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Social Rhythm Disrupting Events Increase the Risk of Recurrence among Individuals with Bipolar Disorder

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Abstract

Objectives—As outlined in the social zeitgeber hypothesis, social rhythm disrupting (SRD) life events begin a cascade of social and biological rhythm disruption that may lead to the onset of affective episodes in those vulnerable to bipolar disorder. Thus, the study of SRD events is particularly important in individuals with this chronic condition. The purpose of the current study was to evaluate 1) the extent to which social rhythm disrupting life events increased the risk of recurrence of a bipolar mood episode, and 2) whether the social rhythm disruption associated with the event conferred an increased risk of recurrence, after accounting for the level of threat associated with the life event.

Methods—We examined the effect of SRD events on recurrence during preventative treatment in a sample of 118 patients with bipolar disorder who achieved remission from an acute episode after receiving psychotherapy and pharmacotherapy. Life events were measured with the Bedford College Life Events and Difficulty Schedule and were rated for degree of SRD and threat.

Results—Time-dependent Cox proportional hazards models showed that that having a higher SRD rating was significantly associated with an increased risk of recurrence, even when accounting for the threat effect of a life event and psychosocial treatment (Hazard Rate = 1.33; 95% CI = 1.04, 1.70; p=0.023). However, this finding fell below conventional levels of statistical significance when accounting for other covariates.

Conclusions—Our findings lend partial support to the social zeitgeber hypothesis.

Keywords

Life events; mood; social rhythms; social zeitgeber; recurrence; threat

Bipolar disorder (BP) is associated with a large economic burden (1). In recent years the disorder was ranked as having the fourth-largest global burden of disease in people aged 10–24 years (2), and it explained 7.4% of non-fatal burden among all mental and substance use disorders (measured by years lived with disability (YLDs)) (3). These findings are particularly troubling given that a replication of the National Comorbidity Survey estimated

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the lifetime prevalence rate of Bipolar I and II disorders at 2.1% in the United States (4). Even so, BP remains “inadequately researched” (5). Thus, greater understanding of the factors that play a role in the etiology and course of the disorder is sorely needed (6).

Because BP is thought to have a biological basis, there has been a focus on the genetic and neurobiological underpinnings of the disorder for many years (e.g.,7;8;9). Additionally, the role of *psychosocial* variables has increasingly come to be appreciated (10–12) with much of the research in this area concentrating on the role of stressful life events, those that are characterized by their level of “threat” or unpleasantness (13;14). The majority of work has supported a role of stressful life events in bipolar episodes, though some findings have been mixed (see10;11;15).

Given that BP is an illness “that is biological in origin yet psychological in expression” (9 p. xxi), etiological models that reflect *both* biological and psychosocial processes are particularly valuable. The social zeitgeber hypothesis (16;17) is one theory that integrates psychosocial and biological factors in understanding their joint role in the development and course of bipolar disorder. In the social zeitgeber model, it is hypothesized that certain life events disrupt an individual’s social rhythms, which are patterns of behavior and cycles of daily life that structure one’s day and help to entrain the biological clock to a 24-hour schedule (18;19). Among vulnerable individuals, the social rhythm instability due to life events is followed by unstable biological rhythms, and eventually the onset of mood symptoms. These sequential changes may be resolved without much incident in those who are *not* vulnerable to a mood disorder, but the progression may not be so easily reversed in those who *are* vulnerable to a mood disorder (16). Moreover, the effect of social rhythm instability is thought to be the same regardless of whether the event has a positive or negative valence.

Though life events that disrupt social rhythms may be considered benign in that they may not be associated with “stress” or “threat” as conventionally defined in the life events literature, they involve changes to daily routines, which may place stress on the body’s ability to maintain synchronized rhythms (20). Still, life events that involve a social rhythm disturbance have been explored to a much lesser extent in bipolar disorder than traditionally defined stressful life events, although evidence is beginning to accrue. Previous analyses from the Maintenance Therapies in Bipolar Disorder study (21) in our group examined the effect of social rhythm disrupting (SRD) events on manic and depressive episode onset among individuals with bipolar I disorder. Between-subjects analyses showed that in the year prior to study entry, SRD events occurring during the eight weeks prior to a bipolar episode were associated with manic but not bipolar depressive episode onset (22). Within-subjects analyses showed that those experiencing mania were more likely to report an SRD event during an eight week pre-onset period than during a different control period in the previous year (22).

Work from the Longitudinal Investigation of Bipolar Spectrum (LIBS) Project prospectively examined the effect of SRD events on affective symptoms among university students with bipolar II disorder or cyclothymia (23). Individuals who reported more SRD events at one time point also reported more depressive symptoms at the following time point, and

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individuals experiencing a depressive episode reported more SRD events prior to the episode than individuals who did not experience an episode. Participants also reported significantly more SRD events in the eight weeks before the onset of a depressive episode than during a control period.

