Min – minutes; REM – rapid eye movement; SD – standard deviation.
[a] Significant inflammation × time (visit) interaction ($p < .05$).
[b] Indicates a significant post hoc difference between baseline and week 8 values ($p < .05$).
[c] Indicates a significant post hoc difference between week 8 values in high versus low inflammation ($p < .05$).

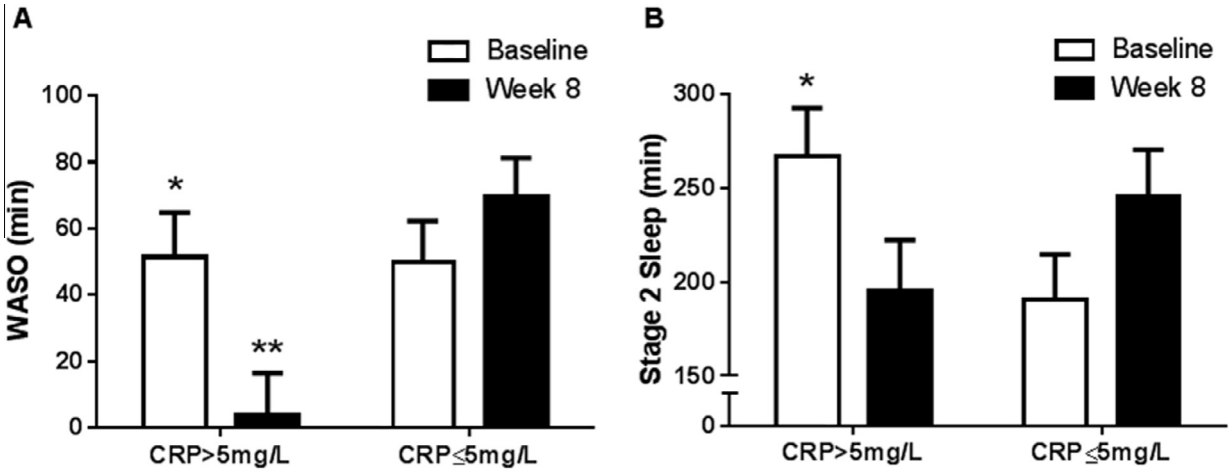

Fig. 1. Impact of infliximab on wake after sleep onset and Stage 2 Sleep in treatment resistant depressed (TRD) patients with high versus low inflammation. Estimated marginal means (including covariates) of wake after sleep onset (WASO) (A) and Stage 2 sleep (B) in minutes significantly decreased from baseline to week 8 in TRD patients treated with infliximab with c-reactive protein (CRP) > 5 mg/L (high inflammation) ($n = 9$) versus those with CRP ⩽ 5 mg/L (low inflammation) ($n = 10$) at baseline. *Indicates a significant difference between baseline and week 8 values ($p < 0.05$). **Indicates a significant difference between week 8 values in high versus low inflammation.

($F[1,11] = 11.99$, $p = 0.005$) and Stage 2 sleep ($F[1,11] = 7.67$, $p = 0.018$) (Table 3). Post-hoc analyses revealed a significant decrease in WASO from baseline to week 8 in infliximab-treated patients with high but not low baseline CRP ($p < 0.05$) (Fig 1A). In addition, WASO was significantly lower in the infliximab-treated patients with high compared to low baseline CRP at 8 weeks ($p < 0.05$). Stage 2 sleep (minutes) also significantly decreased from baseline to week 8 in infliximab-treated patients with high but not low baseline CRP ($p < 0.05$) (Fig 1B). Post hoc tests between specific means of other sleep parameters where there was a significant inflammation by time interaction were not significant ($p > 0.05$). No significant inflammation by time interactions were found for any sleep parameters in placebo-treated subjects.

