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Soehner, Adriane Mary

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You'll Feel Better in the Morning:
Slow Wave Activity and Overnight Mood Regulation in Bipolar Disorder

By

Adriane M. Soehner

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

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Graduate Division

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University of California, Berkeley

Committee in charge:

Professor Allison G. Harvey, Chair
Professor Matthew Walker
Professor Jodi Halpern

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Abstract

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Slow Wave Activity and Overnight Mood Regulation in Bipolar Disorder

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Adriane M. Soehner

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Professor Allison G. Harvey, Chair

Sleep disturbances are among the most prominent correlates of mood episodes and inadequate recovery in bipolar disorder, yet the mechanistic relationship between sleep physiology and mood remains poorly understood. The present study investigated the connection between mood dysregulation and deficient sleep homeostasis during the interepisode phase of bipolar disorder.

Individuals with interepisode bipolar disorder (n = 24) and healthy adult controls (n = 26) slept in the laboratory for 2 baseline nights, a happy mood induction night, and a sad mood induction night. Sleep was recorded using polysomnography and spectral analysis was conducted on the sleep EEG for each of the four overnights. Relative slow wave activity (SWA; 0.75-4.75Hz) during non-rapid eye movement sleep was derived as an index of sleep homeostasis. On the mood induction nights, mood was evaluated using an affect grid pleasantness rating at 3 time points: pre-induction, post-induction and the next morning.

The bipolar and control groups did not exhibit baseline differences in SWA. A greater proportion of bipolar patients experienced a reduction in SWA from baseline to the sad night relative to controls. Reduced SWA following the sad mood induction predicted impaired overnight negative mood improvement in the bipolar group, while this relationship was not observed in the control group. Following the happy mood induction, both groups experienced an increase in SWA, though SWA did not exhibit a significant relationship with overnight mood change for either group.

The present findings indicate that interepisode bipolar patients may be more vulnerable to negative mood-related SWA disruptions, which in turn serve to sustain negative mood from the previous day. Furthermore, positive mood can enhance SWA in both bipolar patients and healthy adults.

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Introduction

Bipolar disorder is fundamentally characterized by mood regulation impairment (1), oscillating between persistently elevated or irritable mood and sustained periods of depressed mood (2). Even between episodes, individuals with bipolar disorder remain seriously symptomatic (3, 4) and exhibit significant mood lability (5-8). Though sleep disturbances are among the most prominent correlates of mood episodes and inadequate recovery in bipolar disorder (9), the precise nature of sleep abnormalities and their relation to negative, and positive, mood dysregulation remains unclear. Disrupted sleep homeostasis, typically indexed via slow waves during non-rapid eye movement (NREM) sleep, is proposed to play an important role in mood regulation impairment in affective disorders (10, 11). However, this hypothesis has primarily been tested in unipolar depression (12). Thus, the aim of the present study was to empirically evaluate the relationship between mood regulation impairment and slow wave activity in interepisode bipolar disorder.

To date, polysomnographic investigations of sleep across the phases of bipolar disorder have principally focused on traditional sleep architecture. In bipolar depression, studies generally suggest that slow wave sleep (SWS; NREM stages 3 and 4) is reduced relative to healthy adults (13-16) and does not significantly differ from unipolar depression (15, 17), though there are some non-replications (18, 19). Increased latency to SWS has also been observed in groups with bipolar and unipolar depression relative to healthy adults (20). SWS findings during mania are less consistent, with one study reporting increased stage 3 percentage relative to healthy adults (21) and others reporting no differences compared to healthy adults (15, 22) and depressed samples (15). No SWS deficits have been reported during the interepisode phase of bipolar disorder (23-25). However, a study conducted in an interepisode bipolar sample reported that baseline SWS percentage positively correlated with manic symptoms at 3-month follow-up (23). Overall, there is some support for reduced SWS during the depressive phase of illness, though the nature of SWS deficits during the manic and interepisode phases remain inconclusive.

Traditional visual scoring of SWS involves assessment of the frequency, amplitude, and proportion of delta (slow) waves during sleep (26, 27). However, delta waves occur throughout all stages of NREM sleep and are not exclusive to SWS. Compared to traditional sleep staging, slow wave activity (SWA), or NREM sleep electroencephalogram power density in the delta frequency range (approximately 1-4.5 Hz), can more accurately capture variation in delta waves during sleep (28, 29). SWA is also an established marker of sleep homeostasis (11, 30). In unipolar depression, it has been proposed that deficient build up of homeostatic sleep pressure during the day results in reduced NREM SWA, known as the S-deficiency hypothesis (11). Though previous investigations have examined homeostatic function using SWA in unipolar depression (12), there is a paucity of work evaluating SWA in bipolar disorder. Only one study in bipolar depression ($n = 8$ per group) has measured SWA, reporting no difference in SWA relative to matched controls (16). To our knowledge, no studies have evaluated SWA during the interepisode phase of bipolar disorder.

To better characterize the role played by sleep homeostasis in bipolar disorder, the present study investigated whether participants with interepisode bipolar disorder are more vulnerable to mood-related disruptions in SWA, and whether disturbed SWA sustains mood impairment. This study involved further analysis of an existing dataset (23, 31). Adults with interepisode bipolar disorder and healthy adult controls spent 4 nights in the sleep laboratory: 2 baseline nights, 1 negative (sad) mood induction night, and 1 positive (happy) mood induction night. The first aim was to assess whether interepisode bipolar patients and healthy adults exhibited an overnight reduction in negative and positive mood following the sad and happy mood inductions, respectively. Due to documented mood regulation deficits in interepisode bipolar disorder (5-8), it was hypothesized that the bipolar group would exhibit a smaller overnight change in mood. The second aim was to

evaluate the effects of the sad and happy mood inductions on SWA relative to baseline. In accordance with the S-deficiency hypothesis (11), it was predicted that the bipolar group would be more vulnerable to mood-related disruptions to sleep homeostasis; specifically, that both mood inductions would lead to reduced SWA in the bipolar group. The final aim was to assess whether reductions in SWA are associated with overnight mood change following the sad and happy mood inductions. It was predicted that reduced SWA would be associated with impaired overnight mood change in bipolar patients.

Methods

Participants

Participants in the present study were selected from a larger protocol, results from which have been described in previous reports (e.g., 23, 31, 32). One prior report in this sample (31) specifically evaluated the effects of sad and happy mood inductions on REM sleep characteristics in participants who had completed polysomnographic recordings (27 bipolar participants, 27 healthy adult controls). The current study extends the traditional sleep staging methods employed in the previous report (31) by evaluating spectral characteristics of the sleep EEG, namely SWA. In order to be included in the present analysis, participants had to have at least one baseline night recording (screening or neutral mood induction) and one mood induction (sad and/or happy) sleep recording. From the original sample, participants were excluded on the basis of poor quality recording and excessive artifact on both baseline nights (control = 1), on the happy mood induction night (bipolar = 5, control = 3) and on the sad mood induction night (bipolar = 1, control = 4). This resulted in inclusion of 24 adults (ages 18–65 years) with bipolar I (n=22) or bipolar II (n=2) disorder who were currently in the interepisode phase and 26 adults with no history of psychiatric or sleep disorders in this report.