The purpose of the current study was to examine the effect of SRD events on bipolar episode relapse or recurrence. To our knowledge, this would be the first study to examine the effect of SRD events in a sample of patients with bipolar I disorder who were carefully diagnosed and followed prospectively, and whose life events were assessed frequently, in order to limit the retrospective nature of the assessment. The study utilized a sample of individuals who were treated to remission with interpersonal and social rhythm therapy (ISPRT) and/or pharmacotherapy, and then followed for up to two years during a preventative treatment phase (24). IPSRT aims to prevent bipolar episodes by enhancing medication compliance, buffering the effects of stressful life events, and improving social rhythm (25;26). IPSRT has been shown to prevent or delay BP episode recurrence and to increase social rhythm regularity (24;27).

Based on the social zeitgeber theory, we hypothesized that a greater level of SRD associated with an event on any given day during the preventative phase would be associated with an increased risk of relapse or recurrence. Furthermore, we hypothesized that this association would remain even after accounting for the level of threat experienced on that day and IPSRT treatment during either the acute or preventative phase. The primary aim of this manuscript was to test these a priori hypotheses. The secondary, exploratory, aims were to determine whether SRD is related to relapse or recurrence after adjusting for other covariates identified in post-hoc analyses and also to determine whether IPSRT treatment alters the relationship between SRD and episode relapse or recurrence.

Methods

Data for this report came from the “Maintenance Therapies in Bipolar Disorder” (MTBD) study (MH29618; E. Frank, PI), which was conducted from 1991–2002 in the Depression Prevention Program at Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center. Participants provided written consent to participate in the study after receiving a thorough description of the study procedures and having the opportunity to ask questions. All study procedures were approved by the Institutional Review Board of the University of Pittsburgh. The study was comprised of an acute phase, in which patients in an episode of bipolar disorder were treated to remission, and a preventative treatment phase, designed to prevent recurrence of bipolar episodes. A full description of study participants and procedures has been published previously (21;24).

Participants

Study participants were 175 adults between 18 and 60 years of age who were diagnosed with bipolar I disorder (n=164) or schizoaffective disorder, manic type (n=11) according to Research Diagnostic Criteria (RCD; (28)). The participants were in an episode of depression or mania upon entering the acute phase of the study. Exclusion criteria included a history of rapid cycling (> 4 episodes/year), meeting RDC for any other psychiatric illness during the

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five years prior to the index episode (except for an anxiety disorder), chronic drug or alcohol use in the five years prior to the index episode, schizophrenia, organic affective syndrome, significant medical illness, refusal to use contraception or pregnancy in females, or unspecified functional psychosis.

Design and Procedure

At study entry, participants scored >7 on the Raskin Severity of Depression Scale (29;30) and >15 on the 17-item Hamilton Rating Scale for Depression (HRSD-17; 31), if the index episode was depression. They had a score of >7 on the Raskin Severity of Mania Scale (29;30) and >15 on the Bech-Rafaelsen Mania Scale (BRMS; 32), if the index episode was mania.

Upon entering the study, participants were randomly allocated to one of two psychosocial treatments: IPSRT (25) or intensive clinical management (ICM). They received this treatment weekly during the acute phase for a minimum of 12 weekly sessions and a maximum of 24 weekly sessions. If a patient switched polarity during the acute phase he or she could receive a maximum of 24 weekly sessions starting after the switch. Once stabilization was achieved patients entered the preventative phase, in which they were re-randomized, either to the psychosocial treatment that they had received during acute treatment or to the alternative one, following a preventative treatment format. If patients experienced a relapse or recurrence they returned to the acute treatment schedule and were treated weekly until stabilization. Of the 175 participants who entered the acute treatment phase, 125 subsequently entered the preventative phase. Of these, 118 completed life events assessments, and their data are used in the present analyses.

All patients also received pharmacotherapy according to an algorithm that aimed to stabilize as many patients as possible on lithium monotherapy or lithium and one adjunctive medication. Please see Frank et al., (24) for a full description of the pharmacotherapy algorithm.

Measures

Mood Symptoms and Episodes—The Schedule for Affective Disorders and Schizophrenia (SADS; 33) and the Structured Clinical Interview for DSM-IV Disorders (SCID-I; 34) were administered at the screening visit to diagnose bipolar disorder (manic or depressive episode at study entry) or schizoaffective disorder, manic phase, for inclusion into the study (the SADS prior to 1995, and the SCID-I beginning in 1995).