Linear regression analyses were conducted to determine the relationship between markers of TNF activity (sTNFR1 and sTNFR2) and those sleep variables with significant inflammation by time interactions in the infliximab-treated group. Relevant clinical covariates including age, race, sex, BMI, psychotropic medication status and change in depression scores from baseline to week 8 were included in the statistical models. Because plasma TNF exhibited a dramatic increase at week 8 [consistent with assay detection of partially saturated TNF-infliximab homotrimers (Chung et al., 2003)], TNF was not included in these models. Decreases in sTNFR1 were predictive of decreases in WASO (beta = 0.536, df = 1.17, $p = .018$) (Fig. 2A) and increases in sleep efficiency (beta = −0.546, df = 1.17, $p = .016$) (Fig. 2B) in the infliximab-treated group as a whole and in patients with CRP > 5 mg/L ($r = 0.667$, $n = 9$, $p = 0.05$ and $r = -0.667$, $n = 9$, $p = 0.05$, respectively, based on Spearman's rank correlation coefficient). No such relationships between inflammatory variables and sleep parameters were found in the low inflammation infliximab group (CRP ⩽ 5 mg/L) or the placebo group. Changes in sleep period time, Stage 2 sleep and spontaneous arousal index were not significantly associated with either inflammatory factor in the infliximab or placebo groups. Of note, these analyses were not corrected for multiple comparisons due to the significant co-linearity among sleep period time, sleep efficiency, WASO, and spontaneous arousal index. Finally, no correlations were found between change in HAM-D-17 scores and sleep period time change, WASO, sleep efficiency, Stage 2 sleep or the spontaneous arousal index in infliximab-treated patients with high inflammation (all $p > 0.5$).

4. Discussion

Our previous study found that infliximab did not have general efficacy in improving depressive symptoms in all patients with TRD but improved depressive symptoms in patients with high

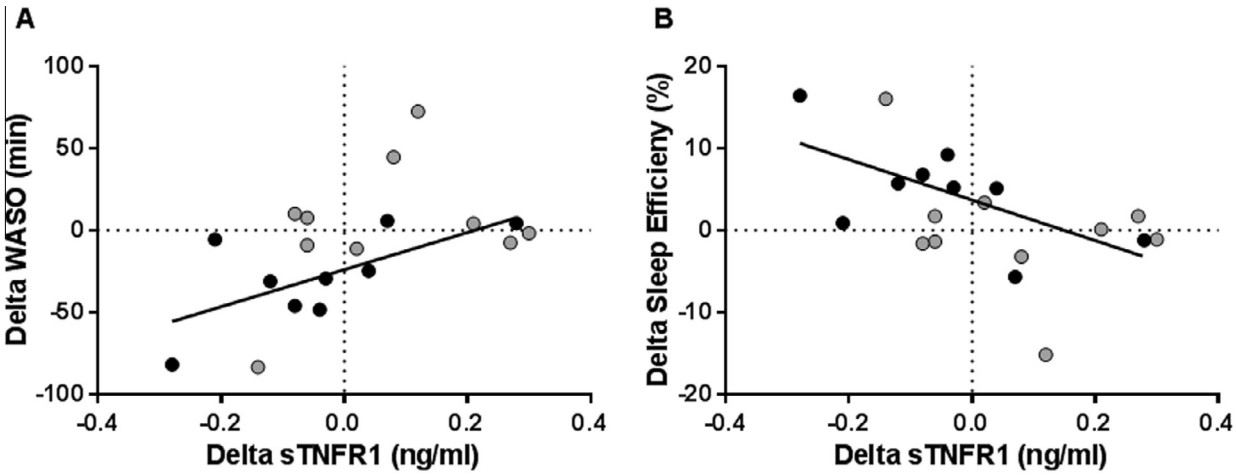

Fig. 2. Change (Delta) in wake after sleep onset and sleep efficiency correlates with change in sTNFR1 in infliximab-treated treatment resistant depressed (TRD) patients with high inflammation. Change (week 8 – baseline) in wake after sleep onset (WASO) measured in minutes (A) and change in sleep efficiency measured in percentage (%) (B) are plotted with change (week 8 – baseline) in soluble tumor necrosis factor receptor 1 (sTNFR1) (ng/ml) in infliximab-treated patients. Decreased WASO and increased sleep efficiency were significantly correlated with decreased sTNFR1 in the group as a whole and in patients with CRP > 5 mg/L ($p < 0.05$). No correlations were found in the group with CRP $\leqslant$ 5 mg/L. Regression lines depict correlations between the indicated variables for the high CRP group only. Highlighted in black are those patients with baseline CRP > 5 mg/L, and those with CRP $\leqslant$ 5 mg/L are depicted in gray.