Participants in the bipolar group were eligible if they (a) met *Diagnostic and Statistical Manual of Mental Disorders (DSM–IV–TR)* criteria for a diagnosis of bipolar I or bipolar II disorder (2); (b) did not meet criteria for a diagnosis of current substance or alcohol abuse or dependence; (c) did not meet criteria for narcolepsy, sleep apnea, restless leg syndrome or periodic limb movement disorder on the basis of polysomnography; (d) were under the care of a psychiatrist; and (e) met criteria for interepisode symptom cutoffs based on prior research (33, 34): a score of ≤7 on the Young Mania Rating Scale (YMRS; 35) and a score of ≤ 11 on the Inventory of Depressive Symptomatology–Clinician Rated (ISD-C; 36); (f) had no history of severe head trauma, stroke, neurological disease, or severe medical illness. Participants with bipolar disorder were not excluded on the basis of comorbidities or psychiatric medication, as these are common characteristics of the disorder (37).

Participants in the healthy adult control group were eligible if they (a) did not meet *DSM–IV–TR* criteria for any past or current Axis I disorder; (b) had scores of ≤7 on the YMRS and ≤ 11 on the IDS-C; and (c) did not meet criteria for any past or current sleep disorder on the basis of either polysomnography or the Duke Structured Interview for Sleep Disorders (DSISD; 38); (d) had no history of severe head trauma, stroke, neurological disease, or severe medical illness.

Clinical Functioning Measures

Structured Clinical Interview for DSM-IV (SCID; 39). All DSM-IV Axis I diagnoses were confirmed using the SCID. Fifteen randomly selected audiotapes of SCID interviews were rated by a set of independent reviewers to check diagnostic reliability for the overall study, a subset of which participated in the present investigation. Ratings matched 100% ($\kappa = 1.00$) of the primary diagnoses made by the original interviewer.

Manic and Depressive Symptoms. Current symptoms of mania were measured using the Young Mania Rating Scale (YMRS; 35). The YMRS is an 11-item, clinician-rated measure of current manic symptoms with scores ranging from 0 to 60, with higher scores indicating greater mania severity. Current symptoms of depression were assessed using the Inventory of Depressive Symptomatology (IDS-C; 36). The IDS-C is a 30-item, clinician-rated measure of current depressive symptoms with scores ranging from 0 to 84, with higher scores indicating greater depressive severity. Both measures have good reliability and validity (35, 36). Scores on the YMRS (≤7) and IDS-C (≤ 11) were used to confirm current interepisode status (i.e., neither currently manic nor depressed) for both groups. Intra-class correlations (ICCs) were strong for both the YMRS (ICC = 0.96) and IDS-C (ICC = 0.98) between the original interviewer and independent rater for participants drawn from the overall study (n = 9), from which a subset will be selected for the present study.

Medication Tracking and Dosage. At the beginning of each visit, medication name, dosage and duration of use were recorded. As medication class and dosing may influence sleep physiology and mood, medication effects were examined using an approach developed by Phillips and colleagues for neuroimaging research (40). Each medication was re-categorized by medication class and dose was categorized as 0 (no medication), 1 (low), or 2 (high) based on published parameters and chlorpromazine-equivalent mean effective daily doses (ED50; 41, 42). Finally, a composite measure of medication load was created for each participant by summing across dosage strength codes and classes, reflecting both dose and diversity of medications taken by each participant (43).

Sleep Measures

Duke Structured Interview for Sleep Disorders (DSISD; 38). The DSISD is a semi-structured interview that assesses research diagnostic criteria for sleep disorders. Potential participants were excluded if they met self-reported criteria for current sleep disorders, including narcolepsy, sleep apnea and periodic limb movement disorder. The DSISD has been shown to have good reliability and validity (44). Fifteen randomly selected audiotapes of DSISD interviews from the overall study were rated by a set of independent reviewers for diagnostic reliability. Ratings matched 100% (κ = 1.00) of the primary diagnoses made by the original interviewer.

Polysomnography (PSG). Overnight PSG recordings took place in individual darkened bedrooms. PSG involves the continuous and simultaneous recording of electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) to score sleep. Data were collected with the Compumedics 802 Siesta device (Compumedics, Charlotte, NC) and software. Recording channels included four EEG derivations (C3/A2, C4/A1, O1/A2, O2/A1), two EOG leads, and two submental EMG sensors. On the first overnight visit, participants' heart rate, blood oxygen, nasal and oral air flow, thoracic and abdominal effort, and leg motion were monitored. Participants will be excluded if they exhibit a respiratory disturbance index (AHI) greater than 5 or a periodic limb movement index (PLMI) greater than 15. PSG data were scored in 30-second epochs using standard criteria for sleep staging (26).

Power Spectral Analysis. Sleep EEG analyses were performed offline in MATLAB R2011b (Mathworks, Natick, MA) and EEGLAB11 (http://sccn.ucsd.edu/eeglab/). Power spectral analysis was carried out in accordance with published methods (e.g., 45, 46, 47). EEG channels were re-referenced to the average of the left and right mastoid (A1, A2), run through high-pass (0.5Hz) and low-pass (55Hz) Finite Impulse Response (FIR) filtering, and split into 5-second epochs. The re-referenced and filtered overnight EEG recordings were visually inspected for 5-second epochs containing muscle, cardiac and eye-movement artifacts. Epochs containing artifact were manually rejected. Subsequent analyses were performed on artifact-free epochs. Power spectral density ($\mu V^2/Hz$) was calculated using a Fast Fourier Transform (FFT) on each hamming-windowed 5-

second epoch at 128Hz, yielding a frequency resolution of 0.2Hz. FFT results were then sorted according to sleep stage and averaged across NREM (stages 2-4). Slow wave activity (SWA) was defined as power density in the 0.75-4.75 Hz range. Relative SWA [(band absolute power/total power)*100] was used for all analyses for two reasons. First, we were interested capturing night-to-night changes in the proportion of SWA, rather than changes resulting from variation in overall absolute spectral power between nights. Second, relative spectral power adjusts for individual differences in overall absolute spectral power that could stem from a variety of inter-individual differences, such as brain to scalp distance, skull thickness, impedance and head size (48).

Mood Ratings

Affect Grid. The affect grid (49) is a self-report rating of pleasure on the horizontal axis (–4 = *extremely unpleasant,* 0 = *neutral,* 4 = *extremely pleasant)* and arousal on the vertical axis (–4 = *extremely low arousal,* 0 = *neutral,* 4 = *extremely high arousal*). This scale has adequate reliability and validity (49).