Depressed and manic mood were assessed at every visit with the HRSD (31;35) and the BRMS (32) (respectively), and they were also used to identify remission and relapse or recurrence. All ongoing mood evaluators were trained to criterion level of agreement (ICC ≥ .80), a level that was re-established every six months. If a relapse or recurrence appeared likely based on HRSD or BRMS scores, the patient was seen by a blinded senior psychiatrist who was not otherwise involved in the conduct of the study. The psychiatrist administered a clinical interview to determine if RDC criteria for relapse or recurrence had been met. This process was bypassed when the participant required immediate hospitalization.

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The Life Events and Difficulties Schedule (LEDS)—The LEDS (13;14) is a semi-structured interview that records and interprets the presence and nature of life events and chronic difficulties. It is designed to rate events based on "contextual" threat, or what most people would consider stressful based on the situation. Under the guidance of Dr. George Brown, we also developed a dictionary that provides a rating for the level of social rhythm disruption associated with the event or difficulty (36). In the current analysis, we evaluated the impact of the social rhythm disruption associated with an event, and, separately, the long-term contextual threat associated with an event (LTC; those that reach their peak threat at one-to-two weeks after the event occurs) (13;37). One benefit of the LEDS is that it allows for multiple unrelated ratings for each event; for example, an event may be rated as positive for SRD but negative for threat, or vice versa (or positive or negative on both ratings). Thus, it is possible to uncouple the SRD and threat rating for each event. Only those events that were given an SRD and LTC rating (whether positive or negative) were included in this analysis, as these ratings are our primary interest.

In this study, the LEDS was administered once initial stabilization was achieved in the acute treatment phase, inquiring about past events that occurred up to one year prior to the onset of the index episode. During the preventative phase, the LEDS was administered every three to four months. If a patient was in an acute episode, the LEDS assessment was delayed in order to avoid a bias in reporting events based on mood symptoms. In that case, the next interview inquired about all events that had occurred since the last interview. The LEDS interviewers were blind to participants' mood ratings and the mood raters were blind to participants' life event ratings.

Though the LEDS was administered throughout the preventative phase, in the current analyses we included only LEDS data up until the point of relapse or recurrence (if applicable). This is because relapse/relapse or recurrence is our outcome variable, so events occurring after this point would not have an impact. If the participant did not experience a relapse or recurrence during the preventative phase we used all preventative LEDS data available. Using this approach, daily SRD and LTC ratings were calculated for each individual from the beginning of their preventative phase until each person had a relapse or recurrence, dropped out of the study, or completed the preventative phase. Each event was scored for SRD (0 = no social rhythm disruption to 3 = most social rhythm disruption) and, separately, for LTC (0 = no threat to 3 = most threat). Ratings for SRD are made independent of ratings for threat, for each event.

To illustrate the meaning of these ratings, several specific examples taken from the participants' charts are listed here: A transatlantic trip would confer the highest likelihood of sleep loss and social rhythm disruption, and so would be given an SRD rating of 3; a spouse's emergency hospitalization would be given an SRD rating of 2, based on the disruption to the schedule of the participant, who would likely travel to the hospital with the spouse; a change of residence would be given an SRD rating of 1; last, hearing about a friend's medical problem would likely confer minimal change to the individual's schedule (perhaps unless the stress associated with it was so high that it affected sleep), and so would be given an SRD rating of 0. Regarding threat ratings: the highest level of stress (3) would be appropriate for an event such as starting an extramarital affair; having an argument with

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one's sister would be given a threat rating of 2; getting married, while a generally positive event, is not without some level of stress, and so would be rated 1; last, having a participant's child return home on a 2-week break from college typically confers minimal stress, and so would be rated 0. To illustrate the independence of the SRD and threat ratings, while having a child home from college may not confer stress, it would be likely to mildly disrupt the participant's daily routine and rhythms, and so would be given an SRD rating of 1.

As noted above, previous analyses from our research group examined the 8-week period prior to onset of a manic or depressive episode for the presence of SRD events (22), presupposing that events within that time may have contributed to episode onset. To be consistent with that work, in the current analysis we maintained the SRD rating of an event for 8 weeks (56 days). Thus, if an SRD-rated event occurred on day one, for example, its rating would persist through day 56 in order to capture the effect of the event in our survival analyses. Similarly, if an LTC-rated event occurred on day one, its rating would persist through day 182 (6 months), consistent with the "most general practice" of examining the 6 months prior to episode onset for stressful life events (38). If a life event occurred in the 56 (for SRD) or 182 (for LTC) days prior to the start of the preventative phase (i.e., during the acute phase), its impact would have carried over into the preventative phase. Thus, we included ratings from these events when calculating the daily SRD and LTC rating during the preventative phase. We assumed that the ratings for SRD, and separately for LTC, were cumulative in nature; thus, if an individual had SRD ratings for more than one event on any given day, they were summed to obtain an overall SRD rating for that day and for the duration of the event's effect. The same was done for LTC ratings.