inflammation (CRP > 5 mg/L). Here we show that blockade of TNF in patients with high inflammation also improved measures of sleep known to be commonly disrupted in depressed patients and/or patients exposed to inflammatory stimuli. Compared to patients with low inflammation, depressed subjects with high inflammation administered infliximab demonstrated improvement in sleep continuity (decreased spontaneous arousals, decreased WASO, and increased sleep efficiency) and decreases in Stage 2 sleep as well as decreases in sleep period time. These improvements were not observed in the placebo group and were apparent when controlling for a variety of covariates including notably the change in depression score. Decreases in WASO and increases in sleep efficiency from baseline to week 8 were further correlated with decreases in sTNFR1 within the infliximab- but not placebo-treated group. Furthermore, this correlation was apparent in infliximab-treated patients with high but not low baseline inflammation as defined by a CRP > 5 mg/L. Given that infliximab is a highly specific antagonist of TNF with few non-immunologic, off-target effects, these data suggest that blockade of inflammation may significantly improve several sleep disturbances relevant to sleep continuity in patients with major depression and possibly other patient populations with increased inflammation.

Previous literature has identified decreases in sleep continuity as a state dependent measure in depression which improves with antidepressant treatment (Kupfer and Ehlers, 1989). This is in contrast to reduced REM latency and decreased SWS which have been shown to persist between depressive episodes (Giles et al., 1993; Thase et al., 1998). Our findings are consistent with these data, given that REM latency and SWS were not significantly changed by infliximab treatment, while measures of sleep continuity significantly improved, independently of improvement in overall depression scores. Our data are also consistent with previous findings of significant improvement in sleep efficiency following infliximab administration in patients with rheumatoid arthritis independent of improvement in joint symptoms (Zamarron et al., 2004). Finally, similar to results in a large cohort of subjects from the Netherlands (Prather et al., 2015), increased CRP was significantly associated with longer sleep duration at baseline. Our findings that sleep period time was significantly reduced by infliximab in patients with high inflammation further confirm this relationship and suggest that inflammation may drive increased sleep time.

It should be noted that in our study, a high percentage (69.4%) of patients were on psychotropic medication. These medications especially antidepressants have been consistently shown to increase REM latency and decrease overall time spent in REM sleep (Hendrickse et al., 1994; Kerkhofs et al., 1990; Mayers and Baldwin, 2005). Indeed, among baseline sleep parameters, there was a significant increase in REM latency from sleep onset and a decrease in total minutes of REM sleep in patients taking an antidepressant (both $p < 0.01$) (data not shown). Nevertheless, whether or not these medication effects interact with inflammation is unknown, and thus it is possible that any effects of blockade of inflammation on REM sleep parameters as was observed in alcoholics with insomnia may have been masked by psychotropic medications in this study (Irwin et al., 2009).

