WHAT IS THE EFFECT OF SOCIAL RHYTHM DISRUPTING EVENTS ON MOOD IN INDIVIDUALS WITH BIPOLAR DISORDER?

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The social zeitgeber hypothesis suggests that life events have the capacity to lead to the onset of affective episodes in those vulnerable to bipolar disorder via biological and social rhythm disruption. However, few studies have systematically evaluated the role of life events that disrupt social routines in the exacerbation of mood symptoms. This report examined the effect of social rhythm disrupting (SRD) events on recurrence during preventative treatment in a sample of 82 patients with bipolar disorder who achieved remission from an acute episode, and assessed whether treatment assignment (interpersonal and social rhythm therapy (IPSRT) vs. intensive clinical management (ICM)) moderated this effect. We also examined the effect of short term (STC) and long term (LTC) threat (unpleasant) events. Recurrence was determined by blinded senior psychiatrists who were not otherwise involved in the conduct of the study and who were asked to determine whether the participant met Research Diagnostic Criteria for a new affective episode. Life events were measured with the Bedford College Life Events and Difficulty Schedule (LEDS) and were rated for degree of SRD and threat. Chi-square tests, Kaplan-Meier survival analyses, and Cox proportional hazards models showed that patients who had a recurrence were more likely to experience independent SRD, STC, and LTC events prior to recurrence than those who survived the two-year preventative phase without a recurrence, and this event occurred closer in time to recurrence than to a corresponding non-recurrence point in

the non-recurrence group. In contrast, events that were rated for SRD *and* threat were not more likely to occur among individuals experiencing a recurrence than events rated for threat only. Nor did such a combined event occur more closely in time to a recurrence than events rated for threat only. Last, among those who experienced an SRD event, those who received preventative IPSRT were *more* likely to have a recurrence than those who received preventative ICM. Future studies should focus on the types of SRD events that are related to mood worsening, as well as on novel methods of examining these scientific aims that make use of longitudinal datasets.

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PREFACE

Many people supported me in the completion of this project and during my time in graduate school, and I would like to thank them here. First and foremost, I would like to thank my advisor and mentor, Ellen Frank. Your wisdom and feedback permeate the pages of this dissertation. I consider myself very fortunate to have had you as a support and guide as I have developed as a researcher and clinician. Thank you for always "having my back," as we say! I am also very grateful to my dissertation committee members, Drs. David Kupfer, Stephen Manuck, Michael Pogue-Geile, and Kathryn Roecklein, for their recommendations and suggestions throughout the genesis, execution, and presentation of this dissertation. Your enthusiasm, curiosity, and expertise made meaningful contributions to this project, and I have appreciated talking with each of you about ways to enrich this work. Thank you to Drs. JeeWon Cheong and Meredith Lotz Wallace, and to Christine Palmer Walther for invaluable statistical consulting. Thanks also to Barbara Anderson, Ph.D., for providing endless knowledge of the intricacies of the LEDS dataset, and to George W. Brown, Ph.D., for sharing his expertise in the study and analysis of life events. To the staff of the Depression and Manic Depression Prevention Program – I have truly enjoyed having you as friends and colleagues over the past seven years. You are a great group! Thank you to my friends and peers for being my sounding board during difficult times, and for making graduate school so much fun. Finally, my deepest thanks to my Mom, my Dad, Josh, and Evan. Your unwavering support and love has been fundamental to my growth as a researcher and clinician, and also as a person. Thank you for always believing in me, for supporting my dreams, and for encouraging me to be myself. I would not be where I am today without you.

1.0 INTRODUCTION

1.1 OVERVIEW

Bipolar disorder is a highly disabling and burdensome condition (Murray & Lopez, 1996). While the biological basis of the disease has long been a focus, the role of psychosocial variables such as life events has come to be appreciated in recent years (Alloy, et al., 2005; Johnson, 2005; Prien & Potter, 1990). The interaction of psychosocial and biological factors in the onset, course, and treatment of the disorder has also been emphasized. Specifically, the social zeitgeber hypothesis (Ehlers, Frank, & Kupfer, 1988; Ehlers, Kupfer, Frank, & Monk, 1993) has described how life events may begin a cascade of social and biological rhythm disruption, which may lead to the onset of affective episodes in those vulnerable to bipolar disorder. Greater understanding of the extent to which life events involving social rhythm disruption affect mood may aid in the elucidation of the mechanisms underlying the disorder and may lead to the development of improved treatment strategies.

The purpose of this work is to examine the effect of social rhythm disrupting (SRD) life events on mood symptoms in a sample of patients with bipolar disorder who have achieved remission from an acute episode. The aim is to add to the literature demonstrating the role of psychosocial stressors in bipolar disorder, as well as to evaluated the social zeitgeber hypothesis.

Since the patients in this sample were treated with two different psychosocial treatments over the course of the study, another aim is to examine whether treatment assignment moderated the effects of SRD events on mood. It is expected that interpersonal and social rhythm therapy (IPSRT; Frank, 2005), a treatment focused on regulating sleep and social rhythms, protects patients with bipolar disorder from a worsening of mood symptoms in the presence of SRD events, as compared to a control treatment.

This report begins with a review of the burden of bipolar disorder and the need to identify the underlying etiology of the disease, making specific arguments for a focus on the effects of social rhythms and life events. After presenting some methodological challenges to the study of life events, the literature on the role of life events in the precipitation of bipolar episodes is reviewed. The social zeitgeber hypothesis and empirical work on social rhythm disruption in affective disorders are presented next, along with the limited evidence documenting the effect of SRD events on mood. The importance of regularizing social rhythms to the success of treatment of bipolar episodes and the prevention of episode recurrence is also discussed. This is followed by a brief discussion of the role of various circadian rhythms in bipolar disorder, emphasizing the importance of social cues and social rhythms in entraining circadian rhythms and how these play a role in bipolar disorder. After stating the aims and hypotheses of this study, the proposed analytic plan is described. As will be explained in greater detail below, the proposed analytic models did not converge using structural equation modeling, limiting our ability to evaluate the hypotheses as originally planned. Thus, revised exploratory analyses are described, as are the results of these analyses. An interpretation of the findings is presented in the discussion section, as well as suggestions for future work.

1.2 THE BURDEN OF BIPOLAR DISORDER AND THE NEED FOR BETTER UNDERSTANDING OF ITS PATHOGENESIS

Bipolar disorder has been identified as a neuropsychiatric condition that contributes to the global burden of disease and has been ranked as the sixth leading cause of disability worldwide (Fajutrao, Locklear, Priaulx, & Heyes, 2009; Murray & Lopez, 1996). Bipolar disorder is characterized by manic, hypomanic, or mixed episodes, and major depressive episodes (APA, 2000). A replication of the National Comorbidity Survey estimated the lifetime prevalence rate of Bipolar I and II disorders at 2.1% in the United States (Merikangas, et al., 2007). Bipolar episodes are likely to recur, and the disorder is associated with higher rates of suicide than all other psychiatric disorders (Miklowitz & Johnson, 2006). Moreover, the majority of individuals with the disorder have at least one comorbid psychiatric or medical condition (Ranga Rama Krishnan, 2005) and they may experience mood symptoms, sleep disturbances, and functional impairment while euthymic (Fagiolini, et al., 2005; Harvey, 2008; Miklowitz & Johnson, 2006) as well as when in an episode. While some pharmacotherapy interventions may be helpful in treating the disorder (e.g., McIntyre, 2010; Van Lieshout & MacQueen, 2010), roughly 40% of patients who attempt to adhere to a drug treatment are only partially adherent (El-Mallakh, 2007). Thus, greater understanding of the etiology of the disorder and the factors that may improve treatment is a high priority.

To achieve this understanding it may be useful to examine factors that affect the onset and course of the disorder. Bipolar disorder is thought to have a biological basis, and there has been a focus on the genetic and neurobiological underpinnings of the disorder for many years (e.g., Bowden, 2008; Carroll, 1994; Goodwin & Jamison, 2007). Indeed, scientists recently suggested that there is a need to “identify the circuits that regulate mood, emotion, energy, and

other relevant functions that are affected in bipolar disorder" (Hyman, 2000, p. 441). There has also been a recent focus on psychosocial factors that play a role in the development of the disorder (e.g., Rush, 2003). Sheri Johnson (2005) notes, "over the past 15 years, a wealth of research has made it abundantly clear that psychosocial variables shape outcomes of this disorder. Much of this psychosocial research has focused on whether life events predict the timing and severity of symptoms within this disorder" (p. 1008). Certainly, stressful life events have been implicated in the development and course of bipolar episodes (Altman, et al., 2006).

The social zeitgeber hypothesis (Ehlers, et al., 1988; Ehlers, et al., 1993) is an example of recent attempts to integrate psychosocial and biological variables in understanding their joint role in the development and course of bipolar disorder. This theory, to be discussed in more detail in later sections of this work, focuses on the extent to which life events have the capacity to disrupt social and biological rhythms, which may lead to the onset of affective episodes in vulnerable individuals. It is hypothesized that certain life events may disrupt an individual's social rhythms, i.e. 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 (Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990; Monk, Kupfer, Frank, & Ritenour, 1991).

While the role of stressful life events in bipolar disorder has been a focus of much of the past 20 years' work, life events that involve a social rhythm disturbance have been explored to a much lesser extent, although evidence is beginning to accrue (e.g., Malkoff-Schwartz, et al., 2000; Malkoff-Schwartz, et al., 1998; Sylvia, Alloy, Hafner, Gauger, & Verndon, 2009). While social and circadian rhythms in individuals with bipolar disorder may be disrupted (e.g., Linkowski, 2003; Szuba, Yager, Guze, Allen, & Baxter Jr., 1992), work that will also be explored in later sections of this paper, the role of social rhythm disrupting *events* in the re-

emergence of bipolar symptoms and episodes is still unclear. The role of these events is unclear in part because previous work has not utilized an empirically defined time window between the occurrence of an event and the presence of mood symptoms or episodes. It may also be unclear because some work has not conducted separate analyses on mood symptom or episode types, which may obscure the results. Thus, further study that clarifies the role of these important factors is warranted, work that may contribute to the development of new treatment strategies and the improvement of existing ones that target these biological and psychosocial factors.

1.3 HOW ARE LIFE EVENTS IMPORTANT TO BIPOLAR DISORDER?

1.3.1 Methodological Challenges

Research has generally supported a positive association between life events and affective episodes (Alloy, et al., 2005; Beyer, Kuchibhatla, Cassidy, & Krishnan, 2008; Johnson, 2005; Johnson & Roberts, 1995; Paykel, 2001, 2003; Tsuchiya, Byrne, & Mortensen, 2003). However, the study of life events presents a number of methodological challenges. First, the types of stressors to study must be considered. In much of the literature life events have been defined as acute incidents and/or as chronic stressors. While the term 'life event' implies a more acute incident than a chronic stressor, an event such as the death of a loved one may have relatively enduring implications, similar to chronic stressors such as ongoing work stress (Dimsdale, 2008). Thus, both acute events and difficulties (chronic stressors) have been considered in this work. 'Stress' in these events has been operationalized by some as the level of "severity of threat or unpleasantness" (Brown, 1989, p. 4; Brown & Harris, 1978), and we too have focused our attention on this rating of the event in this work. Stressful life events that have occurred in the distant past, such as childhood traumas, have been excluded. Historically, past events have had

less of an impact on depressive disorders than life events closer to episode onset (Bebbington, et al., 1993) and they are typically not included in the study of stressful events on depression and mania (e.g., Johnson, 2005). For these reasons, early adversities were not considered. Laboratory stressors were also not considered as they "typically involve a short-term exposure to mild stress," (Kim & Dimsdale, 2007, p. 257), which may be qualitatively different than acute events and chronic stressors.

Most work in this area has relied on retrospective reporting of life events (Paykel, 2003), which can lead to a bias in reporting of events, and in the recall of an event's importance (Alloy, et al., 2005; Johnson, 2005). The capacity to recall life events that precede depressive and manic episodes may differ because manic episodes tend to be relatively shorter than depressive ones (Johnson, 2005), although some very severe forms of mania may involve substantial memory loss (Karmacharya, England, & Öngür, 2008). Capturing a broad range of event types and distinguishing between them is also important in order to identify the varying effects that each type of event may have on mood (Alloy, et al., 2005; Johnson, 2005; Johnson, et al., 2008; Johnson & McMurrich, 2006). Here, life events that are likely to have a disruptive effect on social rhythms have been differentiated from those that are not.

It is also important to keep in mind that psychopathology itself, as well as other comorbid disorders like substance abuse, may lead to subsequent life events (Johnson, 2005; Johnson & McMurrich, 2006; O'Croinin, Zibin, & Byrne, 1994; Paykel, 2001). Thus, if the direction of causality between life events and mood symptoms is not considered, life events that are *dependent* on the current mood state may be mistaken for life events that have *caused* the mood state. Still, it is possible that these events may lead to a worsening of mood symptoms, nonetheless.

Last, while most events are considered discrete entities, there may be a cumulative effect of some events that occur in close proximity to each other, or that may be related in some way. In this case, the cumulative effect of the events may be greater than either event alone. Brown and Harris discuss two possible ways that there may be an additive effect of events, though only modest support is provided for each (Brown, 1989). They noted that we may focus on whether the number of unrelated events has an impact on mood, or we may consider the contribution of related events. In the first, the authors note that "the occurrence of two or more unrelated severe events can apparently appreciably raise risk" of depression (p. 72). In the second, the authors suggest that it is possible to make the case for a cumulative effect of related events, though the impact may be quite modest. Determining the cumulative effect of multiple events can be challenging, both because it is difficult to know how closely in time two events must occur for their effects to be cumulative, and because the combined effects of seemingly unrelated events may be greater than is expected. Studies of the cumulative effect of events have typically focused on childhood traumas (e.g., Chapman, et al., 2004; Wiersman, et al., 2009), or non-stressful events (e.g., Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008) rather than stressful ones or ones that have a social rhythm disrupting component. Moreover, the social zeitgeber hypothesis, which postulates that SRD events ultimately lead to a mood episode, does not necessarily emphasize the impact of cumulative life events, but the impact of one. Though study of the cumulative effects of events is outside the scope of current work, future work should continue recent efforts (Frank, et al., 1996; Lenze, et al., 2008) to investigate this important area.

1.3.1.1. Previous Studies of Life Events and Bipolar Disorder. Stressful life events typically denote events that are characterized by their level of "threat" (Brown, 1989; Brown & Harris, 1978), such as a car accident, health problem, or losing a job. In reviewing the literature in this

area, it became apparent that some authors use the term ‘stressful life event,’ while others use the term ‘negative life event.’ The term used by the study’s author will be maintained here in order to be consistent with the study’s findings, but we understand their meanings to be interchangeable.

Early work in this area focused primarily on establishing a link between stressful life events and bipolar episodes. A number of studies found that individuals with mania reported a significantly greater number of life events prior to their episode than those without a manic episode, and the positive association between life events and hospital admission was stronger among manic patients than controls (Ambelas, 1979; Horesh & Iancu, 2010; Joffe, MacDonald, & Kutcher, 1989; Kennedy, Thompson, Stancer, Roy, & Persad, 1983; Kessing, Agerbo, & Mortensen, 2004). Similar studies noted a greater number of life events prior to patients’ first bipolar episode as compared to subsequent episodes, both for depression and mania (Ambelas, 1979; Dunner, Patrick, & Fieve, 1979; Kennedy, et al., 1983; Kessing, et al., 2004).

With regard to relapse or recurrence, the literature generally supports the role of life events in the appearance of these episodes, although there are some inconsistencies. One retrospective study found that individuals with bipolar disorder who were recently unstable were more likely to relapse after a natural disaster than those who were recently stable, with no differences reported for manic and depressive episodes (Aronson & Shukla, 1987). Other work supports the association of the presence of stressful life events and the likelihood of manic and depressive relapses (Hunt, Bruce-Jones, & Silverstone, 1992), although some work does not separate these effects by episode type (Ellicott, Hammen, Gitlin, Brown, & Jamison, 1990; Hammen & Gitlin, 1997), and some report that this association is only present prior to the return

of manic (Pardoen, et al., 1996) or depressive (Beyer, et al., 2008; Cohen, Hammen, Henry, & Daley, 2004) episodes.

In one study, the increase in stressful life events prior to a depressive episode, relative to a manic one, may have been explained by a preponderance of life events reported by women, who were more likely to report life events and were more likely to be depressed than men (Johnson, Winett, Meyer, Greenhouse, & Miller, 1999), a finding that was replicated more recently (Christensen, et al., 2003). Moreover, life events were associated with higher depression scores, but not manic scores, over time and life events significantly predicted time to recovery from a bipolar episode (Johnson, et al., 1999). An earlier analysis of these data showed that individuals with bipolar disorder who experienced negative stressful life events took more than three times as long to achieve recovery than those without life events (Johnson & Miller, 1997).

However, some work did not find a relationship between life events and the onset of mania (Sclare & Creed, 1990), nor did a within-subjects study find a difference in the number of life events occurring before a bipolar relapse than the number occurring before a non-relapse period (McPherson, Herbison, & Romans, 1993). The authors suggest that events may be more important in the onset of earlier, rather than later episodes. However, these findings may be a function of the methodological differences between these studies and the others cited above, such as low power to detect an event as a result of small sample size, and a variety of methods of defining episode onset, which may have impacted the detection of a life event within a specific period of time. Nevertheless, in general the literature supports the role of stressful life events in the onset and recurrence of manic episodes.

More recently, identifying associations between specific types of life events and bipolar episodes has been the focus, including goal attainment events and social rhythm disrupting

(SRD) events. We will consider goal attainment life events here. These events involve the commitment to and striving toward an interpersonal, occupational, or other type of goal (Johnson, 2005; Johnson & McMurrich, 2006). Three prospective studies assessed goal-attainment life events among individuals with various forms of bipolar disorder. These studies found that this type of event is associated with an increase in (hypo)manic symptoms and episodes, either above and beyond other positive events or as compared to individuals who had not experienced such an event, although the same was not true of depressive symptoms and episodes (Johnson, et al., 2008; Johnson, et al., 2000; Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007). While there was no significant relationship between goal attainment events and depression, one of these studies found that negative stressful life events, not goal attainment ones, were associated with increases in symptoms of depression, but were unrelated to manic symptoms (Johnson, et al., 2008).

Overall, there is a rich literature on the effect of stressful life events on mood, although the evidence for more specific types of events is still developing. The evidence suggests that individuals with bipolar disorder are more likely to experience stressful life events before an episode than controls, and there is a strong association between stressful life events and the likelihood of relapse and recurrence. Yet, the presence of stressful events prior to relapse is observed inconsistently for episodes of depression and mania. Moreover, it seems that women are more likely to experience both depression and stressful life events than men, a trend that may have an impact on the findings. Regarding specific types of life events, the literature suggests that goal attainment life events are associated with manic episodes. Events that involve social rhythm disruption (or SRD events) will be discussed below, after consideration of the social zeitgeber hypothesis.

1.3.2. Measuring Life Events: The Life Events and Difficulties Schedule (LEDS)

There are a number of different ways to measure life events, including the Daily Stress Inventory (DSI; Brantley, Wagonner, Jones, & Rappaport, 1987), the Elder life Stress Inventory (ELSI; Aldwin, 1990), the Psychiatric Epidemiology Research Interview, Modified (PERI-M; Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978), and the Schedule of Recent Changes (Rahe, Pugh, Erickson, Gunderson, & Rubin, 1971). Yet, the Life Events and Difficulties Schedule (LEDS; Bifulco, et al., 1989; Brown, 1989; Brown & Harris, 1978), developed by George Brown and Tirril Harris at Bedford College, is considered the 'gold standard' for recording the presence of life events and interpreting their meanings in a variety of domains.

Unlike self-reports, the LEDS has the advantage of a semi-structured interview format, designed to capture events and difficulties across 10 domains (e.g., education, work, housing). While events, defined in terms of their ability to produce a strong emotional reaction (Brown, 1989), are considered relatively acute occurrences (e.g., buying a house, undergoing an operation), difficulties are long-term conditions lasting at four weeks (Brown, 1989; Brown & Harris, 1978). Incidents are stressful occurrences that are not severe enough to meet the event threshold (Frank, Anderson, Malkoff-Schwartz, & Monk, 1995), based on their likelihood of a lesser emotional impact.

After obtaining biographical information, the LEDS interviewer inquires about possible events and difficulties that may have occurred in the 10 domains, following a set of rules designed to determine whether an occurrence meets the threshold for inclusion as an incident, event, or difficulty (Anderson, Frank, Brown, & Harris, 1995). Then, the event is rated for threat severity and a variety of other interpretations based on "contextual threat," or what Brown and Harris refer to as an interpretation of what *most people* would be likely to experience based on

the person's situation (Brown & Harris, 1978; Brown & Harris, 1989). This rating is made separate from the individual's report of his or her reaction to the event.

Rating events based on contextual threat is an advantage in that it controls for both interviewer bias and the circularity that can come from considering the individual's assessment of the event's impact (Brown & Harris, 1989). An additional advantage is that the LEDS uses a rating system that separates events that may be caused by the person (dependent events) or may be a result of psychopathology (dependent-variable related events (DVR)), from those that are not caused by the person or are related to prodromal symptoms (Anderson, et al., 1995). The LEDS interview may also be conducted as frequently or as infrequently as is desired, with the interviewer asking the patient about any incidents that may have occurred since the last interview. Last, the ratings are reviewed at consensus meetings where the interviewer presents the event to other raters who are blinded to the participant's symptoms and clinical status. This group discusses and votes on the event's ratings, based on a manual of rules that have been set as precedents of over 2000 life events.

1.4 HOW ARE SRD EVENTS IMPORTANT TO BIPOLAR DISORDER?

1.4.1 The Social Zeitgeber Hypothesis

The social zeitgeber hypothesis in affective disorders (Ehlers, et al., 1988; Ehlers, et al., 1993) grew out of a need to integrate biological and psychosocial theories of depression. The theory states that events that disrupt social rhythms have an effect on biological rhythms (of which the sleep system may be one), disruption of which may lead to an affective episode in vulnerable individuals. Social zeitgebers are "personal relationships, social demands or tasks that serve to entrain biological rhythms" (Ehlers, et al., 1988, p. 948; Frank, 2005). Examples include

a work or school schedule, mealtimes, and other social cues that regularize routines (Ehlers, et al., 1988; Frank, 2007). On the other hand, zeitstörers are "time disturbers" (Ehlers, et al., 1993, p. 298). Moving in with a new roommate who keeps you awake at night would be considered a zeitstörer as your social rhythms may be disrupted by his or her presence.

In the social zeitgeber model, a chain of events is triggered when life events involving the loss of a zeitgeber or the introduction of a zeitstörer disturb social rhythms (Ehlers, et al., 1988). This social rhythm instability is followed by unstable biological rhythms, particularly sleep rhythms, and eventually the onset of mood symptoms (Figure 1). As the authors note, these changes may be resolved without much incident in those who are not vulnerable to a mood disorder, but in those who *are* vulnerable to a mood disorder the changes may not be so easily reversed. Note that some life events that set off the sequence of changes may be considered benign in that they are not associated with "stress" as conventionally defined in the life events literature. Yet, they involve changes to daily routines, which may place stress on the body's ability to maintain synchronized rhythms (Frank, Gonzalez, & Fagiolini, 2006). A recent study showed that individuals with bipolar disorder may experience more ambiguous life events in the year before their first manic episode than controls (Horesh & Iancu, 2010). These ambiguous events, such as moving to a different home or getting a new roommate, may not carry stress or threat, but they may involve SRD, which may help to explain why these events had such an impact on manic onset.