The LEDS system is designed for each event to be given several additional descriptors, here called 'dimensions,' that are ratings for whether the event was the consequence of psychopathology (*dependent variable-related events*), caused by the study participant (*dependent events*), and/or had a primary impact only on someone other than the participant (*other-focused*) (13;37;39). Each event is rated on each of these independent dimensions. Past work using the LEDS has varied in terms of which event dimensions were considered (e.g., 40;41;42;43). In this report, we chose to exclude dependent variable-related LTC events, in order to remove the possibility that events that are *the result of* the current mood state may be mistaken for life events that have *caused* the mood state. As an example, if increased symptoms of hypomania (e.g., irritability, inappropriate language, and loud speaking volume) result in receiving a warning at work, this event would be considered *dependent variable-related*. Thus, this event would be excluded because its occurrence was the result of symptoms of mania. *Dependent* and *other-focused* LTC events were also excluded because they are not thought to 'provoke' mood disturbances in Brown and Harris's etiological model (37). Consistent with past work (22), we also excluded *dependent variable-related* SRD events. In this way, any changes to sleep and rhythms that may result from the onset of subsyndromal psychopathology would not be mistaken for a consequence of an SRD event. However, we did include SRD events that may have been caused by the participant (*dependent*) or that may have been primarily focused on someone else (*other-*

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focused). While independence and focus are relevant to *threat* ratings of events, they are not implicated in the social zeitgeber hypothesis.

Statistical Analyses

Descriptive Statistics—For each individual, we calculated the percentage of days with at least one LTC event and the percentage of days with at least one SRD event. This refers to the proportion of days on which an event actually occurred. We then calculated the percentage of days when the SRD rating was > 0, and the percentage of days when LTC rating was > 0. These values reflect the percentage of days affected by an event when the ratings were carried forward for 56 (SRD) or 182 (LTC) days. Last, we calculated the median SRD rating on days when the SRD rating was > 0, and the median LTC rating on days when the LTC rating was > 0. We repeated this same process for all events that were not excluded based on the dimensional ratings: non-dependent variable-related SRD events, and non-dependent variable-related, independent, and self-focused LTC events (all three dimensional qualifiers). We used descriptive statistics to summarize these event ratings across individuals, as well as baseline demographic and clinical characteristics.

Primary Analyses—Time-dependent Cox proportional hazards models were used to test the primary hypotheses that: 1) a higher SRD rating on a given day would be associated with greater risk of relapse or recurrence of bipolar disorder (with or without *dependent variable-related* events), and 2) this relationship would remain after considering the effect of threat and whether IPSRT treatment had been given during acute and/or preventative phase (again, with or without *dependent variable-related* events). By controlling for threat in this second analysis, we are able to examine the unique impact of social rhythm disruption on relapse or recurrence, in addition to the unique impact of threat.

After fitting these models, we assessed statistical and clinical significance of the time-dependent SRD rating using p-values associated with hazard ratios and absolute risk reduction (ARR) effect sizes with 95% bootstrap confidence intervals. The hazard ratio indicates the increase in risk of relapse or recurrence associated with a higher SRD rating. A hazard ratio > 1 indicates that higher SRD increases the risk of relapse or recurrence, or decreases the time one may remain in the preventative treatment phase. A hazard ratio < 1 indicates that higher SRD decreases the risk of relapse or recurrence, or prolongs time in the preventative phase. The ARR evaluates the absolute reduction in the probability of relapse or recurrence within a specified time period when comparing two individuals with different SRD severities (44). We calculated the ARR for a *one-unit* difference in SRD rating over 56 days. The one-unit difference was chosen because this was the median score of an SRD-rated event. Thus, positive ARR effect sizes indicate that an individual who experiences a single SRD event with a rating of 1 has a greater risk of relapse or recurrence than an individual with the exact same characteristics but who did not experience the SRD event. Finally, we determined the difference in SRD ratings that would be required in order to obtain a small (ARR > 0.12), medium (ARR > 0.28), and large (ARR > 0.4) effect size over 56 days.