Improvements in WASO and sleep efficiency, both measures of sleep continuity, were correlated with decreases in sTNFR1 in patients with high inflammation treated with infliximab. This association was not present in infliximab-treated patients with low inflammation or in patients treated with placebo and was not present for sTNFR2 (when entered in linear regression analyses with sTNFR1). Of note, baseline concentrations of both sTNFR1 and sTNFR2 were higher in infliximab responders versus non responders in our previous study (Raison et al., 2010). There is some evidence to suggest that soluble TNF receptors may be more reliable markers of inflammation than TNF (Schroder et al., 1995) and that sTNFR1 may have a special association with neuroinflammation as well as psychiatric syndromes (Barbosa et al., 2011; D'Mello et al., 2009). Moreover, previous studies have shown that sTNFR1 was independently associated with spontaneous movement arousal index scores in patients with obstructive sleep apnea after controlling for age, BMI and sleep apnea severity (Yue et al., 2009). sTNFR1 was also associated with cognitive dysfunction in patients with sleep apnea (Haensel et al., 2009). Nevertheless, it should be noted that sTNFR1 and sTNFR2 were significantly correlated ($r = 0.47$, $p < 0.01$), and similar relationships were observed between delta sTNFR2 and delta sleep efficiency and delta WASO in infliximab-treated patients, although these relationships did not reach statistical significance (both $p > 0.05$). Thus, any specific relationship between sTNFR1 and sleep parameters distinct from sTNFR2 should be interpreted with caution.

An aim of our study was to identify whether the level of baseline inflammatory markers were associated with baseline sleep alterations. Other than increased sleep period time (discussed above) and increased REM latency in patients with high CRP, both of which were previously reported in association with chronic administration of IFN-alpha (Raison et al., 2010), we did not find any consistent relationships between plasma concentrations of CRP, TNF, sTNFR1, or sTNFR2 and sleep parameters at baseline. There are a number of explanations for why we may have not observed such associations. First, our study population had a high average level of inflammation at baseline (mean study CRP of 6.0 mg/L). Moreover, a high percentage of our patients were using psychotropic medications which may have masked baseline relationships especially REM parameters, which are known to be sensitive to psychotropic medication (see above).

It should be noted that because of its large size, infliximab does not readily penetrate the blood–brain barrier (Tweedie et al., 2007), and therefore would not be expected to affect TNF in the brain where it has been shown to affect sleep in laboratory animals (Opp, 2005). Nevertheless, laboratory animal studies have shown that peripheral administration of infliximab significantly reduces depression and anxiety-like behavior in the chronic mild stress model of depression (Karson et al., 2013), suggesting that stress-induced behavioral changes may be a function of activation of peripheral inflammatory responses. These data are consistent with recent studies that inflammatory cells mobilized from the periphery may access the brain during stress to induce a central inflammatory response and alter behavior in laboratory animals (Wohleb et al., 2014). Moreover, there is a rich literature describing how inflammatory cytokines including TNF can access the brain including passage through leaky regions in the blood brain barrier, active transport mechanisms and binding to peripheral afferent nerve fibers including the vagus (Miller et al., 2009; Quan and Banks, 2007). Thus, the ability of infliximab to alter sleep parameters in patients with depression suggests that blockade of inflammatory signals originating in the periphery may be sufficient to impact inflammation-induced effects on sleep in the brain.

Several strengths and limitations of the study design warrant consideration. Strengths include the use of an objective measure of sleep architecture (PSG) in humans with treatment resistant depression prescreened for inflammatory and infectious diseases and uncontrolled medical illnesses and exposed to a standardized dose of a monoclonal antibody targeted specifically to TNF. The use of a placebo-treated, control group not receiving infliximab but administered all study procedures is also a strength, especially given that sleep parameters and depressive symptoms improved (ostensibly nonspecifically) between baseline and week 8 in placebo-treated patients. Weaknesses of our study include the small sample size which was further stratified into groups by treatment and inflammation status, limiting the power of the study. Nevertheless, in instances of negative findings in infliximab-treated patients with high versus low inflammation, power calculations revealed adequate statistical power to detect inflammation by time interactions of moderate effect sizes ($d \geqslant 0.5$). The high percentage of patients on psychotropic medications in our study is also a limitation, especially given the association of antidepressants with alterations in REM sleep (see above). In addition, patients with mild to moderate obstructive sleep apnea were included in the study, and obstructive sleep apnea has been associated with increased inflammatory activity including alterations in the production of TNF (Tamaki et al., 2009). However, no differences in AHI were found between groups, and the mean AHI for subjects in the study was within the normal range (see Table 2). Spectral analysis of PSG was not available for this study which limits quantitative analysis and increases the subjectivity of defining sleep architecture and continuity. Finally, the PSG measure of latency to sleep onset was not included in the analysis because patients in the CRN were not assigned an explicit bedtime. Given that decreased latency to sleep onset has previously been shown to be a reliable marker of depression, this was a missed opportunity.