Mood Induction

Mood Induction. Briefly, the mood induction technique was adapted from well-validated procedures (50-53) that combine continuous music with autobiographical recall in order to elicit neutral, sad and happy moods. For the happy and sad mood inductions, participants were first told that they would listen to a selection of music[1] to assist them in developing a happy (or sad) mood. Participants were then instructed to try hard to develop an intense mood state by concentrating on ideas and images that make them feel happy (or sad). For the neutral induction, participants were asked to focus on neutral topics, such as directions to a familiar place or the layout of furniture at home, while listening to the classical music[1].

During each mood induction, participants rated their current affect, pleasure, and arousal at baseline, 5 minutes after the induction began and every 5 minutes thereafter. Pleasure and arousal were rated on a computerized version of the Affect Grid. For the happy and sad mood inductions, Eich et al. (51) specified Affect Grid mood thresholds on the last rating of at least +3 (pleasure) for the happy induction and at least -3 (pleasure) for the sad induction. If participants met these thresholds, the mood induction ended. In the present study, if the participant did not reach the mood threshold by 40 minutes after the start of the induction, the induction ended and the participant was escorted to bed. For the happy and sad mood inductions, the last rating was used as a manipulation check to ensure that the mood induction had the intended effect. The neutral mood induction was 15 minutes for all participants and there was no mood cut-off at the end.

Procedure

The University of California Berkeley Committee for the Protection of Human Subjects approved all procedures. Participants identified as preliminarily eligible following a telephone screen were invited to a laboratory interview.

Visit 1: Clinical Evaluation. Participants completed written informed consent and were then administered the SCID, DSISD, YMRS, and IDS-C to determine their diagnostic status and mood symptom severity. After eligibility was determined, participants were given an instruction sheet for the day preceding the following four overnight visits. Prior to all overnight visits, participants were asked to: (1) avoid caffeine completely or restrict intake to no more than the equivalent of two cups of coffee before noon and (2) refrain from taking any over-the-counter medications.

Visit 2: Sleep Disorders Screening. For each overnight visit, participants arrived at the laboratory 2 hours prior to their habitual bedtime. The YMRS and IDS-C were then administered to confirm interepisode status. If scores on the YMRS and IDS-C exceeded interepisode cut-offs, participants were assessed for safety, sent home without completing the overnight procedures, and reassessed in

1 month. Their first overnight laboratory visit was to assess for sleep disorders, such as sleep apnea and periodic leg movement disorder. If participants did not meet criteria for sleep disorders, they were invited to complete the next portion of the study.

Visits 3-5: Mood Inductions. The neutral mood induction was conducted on the third laboratory visit, with the happy and sad mood inductions conducted on the fourth or fifth visits (in counterbalanced order). Each mood induction overnight visit was conducted approximately one month after the prior visit. In the overall sample, the time elapsed between sessions did not differ for the bipolar group (M = 31.9 days, SD =15.7 days) and the control group (M = 26.4 days, SD = 12.9 days). Some individuals did not participate in both the happy and sad mood induction nights (bipolar n = 6; control n = 2). The reasons provided for attrition included: unable to recontact (bipolar n = 4, control n = 2), moved out of state (bipolar n =1), and declined to continue participation (bipolar n = 1). Additional participants were excluded from analyses on the basis of poor quality recording and excessive artifact on both baseline nights (control n = 1), on the happy mood induction night (bipolar n = 5, control n = 3) and on the sad mood induction night (bipolar n = 1, control n = 4). Similar to the screening night, participants arrived at the laboratory 2 hours prior to their habitual bedtime and the YMRS and IDS-C were administered to confirm interepisode status. After attaching the PSG equipment, participants were told that they would be participating in two different experiments, a music study and a sleep study, in order to reduce demand effects. Seated in a private experimental room, participants completed baseline Affect Grid ratings and then the mood induction. The final Affect Grid of the mood induction was used as the pre-sleep (post-induction) pleasure and arousal measures. After the mood induction, the participant was immediately escorted to the laboratory bedroom and asked to go to sleep. Participants were awakened at the time they requested, with the constraint that they could not stay in the lab past 9:00am. To reduce the effects of sleep inertia upon morning mood reports, participants completed the Affect Grid roughly 20 minutes after awakening. In the morning following the last visit, participants were debriefed.

Analytic Approach

All analyses were conducted in SPSS 20.0 (IBM Corporation, Somers, NY, 2012). Baseline group differences in demographic, clinical and sleep architecture characteristics were assessed using independent samples t-tests or χ^2 tests. SWA data were derived from the central EEG derivation C4. The C4 derivation was selected for two reasons: (1) to achieve maximal statistical power, as a subset of participants exhibited excessive artifact in C3, necessitating their exclusion (Happy: bipolar=3, control=2; Sad: bipolar=2, control=1) and (2) relative SWA derived from C3 and C4 was highly correlated.

Preliminary Analyses. Correlation analyses were conducted to assess whether age, gender, depressive or manic symptoms scores were meaningfully associated with any mood or sleep EEG outcomes. No significant correlations emerged; therefore these variables were not included as covariates in subsequent analyses.

Main Analyses. The Affect Grid pleasantness rating (–4 = *extremely unpleasant,* 0 = *neutral,* 4 = *extremely pleasant*) was used to evaluate mood just prior to each mood induction (pre-induction), at the end of each mood induction (post-induction) and the morning following the mood induction (morning). A repeated-measures analysis of variance (ANOVA) was conducted for each the sad and happy mood inductions, with Group (bipolar vs. control) serving as the between-subjects variable and Time of mood rating (pre-induction, post-induction, morning) serving as the within-subjects variable. Overnight mood change was evaluated using a difference score, subtracting post-induction affect grid pleasantness rating from the morning rating (morning – post-induction). Independent

samples *t*-tests evaluated group differences in overnight mood change scores.

The effect of pre-sleep sad and happy mood inductions on SWA was examined in two ways. First, a series of 2x2 repeated-measures ANOVA models were performed. Night (sad or happy mood induction vs. baseline) served as the within-subjects variable and Group (bipolar vs. control) served as the between-subjects variable. Baseline sleep was assessed using an average of the first two sleep recording nights (the screening night and neutral mood induction night) following procedures from a previous report in this sample (31). Baseline night means differ slightly for the sad and happy mood induction analyses since a few individuals did not participate in both mood induction overnights. As repeated-measures ANOVA excludes a participant if there is missing data on any of the observation points, separate ANOVAs were conducted to compare each mood induction night to baseline in order to maximize statistical power. Next, changes in SWA were examined categorically based on SWA change from baseline to the mood induction night. Chi-square tests compared the proportions in each group (bipolar, control) who experienced a decrease in SWA (Mood induction SWA< Baseline SWA) on the mood induction night relative to baseline.