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Post-Hoc Exploratory Analyses—We used Cox-proportional hazards models to explore whether each baseline variable had a univariate association with time to relapse or recurrence. Variables with significant relationships were included as covariates in exploratory time-dependent Cox-proportional hazards model along with time-dependent SRD and LTC, and IPSRT treatment. The analysis was repeated after excluding events based on relevant dimensions, as described above. Last, we added interaction terms to each model to determine whether IPSRT treatment altered the relationship between SRD and episode relapse or recurrence

All data were analyzed using SAS for Windows version 9.3 (SAS Institute Inc, Cary, NC) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Sample Characteristics

Of the 118 individuals included in our analyses, 52 experienced a relapse or recurrence during the preventative phase, 50 completed the 2 years of the study without a relapse or recurrence, and 16 dropped out prior to the end of the study. Because the probability of relapse or recurrence never fell below 0.50, the median time to relapse or recurrence is undefined. However, the first time at which the survival probability is less than or equal to 0.75 is week 42 (95% CI = 18.1, 59.3). Demographic and clinical characteristics of the sample are shown in Table 1.

Frequency and Severity of SRD- and LTC-Rated Life Events

Over all participants and all days in the preventative phase, there were a total of 241 life events with an SRD rating > 0. Of these, 236 were not *dependent variable- related*, meaning that they were not thought to be the result of fluctuating mood. There were a total of 374 life events with an LTC rating > 0. Of these, 105 remained after excluding events with all three relevant dimensions. Table 2 further describes the frequency and severity of SRD- and LTC-rated life events during the preventative phase.

Daily SRD ratings (with or without dependent variable-related events) ranged from 0 to 8. Daily LTC ratings ranged from 0 to 20 when including all events. After excluding events based on all three dimensional qualifiers, daily LTC ratings ranged from 0 to 11. These indicate the possible cumulative event rating on any given day for SRD and LTC severity, respectively. It is possible, for example, that an individual may have felt the impact of two severe SRD-rated events (rating of 3) and two mild SRD-rated event (rating of 1) on one day, or eight mild events (rating of 1) on one day, or some combination thereof. As seen in Table 2, individuals experienced social rhythm disruption associated with at least one event on about 15% of days during preventative treatment (with or without *dependent variable-related* events), when SRD ratings were carried forward 56 days. Similarly, individuals experienced threat associated with at least one event on about 70% of days when including all events, and 24% of days after including relevant dimensions, when threat ratings were carried forward 182 days.

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Primary Analyses

Having a higher time-dependent SRD rating was significantly associated with increased risk of relapse or recurrence (Hazard Rate = 1.35; 95% CI = 1.07, 1.70; p=0.01). In this model, an individual with one unit higher social rhythm disruption rating on a given day has 1.35 times greater risk of relapse or recurrence as compared to an individual with a one-unit lower SRD rating. The ARR (95% CI) for an individual with a one unit higher SRD rating across 56 days is 0.016 (95% CI = 0.001, 0.032). Thus, the difference in the *probability* of recurrence occurring for a person with an SRD rating of 1 a compared to a person with an SRD rating of 0 (no SRD event), would be 0.016 across the 56 days, given all other covariates are the same (however in this model, covariates were not included). After adjusting for time-dependent LTC rating and IPSRT treatment, the time-dependent SRD was still significantly associated with increased risk of relapse or recurrence (see Table 3), with an ARR (95% CI) of 0.015 (95% CI =0.000, 0.033). In both models, the ARR effect size for a one-unit SRD difference is less than a “small” effect size; SRD differences of 5, 8, and 9 would result in small, medium, and large ARR effect sizes. However, we note that the largest SRD rating observed in the sample on any given day was 8, making SRD differences > 8 not realistic in this sample.

After removing *dependent variable-related* SRD events and all three relevant dimensions from LTC events, the association of SRD severity and time to relapse or recurrence fell below conventional levels of statistical significance, both before (Hazard Ratio = 1.26; 95% CI = 0.97, 1.62; p=0.08) and after adjusting for time-dependent LTC rating and IPSRT (see Table 4). The ARR for a one-unit SRD difference is 0.013 in both models, with 95% CIs of (−0.005, 0.029) and (−0.008, 0.031). This is less than a “small” effect size. In both models, SRD differences of 6, 9, and 11 would result in small, medium, and large ARR effect sizes, respectively.

Exploratory Analyses

Exploratory, post-hoc analyses showed marital status and weeks in acute treatment to be significantly associated with time to relapse or recurrence in this sample (see Table 1). After adjusting for marital status, weeks in acute treatment, IPSRT treatment, and time-dependent LTC rating, the ARR (95% CI) for an individual with a one unit higher SRD rating across 56 days was 0.012 (95% CI = −0.006, 0.030). SRD differences of 6, 10, and 12 would result in small, medium, and large effect sizes, respectively. After removing *dependent variable-related* SRD events and all three dimensions from LTC events, the ARR (95% CI) was 0.010 (95% CI = −0.008, 0.025). SRD differences of 8, 12, and 14 would result in small, medium, and large effect sizes, respectively.