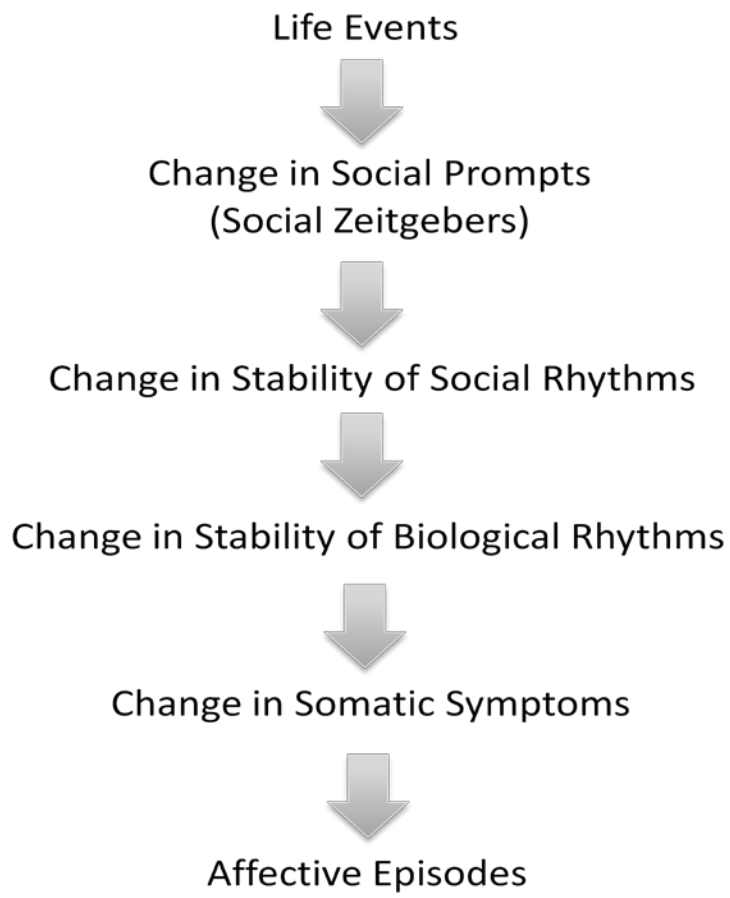

Figure 1. The social zeitgeber hypothesis

As an example, switching to a new job might be an event that has an effect on social rhythms, if an individual must now wake an hour earlier to get to work and arrive home an hour later than at his previous job. While the existing job acted as a social zeitgeber by setting a daily routine, the job change acts as a social zeitstörer, as it changes the individual's sleep and wake schedules, as well as mealtimes. This change to social rhythms may contribute to the unstable biological rhythms seen in bipolar disorder, such as disturbances in melatonin, cortisol, and body temperature rhythms (e.g., Kasper & Wehr, 1992; Kennedy, Kutcher, Raleski, & Brown, 1996; Linkowski, 2003; Nikitopoulou & Crammer, 1976; Pacchierotti, Iapichino, Bossini, Pieraccini,

& Castrogiovanni, 2001; Souetre, et al., 1988). This, in turn, may result in the onset of depressive or manic symptoms.

1.4.2 The Impact of Social Rhythm Disrupting Events on Mood

Recent work has focused on life events involving social rhythm disruption that may or may not involve significant stress, although only a few studies have examined the effect of social rhythm disruption and SRD events on mood. The Wisconsin-Temple research group studied the relationships among social rhythm disrupting (SRD) events, Social Rhythm Metric (SRM; Monk, et al., 1990; Monk, Frank, Potts, & Kupfer, 2002) regularity, and affective symptoms in a group of individuals with bipolar spectrum disorders and normal controls (Sylvia, et al., 2009). These factors were assessed every four months using the SRM, a measure of daily lifestyle regularity, the Life Events Scale (Alloy & Clements, 1992; Needles & Abramson, 1990), and a follow-up interview of life events as a reliability and validity check of the LES. As compared to the control group, the bipolar spectrum group reported more symptoms and less social rhythm regularity at every time point, and more life events at almost all time points. Life events at one time point did not predict social rhythm regularity at the subsequent time point. However, as mentioned above, life events did predict mood scores at the subsequent time points. This effect was stronger for depressive than hypomanic symptoms. There was also a trend for those who experienced more life events to have a shorter time to depressive episode, though the total number of events and negative events did not differ in the 8 weeks prior to a depressive or hypomanic episode as compared to a control period (Sylvia, et al., 2009). However, participants had more SRD events in the eight weeks before the onset of a depressive episode than during a control period, although there were no significant differences for (hypo)manic episodes. Patients with bipolar spectrum disorders also experienced more depressive symptoms (but not

(hypo)manic ones) after an SRD event than before, although the size of this effect was relatively small. The authors suggest that the negative findings pertaining to (hypo)manic symptoms may be due to a low variability of these symptoms in the study sample.

Analyses from the Preventative Therapies in Bipolar Disorder (MTBD) study (Frank, et al., 1997) reported that life events in the year prior to study entry that were characterized by SRD occurring within eight weeks prior to a bipolar episode were associated with manic but not bipolar depressive episode onset (Malkoff-Schwartz, et al., 1998). The findings also suggest that individuals who entered the study with mania were more likely to report an SRD event in the eight weeks before an episode than those who entered the study in a mixed or cycling episode or those with unipolar depression (Malkoff-Schwartz, et al., 2000). Those experiencing mania were also more likely to report an SRD event during an eight week pre-onset period than during a control period (Malkoff-Schwartz, et al., 1998). However, the study from the Wisconsin-Temple group included individuals with "soft" bipolar diagnoses, while the earlier work focused on those with bipolar I disorder, which may have contributed to the differences in the findings.

1.4.3 LEDS Assessment of SRD Events, and Other Relevant Ratings

A manual for rating incidents, events, and difficulties based on social rhythm disruption has also been developed as part of the LEDS (Frank, et al., 1995). In this manual, SRD ratings reflect the potential of a life event to affect the sleep-wake cycle or other routines that may disrupt sleep. The SRD rating of events is made independent of the event's threat rating, and the ratings are to be made conservatively. That is, the rating system was designed so that there must be strong evidence for an event to receive an SRD rating indicating some type of social rhythm disruption. Moreover, some occurrences that would not typically be included in the life chart as events or incidents, because they do not meet LEDS criteria for an event or incident, may be

included in the chart as an “SRD incident” based on its SRD component. An example might be taking the dog out at 3am because you forgot to do so before bedtime. If this type of incident caused sleep disruption of some kind, it might be included as an SRD incident, even though there is little or no threat associated with it. In this rating system, 1=Marked, 2=Moderate, 3=Some, 4=Little/None. Some examples of events with SRD ratings include, a new baby in the household (rating of 1), starting a 20-hour/week part-time job in addition to an existing full-time job (rating of 2), having an outpatient medical procedure requiring early morning arrival to the hospital (rating of 3), ending a romantic relationship in which the partners were not co-habiting (rating of 4). Events that have no social rhythm disruption expected, or those that are thought to increase regularity of routines would be given an SRD rating of 4.

There are additional ratings of each event captured by the LEDS, some of which may be relevant to the present study, including: 1) independence, or the degree to which the individual is or is not an agent in the occurrence of the event; 2) dependent variable-related (DVR) status, referring to the degree to which an event may be contaminated by the presence of prodromal symptoms of an episode; 3) short-term threat, or the unpleasantness experienced within the first few hours following the event; and 4) long-term threat, or the unpleasantness experienced one-to-two weeks following the event (Anderson, et al., 1995; Brown & Harris, 1978). The specific events, difficulties, and incidents that are included in the present analysis, as well as their corresponding ratings, will be discussed in the methods section below.

1.4.4 Additional Life Events Considerations

While previous work has examined the effect of SRD events on mood episodes and symptoms in bipolar disorder, none has reported the use of an empirically defined time window in order to examine the relationship between life events and mood that occur within that time frame.

As the papers have not discussed the use of such a timeframe, we can only assume that the time between life event and mood score chosen was an arbitrary time point or it was based on theory alone. Thus, there has been a need to define a time window in which we would expect these events to have an effect. For example, we would not typically expect one bout of trans-Atlantic travel to affect mood six months later. We identified the time between a life event and episode onset in the pre-onset period of this study, which will be used as our guide for a general timeframe in which we measure the effect of a life event on mood in the preventative phase, the hypothesis-testing portion of this project. Based on these analyses, the median time from most proximal severe life event to mood episode onset, among the events occurring in the four months prior to the acute phase of this protocol was roughly 39 days (Levenson, 2011).

1.5 EVIDENCE FOR SOCIAL RHYTHM DISRUPTION IN BIPOLAR DISORDER

Although evidence is still accruing, both observational and experimental work has explored social rhythm abnormalities among individuals with or at risk for bipolar spectrum disorders. The literature in this area is mixed, although this is not entirely surprising since the social zeitgeber hypothesis does not specifically suggest that euthymic individuals with bipolar disorder will demonstrate disturbed social rhythms. Rather, the hypothesis suggests that these individuals may be particularly vulnerable to rhythm disruption in the face of events and stressors (Ehlers, et al., 1988). Thus, there is a need for those with bipolar disorder to maintain especially regular social rhythms as a way of compensating for this tendency to become disrupted, and as a way of protecting themselves from the disrupting effect of certain events (Ehlers, et al., 1993; Frank, et al., 2006).

Still, it is possible that some individuals with bipolar disorder may demonstrate social rhythm abnormalities even outside of a SRD event. The most common measure of social rhythms, sometimes referred to as daily lifestyle regularity, is the Social Rhythm Metric (SRM; Monk, et al., 1990; Monk, et al., 2002). The short form of this measure (SRM-5; Monk, et al., 2002) includes five items from the original 17 items: 1) Get out of bed, (2) First contact with another person, (3) Start work, housework or volunteer activities, (4) Have dinner, and (5) Go to bed. The timing of these activities, as well as the level of social interaction involved, is recorded by the patient daily. This information is used to calculate multiple measures of weekly social rhythms on a scale of 0-7, with higher scores indicating a higher degree of regularity. Both this measure of social rhythm regularity and the SRD rating of life events have been used in measuring social rhythm disruption in previous work.

Some research on individuals with bipolar I disorder used actigraphy (i.e., a measure of ambulatory activity (Ankers & Jones, 2009; Teicher, 1995)) and SRM scores over one week to assess circadian activity patterns in 19 euthymic patients with bipolar disorder and 19 matched controls (Jones, Hare, & Evershed, 2005). The mean SRM score was lower for the bipolar group than the controls, but the difference did not reach conventional levels of statistical significance. Still, the actigraphy findings showed that intradaily variability of activity patterns was greater for the bipolar group, while interdaily stability was lower. The authors suggest that patients may underestimate rhythm instability, which would account for the measurement differences (Jones, et al., 2005). This suggests that social rhythms may be even more irregular than seen when measured by SRM.

The likelihood of relapse was examined in 20 outpatients with bipolar disorder during the Muslim holiday of Ramadan, a one month period in which eating schedules are altered (Kadri,

Mouchtaq, Hakkou, & Moussaoui, 2000). While 45% of patients who were stable on lithium relapsed during Ramadan, the majority of which were manic relapses, these relapses were not associated with changes in blood lithium level. Even those who did not relapse experienced mood disturbances in the second and third weeks of the month.

Individuals with cyclothymia and bipolar II disorder report fewer regular daily activities than individuals without bipolar disorder, and this decreased regularity prospectively predicted the occurrence of a hypomanic or major depressive episode approximately 13 months after assessing SRM scores (Chang, Alloy, & Abramson, 2003). Regularity also moderated the effect of diagnostic status on likelihood of experiencing a hypomanic episode: cyclothymic individuals who reported low regularity experienced more hypomanic episodes than those with high regularity, although this was not found for individuals with bipolar II or normal controls (Chang, et al., 2003).

Contradicting these results, another study found that individuals with and without bipolar spectrum diagnoses did not differ significantly in the number of activities that they performed regularly or the frequency of engaging in these activities (Shen, Alloy, Abramson, & Sylvia, 2008). Yet, the authors suggest that individuals with bipolar spectrum disorders may be especially sensitive to even minor changes to their daily rhythms, or that controls are able to adapt to these changes more effectively. Moreover, poorer SRM scores, indicating less social rhythm regularity, predicted a shorter time to (hypo)manic episodes. Thus, irregularity of social rhythms may contribute to the onset of bipolar episodes in vulnerable individuals (Shen, Alloy, et al., 2008).

Social rhythm regularity is also important for those *at risk* for having an affective disorder. Based on at least 21 consecutive days of SRM scores, individuals at risk for bipolar

disorder demonstrated lower regularity of daily activities than a control group (Meyer & Maier, 2006). The at risk individuals also showed less stability in their SRM scores over time, although this difference did not reach conventional levels of statistical significance. Another research group also explored the social rhythms and activity levels of individuals at risk for hypomania using a week's worth of actigraphy and a sleep-mood diary (Ankers & Jones, 2009). The at-risk group demonstrated more nighttime activity and less daytime activity than controls, shorter sleep duration than controls, and more variable sleep duration, fragmentation of sleep, and sleep efficiency than controls. Moreover, variability in bedtime was a significant predictor of at-risk vs. control group status, although differences between the groups on the stability or variability of activity rhythms were not significant. Still, the authors suggest that circadian differences may represent a core vulnerability to bipolar disorder

One group also examined the relationship between social rhythm regularity and mood in a group of individuals with rapid cycling bipolar disorder, predicting that the timing and rhythmicity of SRM scores would vary with mood state (Ashman, et al., 1999). Daily SRM scores, activity counts, and solitude ratios (over an average of 95 days) did not vary systematically with mood state for the patient group, but there was a general tendency for morning activities to be delayed when patients were depressed. In general, patients had lower rhythmicity as compared to the control group, and the mean clock times of patients' morning activities was later than controls, suggesting that morning zeitgebers, more than evening ones, may be implicated in the pathophysiology of bipolar disorder (Ashman, et al., 1999). Similarly, a group of inpatients with bipolar and unipolar depression demonstrated more irregular SRM scores at baseline and at follow-up (two weeks later) than a group of control subjects who had regular work schedules, although activity level did not differ among the groups (Szuba, et al.,

1992). This finding was especially remarkable because of the difference in SRM scores, despite the highly structured an inpatient setting.

Overall, this observational work suggests that some individuals with bipolar disorder may have more irregular social rhythms, disturbed sleep and motor activity rhythms, and more intradaily variability of activity patterns than those without bipolar disorder. While some studies did not find differences reaching conventional levels of statistical significance in social rhythm regularity between individuals with bipolar disorder and controls, it is possible that individuals vulnerable to affective episodes may be more sensitive to *changes* in social rhythms. Thus, bipolar episodes may be more likely when these individuals experience rhythm irregularity, even if their typical social rhythms are not significantly different from controls.

1.5.1 Can a Treatment Improve Social Rhythm Regularity?

Based on the importance of social rhythms in these populations, some treatments have emerged that focus on rhythm dysregulation as a target of treatment. One study randomized individuals with cyclothymia either to a condition in which they were instructed to increase lifestyle regularity, or to a condition in which they simply monitored their SRM scores over four weeks (Shen, Sylvia, et al., 2008). The groups did not differ significantly in their depression symptoms over time, even though individuals randomized to the experimental condition were successful in regulating their social rhythms. Yet, those who increased the number of activities regularly performed showed a decrease in depressive symptoms and decreased within-day symptom variability by the end of the study (Shen, Sylvia, et al., 2008). The authors suggest that more than four weeks may be necessary to see the differential effects of increasing lifestyle regularity on mood symptoms.

Of the formal treatments for bipolar disorder, interpersonal and social rhythm therapy (IPSRT; Frank, 2005; Frank, 2007) is perhaps the most well-known for targeting social rhythm disruption. The treatment attempts to prevent the onset of new bipolar episodes by reducing interpersonal stress and regularizing social routines. Interpersonal stressors are a focus of treatment both because of their impact on mood, but also because of their potential effect on the circadian system and daily routine (Frank, 2005; Frank, 2007). IPSRT involves psychoeducation regarding the nature of bipolar disorder, the use of the Social Rhythm Metric (SRM; Monk, et al., 1990) to monitor and modify social routines, and a focus on intervening in an interpersonal problem area that is challenging for the patient. Social rhythms are monitored at the start of treatment to identify targets for improving regularity in routine. The therapist and client strategize ways in which regularity may be increased, and, once social rhythms have become stabilized, they work to anticipate triggers of social rhythm disruption.

A number of studies have demonstrated the efficacy of IPSRT for bipolar disorder. The Preventative Therapies in Bipolar Disorder (MTBD) study reported that IPSRT was efficacious in regularizing the daily routines of individuals recovering from an episode of bipolar disorder, not simply because of monitoring or recording daily routines or because of recovery from an acute episode, but because of increasing social rhythm regularity itself (Frank, et al., 1997). This focus on increasing social rhythm regularity may also impact occupational functioning, as individuals with bipolar I disorder who received IPSRT demonstrated a more rapid improvement in occupational functioning than patients assigned to intensive clinical management (Frank, et al., 2008). The authors suggest that the improvement seen with IPSRT may promote a return to work because of increased rhythm regularity.

Data from the MTBD study will be used for the present analysis. This study used a combination treatment strategy in which individuals in an episode of bipolar disorder were randomly allocated to IPSRT or intensive clinical management (ICM), both in addition to pharmacotherapy (Frank, et al., 2005). Patients were treated to remission, and then entered a 2-year preventative phase in which half remained in the psychotherapy condition to which they were allocated initially, and half received the alternate psychotherapy. Again, all patients received pharmacotherapy; additionally, the frequency of treatment sessions was reduced during the preventative phase. Individuals assigned to IPSRT in the acute phase survived longer without a new episode during the preventative phase, and more regular social rhythms at remission predicted a lower probability of recurrence after controlling for treatment assignment in the acute phase (Frank, et al., 2005). This suggests that increased regularity of daily routines mediated the effect of treatment assignment on likelihood of experiencing a recurrence. Moreover, these findings are consistent with the social zeitgeber hypothesis.

While the studies reviewed here have explored the effect of SRD events on mood, none has observed whether treatment assignment moderates this effect. If it were shown that SRD events have less of an effect on mood among those who receive one treatment, in this case IPSRT, as compared to another, we may make some treatment recommendations based on this observation. Initial analyses of these data showed a longer time to recurrence among patients who initially received IPSRT (Frank, et al., 2005); however, it is unknown if this effect remains among those who experience SRD events. If IPSRT does have a protective effect, we may be preventing one pathway by which stressors lead to mood episodes, according to the social zeitgeber hypothesis, by reducing the impact of SRD events.

We would expect IPSRT to reduce the effect of SRD events because of the treatment's efforts to intervene in two of the three proposed paths to recurrence of bipolar disorder: stressful life events and disruptions in social rhythms (Frank, 2007). While the treatment strategies attempt to reduce the number of interpersonal and social stressors, patients also learn to anticipate the impact of events that may occur and to regularize social rhythms that may begin to be disturbed by returning to the strategies learned earlier in treatment for social rhythm regularization. As Frank and colleagues note, "we also search the 'landscape' of the patient's life for potential triggers to rhythm disruption, such as having house guests or taking a vacation. We then problem-solve with the patient about how to maintain the maximum regularity of routine possible in the face of such disruptions" (Frank, et al., 2006, p. 983). Indeed, an earlier study of stressful life events among depressed women treated with IPT showed that acute and preventative IPT treatment may reduce the effect of conventionally-rated (i.e. rated for stressfulness) life events in precipitating a recurrence of depression (Harkness, et al., 2002).

1.6 THE IMPORTANCE OF BIOLOGICAL RHYTHMS IN BIPOLAR DISORDER

Bipolar disorder is thought to have a biological basis; indeed, Goodwin and Jamison note that it is an illness "that is biological in origin yet psychological in expression" (2007, p. xxi). One major focus in the biological basis of bipolar disorder is the role of circadian rhythm abnormalities, which will be described later in this section; still, work in this area has concentrated on other biological abnormalities as well. Some investigators have searched for genes or genetic regions that may confer susceptibility to the disorder (e.g., Goodwin & Jamison, 2007; McClung, 2007), with recent hypotheses reflecting the idea that many genes of small effect likely contribute to a genetic vulnerability to the disorder, including brain derived

neurotrophin factor (*BDNF*) and D-amino acid oxidase activator (*DAOA*) (Barnett & Smoller, 2009). Exploration into the neurobiological and neuroanatomical underpinnings of the disorder has also intensified in recent years. The role of specific neurotransmitter-related enzymes (e.g., monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT)) has been one such focus (Goodwin & Jamison, 2007), while a recent review of the neurobiological trait abnormalities associated with the disorder noted that "elevated PKA [protein kinase A] activity, altered intracellular calcium signaling, enhanced pro-inflammatory cytokine production [and] glucocorticoid receptor dysfunction" are just some of the trait abnormalities that have been detected (Langan & McDonald, 2009).

Though neither structural nor functional neuroimaging can yet diagnose bipolar disorder, neuroimaging techniques have begun to demonstrate the neuroanatomical abnormalities common to individuals with the disorder (Goodwin & Jamison, 2007). For example, a recent review of functional neuroimaging studies showed altered brain activation in several regions of the cortico-limbic pathway that are responsible for emotion regulation (Cerullo, Adler, Delbello, & Strakowski, 2009).

Although circadian rhythm abnormalities are just one of the biologically based disturbances thought to play a role in the illness, they will be reviewed in greater depth here because they are directly relevant to the underlying hypotheses of the work proposed. Many endogenous human biological rhythms (e.g., body temperature, hormone secretions, sleep, and mood) follow a circadian pattern, or one that typically obeys a 24-hour cycle (Goodwin & Jamison, 2007; Linkowski, 2003). These rhythms are controlled by a master circadian clock located in the suprachiasmatic nuclei (SCN). While these rhythms appear to have a circadian pattern, circadian rhythms that "free run," (i.e., when individuals are isolated from external time

cues) are typically slightly longer than 24 hours (Mills, Minors, & Waterhouse, 1974). The authors note that this may reflect an endogenous timing mechanism. However, these rhythms can be synchronized by environmental zeitgebers or "entraining agent[s]" (Pittendrigh, 1981b), which help to keep our natural biological rhythms on a 24-hour cycle. Indeed, the light/dark cycle is considered the strongest zeitgeber that entrains circadian rhythms in most species (Aschoff, 1981; Pittendrigh, 1981a).

Interest in the role of social factors in the entrainment of biological rhythms is not new. Some of the earliest work emphasized the ability of social zeitgebers to entrain circadian rhythms, perhaps even more than the effect of physical ones (Aschoff, 1981; Aschoff, et al., 1971; Pittendrigh, 1981a; Wever, 1979, 1988). By examining several biological measures of circadian rhythm (e.g., rectal temperature, urinary excretion) one study showed that these rhythms were not significantly different under conditions of an artificial light-dark cycle and continuous darkness (Aschoff, et al., 1971). Yet, the six male participants had knowledge of the time of day, established a living routine, and engaged in social communication during this time. So, while a light-dark cycle was not necessary to entrain circadian rhythms, "knowledge of time of day, living routine, and social communication are powerful zeitgebers for the human circadian system" (Aschoff, et al., 1971, p. 215). Therefore, given how important social cues are to the entrainment of circadian rhythms, we can understand how they may be of even greater importance to individuals with bipolar disorder, whose circadian rhythms may be vulnerable to disruption by disruption of social zeitgebers, according to the social zeitgeber hypothesis.

1.6.1 Circadian Rhythm Disturbances in Bipolar Disorder

An extensive literature on the importance of biological circadian rhythms to the pathophysiology of the disorder has accumulated over roughly 40 years, reflecting the strong

proposal that biological rhythm abnormalities may represent endophenotypes of bipolar disorder (Goodwin & Jamison, 2007). Indeed, Goodwin and Jamison (1990) suggest that instability is the "fundamental dysfunction in manic-depressive illness," a treatment target of which may be to enhance circadian integrity (Goodwin & Jamison, 1990, p. 594). For example, circadian rhythms influence the levels and release of some mood-regulating neurotransmitters (Giglio, et al., 2009), and the therapeutic action of lithium may be related to its effect on the circadian clock (Lamont, Coutu, Cermakian, & Boivin, 2010; LeSauter & Silver, 1993); thus, it would appear logical to search for clues to the pathophysiology of bipolar disorder in the function of the circadian timing system (Wirz-Justice, 2006).

Goodwin and Jamison (2007) describe several proposed mechanisms behind circadian rhythm disturbances that are typical of the disorder, including the desynchronization hypothesis (Georgi, 1947, as cited in Goodwin & Jamison, 2007), Halberg's (1968, as cited in Goodwin & Jamison 2007) free-running hypothesis, and the phase-advance hypothesis. Although they vary slightly, each of these hypotheses focuses on the extent to which one or more circadian rhythms is out of sync with other internal or external (e.g., sunlight) rhythms, which may lead to an affective disturbance. Goodwin and Jamison note that it is difficult to determine if a disturbance in circadian clock function drives the symptoms seen in bipolar episodes, or whether clock dysfunction is a consequence of the symptoms of the disorder. Nonetheless, this dysfunction is an integral piece of the disorder.

Recent work has also focused on circadian genes that may play a role in the manifestation of bipolar disorder (e.g., Lamont, Legault-Coutu, Cermakian, & Boivin, 2007; Mansour, Monk, & Nimgaonkar, 2005; McClung, 2007). For example, a single nucleotide polymorphism (SNP) in the *CLOCK* gene has been associated with greater insomnia and decreased need for sleep in

patients with bipolar disorder, and mice with mutations in the *CLOCK* gene and those that overexpress GSK3β, a circadian clock modulator, display manic-like behaviors (McClung, 2007). Thus, one way that individuals with bipolar disorder may be genetically different from other individuals is based on differences in the CLOCK gene. While we do not have the capacity to examine the effects of genetic mutations in this work, future work should investigate how circadian gene abnormalities play a role in social and circadian rhythm disturbances, particularly in those with bipolar disorder.