For the happy and sad mood induction nights, correlation analyses evaluated whether the percentage change in SWA after the mood induction (100*[Mood Induction SWA-Baseline SWA/Baseline SWA]) was associated with overnight mood change (morning – post-induction affect grid pleasantness ratings) in each group. In accordance with prior reports (54), outliers ± 2.5 standard deviations from the mean were excluded for correlational analyses of SWA with mood outcomes. Finally, exploratory analyses were conducted to examine between-night differences in sleep architecture, the effects of pre-sleep arousal on SWA, and the effects of medication load on SWA. The significance level was set at $p < 0.05$ (two-sided) for all analyses.

Results

Baseline Demographic and Clinical Characteristics

Patient characteristics are described in Table 1. The bipolar and control groups did not significantly differ on any sociodemographic characteristics, though the difference in age reached marginal significance. While the bipolar group exhibited significantly higher baseline manic and depressive symptoms (*p*s<0.001), scores were well below established interepisode cut-offs (33, 34).

Sad Mood Induction

Overnight Mood Regulation. Figure 1a illustrates affect grid mood ratings across the sad mood induction overnight (Pre-Induction, Post-Induction, Morning). There was neither a significant main effect of Group, $F(2, 40)=2.60$, $p=0.115$, nor a significant Group X Time interaction effect, $F(2,40)=0.75$, $p<0.786$. However, there was a significant quadratic main effect of Time, $F(2, 40)=106.21$, $p<0.001$. Posthoc paired samples *t*-tests demonstrated a significant increase in negative mood from pre- to post-mood induction, $t(41)=9.85$, $p<0.001$, and a significant overnight decrease in negative mood from post-induction to morning, $t(38)=-8.73$, $p<0.001$. As shown in Figure 1b, the bipolar and control groups did not differ in the extent to which negative mood decreased overnight based on the affect grid, $t(37)=0.73$, $p=0.471$.

Impact of Mood Induction on SWA. Given that a repeated-measures ANOVA excludes a participant if there is missing data on any of the observation points, the happy and sad mood induction comparisons were conducted separately to maximize statistical power as a few individuals did not participate in both mood induction overnights (see *Procedures*). Figure 1c illustrates SWA means on the baseline and sad mood induction overnights. For the sad mood induction comparisons, there were no significant effects SWA across Group, $F(1,41)=2.46$, $p=0.124$, Night,

$F(1,41)=0.80$, $p=0.377$, or Group X Night, $F(1,41)=0.16$, $p=0.696$. However, a significantly greater proportion of bipolar (55.5%) relative to control participants (21.7%) experienced a reduction in SWA on the sad mood induction night compared to baseline, $\chi^2(1) = 5.07$, $p = 0.024$ (Figure 1d).

Relationship between SWA and Overnight Mood Regulation. For the bipolar group only, percentage change in SWA from baseline to the sad mood induction night exhibited a significant positive correlation with overnight mood change on the affect grid ($r = 0.89$, $p<0.001$) (Figure 2). However, overnight mood change on the affect grid did not significantly correlate with percent change in SWA for the control group on the sad mood induction night ($r = -0.01$, $p=0.968$). Thus, reduced SWA was associated with impaired overnight improvement in negative mood for bipolar participants only.

Happy Mood Induction

Overnight Mood Regulation. Figure 3a illustrates mood ratings across the happy mood induction overnight (Pre-Induction, Post-Induction, Morning). There was neither a significant main effect of Group, $F(2, 41)=0.48$, $p=0.491$, nor a significant Group X Time interaction effect, $F(2,41)=0.05$, $p=0.825$. There was a significant quadratic main effect of Time, $F(2, 41)=36.61$, $p<0.001$. Posthoc paired samples *t*-tests showed a significant increase in positive mood from pre- to post-mood induction, $t(42)=-5.80$, $p<0.001$, and a significant overnight reduction in positive mood from post-induction to morning, $t(42)=5.31$, $p<0.001$. As demonstrated in Figure 3b, the bipolar and control groups did not differ in the extent to which positive mood decreased overnight on the affect grid, $t(38)=-0.12$, $p=0.903$.

Impact of Mood Induction on SWA. Figure 3c shows SWA means on the baseline and happy mood induction overnights. There was a significant main effect of Night, $F(1,41)=4.56$, $p=0.039$, whereby SWA increased on the happy mood induction night relative to baseline in both groups (Figure 3c). The Group, $F(1,41)=0.00$, $p=0.994$, and Group X Night, $F(1,41)=0.13$, $p=0.722$, effects were not significant. The proportion of bipolar (35.0%) and control participants (34.8%) experiencing a reduction in SWA on the happy mood induction night relative to baseline did not significantly differ, $\chi^2(1) = 0.00$, $p = 0.998$ (Figure 3d).

Relationship between SWA and Overnight Mood Regulation. On the happy mood induction night, overnight mood change on the affect grid was not significantly correlated with percentage change in SWA for both the bipolar group ($r = 0.06$, $p=0.790$) and the control group ($r = -0.19$, $p=0.376$).

Sleep Architecture

We also examined whether traditional sleep architecture outcomes differed between the baseline and mood induction nights. Table 2 reports results from repeated measures ANOVAs evaluating sleep architecture variables (TST, TWT, N1%, N2%, SWS%, REM%) on the baseline night vs. mood induction nights. There were no significant effects of Group, Night or Group X Night across sleep architecture variables for both the sad and happy mood induction nights (*p*s>0.05). Baseline sleep architecture has been described in previous reports from this sample (23, 31); the patterns observed in the present study are consistent with earlier findings. As TST has been associated with mood symptoms in bipolar disorder, we also explored the relation between TST and affect grid mood ratings on the induction nights. TST was not significantly associated with morning mood or overnight change in mood on either the sad or happy mood induction nights (*p*s>0.05)

Pre-Sleep Arousal Ratings

To examine the possibility that the magnitude of the pre-sleep arousal influences individual differences in SWA, we conducted an additional set of analyses. On the sad mood induction night, there was not a significant difference between post-induction arousal ratings on the affect grid for

the bipolar and control groups (-1.35 vs. -1.74; $t(41)=-0.71$, $p=0.484$). The bipolar and control groups also did not significantly differ in post-induction affect grid arousal ratings following the happy mood induction (-0.30 vs. -0.35; $t(41)=-0.66$, $p=0.948$). Furthermore, post-induction arousal ratings did not correlate with SWA on the mood induction nights for each group and the overall sample (ps >0.05)

Medication Effects

We also examined the potential effects of medication load on SWA in the bipolar group. Medication load did not significantly differ between the baseline nights (screening and neutral mood induction) and sad mood induction night (3.70 vs. 3.95 vs. 3.85; $F(1,19)=1.21$, $p=0.286$). Similarly, medication load did not significantly differ between the baseline nights (screening and neutral mood induction) and happy mood induction night (3.35 vs. 3.90 vs. 3.75; $F(1,19)=2.45$, $p=0.134$). Further, there were no significant correlations between medication load and SWA on the two baseline nights and the sad mood induction night (ps >0.05). However, medication load exhibited a significant negative correlation with SWA on the happy mood induction night ($r = -0.486$, $p = 0.030$), with greater medication load being associated with lower SWA.