When time-dependent SRD × IPSRT treatment interaction terms were added to each model (with and without dimensional qualifiers, and with and without covariates), IPSRT did not significantly moderate the effect of SRD on episode relapse or recurrence (all *p*-values >0.10). This finding held true when including only participants who received the same psychosocial treatment in both the acute and preventative phase (IPSRT/IPSRT vs. ICM/ICM; all p > 0.20). Because this analysis included only those who received the same treatment throughout the study, we can be confident that treatment did not have a

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meaningful effect on the impact of SRD on relapse or recurrence. Additionally, because being married may serve as a contributor or buffer to social rhythm disruption, we conducted an interaction to determine whether marital status moderated the effect of SRD on time to relapse or recurrence. While there were main effects of marital status and SRD rating, marital status did not moderate the impact of SRD (p=0.30)

Discussion

The purpose of the current study was to examine the effect of SRD events on relapse or recurrence among individuals recently remitted from an episode of bipolar disorder. We found that having a higher SRD rating was significantly associated with an increased risk of relapse or recurrence, even after considering the level of threat experienced on that day and ISPRT treatment. When including only events that were not related to the development of a relapse or recurrence, the increased risk of relapse or recurrence associated with a higher SRD rating fell just below conventional levels of statistical significance.

Only 5 SRD events thought to be related to prodromal mood symptoms (i.e., *dependent variable-related* events) were identified. Thus, it is unlikely that reduced power accounts for the change in significance between SRD events with and without *dependent variable-related* events. It appears that the social rhythm disruption associated with these specific events may be the most predictive of relapse or recurrence, which makes sense because these events were, by definition, related to our outcome variable. On the other hand, further reading of a subset of 10 life charts describing life events revealed that it is very difficult to tease apart whether prodromal symptoms influenced the occurrence of an event. In this subset of 10, there were only one or two events in which influence of the illness was unambiguous.

Across all models, the effect size related to the association of SRD level and risk of relapse or recurrence was very small when considering a one-unit change in SRD severity. This may suggest that a much larger change in social rhythm disruption is needed in order to see a larger effect of SRD on risk of relapse or recurrence. Additionally, it may be that the adverse impact of SRD may be greater among the subset of patients who did not recover, and, thus, did not enter the preventative treatment phase. If we had been able to follow these individuals, we may have seen greater effects. Another reason for the small effect may be that participants in this study were receiving both a psychosocial treatment and protocol driven pharmacotherapy based on lithium, which may have buffered the effects of SRD associated with an event. Furthermore, the majority of individuals included in this report (88/118) had received interpersonal and social rhythm therapy (IPSRT) either in the acute treatment or preventative treatment phase. Focused as it is on helping patients to establish and maintain regular routines, IPSRT may have enabled participants to re-regulate their routines fairly rapidly following an SRD event. Still, previous analysis found no relationship between treatment assignment and risk of relapse or recurrence until a combination of baseline covariates were included in the model (24). Our results showed that IPSRT treatment did not moderate the effect of SRD on risk of relapse or recurrence, nor did IPSRT treatment moderate this effect when including only those participants who received IPSRT in both phases of the study or ICM in both phases. It is possible that individuals with highly

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regular social rhythms (regardless of whether they were naturally more regular or more regular as a result of IPSRT) were protected from the effects of an SRD event on mood.

For patients who are familiar with IPSRT, offering “on demand” sessions during preventative treatment may help them to manage the impact of SRD when it occurs, especially if their rhythms are not highly regular at that time. Additionally, future work should characterize the social rhythm regularity of the sample at the time of the SRD event in order to determine whether what is critical is social rhythm regularity at the time of the event or ability to re-regulate following an event, rather than treatment type.

One unique aspect of the current report is the potential to begin to explore the effect of SRD level over and above that of threat level of any one event. Previous work identified the effects of threat and SRD events on mood among individuals with bipolar disorder, but, to our knowledge, little has attempted to evaluate whether these are independent effects or just different names for the same underlying characteristic of the event. When LTC events were added to the model, having a higher SRD rating was still associated with an increased risk of relapse or recurrence when all events were included. Work in this area begins to investigate the potentially unique contributions of varying event characteristics on mood, in an effort to provide support for proposed mechanisms underlying the onset of mood episodes.

Another unique aspect of this report is the extension of SRD and threat ratings for several weeks or months past the event’s occurrence. For many individuals with bipolar disorder, it may be unlikely that the effect of an event will be resolved shortly after the event’s occurrence. For example, it may take several days or weeks to recover from a sleepless night in the emergency room with a sick child, and the threat effects of that event may persist for even longer. To our knowledge, only one other report has examined the impact of life events over time, but that report examined only stressful life events, extending the impact of the event throughout the duration of the individual’s time in preventative treatment (43).