In addition to circadian genes, there are a number of ways that circadian rhythm abnormalities and their importance in bipolar disorder may be quantified. Disturbances in sleep, a rhythm thought to be regulated by both homeostatic and circadian processes (Borbély, 1982), are frequent during bipolar episodes and are common prodromes to both depression and mania (Harvey, 2008; Jackson, Cavanagh, & Scott, 2003). Several studies have demonstrated a negative cross-correlation between sleep duration and next-day mood in this population, mostly reporting an association between decreased sleep and increased mood (Barbini, Bertelli, Colombo, & Smeraldi, 1996; Bauer, 2008; Bauer, et al., 2006; Leibenluft, Albert, Rosenthal, & Wehr, 1996; Perlman, Johnson, & Mellman, 2006). Experimental work in this area has shown the anti-manic effect of sleep and dark therapy and the antidepressant effect of wakefulness, as well as the effects of light therapy and sleep phase change, which are sometimes used in combination with lithium (Barbini, et al., 2005; Benedetti, et al., 2005; Colombo, et al., 2000; Wehr, et al., 1998; Wirz-Justice, et al., 2005; Wu, et al., 2009). Light therapy and sleep phase advance are thought to sustain the acute antidepressant response brought on by sleep deprivation (Benedetti, et al., 2005; Colombo, et al., 2000; Wirz-Justice, et al., 2005; Wu, et al., 2009).

This empirical evidence fits nicely with theoretical work on sleep disturbances in bipolar disorder, which has focused primarily on mania. Wehr's group hypothesizes that factors that trigger manic episodes may do so via their ability to cause sleep deprivation (Wehr, 1989; Wehr, Sack, & Rosenthal, 1987). The authors propose a bidirectional model in which sleep deprivation leads to mania, but mania also causes sleep reduction. Indeed, the idea that sleep and mood are involved in a bidirectional relationship has endured since first proposed, and is frequently discussed in current work (e.g., Harvey, 2008; Saper, Cano, & Scammell, 2005; Steptoe, O'Donnell, & Wardle, 2008).

It has also been shown that motor activity rhythms and levels may be disturbed when patients with bipolar disorder are in an episode (Teicher, 1995). Actigraphy is a measure of ambulatory activity (Ankers & Jones, 2009; Teicher, 1995) that is increasingly being used in sleep medicine studies (Sadeh & Acebo, 2002). The data provide information about the amount of movement recorded over various time spans (Ankers & Jones, 2009; Buysse, 2005; Teicher, 1995) and may also provide "information for the assessment of biological rhythms" (Teicher, 1995, p. 28). Both early (e.g., Foster & Kupfer, 1975) and more recent (Ankers & Jones, 2009; Harvey, Schmidt, Scarna, Neitzert Semler, & Goodwin, 2005; Jones, et al., 2005) work has shown disturbed rest-activity rhythms in those with bipolar disorder. As noted above, patients with bipolar disorder show greater intradaily variability and lower interdaily stability of activity patterns than a control group (Jones, et al., 2005). Even when euthymic, patients with bipolar disorder may demonstrate lower daytime activity levels than controls (Harvey, et al., 2005).

It has also been shown that there are inter-individual differences in *chronotype*, or the extent to which individuals consistently prefer to be morning-active versus evening-active (Smith, Reilly, & Midkiff, 1989). Individuals with varying tendencies for morningness and

eveningness may demonstrate differences in the timing of certain circadian rhythms, such as body temperature (Baehr, Revelle, & Eastman, 2000; Kerkhof, 1985). Chronotype, commonly measured by the Composite Scale of Morningness (CSM; Smith, et al., 1989), is thought to reflect differences between morning- and evening-types in the phase position of their endogenous circadian oscillators (Kerkof & Vandongen, 1996; Duffy et al., 2001; both as cited in Wood, et al., 2009).

Recent data suggest a tendency toward eveningness among individuals with bipolar disorder. Most recently, one study showed that euthymic patients with bipolar disorder demonstrated a greater tendency toward eveningness than controls (Giglio, et al., 2010). Using the CSM, findings from our group suggest that patients with bipolar I were significantly more likely to be 'evening' types than unscreened controls and patients with schizophrenia or schizoaffective disorder when age was considered (Mansour, Wood, et al., 2005). In a separate study, a sample of adults with bipolar disorder was compared to controls who were drawn randomly from the same residential areas. Individuals with bipolar disorder again were more likely to be 'evening' types, after accounting for potentially confounding variables (Wood, et al., 2009). The analyses also supported a relationship between evening chronotype and more severe depressive mood ratings, and this relationship was demonstrated even among healthy individuals in another study (Hidalgo, et al., 2009).

The finding that patients with bipolar disorder have a tendency toward eveningness appears to apply cross-culturally, as well. A recent study in Korea on chronotype distribution in bipolar I disorder and schizophrenia confirms the preference for eveningness in the bipolar I population (Ahn, et al., 2008). Chronotype may also play a role in the onset of bipolar episodes, as evidenced by a case study of a woman with extreme morning type who developed depressive

symptoms after changing to a night-shift schedule (Meyrer, Demling, Kornhuber, & Nowak, 2009). The authors suggest the possibility of a sensitizing role of chronotype in triggering bipolar episodes when such a drastic switch in the sleep-wake schedule has occurred. Moreover, some have suggested that certain CLOCK polymorphisms play a role in bipolar disorder based on their association with extreme chronotypes, particularly a tendency toward eveningness (Lee, et al., 2010), and that individuals with this polymorphism may be at increased likelihood of bipolar episode recurrence (Benedetti, et al., 2003). This association between evening chronotype, bipolar disorder, and increased depressive symptoms is important because evidence suggests an association between eveningness and low lifestyle regularity (Monk, Buysse, Potts, DeGrazia, & Kupfer, 2004), which is associated with poorer sleep (Monk, Reynolds 3rd, Buysse, DeGrazia, & Kupfer, 2003), factors that may place individuals with bipolar disorder at further risk for developing episodes.

Other biological rhythm abnormalities have been identified in bipolar disorder as well, including disturbances in melatonin, cortisol, and body temperature rhythms, although some of the evidence is inconsistent. For example, there is some suggestion that nocturnal melatonin is elevated during mania (Lewy et al. 1979, Wirz-Justice & Arendt 1980, both as cited in Healy & Williams, 1989), although other evidence suggests that melatonin is decreased during all bipolar mood states as compared to controls (Kennedy, Tighe, McVey, & Brown, 1989). Individuals with bipolar disorder are also thought to have abnormal cortisol profiles, one of the most widely-used markers of the circadian clock, with cortisol hypersecretion often reported among depressed subjects (Linkowski, 2003; Linkowski, et al., 1994; Swann, et al., 1992). With regard to body temperature, some patients with bipolar depression exhibit reduced body temperature when awake, especially during the early morning hours, with elevated nocturnal body temperatures and

a diminished 24-hour rhythm reported in some patients (Nikitopoulou & Crammer, 1976; Souetre, et al., 1988). Yet, more recent work has shown that depressed patients may have abnormal phase variation of temperature rhythms while both manic and depressed patients may demonstrated a lower temperature amplitude than normal controls (Tsujimoto, Yamada, Shimoda, Hanada, & Takahashi, 1990).

1.7 THE CURRENT STUDY

The purpose of the current study is to examine the effect of SRD events on mood, particularly as outlined in the social zeitgeber hypothesis. 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 relatively prospectively. That is, the design of the study aimed to reduce the amount of time between LEDS assessments, limiting the retrospective nature of the assessment. Moreover, an entirely different group of individuals evaluated participants' mood score and life events, reducing evaluator bias.

The patients in the current study received one of two psychotherapeutic treatments, or a combination of the two: IPSRT, a treatment aimed at reducing the effects of social rhythm disruption, or a control psychotherapy. Thus, the second aim of this project is to determine whether IPSRT protects individuals from the effects of SRD events on mood. The study will utilize a sample of men and women with bipolar I disorder who were treated to remission with psychotherapy during an acute treatment phase, and then followed for up to two years during a preventative treatment phase (Frank, et al., 2005). The goal is to determine whether, after achieving remission from an acute bipolar episode, SRD events predict a worsening of bipolar

symptoms, and whether this effect depends on the psychotherapeutic treatment to which the patient was randomly assigned. The following questions are posed:

1.7.1 Does a social rhythm disrupting (SRD) event, predict a worsening in mood symptoms during preventative treatment?

Hypothesis 1a: There will be a significant relationship between the presence of an SRD event and the degree of mood worsening, above and beyond the presence of at least one threat event.

Hypothesis 1b: There will be a significant relationship between the degree of SRD event(s) severity and the degree of mood worsening observed, above and beyond the effect of non-SRD (threat) event severity.

1.7.2 Does treatment assignment moderate the effect of SRD events on mood?

Hypothesis 2: Treatment assignment during the acute and preventative phases will moderate the effect of SRD events on mood worsening during the preventative phase of treatment.

2.0 METHODS

2.1 OVERVIEW

Data for this project come from the "Preventative Therapies in Bipolar Disorder" study (MH29618; E. Frank, PI), which was conducted from 1991-2002 in the Depression Prevention Program at Western Psychiatric Institute and Clinic (WPIC). 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 (preventative) treatment phase, designed to prevent recurrence of bipolar episodes. Only those who entered the preventative phase will be studied in these analyses.

2.2 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). The participants were in an episode of depression or mania upon entering the acute phase of the study, which was at least the third episode that they had experienced during their lifetime. The most recent episode must have occurred within the five years prior to the current episode, with at least 12 weeks of remission between the two episodes. Exclusion criteria included a history of rapid cycling (> 4

episodes/year), meeting Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) for any other psychiatric illness during the 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 or schizoaffective disorder, organic affective syndrome, significant medical illness, refusal to use contraception or pregnancy in females, or unspecified functional psychosis.

2.3 DESIGN AND PROCEDURE

At study entry, participants met RDC criteria for bipolar I disorder or schizoaffective disorder, manic type. They also scored >7 on the Raskin Severity of Depression Scale (Raskin, 1988; Raskin, Schulterbrandt, Reatig, & McKeon, 1969) and >15 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960), if the index episode was depression, or they achieved a score of >7 on the Raskin Severity of Mania Scale (Raskin, 1988; Raskin, et al., 1969) and >15 on the Bech-Rafaelsen Mania Scale (Bech, Bolwig, Kramp, & Rafaelsen, 1979), if the index episode was mania.

Upon entering the study, participants were randomly allocated to one of two psychosocial treatments: IPSRT (Frank, 2005) or intensive clinical management (ICM). They received this treatment weekly during the acute phase for a minimum of 12 weekly sessions, regardless of how quickly they stabilized, and a maximum of 24 weekly sessions. If the patient switched polarity during the acute phase he or she could receive a maximum of 24 weekly sessions starting after the switch. Thus, each patient could have received a maximum of 48 sessions during the acute phase.

Once stabilization was achieved, defined as four consecutive weeks of HRSD-17 and BRMS scores of ≤ 7, patients entered the preventative phase. Of the 175 patients who entered the study, 125 of these individuals entered the preventative phase. Only these patients will be used in

the present analyses. In this phase, the patients were re-randomized, either to the psychosocial treatment that they had received during acute treatment or to the alternative psychotherapy. Treatment visits occurred every other week for the first 12 weeks of preventative treatment, and then monthly for the remainder of the two years of the phase. However, for those patients who received ICM in the acute phase and were then re-randomized to IPSRT during preventative, they received six weekly sessions of IPSRT at the start of this phase, followed by three biweekly sessions, before continuing to monthly treatment. This was done to ease the introduction of IPSRT. As such, the first 12 weeks of the preventative phase are considered 'continuation,' while the remainder is considered 'preventative' treatment. If patients experienced a relapse (during continuation) or recurrence (during preventative) they returned to the acute treatment schedule and were treated weekly until stabilization.

All patients also received pharmacotherapy according to the protocol. The pharmacotherapy algorithm aimed to stabilize as many patients as possible on lithium monotherapy or lithium with one other medication. If lithium was not an acceptable agent, sodium divalproex or cabamazepine was utilized (Frank, et al., 2005). If lithium monotherapy was insufficient to bring about remission of a manic episode, adjunctive antipsychotic pharmacotherapy was initiated. Similarly, if lithium monotherapy was insufficient to bring about remission of a depressive episode, adjunctive antidepressant pharmacotherapy was initiated. However, adjunctive medications were tapered after stabilization in an effort to avoid the switch into mania that can arise with antidepressant use, and to avoid problems with long-term side effects that can arise with antipsychotic use. In the preventative phase, medication regimens were maintained unless adjustments to lithium dosages were required. Moreover, rescue medications were employed when necessary to treat emergent insomnia or acute mania.

2.4 PSYCHOSOCIAL TREATMENTS

2.4.1 IPSRT

Individuals randomized to IPSRT in the acute phase received at least 12, and up to 24 sessions of treatment, with each session lasting roughly 45 minutes. Those randomized to IPSRT in the preventative phase received the treatment biweekly for 12 weeks, and then monthly for the remainder of the two years. However, if they had received ICM in the acute phase, the patients began with six weekly sessions of IPSRT followed by three biweekly sessions, before entering monthly treatment.

IPSRT aims to prevent bipolar episodes by attempting to intervene in three pathways to recurrence: medication non-compliance, stressful life events, and social rhythm disruptions (Frank, 2005; Frank, 2007). The treatment focuses on the amelioration of symptoms via the establishment of highly regular social and sleep/wake routines and the resolution of interpersonal difficulties. Like individuals receiving interpersonal psychotherapy (IPT; Klerman, Weissman, Rounsaville, & Chevron, 1984), those in treatment with IPSRT choose an interpersonal problem area of focus: unresolved grief, grief for the lost healthy self, role transitions, role disputes, or interpersonal deficits. It is thought that addressing interpersonal problems in these areas reduces the social stressors experienced by the patient. In addition, patients monitor social rhythms using the SRM (Monk, et al., 1990; Monk, et al., 2002). The clinician and patient identify areas of irregularity in the patient's social rhythms and attempt to regularize these routines.

Of particular interest to this study, IPSRT focuses on preventing recurrence in the continuation or preventative phase of treatment by the use of several strategies that center on the belief that "social rhythm stabilization can have a long-term prophylactic effect" (Frank, 2005, p. 92). These include searching for triggers of rhythm disruption, finding and maintaining an

appropriate activity level for the patient, and learning to adapt to changes in routine that may occur, whether anticipated or unanticipated changes (Frank, 2007).

2.4.2 Intensive Clinical Management (ICM)

Individuals randomized to ICM in the acute phase received at least 12, but not more than 24 sessions of treatment, with each session lasting roughly 20 minutes. In the preventative phase the patients received 12 biweekly sessions of ICM, followed by monthly sessions for the remainder of two years. The goal of ICM is for the patient to recognize and discuss symptoms of depression and mania, as well as medication side effects. However, techniques for managing these symptoms and side effects are not addressed. Strategies for resolving interpersonal problems are also not discussed, nor are efforts to assist the patient in structuring his or her daily life. If the patient does not present significant symptoms or side effects, a "diary-like" approach is taken, in which the patient is encouraged to discuss activities since the last visit.

2.5 MEASURES

The following assessments were conducted during the study, either to determine eligibility for the protocol or to measure patient variables once in the study. All ongoing assessment evaluators were trained to criterion level of agreement (ICC $\geq$ 0.80), a level that was re-established every six months.

2.5.1 Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960)

The HRSD is an assessment of symptoms of depression that is administered by interview. It was administered at every clinic visit to measure depressed mood, and the scores of the HRSD were used to determine inclusion into the study, to diagnose an index episode of depression, and to identify remission and recurrence. Scores for both the 17- and 25-item scales are available.

2.5.2 Bech-Rafaelsen Mania Rating Scale (BRMS; Bech, et al., 1979)

The BRMS is an assessment of symptoms of mania that is administered by interview. It was administered at every clinic visit to measure manic symptoms, and the scores of the BRMS were used for inclusion into the study, to diagnose an index episode of mania, and to identify remission and recurrence.

2.5.3 Life Events and Difficulties Schedule (LEDS; Brown, 1989; Brown & Harris, 1978)

The LEDS is a semi-structured interview intended to record and interpret the presence and nature of life events and chronic difficulties. It is designed to identify events and difficulties across 10 domains, giving a rating based on "contextual" threat, or what most people would consider stressful. The LEDS also provides a rating for the level of social rhythm disruption associated with the event or difficulty.

In this study, the LEDS was administered once initial stabilization was achieved, 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 first administered during the fourth month of this phase, and then every three months after this point. However, it happened on occasion that an interview may have been delayed if a patient was in an episode; if this was the case, the following interview would inquire about events that occurred since the last interview, so that all time points were captured in a "snapshot" of continuous time over the course of the study, regardless of when the interview was conducted. The LEDS was not administered when the patient was acutely ill to avoid a bias in reporting events based on mood symptoms. Again, the LEDS was administered and rated by an entirely different group of evaluators than those assessing mood symptoms.

Life events, difficulties, and incidents may all be important to the study of the effect of social rhythm disruption on mood; thus, we attempted to include as many measures of these occurrences as possible. Since the social rhythm disruption rating is of greatest interest, only those events that have an SRD rating will be included here. Moreover, we could conceptualize a *change* in the SRD rating of a difficulty as reflecting a type of SRD event. As will be described in more detail below, we attempted to include changes in SRD difficulties, but there were insufficient data to do so. Last, though incidents are not thought to be severe enough to warrant a threat rating, they may disrupt social rhythms. As such, they will be included here. As mentioned above, there are also multiple ways to classify an event. For example, some studies (e.g., Lenze, et al., 2008) consider those events that are rated as "independent" because it is very important to exclude events that are the result of the person's own agency. We have chosen to exclude some event ratings included in the LEDS (e.g., trauma or reconciliation) because they are less relevant to the current research question. The ratings discussed above (DVR, independence, and short-term and long-term threat) are included, either because they are of particular interest to the current project or because they are crucial to the study of life events more generally. In the following analyses, dependent variable-related status will be coded as any possibility of relation to the dependent variable (1) or not dependent variable-related (0); independence will be coded as possibly dependent (1) or independent (0); and short-term threat, long-term threat, and SRD will be coded as 1=Marked, 2=Moderate, 3=Some, 4=Little/None (Anderson, et al., 1995; Brown & Harris, 1978). Each of the hypotheses will be tested using various conceptualizations of each event, based on the ratings of interest identified here. Typically, previous work using the LEDS method has focused on only independent events, or those that are not thought to be the result of the individual's own actions

(e.g., Brown & Harris, 1978; Lenze, et al., 2008). Because of this tendency, this report will focus on independent events, though all events will also be included in some analyses.

2.5.4 Raskin Severity of Depression and Mania Scale (Raskin, 1988; Raskin, et al., 1969)

This is a clinician-rated assessment of depressive and manic symptoms that is based on both the patient's verbal report of symptoms, the patient's behavior, and secondary symptoms. Each of these dimensions is rated on a scale of 1 (not at all) to 5 (very much) for both depression and mania, generating a score for both mood states. This scale was administered at the screening visit and every subsequent clinic visit.

2.5.5 Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978)

The SADS is an interview designed to diagnose psychological disorders according to Research Diagnostic Criteria (RDC; Spitzer & Endicott, 1978). Prior to 1995, the SADS was used to diagnose bipolar disorder or schizoaffective disorder, manic phase, for inclusion into the study. It was administered at the screening visit.

2.5.6 Structure Clinical Interview for DSM-IV Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1997)

The SCID-I is a structured clinical interview that is used to diagnose DSM-IV Axis I disorders. The SCID-I was used after 1995 to diagnose bipolar disorder or schizoaffective disorder, manic phase, for inclusion into the study. It was administered at the screening visit.

2.6 VARIABLES OF INTEREST

The purpose of this study was to examine the effect of life events on mood within one month of the occurrence of the event. As SRD events are thought to have a relatively immediate effect on mood, we expected to see a change in mood just after the occurrence of the event as compared to the mood reported just before the event. Thus, the dependent variable was

conceptualized as the change in mood from one mood assessment point to the next. This was measured individually for symptoms of depression and mania, based on the 25-item Hamilton Rating Scale for Depression (Hamilton, 1960) and the Bech-Rafaelsen Mania Scale (BRMS; Bech, et al., 1979). Given that overall mood change was the variable of interest, the dependent variable may be positive, negative, or zero to indicate mood worsening, improvement, or no change. In addition a dichotomous combined mood outcome variable was examined, by considering any interval that included at least a 4-point worsening in HRSD-25 scores *and* at least a 3-point worsening in BRMS scores as sufficient mixed symptom worsening (coded as '1'). Any interval that included less than a 4-point worsening in HRSD-25 scores or less than a 3-point worsening in BRMS scores was considered insufficient mixed symptom worsening (scored as '0').

This dichotomous scoring was based on recent work identifying clinically meaningful criteria for mixed states in bipolar disorder, which has suggested that the presence of at least three symptoms of depression and three symptoms of mania define a mixed episode (Swann, Steinberg, Lijffijt, & Moeller, 2009). These symptoms were "mild, but definitely present" (Swann, et al., 2009, p. 167). This definition may be equivalent to a 3-point increase on our measures of depression and mania. While some patients may report a mild (i.e., 1-point) worsening on three individual symptoms, others may report a more severe (i.e., 3-point) worsening on one symptom. Nonetheless, the severity of worsening may be the same. If the HRSD-17 were used as our measure of depression, a 3-point worsening as our threshold for depression symptoms would be appropriate here. However, since the HRSD-25 includes 8 additional items that assess anxious/agitated depression, as well as symptoms of atypical depression, a 4-point worsening threshold may be more suitable. Thus, mixed symptom

worsening was defined as a 3-point worsening on the BRMS and a 4-point worsening on the HRSD-25.

Both a categorical and continuous conceptualization of life events for the independent variable were considered to examine the effect of both the *presence* and *severity* of SRD events, taking into account the effect of threat events. As before, threat events are not thought to disrupt social rhythms, but they may have a separate, detrimental effect on mood. The categorical variable was created to examine how the presence of at least one SRD event predicts changes in mood symptoms, controlling for the presence of at least one threat event. Every time window was rated for the presence (‘1’) or absence (‘0’) of an SRD event, and for the presence (‘1’) or absence (‘0’) of a threat event. We planned to include both indicators in the model in order to evaluate the effect of SRD above and beyond the effect of threat.

We also conceptualized a continuous variable, which was though to reflect the level of social rhythm disruption as well as the level of threat. Each event received both an SRD score and a threat score, although these may differ based on the nature of the event. Given any time window, the SRD score was calculated as the sum of the level of social rhythm disruption for each event that occurred during this time window, and the threat score was the sum of the level of threat severity for each even that occurred during this time window. As events are currently scored from ‘1’ (most social rhythm disrupting or most threat) to ‘3’ (least social rhythm disrupting or least threat), these values were reverse coded before summing so that the higher scores indicate higher levels of disruption. Any event that received an initial rating of ‘4’ (no social rhythm disruption or threat expected) was re-coded as ‘0.’ Essentially, these events were not included in the model. Thus, each interval had a score for total level of SRD and total level

of threat. The goal of including both scores in the model was to determine whether SRD event ratings explain more of the variance in mood change than non-SRD event ratings.

Recurrence was determined by blinded senior psychiatrists who were not otherwise involved in the conduct of the study and who were asked to determine whether the participant met Research Diagnostic Criteria for a new affective episode. This process was bypassed when the participant required immediate hospitalization.

2.7 ANALYTIC PLAN

2.7.1 Descriptive Analyses

Limited descriptive analyses were conducted to determine the number of one-month time windows between mood assessments in which life events may have occurred. In the preventative phase protocol mood assessments were scheduled to occur weekly or biweekly for the first 12 weeks, then approximately once per month. Thus, some mood assessment time points were excluded in order to identify the number of non-overlapping, one-month windows between which two mood assessments occurred. The one-month time window was chosen for a few reasons. First, in their hallmark studies of depressed women, Brown and Harris examined "change-points," or significant changes in the patient's psychiatric symptoms (Brown & Harris, 1978). The authors stated that these change-points could not occur more often than every four weeks, other than in clearly exceptional circumstances, methodology that is reflected in our time frame. Second, the decision was based on the time windows that were used in previous studies (e.g., Malkoff-Schwartz, et al., 1998; Sylvia, et al., 2009), which examined life events that occurred within the 2 or 4 months prior to the start of a mood episode. Yet, one may wonder whether a lapse of this nature is too large to see the effects of SRD events on social rhythms, as the effect of SRD events may be more immediate. Moreover, a four-month lapse may be too

large of a window to see the effect of SRD events on hypomanic symptoms, as previous work has suggested that manic episodes may be shorter than depressive ones (Johnson, 2005). As such, a shorter time window, such as one month, may be more appropriate. Third, a one-month window was chosen because the majority of mood assessments were spaced roughly one month apart during the preventative phase, and so it was expected that the one-month time window would maximize the use of the available data. Any assessments that did not fit within our monthly criteria were excluded in order to increase uniformity in this variable as much as possible, especially given the use of a repeated measures model. Last, we measured the median time from most proximal severe life event to mood episode onset, among the events occurring in the four months prior to the acute phase of this protocol. The median time was roughly 39 days (Levenson, 2011). Thus, the chosen one-month window nicely reflects this empirical finding, the timeframes utilized in previous work, and the timing of the mood assessments in the preventative phase of the trial.

To maximize the number of windows that are close to the one-month interval, mood assessments that were between 21-35 days apart were searched. This allows for the fact that patients may not have been able to make it into the clinic exactly every 28 days. If mood assessments occurred less than 3 weeks or greater than 5 weeks apart, the window was excluded. Each window was coded to indicate whether at least one SRD event occurred and whether at least one non-SRD event occurred.