Discussion

This study tested the relationship between SWA and mood regulation impairment in interepisode bipolar disorder. The data show that (1) overnight mood regulation in interepisode bipolar disorder does not significantly differ from healthy adults, (2) inducing negative and positive mood states prior to sleep can impact SWA in bipolar patients and healthy controls, though the effects on SWA differ by mood valence and disorder status and (3) negative mood-induced reductions in SWA are associated with impaired overnight mood regulation for bipolar patients, while positive mood-induced changes in SWA were not.

Taking findings from the sad mood induction first, the initial prediction that the bipolar group would exhibit impaired overnight mood regulation was not supported. Both the bipolar and control groups exhibited intact overnight mood regulation, with negative mood prior to sleep generally regularizing to a neutral rating by the morning. This is consistent with previous research indicating that negative mood typically improves overnight in healthy adults (64, 65). Impaired mood regulation during the interepisode phase of bipolar disorder might only be evident after shorter spans of time during waking hours, though to our knowledge this question has not yet been systematically investigated. The present findings indicate that *overnight* mood regulation capabilities in interepisode bipolar disorder may generally be comparable to healthy adults.

However, the sad mood induction did have differential effects on SWA across the two groups. A significantly greater proportion of participants in the bipolar group experienced reduced SWA following the sad mood induction compared to controls, though there was not a significant difference in the magnitude of change in SWA between groups. This partially supports our hypothesis, and suggests that there may be a subgroup of bipolar patients who are more vulnerable to negative mood-induced SWA reduction. In support of our final prediction, reduced SWA following the sad mood induction was related to impaired overnight improvement in negative mood for the bipolar group only. The overall pattern of findings largely coheres with predictions of the S-deficiency hypothesis (10), which proposes that negative mood can lead to decrements in SWA that in turn serve to sustain negative mood. Further, these results raise the possibility that disrupted sleep homeostasis might contribute to negative mood regulation difficulties in bipolar disorder.

Predictions for the happy mood induction night were generally not supported. On average, positive mood state prior to sleep decreased to a neutral rating by morning for both groups, thus the

bipolar group did not exhibit impaired overnight mood regulation relative to controls. Also contrary to our hypothesis, both groups exhibited increased SWA following the happy mood induction and the proportion of participants with reduced SWA did not differ between groups. Finally, there was not a significant association between SWA and overnight change in positive mood. The absence of a statistically significant relationship between SWA and overnight change in positive mood, in the presence of positive mood-induced SWA changes and a reduction in positive mood from night to morning, raises the possibility that sleep homeostasis may not be driving overnight change in positive mood. Perhaps overnight changes in positive versus negative mood are driven by different sleep-wake regulatory mechanisms. In the past decade, tightly controlled forced desynchrony and constant routine protocols have determined that there is a circadian pattern in positive affect (55, 56). There is less evidence for a clear 24-hr rhythm in negative affect (55). Thus, overnight change in positive mood may primarily be modulated by circadian, rather than homeostatic factors.

It is intriguing to note that the happy mood induction led to increased SWA relative to baseline in both groups. This pattern of SWA change could represent a favorable process for both groups. Positive affect has been observed to be beneficial for sleep quality and efficiency in some studies (57, 58), though this is the first study to our knowledge that has explored the effects of positive mood on SWA. Further, these results provide insight into one potential pathway for improving deficient SWA – increasing pre-sleep positive mood. Interestingly, greater medication load was associated with lower SWA on the happy mood induction night for the bipolar group. Perhaps medication buffered or blunted the extent to which SWA increased in the bipolar sample. This stands in contrast to neuroimaging findings in medicated bipolar participants, which generally indicate that medication has a normalizing effect on affective neural circuitry, with medicated bipolar participants more closely resembling healthy adults than their unmedicated counterparts (59).

These findings should be interpreted in light of several limitations. Participants in this sample, particularly the bipolar group, were predominantly female. In studies of unipolar depression, gender differences in sleep homeostasis have been observed, with some reports observing that females demonstrated greater, rather than reduced, SWA relative to healthy adults (62, 80). Due to the small sample size of the present investigation, there was not sufficient statistical power to conduct sub-group analyses based on gender. The current study was also limited to analysis of central EEG derivations. SWA deficits can be more pronounced in prefrontal and frontal areas (54, 60), thus future studies of sleep in bipolar disorder would benefit from utilizing hdEEG to explore topographic hypotheses. Another important consideration is that this was a medicated sample of bipolar participants. Though medication load was not associated with overnight mood change, there was some indication that medication could be affecting sleep physiology. Because this study was conducted across a span of several months, an unmedicated or medication naïve sample would be unfeasible and unsafe. More broadly, research on severe mental illness would be seriously hindered and lack generalizability if it is done on only medication-free samples (47). The present findings remain clinically important given that the vast majority of patients with bipolar disorder are medicated.

In summary, the present findings provide support for a relationship between mood and SWA in interepisode bipolar disorder. Pre-sleep negative mood is associated with reduced SWA in bipolar participants, which in turn is associated with sustained negative mood the following morning. Conversely, pre-sleep negative mood did not affect SWA and SWA did not significantly relate to overnight mood regulation in the control group. Pre-sleep positive mood had a SWA-enhancing effect for both groups, though it did not relate to change in mood by morning. The present findings highlight the interplay between mood and SWA that could influence, and possibly perpetuate, mood dysregulation or sleep-wake disturbances during the interepisode phase of bipolar disorder.

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Footnotes

[1] The music selection for the mood inductions was based on the protocol development by Eich et al. (51). The music for the happy mood induction included the Allegro and the Rondo from Mozart's *Eine Kleine Nachtmusik;* the Finale from Mozart's Serenade no. 9 in D Major ("Posthorn"), K. 320; the Allegro from Bach's Brandenburg Concerto no. 3; "Waltz of the Flowers," "Trepak," and "Dance of the Flutes" from Tchaikovsky's *Nutracker;* the Allegro from Dvorak's Piano Quartet in E-flat Major; the Presto from Dvorak's Slavonic Dance no. 1 in C Major, op. 46, no. 1; the Allegretto from Dvorak's Slavonic Dance no. 6 in D Major, op. 46, no. 6; the Allegro from the "Spring" movement of Vivaldi's *Four Seasons;* and Brahms's Hungarian Dance no. 7 in F Major. The music for the sad mood induction included the Adagio from the "Autumn" movement of Vivaldi's *Four Seasons;* "Lullaby" from Stravinsky's *Firebird;* Chopin's Prelude in E Minor, op. 28, no. 4; Faure´'s Piano Quintet no. 1 in D Minor, op. 89; Faure´'s Quartet no. 1 in C Minor, op. 15; Rachmaninov's *Vocalise,* op. 34, no. 14; Mahler's Symphony no. 5; Suite no. 1 from Grieg's *Peer Gynt;* and Albinoni's Adagio in G Minor. Finally, the music for the neutral induction included Fauré's Ballad for Piano and Orchestra, op. 19, and the second and third movements from Brahms's Symphony no. 3 in F Major, op. 90.