In summary, results from this study support the notion that blockade of TNF can improve sleep continuity independently of depressive symptoms in patients with treatment resistant depression and high inflammation. Moreover, decreases in sTNFR1 were associated with the improvements in both sleep efficiency and WASO. Given the relationship of TNFR1 with alterations in sleep continuity in primary sleep disorders such as apnea, these data suggest that TNF antagonists may warrant further study in patients with other sleep disorders with increased inflammation including insomnia as well as in patients with depression and high inflammation. Nevertheless, given the modest sample size, these results should be considered preliminary and in need of further exploration.

Financial disclosure

In the prior 12 months, Charles L. Raison has served as a consultant for Pamlab, Lilly, and Otsuka-Lundberg; has been on the speakers bureau for Pamlab and Sunovion, has served on the steering committee for North American Center for Continuing Medical Education (NACCME) and has prepared and delivered continuing medical education material for NACCME, Haymarket CME, Medscape and CME Incite. All other authors have no conflict of interest or financial relationships to disclose.

Acknowledgments

This work was supported in part by grants from the National Institute of Mental Health (R03MH100273 and R21MH0771172) and the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR000454). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

Abad, V.C., Sarinas, P.S., Guilleminault, C., 2008. Sleep and rheumatologic disorders. Sleep Med. Rev. 12, 211–228.

Arfken, C.L., Joseph, A., Sandhu, G.R., Roehrs, T., Douglass, A.B., Boutros, N.N., 2014. The status of sleep abnormalities as a diagnostic test for major depressive disorder. J. Affect. Disord. 156, 36–45.

Barbosa, I.G., Huguet, R.B., Mendonca, V.A., Sousa, L.P., Neves, F.S., Bauer, M.E., Teixeira, A.L., 2011. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 261, 139–143.

Benca, R.M., Peterson, M.J., 2008. Insomnia and depression. Sleep Med. 9, S3–9.

Benedict, C., Scheller, J., Rose-John, S., Born, J., Marshall, L., 2009. Enhancing influence of intranasal interleukin-6 on slow-wave activity and memory consolidation during sleep. FASEB J. 23, 3629–3636.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652.

Chung, E.S., Packer, M., Lo, K.H., Fasanmade, A.A., Willerson, J.T., 2003. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 107, 3133–3140.

D'Mello, C., Le, T., Swain, M.G., 2009. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. J. Neurosci. 29, 2089–2102.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.

EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association, 1992. Sleep 15, 173–184.

Faul, F., Erdfelder, E., Lang, A., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191.