2.7.2 Preliminary Analyses

All preliminary analyses were conducted with PASW Statistics version 18.0 for Mac. Chi-square tests and Mann-Whitney U tests examined differences in demographic and clinical variables among patients who received LEDS interviews and those who did not, among those

patients who entered the preventative phase and those who did not, and among patients who had at least one pair of mood assessments that were one month apart and those who did not.

2.7.3 Hypothesis Testing Analyses

Hypothesis-testing analyses were conducted in MPLUS version 6 for Windows. We planned to test each of these hypotheses using intercept-only growth curve models, with the mood change scores included as repeated measures. Since it was not expected that the mood change score would increase or decrease over time, it was decided to model the overall level of mood change within a one-month window over time using the intercept-only growth model, rather than linear growth curve model. In this modeling approach, the average of the overall mood change across all included time points and the individual differences in the overall mood change were to be estimated by the mean and the variance of the intercept factor, respectively. In addition, we planned to include the life event types or severity of SRD during each time window as time varying covariates affecting the level of mood change at each time window. This analytic method allows for testing the effects of the SRD events on the mood change, utilizing the multiple life events and mood scores captured during the preventative phase. Incomplete data were assumed to be missing at random. Under this assumption, mixed effects models for longitudinal data using maximum likelihood estimation still provide valid statistical tests in the presence of incomplete data.

2.7.4 Hypothesis 1a: There will be a significant relationship between the presence of an SRD event and the degree of mood worsening, above and beyond the presence of at least one threat event.

To test this hypothesis, the dependent variable was originally conceptualized as the change in continuous measure of depression and/or mania from the start to the end point of the

one-month time window. Analyses testing this hypothesis planned to examine how the presence of at least one SRD event predicted changes in mood symptoms, controlling for the presence of at least one threat event. Using the intercept-only growth curve model, every time window was rated as 0 or 1 for the absence/presence of an SRD event and 0 or 1 for the absence/presence of a threat event. We planed to enter these indicators into the model predicting change in mood, allowing us to examine the effect of each event type simultaneously. We intended to conduct the analyses separately for depression (HRSD-25) and mania (BRMS), and together using a dichotomized HRSD-25-BRMS score.

In addition, we intended to conduct these analyses after taking into consideration the effect of events that are or are not considered to be independent of the current mood state, and those that are not thought to be the result of prodromal symptoms.

2.7.5 Hypothesis 1b: There will be a significant relationship between the degree of SRD event(s) severity and the degree of mood worsening observed, above and beyond the effect of threat event severity.

The analytic plan included intercept-only growth curve modeling to test whether the total level of social rhythm disruption (conceptualized as a continuous variable with a value between 1 and 3) or the severity of SRD difficulty change predicted worsening in mood score from one mood assessment time point to the next. The total level of threat event severity was to be included in this model prior to entering SRD severity. As above, we intended to conduct these analyses separately for depression (HRSD-25) and mania (BRMS) scores, as well as together using a combined dichotomous score.

In addition, we planned to conduct these analyses after considering events that are or are not considered to be independent of the current mood state, and those that are not thought to be the result of prodromal symptoms.

2.7.6 Hypothesis 2: Treatment assignment during the acute and preventative phases will moderate the effect of SRD events on mood worsening during the preventative phase of treatment.

To test this moderation hypothesis, we planned to repeat the latent intercept-only growth curve analyses outlined in hypotheses 1a & 1b, adding acute and preventative treatment assignments in a second step with the life event variable. The third step included the interaction of the life event and treatment assignment to determine if the effect of the SRD events varied by the treatment received. Again, this was to be done separately for depression (HRSD-25) and mania (BRMS) scores and together using a combined dichotomous score.

2.7.7 Exploratory Analyses

As will be described in greater detail below, the proposed analytic models did not converge using structural equation modeling, limiting our ability to evaluate the hypotheses as originally planned. Thus, alternate methods were used to evaluate whether individuals who experienced a recurrence were more likely to have an event prior to recurrence than a non-recurrence control group. Similar to analyses utilized in previous studies examining the association of life events and mood episode (Frank, Anderson, Reynolds 3rd, Ritenour, & Kupfer, 1994), we used a backward survival analysis technique in which the onset of mood recurrence was set as time zero and we searched backward in time for the closest life event. We expected the recurrence group would be more likely to have an event prior to recurrence than the

control group, and that this event would occur closer in time to the recurrence than to a corresponding non-recurrence point in the control group.

3.0 RESULTS

3.1 PRELIMINARY ANALYSES

Of the 175 participants who originally entered the acute phase of the study, 125 completed acute and entered the preventative phase, also called the maintenance phase. Table 1 shows the demographic and clinical characteristics of the 125 who entered preventative, and the 50 who did not. Those who entered the preventative phase were more likely to be Caucasian than those who completed acute only (X^2=5.48, p=0.02), and there was a trend (X^2=3.33, p=0.07) for individuals who entered the preventative phase to be more likely working (part-time or full-time) or attending school, while those who completed acute only were more likely to be homemakers, not working, or retired. When individuals entered the acute phase of treatment their mood episode was ultimately classified as depressed, manic, or mixed/cycling. Individuals who entered the preventative phase were less likely to have a mixed or cycling episode upon entering the acute treatment phase than individuals who participated in acute only (X^2=14.39, p=0.001). Individuals who entered the preventative phase had significantly lower mean depression scores at entry on the 25-item HRSD (Mann-Whitney U p<0.0001), significantly higher scores at entry on the BRMS (Mann-Whitney U p=0.001), and fewer previous depressive episodes (Mann-Whitney U p=0.02). However, individuals in the preventative group only had one fewer depressive

episode than those in the acute only group, calling into question the clinical significance of this difference.

Table 1

Demographics and Clinical Characteristics of Participants in the Acute Phase Only and Those in the Acute and Preventative Phases

	Preventative Phase (n=125)	**Acute Phase Only (n=50)**	**X^2 or Mann-Whitney U**
Mean (S.D.) Age	35.42 (10.48)	34.56 (10.78)	U p=0.56
Gender (% Female)	59.20%	50.0%	1.23
Marital Status			3.04
Single	46.40%	32.0%	
Divorced/Separated	20.0%	26.0%	
Married/Living as Married	33.6%	42.0%	
Working Full-Time, Part-Time, or Student	59.2%	44.0%	3.33*
Caucasian	93.6%	82.0%	5.48**
Mean (S.D.) Baseline 25-item Depression Score	17.40 (9.44)	25.32 (8.53)	U p<0.0001
Mean (S.D.) Baseline Mania Score	12.81 (13.24)	5.44 (8.06)	U p=0.001
Mean (S.D.) Baseline Global Assessment of Function	48.15 (9.07)	48.36 (8.65)	U p=0.87
Mean (S.D.) Years of Education	14.71 (1.95)	15.06 (1.87)	U p=0.34
Mean (S.D.) Age of Manic Episode Onset	26.54 (9.20)	24.45 (8.77)	U p=0.09

Table 1 (continued)

Mean (S.D.) Age of Depressive Episode Onset	22.75 (8.20)	20.90 (6.63)	U p=0.30
Number of Previous Manic Episodes			U p=0.19
Mean (S.D.)	3.56 (3.68)	4.5 (6.41)	
Median	2.00	3.00	
Number of Previous Depressive Episodes			U p=0.02
Mean (S.D.)	5.09 (6.83)	6.03 (5.74)	
Median	3.00	5.00	
Mean (S.D.) Weeks in Acute Treatment	35.38 (21.16)	28.26 (20.75)	U p=0.02
Acute Treatment (% IPSRT)	48.8%	52.0%	0.15
Preventative Treatment (% IPSRT)	47.2%	N/A	N/A
Acute Phase Treatment Group			14.39**
Depressed	46.4%	68.0%	
Manic	30.4%	4.0%	
Mixed/Cycling	23.2%	28.0%	

*p<0.10, **p<0.05

With regard to life events, 114 of the 125 participants had life events data available. We compared individuals who completed the LEDS and those who did not, finding only one notable difference. There was a trend for individuals with LEDS data to have significantly lower Global Assessment Scale (Endicott, Spitzer, Fleiss, & Cohen, 1976) scores (Mann-Whitney U p=0.07) than those without LEDS data. We excluded events in which the SRD rating was missing (n=9 out of n=3406 total events reported by study participants). Since this was our main variable of interest, events without an SRD rating seemed non-informative to the current research questions. As there were only eight improvements and three exacerbations to the SRD rating of difficulties (of 267 possible ratings during the preventative phase), we decided to forego these analyses due to limited variability of the data.

Of the 125 participants in the preventative phase, 119 had at least one pair of mood assessments that were roughly one month apart to be used in the hypothesis-testing analyses. We compared individuals with at least one pair of mood scores to those without a pair of mood scores to examine differences between the groups. Individuals with at least one pair of mood scores were significantly older at the time of their first manic episode than those without a pair of mood scores (Mann-Whitney U p=0.02). The 114 participants with LEDS and mood assessments had an average of 9.80 (S.D. = 5.51) mood windows with which to measure the effect of life events on mood (range = 0-23).

At very few of these time points, only the HRSD (n=12) or BRMS (n=4) was reported. In these cases, we maintained the assessment time point for the analyses in which we planned to examine depressive and manic mood separately, though we intended only to include time points where both the HRSD and BRMS were present for the dichotomous mood measure. Still, only 28 participants of the 119 with at least one pair of mood assessments actually met criteria for a

combination mood change at one or more time points. Given that HRSD and BRMS scores were missing at relatively few time points, it is unlikely that the limited variability of the combination mood change data was related to these missing observations.

3.2 ORIGINAL HYPOTHESIS TESTING ANALYSES

We began the hypothesis testing analyses by running a confirmatory factor analysis (CFA) to determine how the observed HRSD-25 change scores fit a latent factor. We began with the change in depression score variable because it was vital to the outcome of nearly all of the analyses. Because we were interested in only the mood change scores that occurred during the preventative phase, Visit 2 change score was the first data point that we included, which examined mood change from Visit 2 as compared to Visit 1. The CFA model did not converge using all time points, which may have been because of missing data at later time points, perhaps due to participants dropping out. Figure 2 shows the frequencies of HRSD-25 observations at each computer-generated time point (the number of HRSD-25 observations over the preventative phase for each participant is shown in Figure 3). As described above, to maximize the number of windows that were close to the one-month interval, mood assessments that were between 21-35 days apart were searched, and mood assessments that occurred less than 3 weeks or greater than 5 weeks apart were excluded. Because of the spacing of assessments, and the use of an analytic code that searched for mood assessments that were 28 days (+/- 7 days) from the most recent mood assessment point, participants may have had mood scores that fit into any one of 28 “time points.” This does not indicate that participants had up to 28 mood assessments, rather that the computer program used these 28 time points as place holders based on the dates and spacing of assessments. At time point 16, 50% of participants had mood scores available based on the monthly pairing of mood assessments that we generated. As such, we chose this time point as the

place to truncate the data, in order to determine if a CFA with better fit would emerge. The model did not converge when we used Visits 2-16, so we re-ran the model dropping Visits 16, and then Visits 15. When we used only Visits 2-14 the model still did not converge. At this point, we chose to forego the CFA to fit the observed measures to the latent factor because of the lack of model convergence and the fact that we are only examining an intercept-only model, not a growth curve model, which assumes constant variance of the factors (Curran, Obeidat, & Losardo, 2010). Thus, the lack of CFA model convergence indicates that the observed HRSD-25 change scores fit poorly to a latent factor.

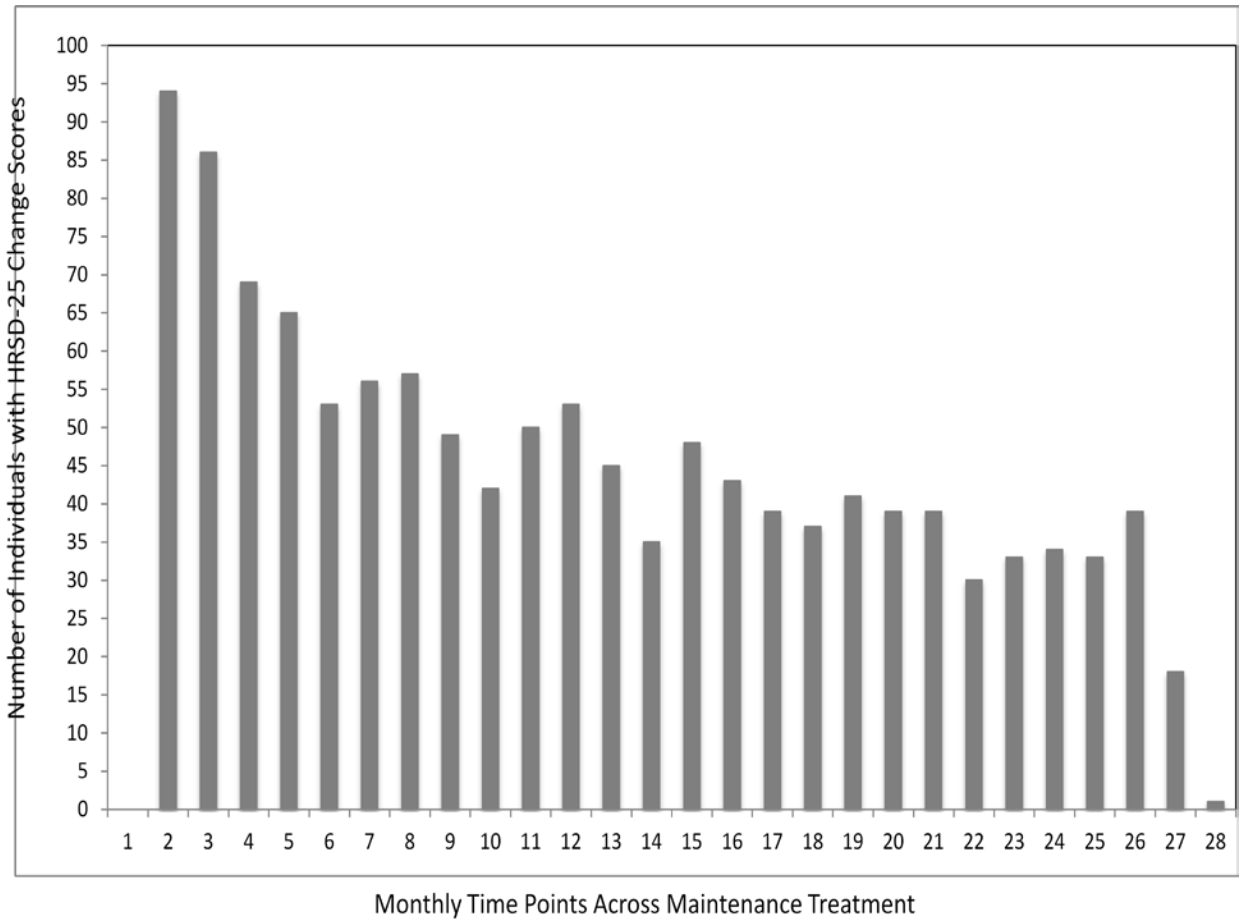

Figure 2. HRSD-25 change scores available at each time point.

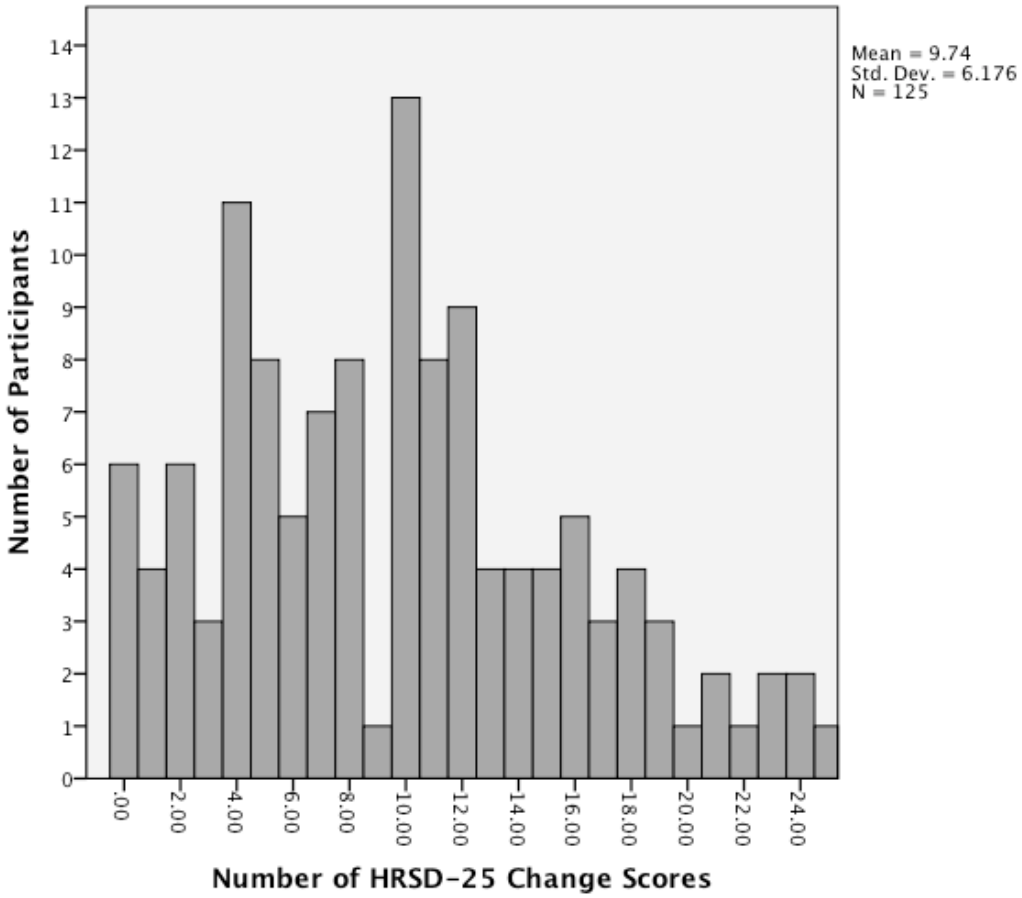

Figure 3. Number of total HRSD-25 change scores per participant

Next we evaluated the intercept-only structural equation model by first setting the factor loadings of each of the indicators to one. Though the model converged, the fit was quite poor ($X^2(89)=381.21$ $p<0.0001$; RMSEA=0.15, $p<0.0001$). In an attempt to improve model fit, the adjacent residual variances were correlated, but the model fit did not improve meaningfully ($X^2(77)=191.43$, $p<0.0001$; RMSEA=0.11, $p<0.0001$). Moreover, the variance of the latent factor was negative, indicating a flaw in the model.

Identical analyses were conducted using BRMS change scores and combination mood change scores. Similar results were found when examining BRMS change scores, with very poor

CFA model convergence when using time points 2-12 ($X^2(44)=176.32$ $p<0.0001$; RMSEA=0.16, $p<0.0001$), and again with negative latent factor variance, and poor model fit when examining the BRMS intercept-only model, even when adjacent residual variances were correlated ($X^2(77)=458.68$ $p<0.0001$; RMSEA=0.20, $p<0.0001$). Because so few individuals met the criteria for combination mood change (n=28 HRSD-25 and BRMS), only time points 2-7 were able to be used in the combination mood change CFA. This is because the remainder of the time points had too little variance. The CFA model did not converge, and the intercept-only model using these combination mood change scores had very poor fit ($X^2(13)=165.09$ $p<0.0001$; RMSEA=0.31, $p<0.0001$). The poor fit of each of these three models (HRSD, BRMS, and combination) is problematic because even if we found significant results when testing our hypotheses, we would not be confident in the findings because model fit was so poor. Given that the mood change scores were so vital to nearly all of the hypotheses, it became necessary to forgo the remainder of the original hypothesis testing analyses.

3.3 EXPLORATORY ANALYSES

3.3.1 Statistical Methods

Though it was not possible to proceed with the planned analyses, the effect of life events on mood in this population was still of great interest. In order to examine the effect using a method that would make use of the data successfully we inquired about the presence and temporal association of a life event preceding a recurrence. Again, recurrence was determined by blinded senior psychiatrists who were not otherwise involved in the conduct of the study and who were asked to determine whether the participant met Research Diagnostic Criteria for a new affective episode. This process was bypassed when the participant required immediate hospitalization.

To address the original question, “does a social rhythm disrupting (SRD) event, predict a worsening in mood symptoms during preventative treatment?” we instead asked, “are individuals who experienced a recurrence during the preventative phase more likely to have had an event prior to the recurrence than those who survived two years in the preventative phase?” and “is the time from life event to recurrence (among those who had a recurrence) shorter than the time from life event to an analogous time point (among those who did not have a recurrence)?” A modified statistical plan was generated that included chi-square tests, and survival analyses utilizing Kaplan-Meier and Cox proportional hazard models. In each test, the probability of having an event (or the time to an event) was considered the outcome variable, based on whether or not the participant had a recurrence in the preventative phase. In addition, we originally hypothesized that the presence and event severity of an SRD event would be associated with mood worsening, above and beyond threat events. The specific method used to test a similar hypothesis utilizing new methodology is described below, in the section “The Effect of SRD Above Threat.”

To address the second original question, “does treatment assignment moderate the effect of SRD events on mood?” we instead asked, “among those experiencing an SRD event, is the likelihood of having a recurrence dependent on acute and/or preventative treatment?” We originally hoped to use treatment randomization in both phases as moderators, but preventative treatment randomization cannot be considered a moderator because, by definition, moderators must be “baseline or prerandomization characteristic[s]” (Kraemer, Wilson, Fairburn, & Agras, 2002, p. 879). Instead, using chi-square tests we examined the likelihood of having a recurrence based on treatment assignment over acute and preventative phases among those who experienced an SRD event.

Since those participants who did not experience a recurrence, by definition, spent more time in the preventative phase and, thus, had a longer opportunity to experience events, to conduct these analyses a set of matched pairs was created in order to equate the amount of time that participants could potentially experience events. One member of the pair experienced a recurrence, while the other did not. The members were matched on sex and age (within 2 years). Of the 114 individuals with LEDS data, we were able to create 41 pairs (n=82). Figure 4 displays the process of determining the time points in which to search for an event. To do so, we first identified the length of time (in days) between entry into the preventative phase and the date of recurrence among each of the individuals in the 41 pairs who experienced a recurrence (recurrence group). We used this time span to determine the corresponding interval for each individual in the matched pairs who did not experience a recurrence (control group) by projecting forward from the date of entry into the preventative phase the same number of days as the control individual's matched pair. In this way, we were able to identify identical time intervals for each matched pair within which to search for a life event.