Table 1. *Sociodemographic and clinical characteristics by diagnostic group.*

Demographic	Bipolar *n* = 24	Control *n* = 26	Statistic	*p*
Age (Years)	33.42 (10.22)	39.50 (12.37)	$t(48) = 1.89$	0.065
Gender (%)			$\chi^2(1) = 2.02$	0.155
Male	2(8.3%)	6(23.1%)		
Female	22(91.7%)	20(76.9%)		
Ethnicity (%)			$\chi^2(5) = 4.96$	0.421
African American	1(4.2%)	2(7.7%)		
Asian/Pacific Islander	1(4.2%)	5(19.2%)		
Hispanic	1(4.2%)	2(7.7%)		
Native American	1(4.2%)	0(0.0%)		
White	18(75.0%)	14(53.8%)		
Other	2(8.3%)	3(11.5%)		
Education (%)			$\chi^2(5) = 3.97$	0.553
High school	1(4.2%)	1(3.8%)		
Some college	7(29.2%)	5(19.2%)		
2yr college	2(8.3%)	4(15.4%)		
4yr college	11(45.8%)	10(38.5%)		
Master's	2(8.3%)	6(23.1%)		
Doctorate	1(4.2%)	0(0.0%)		
Employed (%)			$\chi^2(2) = 3.98$	0.136
Full-time	9(37.5%)	17(65.4%)		
Part-time	9(37.5%)	6(23.1%)		
Unemployed	6(25.0%)	3(11.5%)		
Clinical				
YMRS	2.87 (2.26)	0.83 (1.17)	$t(45) = -3.85$	<0.001
IDS-C	7.05 (3.63)	2.75 (2.34)	$t(44) = -4.81$	<0.001
BD Age of Onset (years)	18.29 (8.93)	-	-	-
BD Illness Duration (years)	15.42 (8.72)	-	-	-
# (Hypo)manic Episodes	7.83 (7.52)	-	-	-
# Depressive Episodes	10.58 (10.41)	-	-	-
Psychotropic Medications		-	-	-
Polytherapy (%)	24(79.2%)	-	-	-
Mood Stabilizer (%)	19(79.2%)	-	-	-
Antipsychotic (%)	10(41.7%)	-	-	-
Antidepressant (%)	18(75.0%)	-	-	-
Anxiolytic (%)	4(16.7%)	-	-	-
Sedative Hypnotic (%)	2(8.3%)	-	-	-
Stimulant (%)	1(4.2%)	-	-	-
Medication Composite	3.67 (2.2)	-	-	-

Note. Mean values are displayed with standard deviations in parentheses where applicable; BD = Bipolar Disorder; YMRS = Young Mania Rating Scale; IDS-C = Inventory of Depressive Symptoms-Clinician Rated.

Table 2. *Sleep architecture on the baseline and mood induction nights.*

	Sad Mood Induction Analysis[a]									
	Baseline		Sad Night		Group		Night		Group X Night	
Sleep Variable	Bipolar	Control	Bipolar	Control	*F*	*p*	*F*	*p*	*F*	*p*
TST (min)	430.92(72.33)	401.39(64.84)	438.93(93.61)	417.87(60.85)	1.98	0.167	0.84	0.365	0.10	0.753
TWT (min)	53.16(50.52)	35.03(25.42)	45.58(66.80)	28.96(26.37)	2.81	0.101	0.01	0.932	0.58	0.444
N1 (%)	6.93(4.18)	8.42(5.32)	9.26(18.70)	5.58(4.02)	0.21	0.649	0.02	0.890	2.00	0.165
N2 (%)	49.33(10.73)	52.04(8.19)	49.99(14.92)	51.95(7.27)	0.84	0.365	0.02	0.885	0.04	0.849
SWS (%)	19.5(10.04)	17.36(7.14)	18.88(13.83)	19.54(10.04)	0.07	0.783	0.27	0.607	0.95	0.335
REM (%)	24.20(6.23)	22.18(6.58)	21.86(7.15)	22.93(5.84)	0.09	0.770	0.47	0.497	1.78	0.190
	Happy Mood Induction Analysis[b]									
	Baseline		Happy Night		Group		Night		Group X Night	
Sleep Variable	Bipolar	Control	Bipolar	Control	*F*	*p*	*F*	*p*	*F*	*p*
TST (min)	431.59(77.79)	396.78(76.19)	405.35(104.49)	383.09(75.16)	1.50	0.228	3.56	0.066	0.35	0.557
TWT (min)	47.26(51.68)	32.55(24.22)	62.92(85.34)	30.13(34.53)	3.57	0.066	0.43	0.516	0.80	0.376
N1 (%)	6.42(4.47)	8.72(5.67)	7.72(5.07)	7.20(3.66)	0.49	0.486	0.03	0.874	3.86	0.056
N2 (%)	45.73(10.74)	49.72(11.16)	47.05(10.84)	49.23(10.65)	1.11	0.298	0.07	0.793	0.33	0.579
SWS (%)	23.13(10.37)	19.18(10.42)	23.18(12.61)	21.90(5.83)	1.07	0.307	0.65	0.425	0.60	0.442
REM (%)	24.71(6.21)	22.37(6.01)	22.05(7.78)	21.67(11.40)	0.64	0.428	0.83	0.367	0.28	0.367

Note. Mean (standard deviation) are presented. Baseline night means differ slightly between the sad and happy mood induction nights since a few individuals did not participate in both mood nights and a repeated measures analysis of variance excludes a participant if there is missing data on any of the observation points. Sleep architecture variables are presented as percentage of total sleep time. TST = total sleep time; TWT = total wake time; N1 = NREM Stage 1; N2 = NREM Stage 2; SWS = Slow wave sleep or NREM Stages 3 and 4; [a]Bipolar $n = 20$, control $n = 23$; [b a]Bipolar $n = 20$, control $n = 23$.