First MB, S.R., Gibbon, M., Williams, J.B., 1997. Structured Clinical Interview for DSM-IV. American Psychiatric Press, Washington, DC.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Franzen, P.L., Buysse, D.J., Rabinovitz, M., Pollock, B.G., Lotrich, F.E., 2010. Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment. Psychiatry Res. 177, 240–245.
Giles, D.E., Jarrett, R.B., Rush, A.J., Biggs, M.M., Roffwarg, H.P., 1993. Prospective assessment of electroencephalographic sleep in remitted major depression. Psychiatry Res. 46, 269–284.
Haensel, A., Bardwell, W.A., Mills, P.J., Loredo, J.S., Ancoli-Israel, S., Morgan, E.E., Heaton, R.K., Dimsdale, J.E., 2009. Relationship between inflammation and cognitive function in obstructive sleep apnea. Sleep Breath 13, 35–41.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hendrickse, W.A., Roffwarg, H.P., Grannemann, B.D., Orsulak, P.J., Armitage, R., Cain, J.W., Battaglia, J., Debus, J.R., Rush, A.J., 1994. The effects of fluoxetine on the polysomnogram of depressed outpatients: a pilot study. Neuropsychopharmacology 10, 85–91.
Imeri, L., Opp, M.R., 2009. How (and why) the immune system makes us sleep. Nat. Rev. Neurosci. 10, 199–210.
Irwin, M.R., Wang, M., Campomayor, C.O., Collado-Hidalgo, A., Cole, S., 2006. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch. Intern. Med. 166, 1756–1762.
Irwin, M.R., Wang, M., Ribeiro, D., Cho, H.J., Olmstead, R., Breen, E.C., Martinez-Maza, O., Cole, S., 2008. Sleep loss activates cellular inflammatory signaling. Biol. Psychiatry 64, 538–540.
Irwin, M.R., Olmstead, R., Valladares, E.M., Breen, E.C., Ehlers, C.L., 2009. Tumor necrosis factor antagonism normalizes rapid eye movement sleep in alcohol dependence. Biol. Psychiatry 66, 191–195.
Karson, A., Demirtas, T., Bayramgurler, D., Balci, F., Utkan, T., 2013. Chronic administration of infliximab (TNF-alpha inhibitor) decreases depression and anxiety-like behaviour in rat model of chronic mild stress. Basic Clin. Pharmacol. Toxicol. 112, 335–340.
Kerkhofs, M., Rielaert, C., de Maertelaer, V., Linkowski, P., Czarka, M., Mendlewicz, J., 1990. Fluoxetine in major depression: efficacy, safety and effects on sleep polygraphic variables. Int. Clin. Psychopharmacol. 5, 253–260.
Krueger, J.M., 2008. The role of cytokines in sleep regulation. Curr. Pharm. Des. 14, 3408–3416.
Krueger, J.M., Obal, F.J., Fang, J., Kubota, T., Taishi, P., 2001. The role of cytokines in physiological sleep regulation. Ann. N. Y. Acad. Sci. 933, 211–221.
Kupfer, D.J., Ehlers, C.L., 1989. Two roads to rapid eye movement latency. Arch. Gen. Psychiatry 46, 945–948.
Lam, R.W., 2006. Sleep disturbances and depression: a challenge for antidepressants. Int. Clin. Psychopharmacol. 21 (Suppl 1), S25–29.
Mayers, A.G., Baldwin, D.S., 2005. Antidepressants and their effect on sleep. Hum. Psychopharmacol. 20, 533–559.
Mehta, D., Raison, C.L., Woolwine, B.J., Haroon, E., Binder, E.B., Miller, A.H., Felger, J.C., 2013. Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. Brain Behav. Immun. 31, 205–215.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.
Motivala, S.J., Sarfatti, A., Olmos, L., Irwin, M.R., 2005. Inflammatory markers and sleep disturbance in major depression. Psychosom. Med. 67, 187–194.
Mullington, J., Korth, C., Hermann, D.M., Orth, A., Galanos, C., Holsboer, F., Pollmacher, T., 2000. Dose-dependent effects of endotoxin on human sleep. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278, R947–955.
Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966.
Nutt, D., Wilson, S., Paterson, L., 2008. Sleep disorders as core symptoms of depression. Dialogues Clin. Neurosci. 10, 329–336.
Opp, M.R., 2005. Cytokines and sleep. Sleep Med. Rev. 9, 355–364.
Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon 3rd, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., Rifai, N., Smith Jr., S.C., Taubert, K., Tracy, R.P., Vinicor, F., 2003. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107, 499–511.