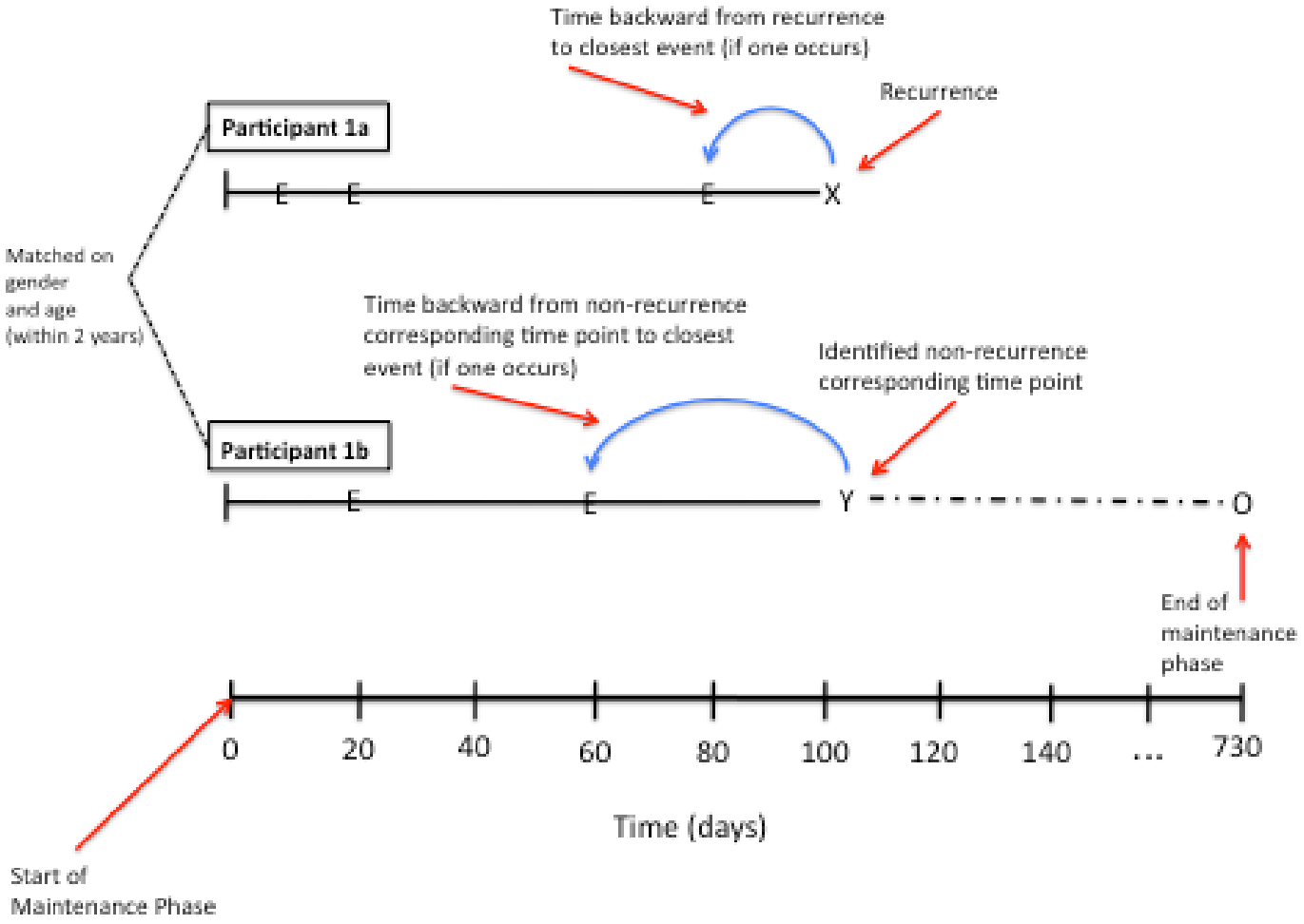

Figure 4. Method used to identify events among matched pairs of participants

Then, starting at the recurrence time point (or corresponding non-recurrence time point for the control group), we searched *backward* in time for a life event that occurred closest to this date, recording whether any event occurred during this time, and the length of time in days between the life event (if one occurred) and the identified recurrence/non-recurrence time point. The three event types of interest are SRD events (events rated 1-3 but not 4 on the SRD scale), events rated as having short-term contextual threat (STC events; events rated 1-3 but not 4 on the STC scale), and events rated as having long-term contextual threat (LTC events; events rated 1-3 but not 4 on the LTC scale). Short-term threat is thought to have reached its peak threat or unpleasantness within the first day after that event, while long-term threat is rated at one-to-two weeks after the event occurs (Anderson, et al., 1995; Brown & Harris, 1978). The presence, rating, and date of SRD events were recorded, as were the ratings for independence and dependent-variable related-status (DVR) of this event. The same procedure was completed for STC and LTC events. Sometimes these ratings pertained to the same event (for example, if an event was thought to carry a social rhythm disrupting effect, as well as short- and long-term threat), although at other times only one category was rated (if an event was only thought to carry short-term threat, but not long-term threat or a social rhythm disrupting effect). Overall, each event was rated on several different scales depending on the nature of the event.

3.3.2 Differences between Included and Excluded Samples

We compared the matched individuals who were included in the exploratory analyses with those who were not able to be matched (and therefore were excluded from these analyses) on demographic and clinical variables. Individuals excluded from these analyses were significantly older (t=2.85, p=0.01), there was a trend for them to be younger when they had their first depressive episode (Mann-Whitney U p=0.06), and there was a trend for more females

to be matched in the exploratory dataset than males (X^2=2.742, p=0.10). However, this gender difference reflects the higher proportion of females in the preventative portion of the study overall (female n=74, male n=51). Moreover, individuals who had a recurrence were purposely over-selected for our exploratory analyses, contributing to the trend-level chi-square statistic that tested for differences in preventative phase outcome (completer vs. dropout vs. recurrence) between the groups (X^2=5.45, p=0.07). This was done to create a set of individuals with and without a recurrence who were matched on age and sex. Table 2 shows the demographic and clinical characteristics of the 82 participants ultimately included in the exploratory analyses, by recurrence group status. Participants in these groups differed only on the proportion of individuals receiving IPSRT in the preventative phase, with more individuals receiving IPSRT in the recurrence group than the control group (X^2=3.12, p=0.07). However, this finding did not reach conventional levels of statistical significance. Last, of the 11 individuals diagnosed with schizoaffective disorder (manic type) in the study, 6 of them were included in the matched sample. We did not detect significant differences between the two diagnostic groups on demographic or clinical variables using chi-square analyses and Mann-Whitney U tests, though power to detect such an effect is likely to have been quite small. Still, an examination of these characteristics by group suggested that, in terms of clinical significance, the group diagnosed with schizoaffective disorder scored an average of nine points lower on the HRSD-25, five points higher on the BRMS, and suffered from the illness an average of five years fewer than those with bipolar disorder. However, the differences in entry mood scores are likely due to the fact that participants with schizoaffective disorder were required to be in a manic episode upon entry into the study, whereas participants with bipolar disorder could be in a manic or depressive episode.

Table 2

Demographics and Clinical Characteristics of Matched Groups

	Recurrence Group (n=41)	**Non-Recurrence Group (n=41)**	**X^2 or Mann-Whitney U**
Mean (S.D.) Age	33.27 (9.52)	33.73 (9.69)	U *p*=0.84
Gender (% Female)	63.4%	63.4%	0.00
Marital Status			0.44
Single	56.1%	48.8%	
Divorced/Separated	17.1%	19.5%	
Married/Living as Married	45.8%	31.7%	
Working Full-Time, Part-Time, or Student	63.4%	70.7%	0.50
Caucasian	87.8%	95.1%	1.41
Mean (S.D.) Baseline 25-item Depression Score	19.20 (10.26)	16.34 (9.34)	U *p*=0.11
Mean (S.D.) Baseline Mania Score	12.27 (13.02)	13.71 (14.16)	U *p*=0.88
Mean (S.D.) Baseline Global Assessment of Function	48.17 (9.31)	48.28 (8.98)	U *p*=0.99
Mean (S.D.) Years of Education	14.80 (1.89)	14.76 (1.89)	U *p*=0.88
Mean (S.D.) Age of Manic Episode Onset	25.76 (8.40)	25.58 (8.67)	U *p*=0.82

Table 2 (continued)

Mean (S.D.) Age of Depressive Episode Onset	21.87 (7.06)	20.54 (5.90)	U p=0.56
Number of Previous Manic Episodes			U p=0.23
Mean (S.D.)	3.21 (2.61)	2.95 (3.33)	
Median (IQR)	2.00 (2)	2.00 (2)	
Number of Previous Depressive Episodes			U p=0.30
Mean (S.D.)	6.27 (9.20)	4.18 (5.25)	
Median	3.00 (4)	2.50 (3)	
Mean (S.D.) Weeks in Acute Treatment	39.31 (23.40)	31.62 (19.25)	U p=0.096
Acute Treatment (% IPSRT)	46.3%	43.9%	0.049
Preventative Treatment (% IPSRT)	58.5%	39.0%	3.34*
Acute Phase Treatment Group			1.31
Depressed	48.8%	51.2%	
Manic	24.4%	31.7%	
Mixed/Cycling	26.8%	17.1%	

*p<0.10

3.3.3. Covariate Identification

Covariates were determined by examining which demographic and clinical variables were related to the presence of an SRD, STC, or LTC event using logistic regression analyses. The results suggested that only age of first manic episode (Exp(ß)=0.93, p=0.02) was significantly associated with the presence of an SRD event. Baseline depression score, as measured by HRSD-25 (Exp(ß)=1.05, p=0.04), as well as age of first depressive episode (Exp(ß)=0.90, p=0.01), were significantly associated with the presence of an STC event. Last, baseline depression score, measured by HRSD-25 (Exp(ß)=1.08, p=0.002), baseline mania score, measured by BRMS (Exp(ß)=0.96, p=0.03), and global assessment scale (Exp(ß)=1.08, p=0.01) were significantly associated with the presence of an LTC event. Because HRSD-25 was highly correlated with GAS (r=0.42, p<0.0001) and BRMS (r=0.77, p<0.0001), only HRSD-25 was included as a covariate in order to avoid multicollinearity.

3. 3.4 Likelihood of Having an Event by Recurrence Group

We began by comparing the recurrence group with the control group on the proportion of each group who experienced an event. Chi-square analyses, as seen in Table 3, showed that when including only those events that were rated as independent of the individual's influence (independent), the recurrence group was significantly more likely to experience SRD (X^2=5.19, p=0.02), STC (X^2=5.92, p=0.02), and LTC (X^2=7.03, p=0.01) events in the period of interest than the control group. Similar results were observed when examining only STC (X^2=3.95, p=0.047) and LTC (X^2=4.90, p=0.03) events that were independent *and* not thought to be caused by the patient or related to his or her psychopathology (non-DVR), though this difference fell to a trend level when examining this type of SRD event (X^2=3.46, p=0.07). Because some events have a relatively immediate effect on mood, we identified the proportion of events per recurrence

group when examining only the one-month and four months prior to recurrence (or the corresponding control time point), with no significant differences between the groups (all $p>0.05$). When all events were considered, the groups did not differ significantly on the proportion of each group who had an SRD ($X^2=0.20$, $p=0.66$), STC ($X^2=0.52$, $p=0.47$), or LTC ($X^2=2.61$, $p=0.11$) event prior to recurrence or the corresponding non-recurrence time point. Thus, the results differed in meaningful ways when considering only independent and non-DVR events as compared to all events.

Table 3

Event Proportions by Recurrence Group

Event Type (Number Included in Analysis)	**Recurrence**	**Non-Recurrence**	**All**	**X^2**
SRD All (n=82)	51.2% (n=11)	46.3% (n=11)	48.8% (n=14)	0.20
STC All (n=82)	73.2% (n=19)	65.9% (n=9)	69.5% (n=28)	0.52
LTC All (n=82)	73.2% (n=20)	56.1% (n=10)	64.6% (n=30)	2.61
SRD Independent Only (n=82)	36.6% (n=15)	14.6% (n=6)	25.6% (n=21)	5.19**
STC Independent Only (n=82)	65.9% (n=27)	39.0% (n=16)	52.4% (n=43)	5.92**
LTC Independent Only (n=82)	63.4% (n=26)	34.1% (n=14)	48.8% (n=40)	7.03**
SRD Independent and Non-DVR Only (n=82)	31.7% (n=13)	14.6% (n=6)	23.2% (n=19)	3.56*
STC Independent and Non-DVR Only (n=82)	61.0% (n=25)	39.0% (n=16)	50.0% (n=41)	3.95**
LTC Independent and Non-DVR Only (n=82)	58.5% (n=24)	34.1% (n=14)	46.3% (n=38)	4.90**

Table 3 (continued)

SRD within one month (n=12)	88.9% (n=8)	66.7% (n=2)	83.3% (n=10)	Fisher's Exact *p*=0.46
SRD within four months (n=47)	57.7% (n=15)	47.6% (n=10)	53.2% (n=25)	0.47
STC within one month (n=28)	100.0% (n=20)	87.5% (n=7)	96.4% (n=27)	Fisher's Exact *p*=0.29
STC within four months (n=56)	77.4% (n=24)	68.0% (n=17)	73.2% (n=41)	0.63
LTC within one month (n=23)	100.0% (n=17)	83.3% (n=5)	95.7% (n=22)	Fisher's Exact *p*=0.26
LTC within four months (n=52)	75.9% (n=22)	60.9% (n=14)	69.2% (n=36)	1.35
SRD, severe events only (n=82)	29.3% (n=12)	31.7% (n=13)	30.5% (n=25	0.06
STC, severe events only (n=82)	63.4% (n=26)	56.1% (n=23)	59.8% (n=49)	0.46
LTC, severe events only (n=82)	51.2% (n=21)	34.1% (n=14)	42.7% (n=35)	2.44

*$p<0.10$, **$p<0.05$

3. 3.5 Survival Analyses Examining Differences Between Groups in Time to Events

To examine the temporal association of events between the two groups, Kaplan-Meier survival analyses and the Cox proportional hazards model were used. This survival method uses a modified version of these analyses, in which the date of recurrence or the comparable time point for the matched individual in the control group is set as time zero, working backward to find the closest SRD, STC, and LTC event for each participant, if one occurred. Survival analyses were first conducted examining only those events that are thought to be independent of the individual's own agency. In this case, the recurrence group experienced an independent SRD event (X^2=6.01, p=0.01), an independent STC event (X^2=14.56, p<0.0001), and an independent LTC event (X^2=10.41, p=0.001) within a significantly shorter time prior to the recurrence date than the control group's analogous end point. Kaplan-Meier survival curves of these three effects are shown in Figures 5, 6, and 7, respectively. The low proportion of subjects in the non-recurrence group experiencing an independent SRD event precluded the calculation of a median time for that group, though median time backward to an event for the recurrence group was 310 days (S.E.=109.51). However, when quartiles were examined, we found that 50% of the subjects in the recurrence group had an independent SRD within 124 days prior to recurrence, while the control group had an independent SRD event within 203 days prior to the corresponding non-recurrence point. Median event times highlight the shorter duration from recurrence or corresponding non-recurrence point backward to an event for STC (control=414 days (S.E.=42.14), recurrence=138 days (S.E.=75.79)) and LTC (control=486 days (S.E.=65.63), recurrence=180 days (S.E.=44.08)).

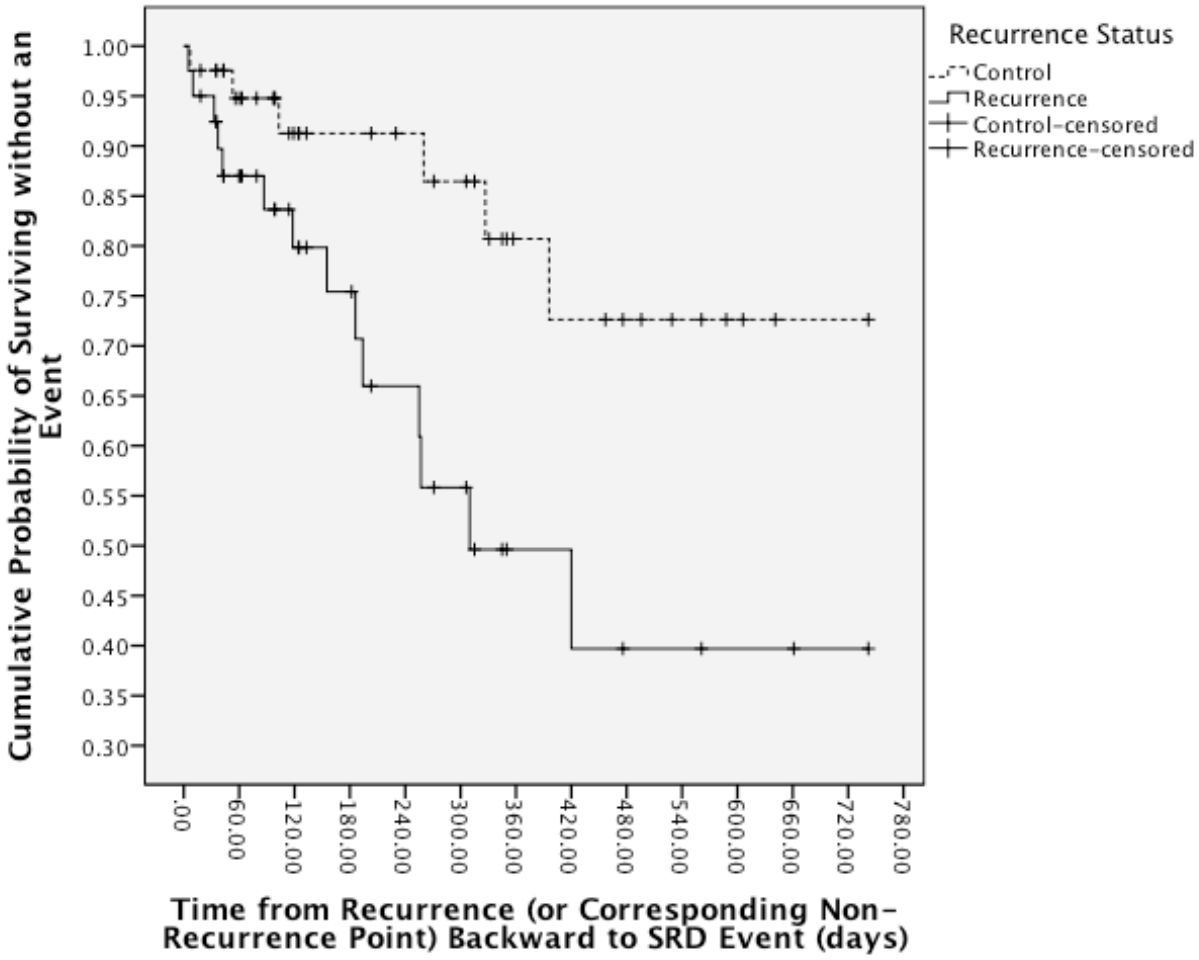

Figure 5. Kaplan-Meier survival analysis depicting time backward to an independent SRD event by recurrence status.

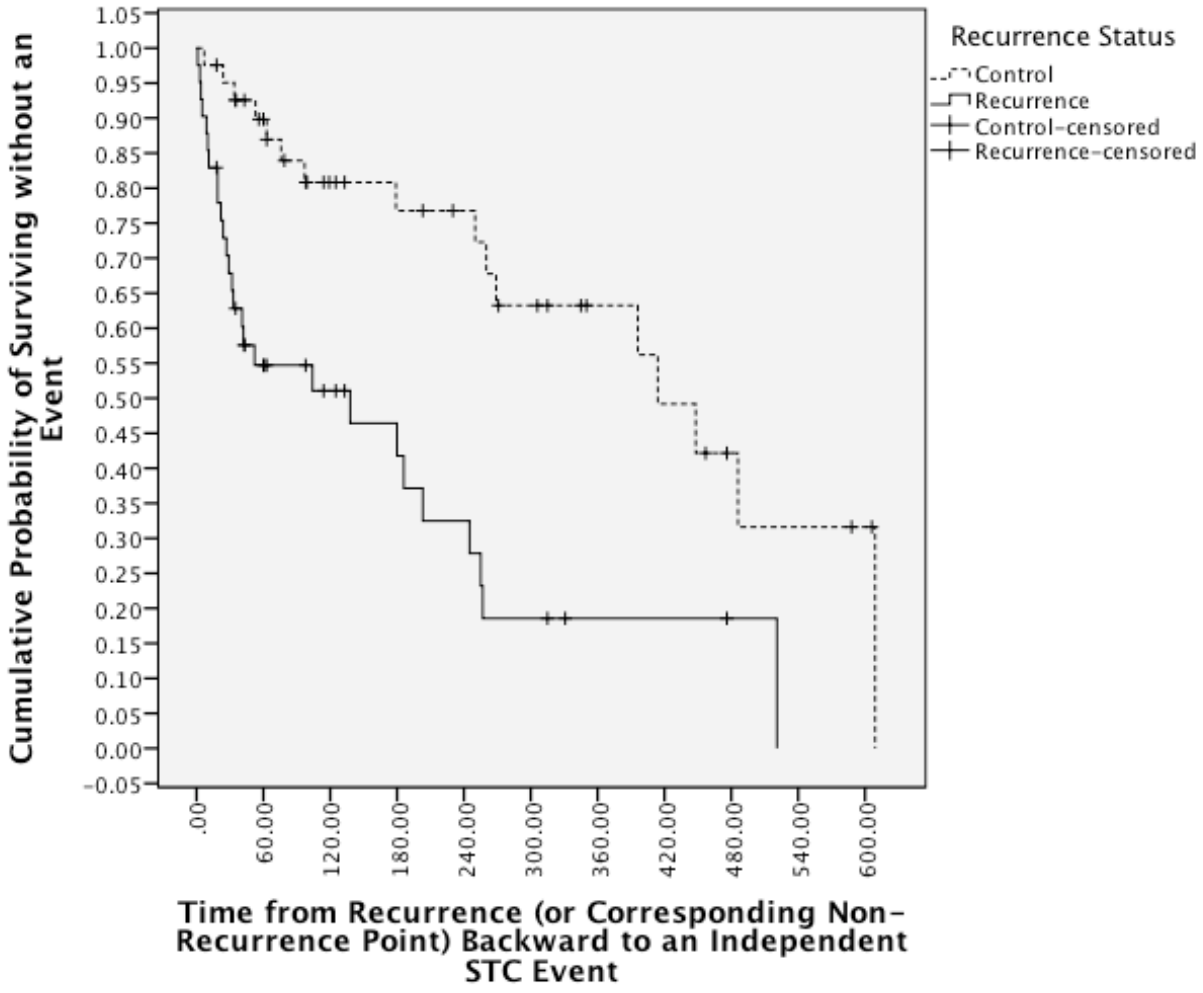

Figure 6. Kaplan-Meier survival analysis depicting time backward to an independent STC event by recurrence status.

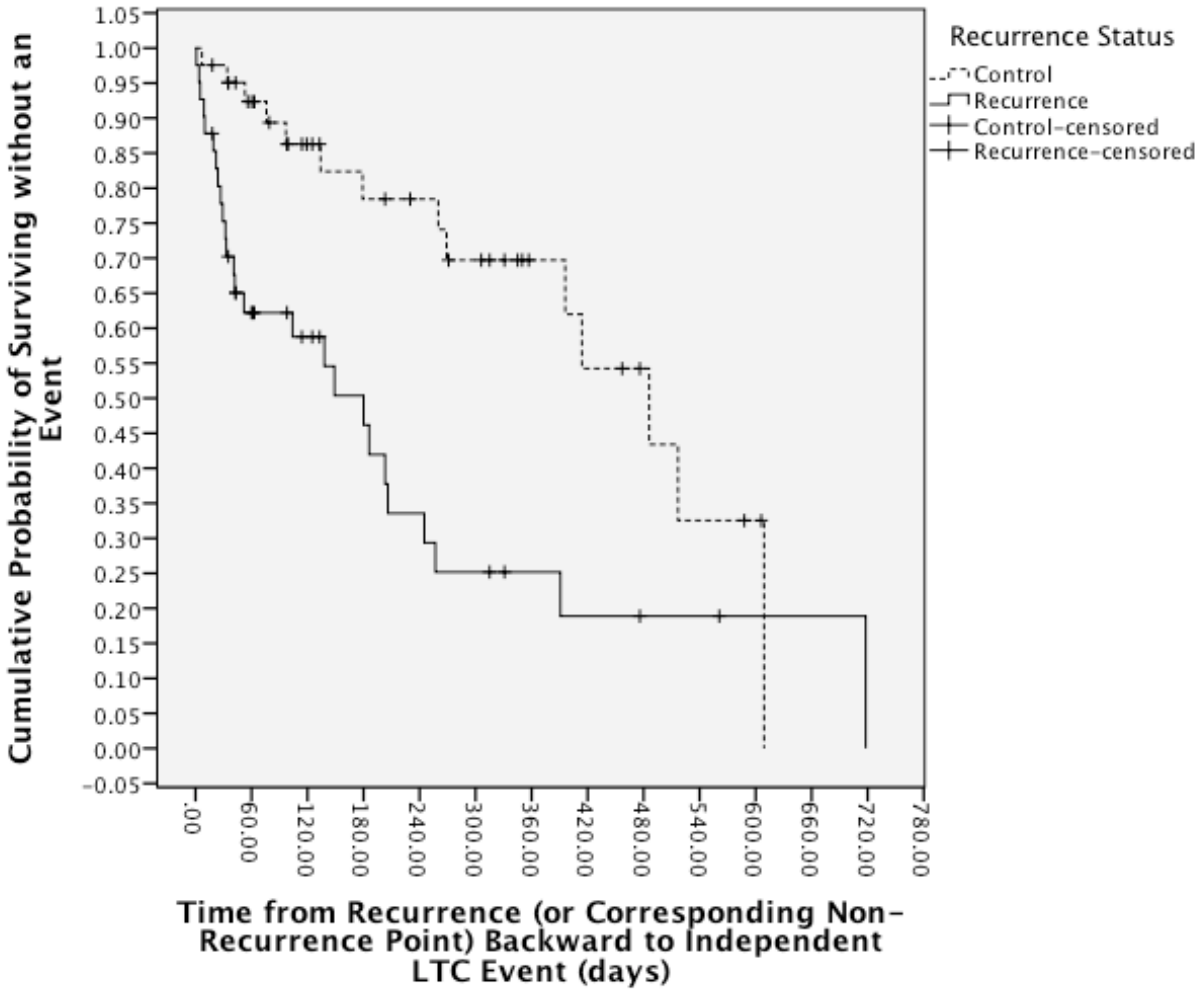

Figure 7. Kaplan-Meier survival analysis depicting time backward to an independent LTC event by recurrence status.

Next, we conducted Kaplan-Meier survival analyses examining only those events that are thought to be independent of the individual's own agency *and* not related to the individual's psychopathology (non-DVR). In this case, the recurrence group experienced an independent/non-DVR SRD event (X^2=4.82, p=0.03), an independent/non-DVR STC event (X^2=9.59, p=0.002), and an independent/non-DVR LTC event (X^2=8.00, p=0.01) within a significantly shorter time prior to the recurrence date than the control group's analogous end point. Kaplan-Meier survival

curves of these three effects are shown in Figures 8, 9, and 10, respectively. The low proportion of subjects in the non-recurrence group experiencing an independent SRD event precluded the calculation of a median time for that group, though median time backward to an event for the recurrence group was 420 days (S.E.=108.78). However, when quartiles were examined, we again found that 50% of the subjects in the recurrence group had an independent SRD within 124 days prior to recurrence, while the control group had an independent SRD event within 203 days prior to the corresponding non-recurrence point. Median event times highlight the shorter duration from recurrence or corresponding non-recurrence point backward to an event for STC (control=414 days (S.E.=30.79), recurrence=180 days (S.E.=52.77)) and LTC (control=486 days (S.E.=55.42), recurrence=180 days (S.E.=33.37)). Thus, when considering only independent events, as well as independent and non-DVR events, those who had a recurrence experienced each type of event sooner prior to the event than those who did not have a recurrence.