Figure Captions

Figure 1. (a) Affect grid pleasantness ratings for bipolar and control groups assessed at the beginning of the sad mood induction (Pre-Induction), at the end of the sad mood induction (Post-Induction) and upon awakening the following morning (Morning); **(b)** Sad mood induction overnight mood change (Morning – Post-Induction) for the bipolar and control groups; **(c)** Mean relative slow wave activity (SWA) on the baseline and sad mood induction nights; **(b)** Proportion of bipolar and control participants with reduced SWA on the sad mood induction night relative to the baseline nights (Sad Mood Induction SWA<Baseline SWA); Baseline night means differ slightly between the sad and happy mood induction analysis since a few individuals did not participate in both mood induction nights (Bipolar $n = 20$, Control $n = 23$); *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Figure 2. Overnight mood change on the affect grid pleasantness ratings as a function of percentage change in SWA (100*[Sad Night SWA – Baseline SWA/Baseline SWA]) for the bipolar and control groups on the sad mood induction night.

Figure 3. (a) Affect grid pleasantness ratings for bipolar and control groups assessed at the beginning of the happy mood induction (Pre-Induction), at the end of the happy mood induction (Post-Induction) and upon awakening the following morning (Morning); **(b)** Happy mood induction overnight mood change (Morning – Post-Induction) for the bipolar and control groups; **(c)** Mean relative slow wave activity (SWA) on the baseline and happy mood induction nights **(d)** Proportion of bipolar and control participants with reduced SWA on the happy mood induction night relative to the baseline nights (Happy Mood Induction SWA<Baseline SWA); Baseline night means differ slightly between the sad and happy mood induction analysis since a few individuals did not participate in both mood induction nights (Bipolar $n = 20$, Control $n = 23$); *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Figure 1.

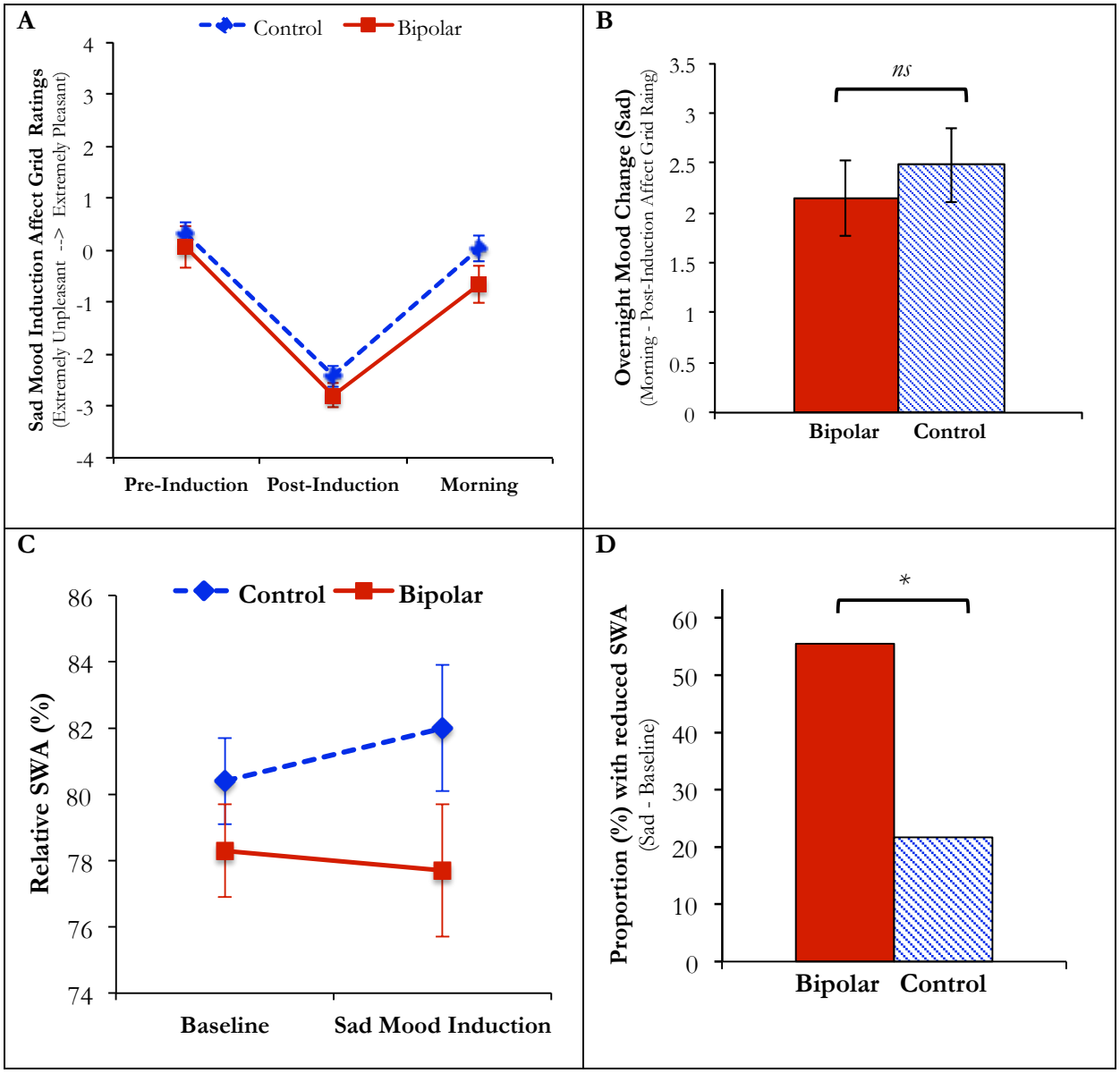

A
Control
Bipolar
Sad Mood Induction Affect Grid Ratings
(Extremely Unpleasant --> Extremely Pleasant)
4
3
2
1
0
-1
-2
-3
-4
Pre-Induction
Post-Induction
Morning
B
ns
Overnight Mood Change (Sad)
(Morning - Post-Induction Affect Grid Rating)
3.5
3
2.5
2
1.5
1
0.5
0
Bipolar
Control
C
Control
Bipolar
Relative SWA (%)
86
84
82
80
78
76
74
Baseline
Sad Mood Induction
D
*
Proportion (%) with reduced SWA
(Sad - Baseline)
60
50
40
30
20
10
0
Bipolar
Control

Figure 2.