Then again, the extension of event ratings may constitute one possible limitation of our approach; that is, we assumed that the SRD and LTC ratings stayed constant over a specified time period and then dropped off at a specific time point. In reality it may be that the effect of an event tapers off more gradually than our analyses have accounted for. Work in this area has not yet explored changes in the magnitude of the effect of an event in the weeks and months after the event’s occurrence, the rate at which the effect of an event tapers off or whether the effects of some events taper off while others grow (e.g., change to a rotating shift job, which may disturb social rhythms more and more with time). Future studies should include measures of the effect of an event over time and should incorporate such data into statistical analyses.

Additionally, it is outside the scope of the current paper to examine whether the effect of multiple co-occurring events is additive or synergistic. In the current analyses we have assumed an additive effect, but it is possible that a pattern of several events may confer varying levels of SRD and threat depending on whether or not the events are related. A sequence of related events (e.g., pregnancy, birth of a child, living with a newborn) may be easier to anticipate than several unrelated events that occur unexpectedly. Being able to

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anticipate the occurrence of social rhythm disturbances may be beneficial because the individual may be able to make efforts to prepare for such disruption. Indeed, known triggers to social rhythm disruption are discussed between therapist and patient in IPSRT, and the coming weeks and months are examined to identify possible disturbances. The pair then works to minimize social rhythm disruptions that are malleable, or to manage the effects of the disruptions that are unavoidable.

Interestingly, LTC events were not predictive of bipolar episode relapse or recurrence in our study population. While stress events have been implicated in bipolar episode relapse or recurrence in some reports, others have suggested that these events are episode-specific, or are relevant to characteristics of the individual (10;11;15). Thus, in future analyses it will be important to perform moderator analyses to characterize baseline profiles of individuals that may have had different types of reactions to LTC and SRD events.

Our findings should be interpreted in light of several additional strengths. As noted above, this is the first study to examine the effect of SRD events in a sample of patients with bipolar I disorder who were carefully diagnosed and followed *prospectively* using the LEDS assessment. The use of the LEDS is a strength because this measure allows for several unrelated ratings of one event. In addition, LEDS events were not assessed while participants were in a mood episode, limiting the influence of mood symptoms on recollection or reporting of events, and an entirely different group of individuals evaluated participants' mood score and life events, reducing evaluator bias.

Future Directions

The findings reported here suggest several lines of future research. First, future work should aim to validate our findings in a separate, larger sample of individuals with bipolar disorder, which will allow for independent replication of the findings of this report. Only 54 of the 125 patients who entered the preventative treatment phase had a relapse or recurrence over two years of preventative treatment, perhaps because they were effectively treated during the acute phase and closely followed during the preventative phase. Observational, non-treatment studies may provide more opportunity to study predictors and moderators of relapse or recurrence if they occur more often when active treatment is not being delivered.

An alternate approach would be to examine the role of social rhythm disruption, as measured by the Social Rhythm Metric (18;45), in the relationship between SRD events and mood exacerbation. SRD ratings of events reflect the *expected* disruption of social rhythms that results from an event, but they do not describe the amount of SRD that is associated with that event. Examining the effect of SRD events on mood exacerbation among only those SRD events that actually contribute to worsening in social rhythm regularity would allow us to determine the extent to which the SRD ratings reflect subsequent dysregulation of social rhythms, and to identify the effect of SRD events on mood when we are more confident that the event has actually produced social rhythm disruption.

Our exploratory analyses demonstrated the importance of marital status and number of weeks in acute treatment in evaluating risk of relapse or recurrence of a mood episode. In this model, being married or living as married reduced likelihood of having a relapse or

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recurrence, but marital status did not moderate the impact of SRD on relapse or recurrence. Thus, while being married may be protective against *relapse or recurrence*, being married does not specifically affect an individual's ability to cope with SRD. Rather, marital status may serve as a proxy for level of functioning or overall illness severity, which may help to determine likelihood of relapse or recurrence.This exploratory work should serve a foundation for future analyses, which might study marital status and/or weeks in acute treatment as *a priori* hypotheses.

Last, stressful and SRD events often occur in the face of ongoing LEDS-rated difficulties and acute incidents, perhaps contributing to an additive effect of stress and social rhythm disruption. Future work should focus on this area to investigate more complex conceptualizations of the effect of life events.