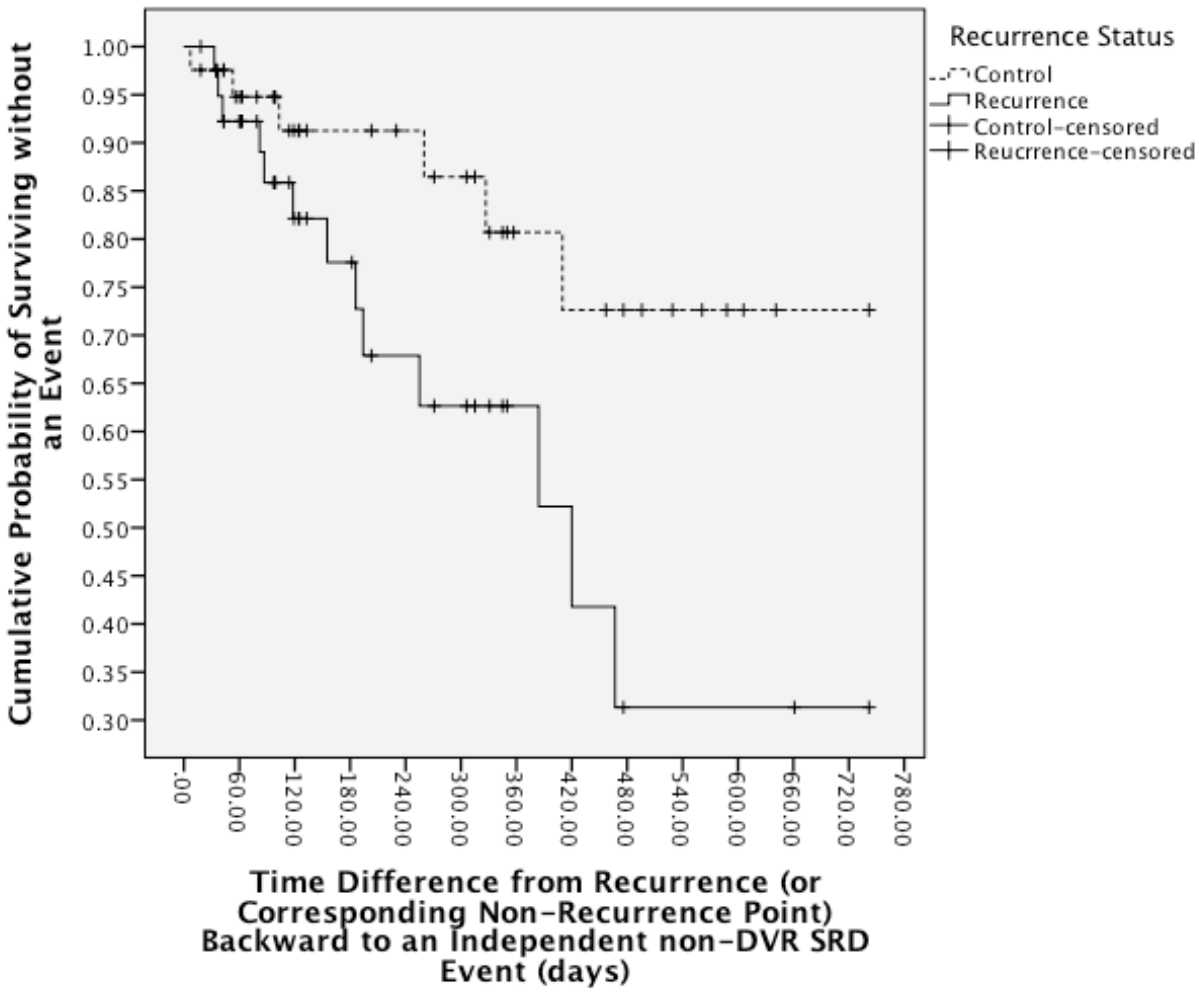

Figure 8. Kaplan-Meier survival analysis depicting time backward to an independent non-DVR SRD event by recurrence status.

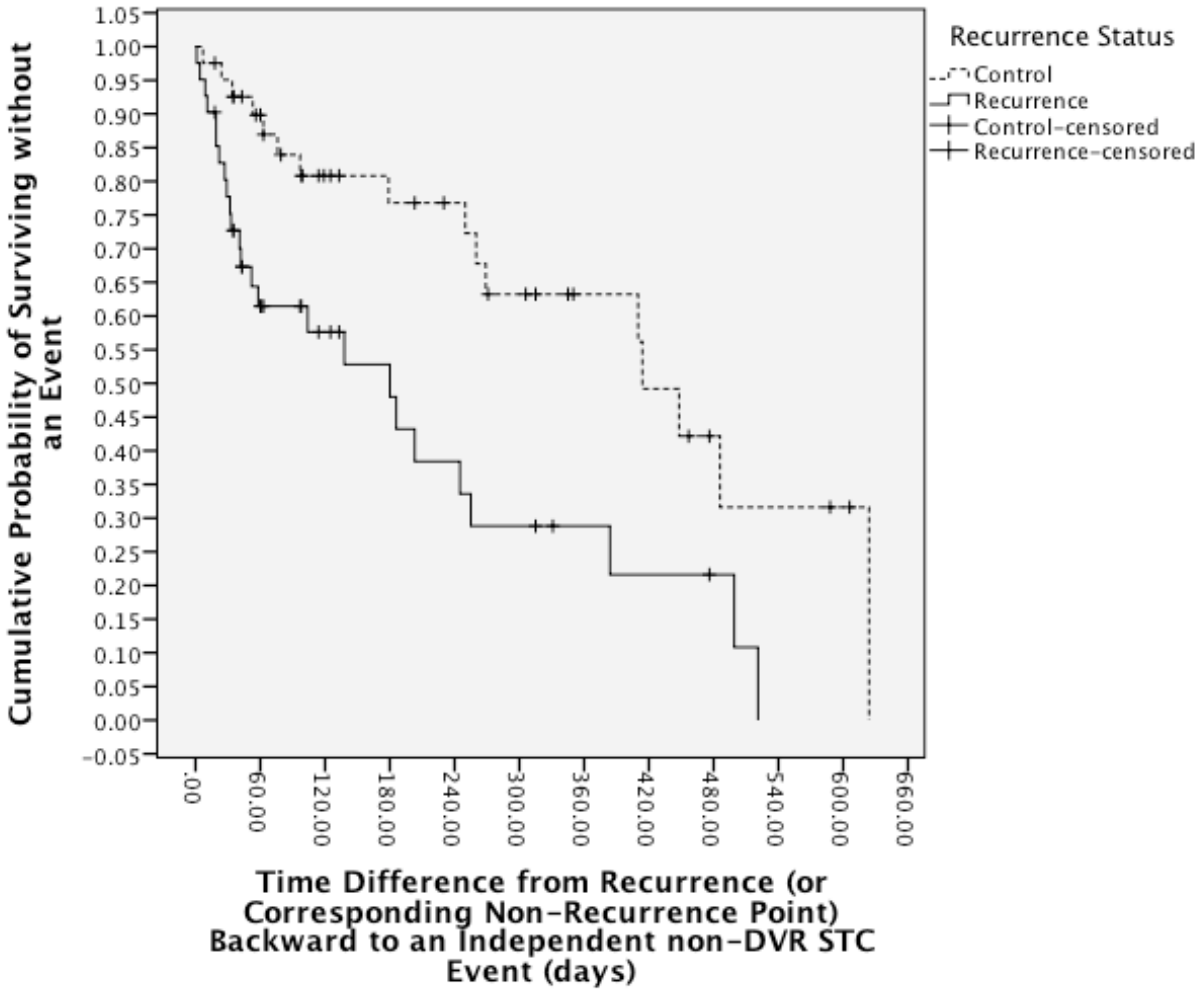

Figure 9. Kaplan-Meier survival analysis depicting time backward to an independent non-DVR STC event by recurrence status.

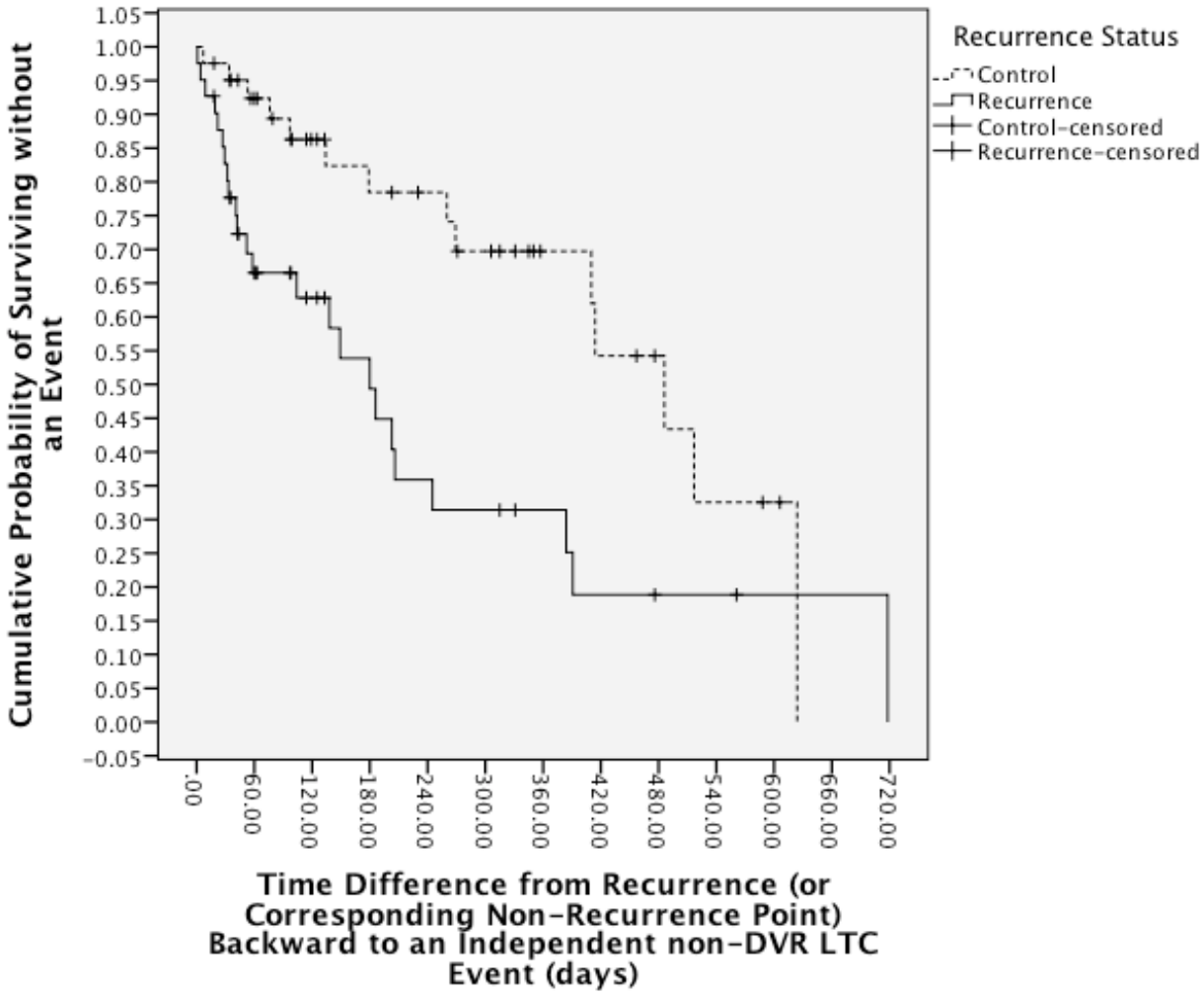

Figure 10. Kaplan-Meier survival analysis depicting time backward to an independent non-DVR LTC event by recurrence status.

Survival analyses were repeated when examining only the one month, and four months prior to recurrence, again considering all events. The difference between groups in time to an SRD (X^2=0.30, p=0.58), STC (X^2=0.02, p=0.88), or LTC (X^2=0.14, p=0.71) event within one month prior to recurrence was not significantly different, nor was it significant for the difference between groups in time to an SRD event within the four months prior to recurrence (X^2=1.85,

p=0.17). However, there was a trend for individuals in the recurrence group to experience an STC event sooner prior to recurrence than the control group, when examining only the four months prior to recurrence (X^2=3.36, *p*=0.07), and the groups differed significantly on time to an LTC event (X^2=5.57, *p*=0.02) during this time period as well (see Figure 11).

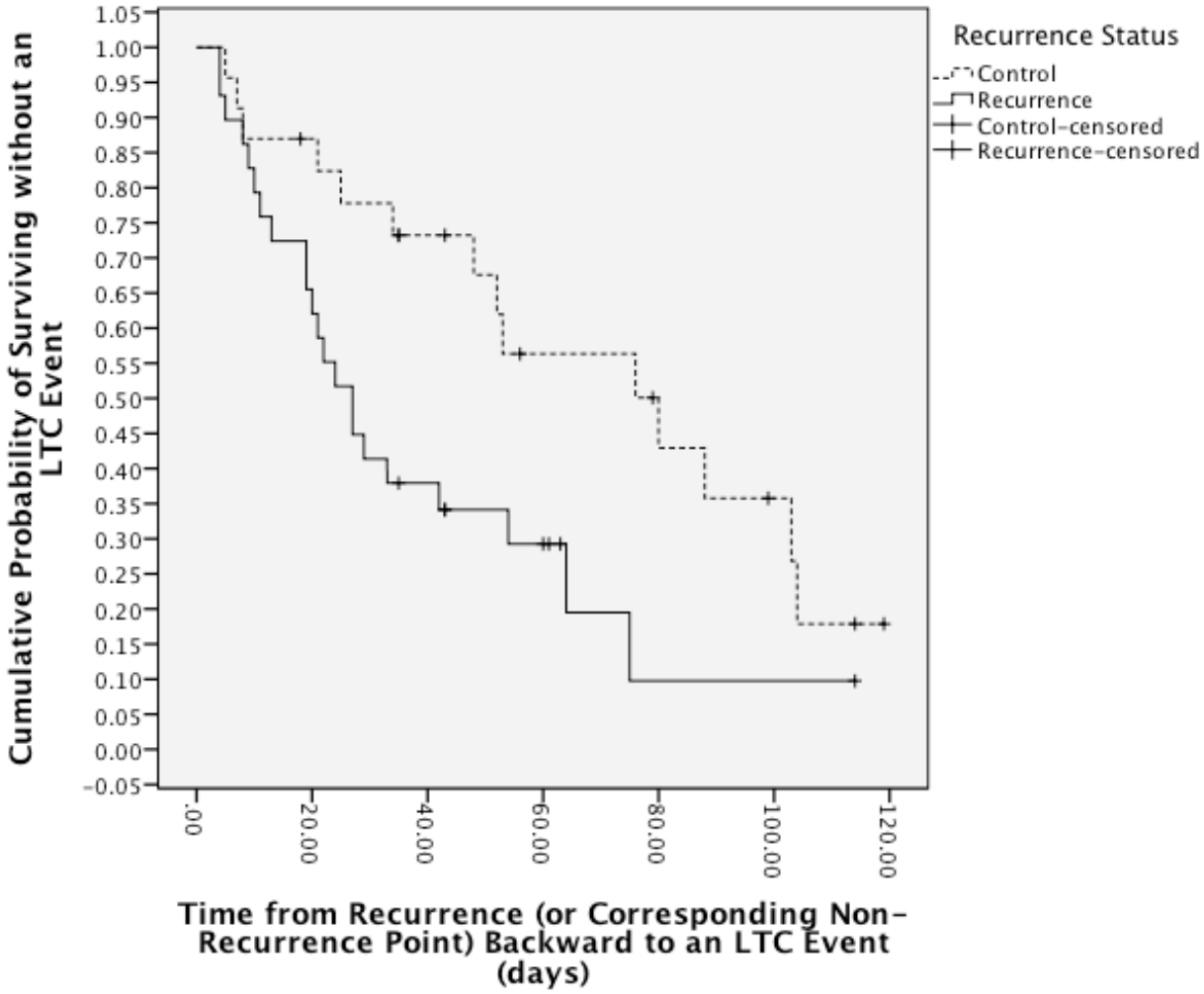

Figure 11. Kaplan-Meier survival analysis depicting time backward to an LTC event within four months of recurrence or corresponding non-recurrence time point by recurrence status.

Last, when all event types were included we found that the recurrence group experienced a shorter time to event for the three event types. The difference between groups was significant

for time to an STC (Log Rank X^2=5.17, p=0.002) and LTC (X^2=8.15, p=0.004) event, but not for an SRD (X^2=1.66, p=0.20) event. Kaplan-Meier survival curves of these three effects are shown in Figures 12, 13 and 14, respectively. Median event times highlight the shorter duration from recurrence or corresponding non-recurrence point backward to an event for SRD (control=289 days (S.E.=64.26), recurrence=186 days (S.E.=60.71)), STC (control=134 days (S.E.=21.72), recurrence=29 days (S.E.=11.26)), and LTC (control=242 days (S.E.=80.08), recurrence=54 days (S.E.=23.78)). Table 4 shows the effect sizes (in terms of absolute risk reduction (ARR) and number needed to treat (NNT)) for survival analyses reaching statistical significance. ARR presents the difference in estimated survival probabilities of having an event between the two groups at a specified time point, while NNT describes the number of patients who would need to be in the non-recurrence group in order to avoid having an event at a specified time point (Altman & Andersen, 1999). The top half of the table shows the effect sizes of the survival probability of having an event based on results from the Kaplan-Meier analyses, which do not include covariates. The effect sizes are shown for multiple time points per test, with most effect sizes in the small to medium range.

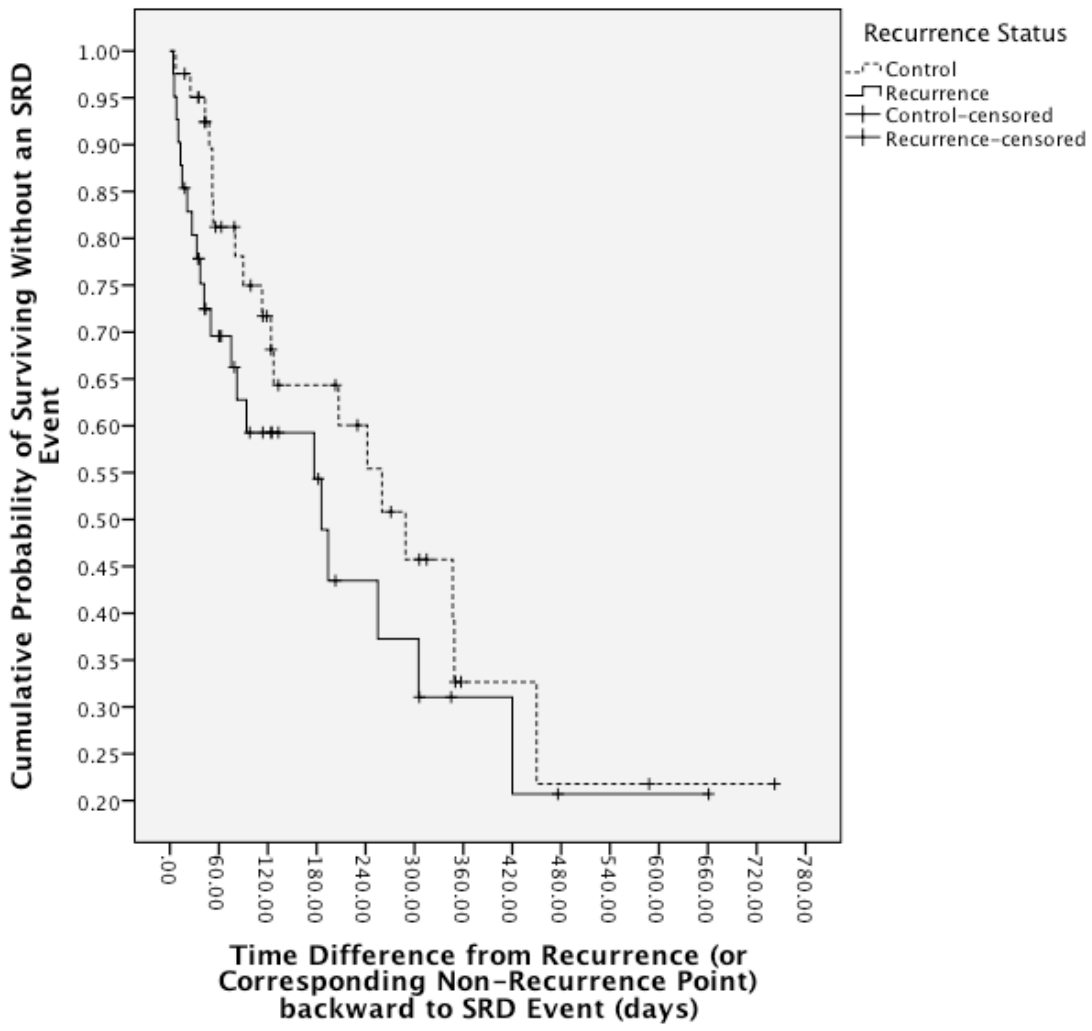

Figure 12. Kaplan-Meier survival analysis depicting time backward to an SRD event by recurrence status.

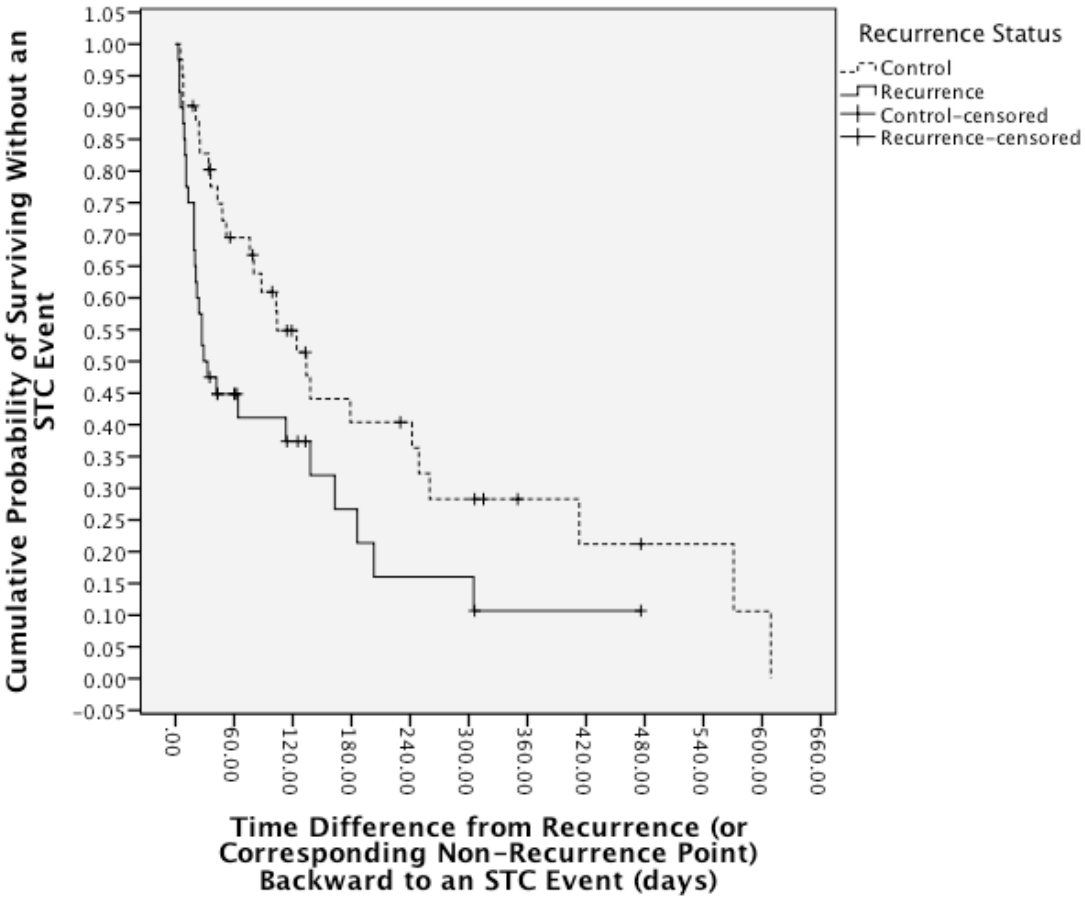

Figure 13. Kaplan-Meier survival analysis depicting time backward to an STC event by recurrence status.