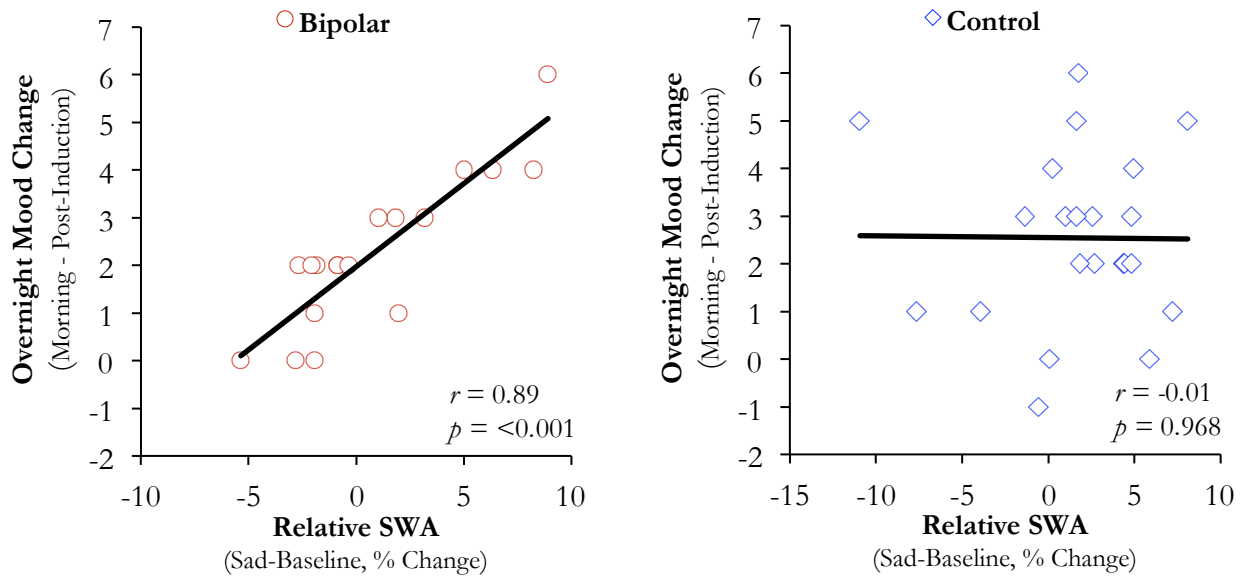
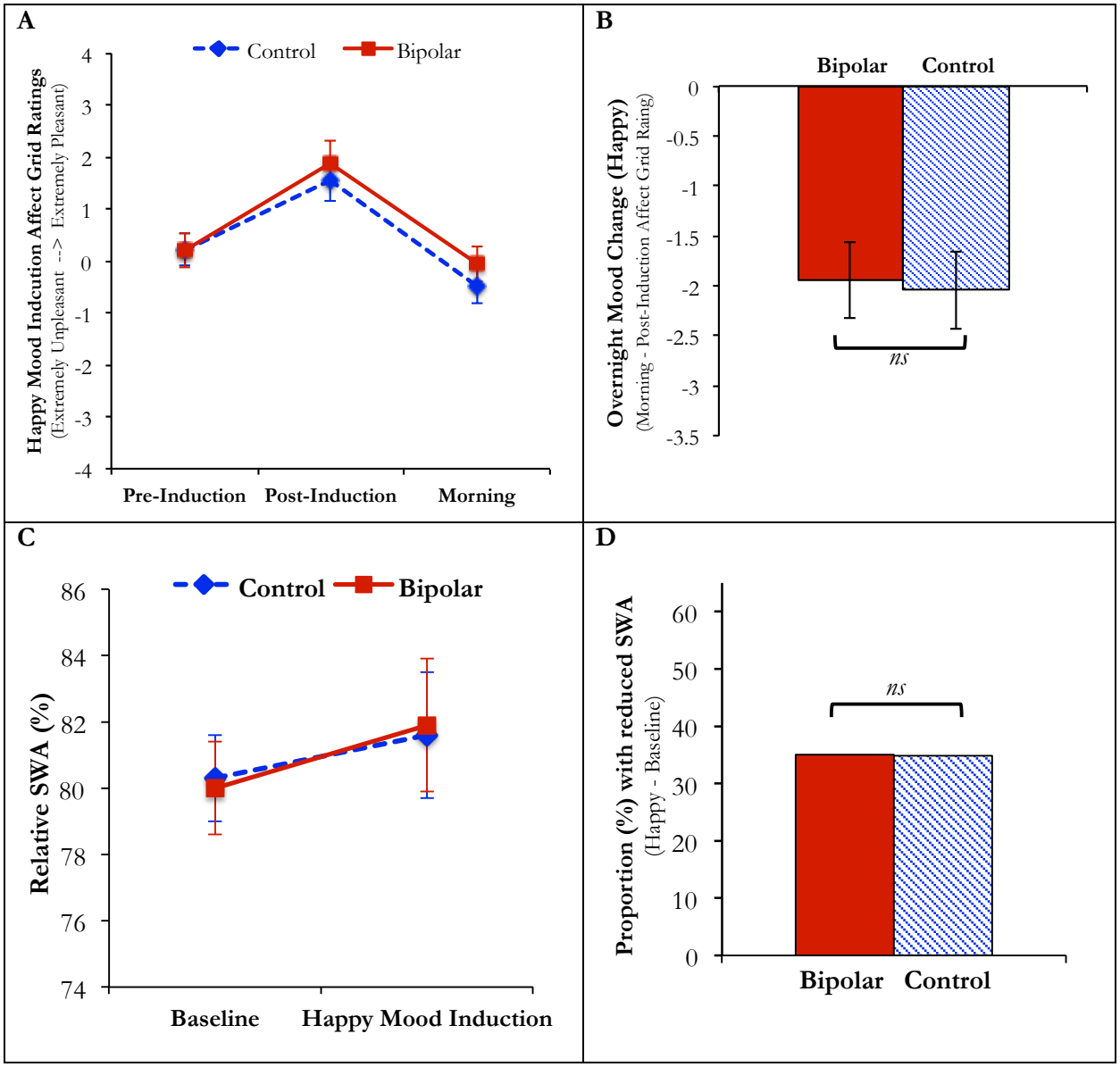

Bipolar
Overnight Mood Change
(Morning - Post-Induction)
7
6
5
4
3
2
1
0
-1
-2
-10
-5
0
5
10
Relative SWA
(Sad-Baseline, % Change)
r = 0.89
p = <0.001
Control
Overnight Mood Change
(Morning - Post-Induction)
7
6
5
4
3
2
1
0
-1
-2
-15
-10
-5
0
5
10
Relative SWA
(Sad-Baseline, % Change)
r = -0.01
p = 0.968

Figure 3.


A
Control
Bipolar
Happy Mood Indcution Affect Grid Ratings
(Extremely Unpleasant --> Extremely Pleasant)
4
3
2
1
0
-1
-2
-3
-4
Pre-Induction
Post-Induction
Morning
B
Bipolar
Control
Overnight Mood Change (Happy)
(Morning - Post-Induction Affect Grid Raing)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
ns
C
Control
Bipolar
Relative SWA (%)
86
84
82
80
78
76
74
Baseline
Happy Mood Induction
D
Proportion (%) with reduced SWA
(Happy - Baseline)
60
50
40
30
20
10
0
ns
Bipolar
Control