Conclusions

Supporting our original hypotheses, we found that having a higher SRD rating was significantly associated with an increased risk of relapse or recurrence, even after controlling for threat ratings and IPSRT treatment. It appears that dependent variable-related events drove this relationship, as the impact of SRD rating on relapse or recurrence fell below conventional levels of statistical significance when including only events that were not related to the development of a relapse or recurrence. Moreover, most of our effects were less than small in size, indicating that a large amount of social rhythm disruption is required in order to observe a clinically meaningful effect on relapse or recurrence. Our findings lend support to the effect of SRD events on mood, as outlined in the social zeitgeber hypothesis.

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Table 1

Baseline characteristics and exploratory univariate associations with time to relapse or recurrence (N=118).

Baseline Characteristic	Mean (SD) or Median (Q1, Q3)	Hazard Ratio	95% CI for Hazard Ratio	p-value
Age	35.3 (10.6)	.98	(.95, 1.00)	.080
Baseline 25-item Depression Score	17.3 (9.6)	1.02	(.99, 1.05)	.314
Baseline Mania Score	12.9 (13.2)	.99	(.97, 1.02)	.603
Baseline Global Assessment of Function[a]	48.0 (9.2)	1.00	(.97, 1.03)	.787
Years of Education	14.7 (1.9)	.97	(.84, 1.11)	.646
Age of Manic Episode Onset[a]	26.5 (9.0)	.99	(.95, 1.02)	.360
Age of Depressive Episode Onset[b]	22.6 (8.0)	.98	(.95, 1.02)	.382
Weeks in Acute Treatment	35.5 (21.4)	1.01	(1.00, 1.03)	.036
Weeks in Index Episode	17.3 (8.7, 38)	1.00	(.99, 1.00)	.468
Number of Past Manic Episodes	2.5 (1, 5)	1.00	(.99, 1.01)	.923
Number of Past Depressive Episodes[a]	4 (2, 8)	1.00	(.99, 1.01)	.621
	% (n)			
IPSRT in Acute Treatment	49.2% (58)	.90	(.52, 1.55)	.700
Female	59.3 (70)	1.54	(.86, 2.75)	.145
Married or Living as Married	33.9% (40)	.44	(.23, .84)	.012
Working Full-Time, Part-Time, or Student	58.5% (69)	.96	(.55, 1.67)	.885
Caucasian	93.2% (110)	.52	(.22, 1.23)	.137

[a] N=117;

[b] N=109;

IPSRT: Interpersonal and Social Rhythm Therapy

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Table 2

Life events summarized for each individual throughout preventative treatment.

	Q1	Median	Q3
SRD Events			
Percentage of Days with at least 1 Event	0	.25	.57
Percentage of Days with SRD Rating > 0 (Rating carried forward)	0	15.13	28.44
Median SRD Rating on days when SRD > 0	1	1	2
SRD Events (Not Dependent Variable Related)			
Percentage of Days with at least 1 Event	0	.18	.55
Percentage of Days with SRD Rating > 0 (Rating carried forward)	0	14.87	28.22
Median Rating on days when SRD > 0	1	1	2
LTC Events			
Percentage of Days with at least 1 Event	0	.53	1.07
Percentage of Days with LTC Rating > 0 (Rating carried forward)	37.53	70.37	95.57
Median SRD Rating on days when LTC > 0	2	3	4
LTC Events (All Qualifiers)			
Percentage of Days with at least 1 Event	0	0	.27
Percentage of Days with LTC Rating > 0 (Rating carried forward)	0	24.43	49.52
Median SRD Rating on days when LTC > 0	1	1.25	3

SRD: Social Rhythm Disruption; LTC: Long Term Contextual Threat

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Table 3

Time-dependent Cox proportional hazards model for daily SRD rating.

Variable	Hazard Ratio	95% CI for Hazard Ratio	p-value
Daily SRD Rating (time-dependent)	1.33	(1.04, 1.70)	.023
Daily LTC Rating (time-dependent)	1.03	(.93, 1.14)	.599
IPSRT (Acute or Preventative)	1.92	(.93, 3.94)	.076

SRD: Social Rhythm Disruption; LTC: Long Term Contextual Threat; IPSRT: Interpersonal and Social Rhythm Therapy

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Table 4

Time-dependent Cox proportional hazards model for daily SRD rating after excluding events with relevant qualifiers.

Variable	Hazard Ratio	95% CI for Hazard Ratio	p-value
Daily SRD Rating (time-dependent)	1.27	(.98, 1.63)	.070
Daily LTC Rating (time-dependent)	1.02	(.83, 1.23)	.879
IPSRT (Acute or Preventative)	1.91	(.93, 3.92)	.080

SRD: Social Rhythm Disruption; LTC: Long Term Contextual Threat; IPSRT: Interpersonal and Social Rhythm Therapy