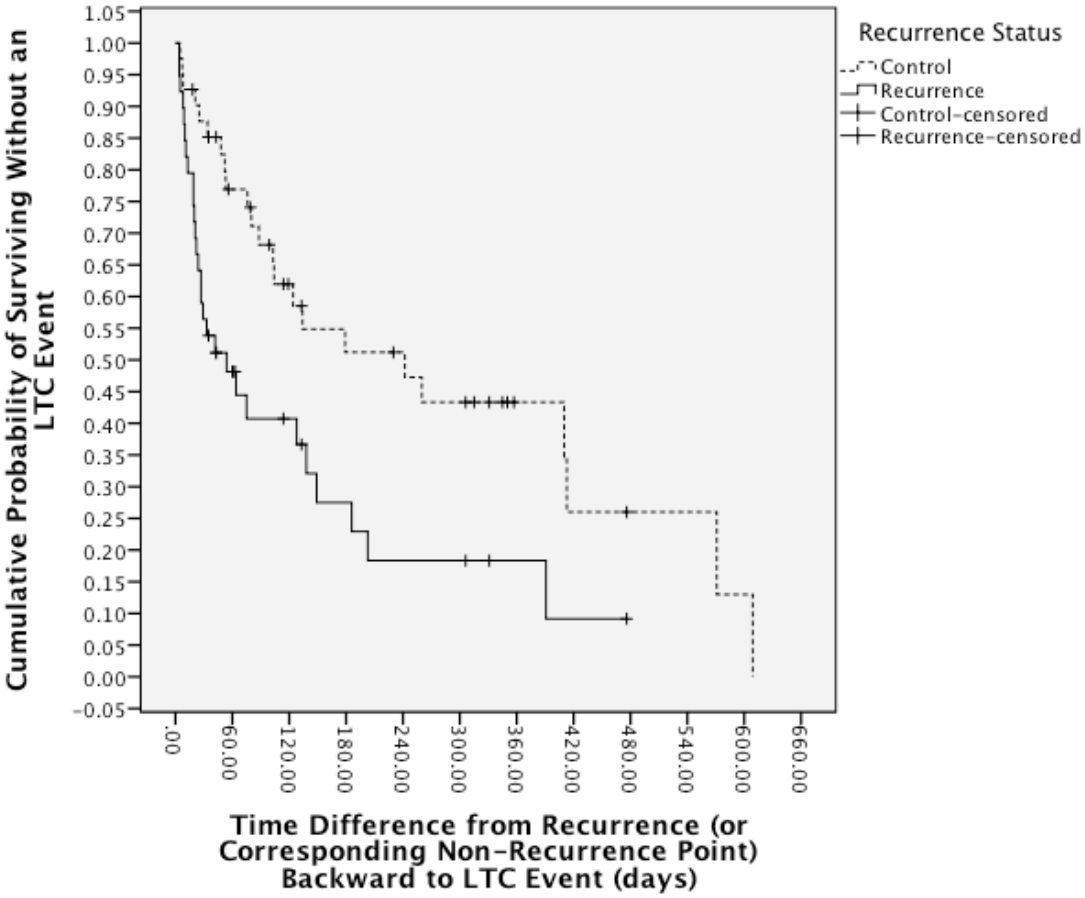

Figure 14. Kaplan-Meier survival analysis depicting time backward to an LTC event by recurrence status

Table 4

Number Needed to Treat and Absolute Risk Reduction at Various Times Prior to Recurrence for Patients With and Without Each Event Type

Survival Analysis	**Event Type**	**Time Prior to Recurrence (days)**	**Number Needed to Treat (NNT)**	**Absolute Risk Reduction (ARR)***	**95% CI**
Kaplan-Meier	STC, all events, without covariates	60	4.15	0.24	0.03-0.45
		120	5.75	0.17	-0.05-0.40
		240	4.90	0.20	-0.03-0.43
	LTC, all events, without covariates	60	3.47	0.29	0.08-0.50
		120	4.69	0.21	-0.02-0.44
		240	3.04	0.33	0.10-0.56
	LTC, events within 4 months, without covariates	60	3.70	0.27	-0.01-0.55
		120	N/A	N/A	N/A
		240	N/A	N/A	N/A

Table 4 (continued)

	SRD, independent events only, without covariates	60	12.82	0.08	-0.05-0.21
		120	8.70	0.12	-0.05-0.28
		240	3.95	0.25	0.05-0.46
	STC, independent events only, without covariates	60	2.85	0.35	0.17-0.54
		120	3.37	0.27	0.09-0.50
		240	2.26	0.44	0.21-0.67
	LTC, independent events only, without covariates	60	3.32	0.30	0.13-0.47
		120	3.64	0.28	0.08-0.47
		240	2.23	0.45	0.22-0.68
	SRD, independent non-DVR events, without covariates	60	38.46	0.02	-0.08-0.14
		120	10.87	0.09	-0.07-0.26
		240	5.38	0.19	-0.04-0.40
	STC, independent non-DVR events, without covariates	60	3.53	0.28	0.10-0.46
		120	4.31	0.23	0.02-0.44
		240	2.60	0.39	0.15-0.62

Table 4 (continued)

	LTC, independent non-DVR events, without covariates	60 120 240	3.88 4.26 2.30	0.26 0.24 0.44	0.09-0.43 0.04-0.43 0.20-0.67
Cox proportional hazards model	SRD, independent events only with covariates	60 120 240	9.90 6.12 4.48	0.10 0.16 0.22	0.03-0.13 0.05-0.21 0.07-0.28
	STC, all events, with covariates	60 120 240	3.94 3.51 3.61	0.25 0.28 0.28	0.08-0.37 0.08-0.44 0.07-0.47
	STC, events within 4 months of recurrence, with covariates	60 120 240	2.87 N/A N/A	0.35 N/A N/A	0.07-0.56 N/A N/A
	STC, independent events only, with covariates	60 120 240	3.66 3.06 2.67	0.27 0.37 0.38	0.15-0.34 0.18-0.42 0.19-0.49

Table 4 (continued)

	LTC, all events, with covariates	60 120 240	4.19 3.48 3.26	0.24 0.29 0.31	0.09-0.34 0.10-0.42 0.10-0.48
	LTC, independent events only, with covariates	60 120 240	4.93 4.45 3.04	0.20 0.23 0.33	0.10-0.26 0.11-0.29 0.14-0.45
	LTC, events within 4 months of recurrence, with covariates	60 120 240	3.68 N/A N/A	0.27 N/A N/A	0.02-0.46 N/A N/A
	SRD, independent non-DVR events, with covariates	60 120 240	14.10 7.54 4.73	0.07 0.13 0.21	0.02-0.09 0.03-0.17 0.05-0.27
	STC, independent non-DVR events, with covariates	60 120 240	5.29 4.32 3.48	0.20 0.23 0.29	0.07-0.26 0.08-0.33 0.09-0.41

Table 4 (continued)

	LTC, independent non-DVR events, with covariates	60	5.93	0.17	0.07-0.23
		120	5.28	0.19	0.07-0.26
		240	3.41	0.29	0.10-0.42

*Cutoffs for effect size estimates: Small=ARR>0.112, Medium=ARR>0.276, Large=ARR>0.428 (Kraemer & Kupfer, 2005)

3.3.6 Survival Analyses Examining Differences Between Groups in Likelihood of Having an Event

The Cox proportional hazard model was conducted in order to determine the likelihood of each group having an event while taking into account the amount of time studied prior to event or censoring. The identified covariates appropriate for each event type (described above) were included in the models, along with recurrence group status in predicting the likelihood of having each type of event. Including covariates, individuals who had a recurrence were more likely to experience an independent SRD event (Exp(ß)=3.78, p=0.01; see Table 5), an independent STC event (Exp(ß)=3.42, p<0.0001; see Table 6), and an independent LTC event (Exp(ß)=2.94, p=0.002; see Table 7). The same was true when only independent *and* non-DVR SRD (Exp(ß)=1.82, p=0.02; see Table 8), STC (Exp(ß)=2.68, p=0.01; see Table 9), and LTC (Exp(ß)=2.15, p=0.01; see Table 10) events were included. When only the four months prior to recurrence or the corresponding non-recurrence point were included, individuals experiencing a recurrence were again more likely to have an STC (Exp(ß)=2.68, p=0.01; see Table 11) or LTC (Exp(ß)=2.15, p=0.04; see Table 12) event, though the groups did not differ on the likelihood of having an SRD event (Exp(ß)=1.63, p=0.24). The differences between groups in likelihood of having an SRD, STC, or LTC event prior to recurrence within one month prior to the endpoint were not statistically significant (all p>0.05). Last, when all events were including there was a trend for individuals who had a recurrence to be more likely to experience an SRD event (Exp(ß)=1.82, p=0.07), though individuals who had a recurrence were significantly more likely to experience an STC event (Exp(ß)=2.25, p=0.01; see Table 13) and an LTC event (Exp(ß)=2.37, p=0.004; see Table 14) than the control group. The bottom half of Table 4 shows the ARR and NNT effect sizes for Cox proportional hazard models reaching conventional levels

of statistical significance. These effect sizes are shown for multiple time points per test when taking into account covariates (Altman & Andersen, 1999), with most effect sizes in the small to medium range. It is important to note, however, that covariates are included in the Cox models, so the effect sizes may vary slightly in subpopulations defined by the covariates (H.C. Kraemer, personal communication, April 20, 2012). Overall, however, the sizes of most effects are modest, despite many statistically significant results.

Table 5

Cox Regression Predicting SRD Independent Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	3.78	1.34-10.64	0.01
Age of Manic Episode Onset	0.97	0.92-1.03	0.34

Table 6

Cox Regression Predicting STC Independent Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	3.42	1.74-6.75	0.0001
Baseline 25-item Depression Score	1.03	0.999-1.07	0.06
Age of Depression Episode Onset	0.96	0.91-1.02	0.18

Table 7

Cox Regression Predicting LTC Independent Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.94	1.51-5.75	0.002
Baseline 25-item Depression Score	1.04	1.01-1.08	0.02

Table 8

Cox Regression Predicting SRD Independent non-DVR Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	1.82	0.95-3.48	0.02
Age of Manic Episode Onset	0.98	0.90-0.99	0.38

Table 9

Cox Regression Predicting STC Independent non-DVR Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.68	1.22-5.90	0.01
Age of Depressive Episode Onset	0.98	0.93-1.04	0.46
Baseline 25-item Depression Score	1.031	0.996-1.07	0.08

Table 10

Cox Regression Predicting LTC Independent non-DVR Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.15	1.05-4.42	0.01
Baseline 25-item Depression Score	1.04	1.01-1.08	0.02

Table 11

Cox Regression Predicting STC Events within Four Months by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.68	1.22-5.90	0.01
Age of Depressive Episode Onset	0.90	0.83-0.98	0.01
Baseline 25-item Depression Score	0.37	0.95-1.02	0.98

Table 12

Cox Regression Predicting LTC Events within Four Months by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.15	1.05-4.42	0.04
Baseline 25-item Depression Score	1.02	0.98-1.06	0.33

Table 13

Cox Regression Predicting STC Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.25	1.25-4.00	0.01
Baseline 25-item Depression Score	0.98	0.95-1.02	0.37
Age of Depression Episode Onset	0.90	0.82-0.98	0.01

Table 14

Cox Regression Predicting LTC Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.37	1.32-4.25	0.004
Baseline 25-item Depression Score	1.03	1.00-1.06	0.03

3.3.7 The Effect of SRD Above Threat

As mentioned above, we were also interested in the SRD effect of an event, above and beyond the threat effect of an event. Here we asked, "is the time backward from recurrence to an event rated for *both* SRD and threat shorter than the time backward to an event rated for threat only?" To examine this question we selected individuals who experienced a recurrence and also an independent threat event prior to recurrence (see Figure 15). Some of these threat events were also rated for SRD, while some were not. Table 15 depicts the frequencies of having an

independent event rating for SRD, short-term threat, or both, among those who experienced a recurrence. Using Kaplan-Meier survival analyses, we examined whether the time backward from recurrence to the event was shorter for events rated for both threat *and* SRD than events rated for threat only. The time difference was not significantly different between the groups when including only independent events, nor was it different when all events were included (all $p>0.05$). However, power to detect such an effect was likely quite low, as there were only 27 participants who had a recurrence that also experienced an independent threat event (n=20 with a threat only event, n=7 with an event rated for SRD and threat).Thus, findings may have differed if power to detect an effect was increased.

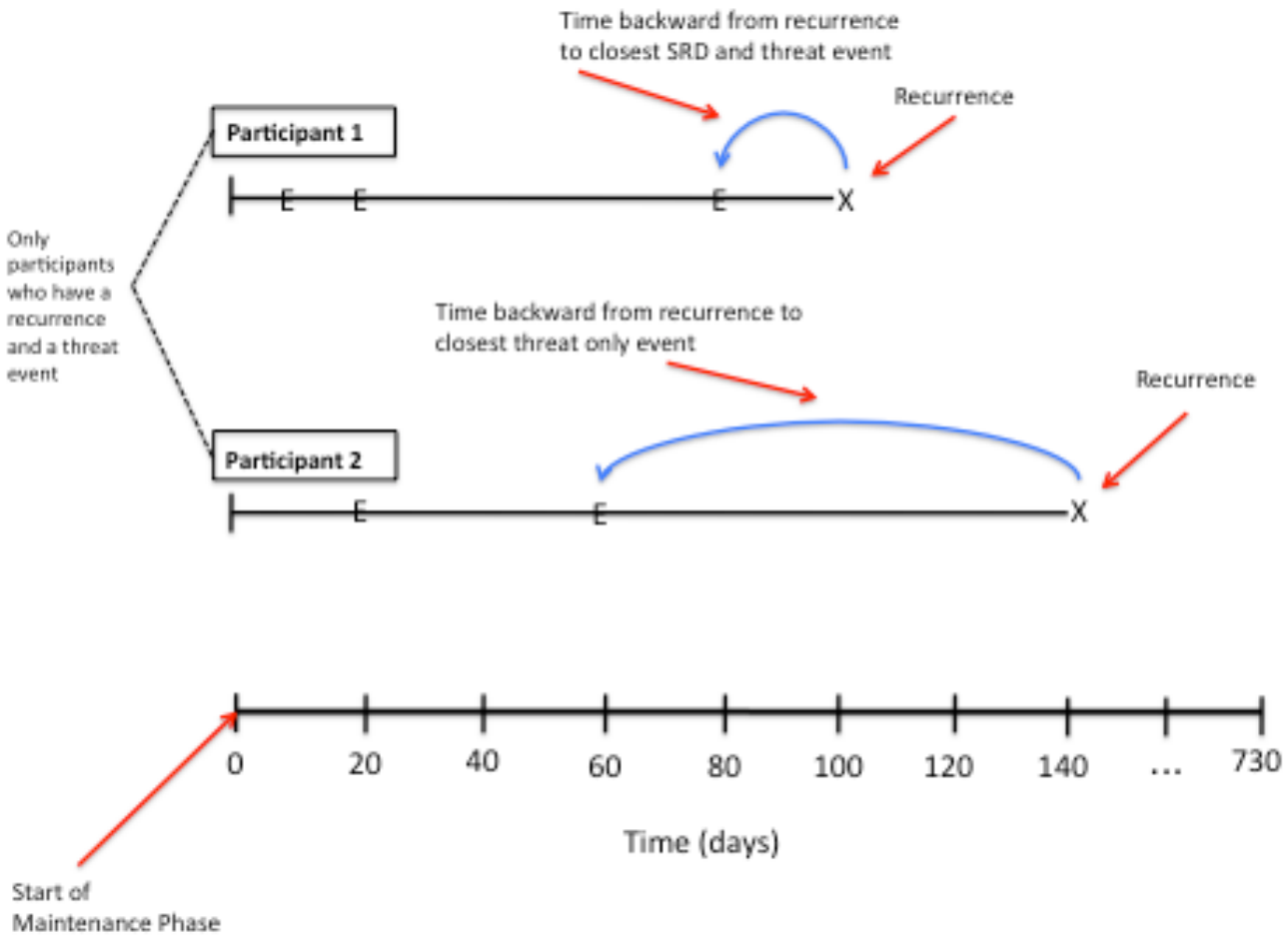

Figure 15. Method of identifying closest event prior to recurrence among those experiencing an event rated for SRD and threat, and those rated for threat only

Table 15.

Frequency of Independent SRD and/or STC Event among Those Having a Recurrence

	STC Present	**STC Absent**	**Total**
SRD Present	7	0	7
SRD Absent	20	14	34
Total	**27**	**14**	**41**

3.3.8 The Effect of Treatment Randomization

One of our original aims was to determine whether treatment with IPSRT buffered the effect of having an event on mood. Because preventative treatment randomization occurred at the start of the preventative phase, and is not considered a pre-randomization characteristic (Kraemer, et al., 2002) we cannot examine it as a moderator. Still, we are interested in whether receiving IPSRT in the acute and/or preventative phases protected individuals from the effects of events on mood. To do so, we examined the likelihood of having a recurrence in the face of an SRD event depending on whether or not patients had received an adequate dose of IPSRT. Those in the "IPSRT" group received between 8 and 103 sessions (mean= 26.95 (S.D.=2.22), median= 22.5) of the treatment over the course of the acute and preventative study phases. The vast majority of participants in the "non-IPSRT" group did not receive any IPSRT sessions, though three participants received just a few (2, 3, or 5 sessions). Contrary to expectation, Table 16 shows that in the face of an SRD event, those who had 6 or more sessions of IPSRT were more likely to experience a recurrence than those with 5 or less sessions of IPSRT (Fisher's Exact p= 0.001).

Table 16.

Recurrence Rate among Those Having an SRD Event by Number of IPSRT Sessions Received

	Recurrence (n=13)	**No Recurrence (n=6)**	**Total (n=19)**
6 or more IPSRT Sessions	84.6% (n=11)	0.0% (n=0)	57.9% (n=11)
5 of fewer IPSRT Sessions	15.4% (n=2)	100.0% (n=6)	42.1% (n=8)

3.3.9 The Role of Incidents

As mentioned previously, incidents are stressful occurrences that are not severe enough to meet the event threshold (Frank, et al., 1995), based on their likelihood of a lesser emotional impact. Though they are not included in the life chart as events because they do not meet LEDS criteria for an event, they may be included in the chart as an "SRD incident" based on its SRD component. We repeated the analyses described above, using incidents instead of events. As incidents do not include a threat rating, only SRD events were studied. The proportion of incidents in each recurrence group did not differ significantly, according to chi-square tests (X^2=0.05, p=0.82). Kaplan-Meier analyses did not suggest a significant difference between the recurrence and control groups in time from recurrence or the corresponding non-recurrence time point to an SRD incident (X^2=0.02, p=0.90). Similarly, the Cox proportional hazards model did not suggest a significant difference in the likelihood of having an SRD incident based on

recurrence status (Exp(ß)=2.10, p=0.38). Because incidents may lead to a recurrence within a relatively short amount of time, we again examined only those events that occurred within the one month and four months prior to recurrence (or corresponding non-recurrence time point) without meaningful differences to the results (all p>0.05). With respect to treatment effects, we repeated the chi-square analysis above that examined the likelihood of having a recurrence by treatment type in the face of an SRD incident. The results suggested that in the face of an SRD incident, those who had 6 or more sessions of IPSRT did not differ significantly from those with 5 or less sessions of IPSRT in terms of their likelihood of having a recurrence (Fisher's Exact p=0.49). Thus, the presence of incidents does not appear to be related to recurrence group status.

3.3.10 The Effect of Severe Events

One of our original aims sought to examine the differential effect of event severity on mood exacerbation. To do so in the present analyses, all chi-square, Kaplan-Meier and Cox proportional hazards models were repeated when only considering severe events. On a scale from 1-4, events rated as "3" or "4" are considered only mildly threatening, if at all (Anderson, et al., 1995). Thus, for the purpose of these analyses, events rated as "1" or "2" will be considered severe. In the current dataset, 25 individuals had severe SRD events, 49 had severe STC events, and 35 had severe LTC events. The proportion of SRD, STC, and LTC severe events in each recurrence group did not differ significantly according to chi-square tests (all p>0.05). The groups did not differ significantly on time backward to a severe SRD event (X^2=0.03, p=0.86) or severe STC event (X^2=2.03, p=0.16), nor did they differ on the likelihood of having a severe SRD event (Exp(ß)=1.08, p=0.86) or severe STC event (Exp(ß)=1.37, p=0.30). However, the recurrence group experienced a significantly shorter time to a severe LTC event than the control group (X^2=4.04, p=0.04) and they also were more likely to have a severe LTC (Exp(ß)=2.04,

p=0.04) event, even when covariates were included (see Table 17). Here, the effect of severe events remained only when considering LTC events.

Table 17

Cox Regression Predicting Severe LTC Events by Recurrence Status

Variable	**Exp(ß)**	**95% CI**	**p-value**
Recurrence Status	2.37	1.32-4.25	0.004
Baseline 25-item Depression Score	1.03	1.00-1.06	0.03

4.0 DISCUSSION

4.1 OVERVIEW

Though some evidence suggests that individuals with bipolar disorder are more likely to experience stressful life events before an episode than controls, there has been a relative dearth of studies examining the association between life events and the onset of bipolar episodes overall. This is especially true of life events that are thought to disrupt social rhythms, which may have a unique impact on mood. The social zeitgeber hypothesis has described how life events may begin a cascade of social and biological rhythm disruption, which may lead to the onset of affective episodes in those vulnerable to bipolar disorder. Thus, it follows that evaluating the social rhythm disrupting effect of life events on mood, in addition to the level of stress or threat, is essential to understanding the true association between life events and mood disturbances, and the mechanisms by which life events lead to the onset of mood episodes. Still, only a handful of studies have begun to explore this area.

The purpose of the current study was to examine the effect of SRD events on mood, particularly as outlined in the social zeitgeber hypothesis. To our knowledge, this was 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 relatively prospectively using the 'gold standard' LEDS assessment method. The design of the

study aimed to reduce the amount of time between LEDS assessments, limiting the retrospective nature of the assessment, and an entirely different group of individuals evaluated participants' mood score and life events, reducing evaluator bias.

4.2 PROPOSED ANALYSES

The original goal of the study was to determine whether, after achieving remission from an acute bipolar episode, SRD events predicted a worsening of bipolar symptoms, and whether this effect depended on the psychotherapeutic treatment to which the patient was randomly assigned. We hypothesized: 1) There will be a significant relationship between the presence of an SRD event and the degree of mood worsening, above and beyond the presence of at least one threat event; 2) there will be a significant relationship between the degree of SRD event(s) severity and the degree of mood worsening observed, above and beyond the effect of threat event severity; and 3) treatment assignment during the acute and preventative phases will moderate the effect of SRD events on mood worsening during the preventative phase of treatment.

However, we were unable to evaluate any of these hypotheses using the methodology originally planned because the proposed model did not fit the data. Specifically, we were unable to obtain sufficient model fit for the individual intercept-only models of depression, mania, and combination mood scores over time. Though it was possible to have run the full structural equation model examining the effect of SRD events on mood change scores, it would have been futile to do so because poor model fit of the outcome variables would have substantially lowered our confidence in the validity of the results, even if the findings of the full SEM model were significant with large effect sizes.

One possible reason for the poor model fit is based on using mood change scores over time. The negative residual variance of the observed measures that was reported may have

resulted from negative values of some mood change scores (depicting a decrease in mood symptoms from one time point to the next). Regardless of the fact that this accurately reflects the data, models with negative variance typically have very poor fit. More broadly, the use of statistical analyses that rely on fitting a latent factor for mood change scores may not have reflected our clinical conceptualization of these data. The fit of the latent factor is based on how well the observed scores fit together. While we would expect actual mood scores for any given participant to be related to one other over time, we would not expect that the *change* in mood scores from one time point to the next is related to the change at other time points. On the contrary, participants may have an increase in depression score by 2 points one month, but a decrease by 3 points the next month, and no change during the third month. While those actual scores resemble each other (within 5 points), the changes in the scores do not.

A second possibility is that monthly mood assessments may have been too infrequent to see the effects of events on mood, suggesting that we may have calculated mood change scores based on the wrong timeframe. The effect of some events (particularly SRD events) on mood may have been more immediate (e.g., staying home from work with the flu), but may have resolved by 3 or 4 weeks after the event. Thus, the change in mood score that is assessed 3 or 4 weeks after the event may have reflected something *other* than the consequences of the event, or simply normative fluctuations in mood. Mood score changes may have been less discrepant if we were more confident that the observed change in mood was a direct result of the event itself. Future studies should examine day-to-day or week-to-week changes in mood scores to identify more acute effects of events on mood, and potentially more congruent mood change scores. This may not only better reflect the effect of events, but it may also allow for improved model fit.