Persoons, P., Vermeire, S., Demyttenaere, K., Fischler, B., Vandenberghe, J., Van Oudenhove, L., Pierik, M., Hlavaty, T., Van Assche, G., Noman, M., Rutgeerts, P., 2005. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment. Pharmacol. Ther. 22, 101–110.
Petersen, T., Papakostas, G.I., Posternak, M.A., Kant, A., Guyker, W.M., Iosifescu, D.V., Yeung, A.S., Nierenberg, A.A., Fava, M., 2005. Empirical testing of two models for staging antidepressant treatment resistance. J. Clin. Psychopharmacol. 25, 336–341.
Prather, A.A., Rabinovitz, M., Pollock, B.G., Lotrich, F.E., 2009. Cytokine-induced depression during IFN-alpha treatment: the role of IL-6 and sleep quality. Brain Behav. Immun. 23, 1109–1116.
Prather, A.A., Vogelzangs, N., Penninx, B.W., 2015. Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands Study of Depression and Anxiety (NESDA). J. Psychiatr. Res. 60, 95–102.
Quan, N., Banks, W.A., 2007. Brain-immune communication pathways. Brain Behav. Immun. 21, 727–735.
Raison, C.L., Rye, D.B., Woolwine, B.J., Vogt, G.J., Bautista, B.M., Spivey, J.R., Miller, A.H., 2010. Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. Biol. Psychiatry 68, 942–949.
Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70, 31–41.
Ranjbaran, Z., Keefer, L., Stepanski, E., Farhadi, A., Keshavarzian, A., 2007. The relevance of sleep abnormalities to chronic inflammatory conditions. Inflamm. Res. 56, 51–57.
Rechtschaffen, A.K.A., 1968. A Manual of Standard Terminology: Techniques and Scoring System for Sleep Stages in Human Subjects. U.S. Government Printing Office, Washington, DC.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatry 163, 1905–1917.
Rutgeerts, P., Feagan, B.G., Lichtenstein, G.R., Mayer, L.F., Schreiber, S., Colombel, J.F., Rachmilewitz, D., Wolf, D.C., Olson, A., Bao, W., Hanauer, S.B., 2004. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 126, 402–413.
Schroder, J., Stuber, F., Gallati, H., Schade, F.U., Kremer, B., 1995. Pattern of soluble TNF receptors I and II in sepsis. Infection 23, 143–148.
Tamaki, S., Yamauchi, M., Fukuoka, A., Makinodan, K., Koyama, N., Tomoda, K., Yoshikawa, M., Kimura, H., 2009. Production of inflammatory mediators by monocytes in patients with obstructive sleep apnea syndrome. Intern. Med. 48, 1255–1262.
Thase, M.E., Fasiczka, A.L., Berman, S.R., Simons, A.D., Reynolds 3rd, C.F., 1998. Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. Arch. Gen. Psychiatry 55, 138–144.
Thase, M.E., 2006. Depression and sleep: pathophysiology and treatment. Dialogues Clin. Neurosci. 8 (2), 217–226.
Trivedi, M.H., Rush, A.J., Ibrahim, H.M., Carmody, T.J., Biggs, M.M., Suppes, T., Crismon, M.L., Shores-Wilson, K., Toprac, M.G., Dennehy, E.B., Witte, B., Kashner, T.M., 2004. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol. Med. 34, 73–82.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66, 1254–1269.
Tweedie, D., Sambamurti, K., Greig, N.H., 2007. TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. Curr. Alzheimer Res. 4, 378–385.
Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., Cella, D., Krishnan, R., 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367, 29–35.
Wohleb, E.S., McKim, D.B., Shea, D.T., Powell, N.D., Tarr, A.J., Sheridan, J.F., Godbout, J.P., 2014. Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain. Biol. Psychiatry 75, 970–981.
Yue, H.J., Mills, P.J., Ancoli-Israel, S., Loredo, J.S., Ziegler, M.G., Dimsdale, J.E., 2009. The roles of TNF-alpha and the soluble TNF receptor I on sleep architecture in OSA. Sleep Breath 13, 263–269.
Zamarron, C., Maceiras, F., Mera, A., Gomez-Reino, J.J., 2004. Effect of the first infliximab infusion on sleep and alertness in patients with active rheumatoid arthritis. Ann. Rheum. Dis. 63, 88–90.