4.2.1 Why Not Use Actual Mood Score?

Since actual mood scores may fit a latent factor model with much better fit, the logical next question is why we do not use these scores over time as our outcome measure. Though we are interested in the relatively short-term effect of events on mood exacerbation, using actual mood scores over time does not take into account the individual's mood just prior to the event's occurrence. For example, the loss of a spouse may be associated with an HRSD-25 score of 30 the following week or month, and we could argue that this event was associated with severe depression. This assertion would be compelling if the previous month's score was 12 (indicating a large change in mood if the death was unexpected), but it would be misleading if the previous month's score was 27 (indicating a smaller mood worsening if the death followed a long battle with a chronic illness, for example). Thus, we might be mistakenly assuming that the death event caused the subsequent mood score.

4.2.2 How Could We Use Data of this Kind More Effectively in the Future?

There may be other possibilities for testing our original hypotheses utilizing longitudinal data. Because structural equation modeling may be quite sensitive to small sample sizes, one method would be to gather data on a much larger sample of individuals with bipolar disorder, which may improve our power to detect an effect. However, this does not address the negative variance and poor CFA model fit that we observed. Mood changes that are a more immediate and direct result of SRD events may be more similar if we can be sure that we have captured the change in mood within the time frame of risk. This may be in a much shorter time period after the occurrence of the event than we had originally conceptualized. Thus, as noted above, future studies should examine day-to-day or week-to-week changes in mood scores to identify more acute effects of events on mood, and potentially more congruent mood change scores.

Furthermore, future work should aim to identify the approximate length of this crucial interval in which we expect events to have an effect on mood. For some events the time of risk may be relatively short, but for others it may be substantially longer.

Last, future work should aim to increase the attention to the specificity of life event subtypes that are studied. Certain kinds of SRD events may increase mood (such as sleep loss that results from staying up until the wee hours of the morning on New Year's Eve), while others may decrease mood (such as decreased social interaction that results from a job loss). Investigation of specific SRD events may increase the similarity in observed mood change scores that follows each event type.

4.3 EXPLORATORY ANALYSES

4.3.1 Why Was Matching Necessary?

Of the 114 individuals with LEDS data, 54 had a recurrence at some point during preventative treatment. Had we included all 114 individuals in the exploratory analyses, we would have compared groups with unequal sample size and varying age and gender compositions, because individuals were not randomly assigned to having a recurrence or not. Most relevant to the question at hand, however, since those participants who did not experience a recurrence, by definition, spent more time in the preventative phase and, thus, had a longer opportunity to experience events, we chose to create a set of matched pairs in order to equate the amount of time that participants could potentially experience events. Overall, matching allows for increased control over unwanted differences in age, gender, and preventative treatment time, which may have affected the likelihood of having a recurrence or an event.

4.3.2 STC and LTC Events

Returning to the original scientific question, we planned to test our hypotheses using modified statistical methods. A number of our findings pertaining to threat events provide additional support for the link between stressful life events and the onset of mood symptoms and mood episodes that is established in the literature. Though the groups did not differ on the proportion having an STC or LTC event, there were significant differences when only independent events were considered, and when only independent *and* non-DVR events were considered. Using survival analyses, the recurrence and control groups differed significantly on the likelihood of having an STC or LTC event (and in the time to these events) when independent events were included and when only events occurring within the four months prior to relapse were included. Similarly, the groups differed on the likelihood of having an LTC event when only severe events were included. Indeed we detected that the sizes of these effects were medium and large at some time points, suggesting a clinically meaningful difference in the likelihood of having an event based on recurrence status, the nature of the event (e.g., independent), and the time point at which the event occurred.

The findings of this report also corroborate previous work demonstrating the importance of independent and severe threat events in the onset of a recurrence (Horesh & Iancu, 2010; Hunt, et al., 1992), and they provide further support for the established practice of considering only these type of events in studies of the effect of life events on mood symptoms and episodes (e.g., Brown & Harris, 1978; Frank, et al., 1994; Lenze, et al., 2008). Last, these findings suggest that the *nature* of an event (e.g., independent, non-DVR, etc.) and the *timing* of an event (e.g., within four months prior to recurrence) may play a more important role in determining the effect of threatening events on episode recurrence than simply the presence of any event using an

analysis that does not consider event characteristics. This may be especially true among patient populations that have a high number of previous episodes. Recent work has shown a decreasing depressogenic effect of stressful life events with increasing numbers of episodes, up to nine depressive episodes (Kendler, Thornton, & Gardner, 2000). Given that all MTBD study participants had at least two prior bipolar episodes prior to entering the study, with a mean of 8.28 (5.27 depressive and 3.01 manic) and a median of 5 previous episodes (3 depressive and 2 manic), one reading of our results suggests that events that have a weaker association with mood symptoms based on their nature (e.g., mild events) may have less of an impact on mood with a longer history of bipolar episodes.

The lack of group differences when considering only events that occurred within the one month prior to recurrence may be due to low power to detect this effect, as a result of the small number of events that occurred within this time frame. There were 26 individuals who had STC events and 22 individuals who had LTC events within the month prior to recurrence (or the corresponding non-recurrence time point). One interpretation of the significant difference between groups when examining the four months prior to recurrence (or corresponding non-recurrence time point) is that the majority of the effect of STC and LTC events is felt within the four months after the event occurs. This can be used to guide clinicians to be wary of a substantial change in mood that may be observed in the few months after the occurrence of a threatening event. Though some events may have an effect on mood sooner (i.e., within the month), our sample size may have been too small to observe such an effect.

4.3.3 SRD Events

This report also adds to the literature on the effect of SRD events, a much less frequently studied area. Here, too, we did not detect significant differences between the recurrence and

control groups when all SRD events were included, but we did find differences between the groups when we examined only those events that were thought to be independent of the individual's influence, both in terms of the proportion in each group with this type of event, and in terms of the time backward from recurrence (or corresponding non-recurrence time point) to this type of event. These findings remained even when covariates were included. This was also true when only events that were independent *and* non-DVR were included. Still, the majority of effects were small in size, indicating that, though the differences reached statistical significance, the clinical significance of the effect between the two groups may be more modest.

An independence rating does not consider the individual's mental health. Rather, raters are instructed to "consider how independent of the person's agency would we rate this event for any subject, regardless of his/her psychiatric condition" (Anderson, et al., 1995, p. 17). For example, events that are entirely independent from the person, such as an earthquake or hurricane, or serious illness of a family member are considered independent events. These events may be less expected than a dependent event, and it may be that the possibility of anticipating a dependent event lessens its effect on mood, regardless of SRD rating. Including only independent and non-DVR events is also vital because when all other events (dependent and DVR) are considered it is difficult to determine whether the event is a cause or an effect of a mood episode. That is, it is not often possible to disentangle dependent and DVR events from the start of a mood episode or from the individual's own actions, which may potentially mask the true effect of the event on mood. As an example, it is very difficult to determine whether a romantic relationship break-up brings about a depressive episode, or whether the break-up may be the result of prodromal depressive symptoms (Anderson, et al., 1995; Brown & Harris, 1978). Overall, evidence for the role of events demonstrated in this report suggests that only

independent and non-DVR events should be considered when examining their effect on various mood states, particularly because of the difficulty sorting out their cause and effect.

Somewhat to our surprise, we did not observe significant differences between the groups when evaluating events that occurred within the month or four months prior to recurrence or the corresponding non-recurrence time point. This is important because we believe the social rhythm disrupting nature of an event to have a relatively immediate impact on mood. This negative finding may be the result of small of a sample size, as only 10 participants experienced an SRD event in the month prior to recurrence. Alternatively, the finding may indicate that SRD events do not have as immediate an effect as initially hypothesized. A third possibility is that one month and four months is still too long a time after the occurrence of an SRD event in which to observe the effects of the event. As noted above, more finely tuned day-to-day mood changes should be assessed and evaluated for their relevance to the occurrence of an SRD event.

Similarly, the absence of a significant difference related to severe SRD events may be related to the fact that only 25 individuals experienced this type of event, again reducing our power to detect an effect. Alternatively, this may indicate that even mild social rhythm disruption rating that is associated with an event may have the capacity to dysregulate social and biological rhythms, leading to bipolar episodes. An example of an event rated “3” (or mild) on SRD is a two-day hospital admission of a patient’s child, or change in job status such that the patient a must increase his daylight working hours while his lunch break has been eliminated. Previous work has also found an association between SRD events and subsequent depressive symptoms and episodes among individuals with bipolar spectrum disorders, even when more mild SRD-rated events were included, in addition to severe SRD event (Sylvia, et al., 2009). The majority of the general population is not likely to experience a dysregulation in mood as a result of this

type of change, but individuals with bipolar disorder, who are acutely vulnerable to changes in social rhythms, may experience even this "mild" social rhythm disruption as disruptive and troublesome to their mood. Future work should include larger samples that have sufficient power to examine the effect of only severe events to determine if severe SRD events have an effect on mood above and beyond mild SRD events.

4.3.4 Effect of Treatment

One of the original aims was to determine whether IPSRT treatment moderated the effect of events on mood. We had originally hypothesized that those who received IPSRT would experience less of an effect of life events on mood than those who received ICM. Because preventative treatment cannot be considered a moderator (Kraemer, et al., 2002), we chose to examine the proportion of individuals who had a recurrence during the preventative phase based on the dose of IPSRT that they received, among those who experienced an SRD event. The result was in the opposite direction of our expectation, indicating that those who received IPSRT (6 sessions or more) were *more* likely to have a recurrence. It is unlikely that individuals receiving IPSRT did not have sufficient treatment sessions in which to learn and integrate the strategies for social rhythm regulation by the time the event occurred, as the median number of IPSRT sessions received in the "IPSRT group" was 22.5 (mean=26.95, S.D.=2.22).

Still there may be other reasons underlying the poorer outcome of the IPSRT group. First, this finding may have been due to small sample size, as only 13 individuals in this group who had an SRD event in the preventative phase experienced a recurrence. Second, it is possible that individuals with highly regular social rhythms were protected from the effects of an SRD event on mood. However, not all individuals receiving IPSRT may have had highly regular rhythms at the point at which the event occurred, and some patients receiving ICM may have had regular

rhythms. This possibility calls for future work to characterize the social rhythm regularity of the sample at the time of the event in order to determine if we should examine subgroups based on regularity, rather than treatment type. This is especially relevant given previous work demonstrating the importance of social rhythm regularity in its role in the risk of episode recurrence (Frank, 2005) and the association of increased regularity of activities with decreased depressive symptoms (Shen, Sylvia, et al., 2008). If highly regular rhythms were found to protect patients from the effects of SRD events, it would be of great interest to examine the likelihood of recurrence based on *both* treatment type and social rhythm regularity to determine if the protective effect of regular rhythms is even more potent in the face of treatment that works to resolve interpersonal difficulties. Answering these questions necessitates that future work study sufficiently large samples of patients with bipolar disorder whose social rhythm regularity is measured with sufficient frequency as to evaluate their rhythm regularity at the time of an SRD event.

Third, the relatively high numbers of past manic (IPSRT mean=3.16, ICM mean=3.06) and depressive episodes (IPSRT mean=5.37, ICM mean=4.29), and nearly a dozen or more years suffering from bipolar illness (15.13 years IPSRT group vs. 11.23 years ICM group) point to a severe and chronic course of bipolar disorder among at least some study participants. It may be, as Vieta and colleagues (Vieta, et al., 2005) suggest, that treatment may not benefit as highly those patients with long-standing bipolar disorder who experience frequent mood swings. Likewise, in these patients in particular, active treatment may not be effective in protecting against the effects of SRD events when the course of the disorder has been so chronic and turbulent.

4.3.5 The Effect of SRD Above and Beyond Threat

We were not able to detect a shorter time from recurrence back to an event rated for *both* SRD and threat, as compared to an event rated only for threat. One reason for the negative finding may be related to the methods used to explore this question, which reduced our sample size for this analysis. That is, to ensure that the effect of SRD was over and above the effect of threat, we needed to select only those individuals who had a recurrence who also had an event that was rated for at least threat (and some were also rated for SRD as well). This reduced our sample size to 20 individuals with a threat only event, and 10 individuals with a threat and SRD rated event, limiting the power to detect an effect. Moreover, this method did not take into account the event's ratings, which may have distorted the outcome if the difference in threat and SRD ratings resulted in differences in the effect of the event on mood. For example, an event such as a child's two-day hospital stay for asthma-related complications, which may have mild SRD and threat ratings, may take longer to affect mood than the loss of a close friend who lived out of town, which may have a severe threat rating, but no SRD rating. Future work should explore methodology that allows for the consideration of the level of SRD and threat ratings when examining the effect of SRD above and beyond threat.

4.3.6 The Timing of Events

This analysis also raises the subject of the timing of events in relation to mood. One important assumption we have made in these analyses is that the event occurring closest in time prior to recurrence has the greatest effect on mood. In some cases, this is a straightforward claim to make, as, for example, most readers would accept the idea that a severe SRD event occurring one week prior to recurrence is most likely more strongly related to recurrence than a mild SRD event that occurred four months prior. But some situations are more complex, as in the case of an

SRD event rated “3” that occurs one week prior to recurrence, and an SRD event rated “1” that occurs two weeks prior to recurrence. An example of this circumstance would be a student staying up all night to study for college final exams (SRD=1), followed by a two-week winter holiday break (SRD=3). An alternative situation might be staying up all night to accompany a friend who has broken his leg to the ER (SRD=1), followed by inviting the friend to move in the next week because of his limited mobility (SRD=3). The methodology utilized here assumes that the event closest to the recurrence is the most strongly related to the recurrence, and it is the one we should study. But might it be possible that the effects of the earlier event, which truly disrupts rhythms, are still being felt two weeks later, and that the later event is really just an annoyance? Or, is it possible that the effect of the mild SRD event in the face of established social rhythm dysregulation is enough to lead to a recurrence? Future work should explore additional methods of identifying an event of interest for each participant, such as choosing the event with the most severe rating (as opposed to the one closest in time to recurrence), or considering the cumulative effect of two or more events that occur within a set amount of time (e.g., one or two weeks).

4.3.7 SRD Incidents

The lack of findings pertaining to SRD incidents was somewhat unexpected. Though incidents are not thought to carry sufficient threat to meet criteria for an event, they may carry substantial SRD. Nevertheless, a reading of roughly 15 LEDS life charts suggested that many SRD incidents are repeated over time. For example, an individual’s child returning from a semester away at college is given an SRD incident rating of 3 for the parent (the patient). As this SRD incident occurred roughly eight times per year over four years, it is possible that the parent may have grown accustomed to the transition and was able to prepare for the social rhythm disruption that accompanied the child’s coming and going. Though not discussed in the SRD

manual, another possibility is that the SRD level of these incidents may have been slightly milder than those associated with an event. Future work should consider ways to evaluate the additive effects of events and incidents, to examine their joint effect on mood.

4.3.8 Representativeness of Sample

Not all individuals who originally entered the acute phase of the study participated in the preventative phase, nor did all complete LEDS assessments. As compared to those who originally entered the study whose data were not included in the originally proposed analyses (n=61), those who were included (n=114) were more likely to be Caucasian, were more likely to be working (at a trend level), had lower depression scores and higher mania scores at entry, were less likely to enter the study with a mixed/cycling episode, and had on average one fewer depressive episode. Moreover, data from only 82 of the 114 individuals set for inclusion in the original hypothesis-testing analyses were actually included once the case-control matching was complete. These 82 individuals were younger than the 32 who were not included. Overall, these differences may speak to the fact that our findings may hold less relevance for certain populations of patients with bipolar I disorder, such as older adults, individuals who are not working, and those with a tendency toward mixed episodes. This should be considered when generalizing the findings reported here. Moreover, it may be that some characteristics of the individuals included in the final sample, such as younger age, the ability to work full-time or part-time, fewer past episodes, and lower depression scores, may speak to an overall less severe form of bipolar disorder in these individuals, which may have protected them from the effects of SRD events.

4.4 STRENGTHS

To our knowledge 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*. The fact that the same clinicians treated participants in both treatment conditions is a substantial advantage in this study as a participant's clinician was retained even when the participant switched treatment modalities when entering the preventative phase.

The use of the LEDS, the 'gold standard' life events assessment, is a strength in its own right. This measure allows for several unrelated ratings of one event, such as dependent-variable related status, independence, and social rhythm disruption. LEDS events were not assessed while participants were in a mood episode, limiting the influence of mood symptoms on recollection or reporting of events. Moreover, an entirely different group of individuals evaluated participants' mood score and life events, reducing evaluator bias. The design of the study aimed to reduce the amount of time between LEDS assessments, limiting the retrospective nature of the assessment. Indeed, during the preventative phase individuals were asked about life events at approximately regular intervals, limiting the recall bias associated with recollecting events.

One unique aspect of the current report is the ability to begin to explore the effect of SRD level over and above that of threat level of any one event. Previous work has identified the individual 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. 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.

4.5 LIMITATIONS

Limitations of this study should also be considered. Though the dataset is rich with multiple observations of several measures across the length of the preventative phase, the proposed analyses were not able to make use of much of these data because of poor model fit. This is not an uncommon occurrence when data are extracted from a study that was not originally designed to answer the scientific question at hand. Still, the cross-sectional design of the exploratory analyses included in this report limits our ability to draw conclusions about cause and effect. Another related limitation is the relatively small size of the sample. It is likely that we would have had sufficient power to detect additional effects with increased sample size, particularly among current trend level significance findings. Still, several findings, even pertaining to the effect of SRD events, reached statistical significance. This highlights the need for replication with larger samples that will allow for exploring the specific effects of various types of life events that have occurred, as well as the effect of these events on individual mood exacerbations (depression, mania, mixed) that may be the result.

The relatively small size of the sample also meant that power to detect a moderation effect in this study was relatively low. This is particularly important when considering the effect of factors that may protect against the stressful and SRD effects of life events on mood, such as social support, lifestyle regularity, lifetime illness duration, melatonin and cortisol dysregulation, and genetic vulnerabilities. Though the inclusion of these additional moderators was not an aim of this report, future work should aim to replicate our analyses with sufficient power as to examine these additional moderators.

Another limitation is the monthly assessment of mood in the preventative phase, which may not have been frequent enough to capture acute mood fluctuations that likely resulted from

social rhythm disruption. Mood score changes may have been less discrepant if we were more confident that the change in mood was a direct result of the event itself. Future studies should examine day-to-day or week-to-week changes in mood scores to identify more acute effects of events on mood, and potentially more congruent mood change scores. This may not only better reflect the effect of events, but it may also allow for improved model fit.

We cannot overlook the fact that all individuals in this study were prescribed one or more psychiatric medications, which may have differed across participants and/or across the duration of the study. These medications may have increased mood stability over the course of treatment, and they may also have protected against the effects of stressful or SRD events based on the sedating, alerting, or rhythm-stabilizing effects of the medications. The cross-sectional nature of the final analyses did not allow for examination of the time-varying nature of changes to medication prescriptions over the preventative phase, although these should have been relatively few as the medication regimens in this phase were maintained unless adjustments to lithium dosages were required, or if rescue medications were necessary. Moreover, it is not only unfeasible but also unethical to study a group of patients with bipolar disorder who are medication free. Future work should investigate the differential protective effect of pharmacotherapy based on various combinations and dosages of psychiatric medications.

Last, though the recurrence and control groups were matched on age and gender, and they were equated with respect to the amount of time that participants could potentially experience events, there were six individuals diagnosed with schizoaffective disorder in this sample. This may have increased the heterogeneity of the participants in the matched groups, though we did not detect significant differences between those diagnosed with bipolar disorder and those diagnosed with schizoaffective disorder on demographic or clinical variables. Moreover, the

recurrence and control groups differed in the proportion of each group that received IPSRT in the preventative phase at a trend levels, as well as possibly on other unmeasured variables of interest. Though it would have been useful to utilize a within–subjects design to compare a pre-recurrence period with a control period of equal duration among the recurrence group only, this was not feasible in the current study because 1) some participants only remained in the preventative phase for less than a month, eliminating the possibility of identifying a control period for these participants, and 2) thus far we have been unable to determine empirically an appropriate length of time prior to a recurrence in which to search for potentially related events, so any interval set a priori might be invalid. An important parallel line of research would be to identify the interval of time prior to a recurrence in which an event has occurred that is thought to be related to the recurrence.

4.6 FUTURE DIRECTIONS

The findings reported here suggest several lines of future research. First, future work should aim to cross-validate our findings in a separate, larger sample of individuals with bipolar disorder. A larger sample will allow for sufficient power to detect moderation effects, such as differences based on the type of recurrence episode type. There were only 54 participants who had a recurrence over two years of maintenance treatment, perhaps because they were treated so well during the acute phase and closely followed during the preventative phase. As such, the sample size of each cell in moderator-type analyses became quite small. Observational, non-treatment studies, or the wait-list control arm of such a study, may provide more opportunity to study recurrences if they occur more often when active treatment is not being delivered. Moreover, it will be particularly important to replicate the unique findings of this report, that of a significant difference in time from an independent SRD event and recurrence/non-recurrence

time point between groups, and in the difference in likelihood of having independent SRD events between the recurrence and control groups. Future work should also focus on characterizing independent events to generate hypotheses about the mechanisms by which these events affect mood, while dependent events do not.

Although we did not have sufficient data here, an alternate approach would be to examine the role of social rhythm disruption, as measured by the Social Rhythm Metric, in the relationship between SRD events and mood exacerbation. At present, SRD ratings of events reflect the *expected* disruption of social rhythms that results from an event, but they do not actually describe the amount of SRD that is associated with that event. It would be useful to examine the effect of SRD events on mood exacerbation among *only* those SRD events that predict worsening in social rhythm regularity, which would first require an examination of how well SRD ratings of events reflect the social rhythm disruption that actually follows. This line of exploration would allow us to 1) determine the reliability of the SRD ratings, and 2) identify the true effect of SRD events on mood when we are more confident that the event will actually produce social rhythm dysregulation.

Future work should also examine the presence of routinizing factors and the level of change in exposure to light associated with an event as moderators of the main effect studied here. These additional ratings may imply social and/or biological rhythm disruption that is measured differently (and is, perhaps, qualitatively different as well) from SRD events. It has been suggested that even a weak light stimulus can phase shift endogenous melatonin and cortisol rhythms (Boivin & Czeisler, 1998), neuroendocrine factors that are thought to affect sleep. Conversely, even a highly disruptive SRD event may have little effect on mood in the face of other factors that regularize routines, such as a highly regular work schedule. The inclusion of

the social rhythm metric, as well as measurement of other routinizing factors may allow us to examine social rhythm regularity as a buffer for SRD events in future work.

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. It may be that an SRD event is not sufficient to bring on a mood episode for some individuals, but when this event occurs in the context of an ongoing difficulty the likelihood of recurrence may be higher. It was outside the scope of the current project to examine the additive nature of these stressors, but future work should surely focus on this area to investigate more complex conceptualizations of the effect of life events. Such work would need to account for the severity of the event, and perhaps for an additive event/difficulty severity rating, in order to evaluate the additive effect.

Similarly, future work should take into account the goal attainment rating associated with an event, perhaps generating a combined score for the SRD and goal/reward attainment that is associated with any event. Goal/reward attainment events are events that involve the pursuit and/or attainment of a reward, such as studying for and taking final exams. As noted above, these events are important because the behavioral approach system (BAS) model proposes that some individuals with bipolar disorder demonstrate BAS dysregulation, which regulates engagement in the pursuit of goals, attention to reward, cognition, and affect (Depue & Iacono, 1989; Johnson & McMurrich, 2006; Johnson & Roberts, 1995; Urosevic, Abramson, Harmon-Jones, & Alloy, 2008). Some individuals with bipolar disorder may be more sensitive to goal-directed behavior and reward based on weak regulation of the BAS, resulting in extreme BAS activation and deactivation, and consequently, the highs and lows that characterize the disorder (Depue & Iacono, 1989; Urosevic, et al., 2008). Thus, it follows that goal/reward-striving and reward

attainment relevant events have been shown to trigger hypo/manic episodes (Johnson, et al., 2000). Given that many reward-relevant events can disrupt social rhythms, future work should consider the potentially combined effect of SRD and goal attainment ratings of an event, such as staying up until 3am to make holiday gifts for each member of a family, on mood.

Last, future work should continue to explore the extent to which lifetime illness duration (or number of previous episodes) moderates the main effects examined here. This work should ensure sufficient sample size as to explore the effect of illness duration or episode history as a moderator of the effect of life events on recurrence or symptom worsening, in line with previous work referenced here.

4.7 CONCLUSIONS

We examined the effect of SRD events on mood among individuals remitted from an episode of bipolar disorder who had been treated with IPSRT and/or ICM. Adding support to established findings, we detected that threatening events were more likely to occur prior to a recurrence than a non-recurrence control point, and these events occurred closer in time to a recurrence than to a control point in the life of a patient who did not recur. Supporting our original hypotheses, individuals who experienced a recurrence were also more likely to experience an independent SRD event than those who did not, and again this event occurred closer in time to a recurrence than to a corresponding non-recurrence point in the life of those in the control group. In contrast to initial hypotheses, SRD events do not appear to have an effect on recurrence above and beyond the effect of threat events. Future studies should continue to focus on the types of SRD events that are related to mood worsening, and they should consider ways of evaluating the combined effect of events and incidents, as well as the additive effect of

related event ratings. Last, future work should explore alternative conceptual and statistical methods of studying these scientific aims that make use of longitudinal datasets.

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