UNIVERSITY OF CALIFORNIA, SAN DIEGO
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Interactive Effect of the Serotonin Transporter (5-HTTLPR) Genotype and Life Stress Predicting Bipolar Symptomatology

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in
Clinical Psychology
by
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The dissertation of Amelia Kotte is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

I would like to dedicate this work to my aunts, Viviana and Meri Gjerga, to my uncle Vasil Gjerga, to my mother, Irma Gjerga and to my sister, Ester Kotte, for their ceaseless faith, sacrifice, and love, always, across time and continents.

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ABSTRACT OF THE DISSERTATION

Interactive Effect of the Serotonin Transporter (5-HTTLPR) Genotype and Life Stress Predicting Bipolar Symptomatology

by

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University of California, San Diego, 2011

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In patients with bipolar disorder, the serotonin transporter gene polymorphism (5-HTTLPR) is associated with effectiveness of lithium prophylaxis and with affective instability in response to environmental stress. This cross-sectional study investigated whether bipolar symptomatology at the baseline for a lithium treatment study is consistent with the diathesis-stress model.

Forty-two participants with bipolar disorder completed a battery of measures assessing demographic information, life stress, and symptoms of bipolar disorder. Participants underwent phlebotomy procedures for genotyping.

MANOVA tests showed a significant main effect for event severity (Wilk's λ = .714, F [4,31] = 2.20, p =.029). Participants with presence of a severe event scored significantly higher in depressive symptoms and were deemed more ill by the clinicians. There was a significant omnibus 3-way interaction between severe events, 5- HTTLPR,

and lithium status (Wilk's $\lambda = .367$, $F [4, 33] = 3.020$, $p = .031$). A trend toward significance for 5-HTTLPR was found; i.e., lower depression scores were present in *s/s* and *s/l* and participants taking lithium, as opposed to *l/l* participants, when severe events were present but not when severe events were absent. There was a main effect for loss events predicting manic symptoms ($F[1,38] = 4.15$, $p = .04$). Participants with a loss event reported higher manic symptoms than those without. There was an interaction between loss events and lithium status at baseline: in participants with a loss event taking lithium, manic scores were significantly lower ($\mu = 1.70$) than in patients not taking lithium ($\mu = 9$). There was a main effect for goal-attainment events predicting symptoms of depression ($F[1,38] = 5.95$, $p = .01$). Participants with at least one goal-attainment event reported lower depressive symptoms than those without.

Findings were partially consistent with the diathesis-stress model. No interaction was found between 5-HTTLPR genotype and event severity predicting bipolar symptomatology. The results suggest lithium prophylaxis is effective in buffering against depressive symptoms when bipolar patients with at least an *s* 5-HTTLPR allele experience severe environmental events. Results increase understanding of gene by environment mechanisms, imply improvement of identification of patients at risk for poor prognosis and help direct therapeutic techniques.

I. INTRODUCTION

A. Background

Bipolar disorder is one of the most common, severe and devastating psychiatric disorders affecting approximately 1.3-1.5% of the US population (Narrow, Rae, & Robins, 2002) and approximately 3-5% of the worldwide population (Benazzi, 2003). It is characterized by a chronic nature with a rate of occurrence of 90% (Gitlin et al., 1995), which leads to high levels of disability and interferes with sustained individual employment (Murray & Lopez, 1996) as well as decreased quality of life for patients and their families. Patients with bipolar disorder incur double the amount of annual out-of-pocket expenses when compared to expenses incurred by all other psychiatric patients (Peele, Xu & Kupfer, 2003). Suicidal ideation, acts, and completed attempts are extraordinarily high, (Harris & Barraclough, 1997; Tondo, Isacsson & Baldessarini, 2003; Valtonen et al., 2005).

The etiology of bipolar disorder is complex, but research suggests it is a genetically heritable disorder that tends to aggregate in families (Badner, Gershon, & Goldin, 1998) with heritability estimates of 80 to 90% (Craddock & Forty, 2006), a .43 concordance rate for monozygotic twins and .06 for dizygotic twins (Craddock & Jones, 1990, 1999; Kieseppa et al., 2004). Recent advances in molecular genetics have made it possible to identify many of the susceptibility and candidate genes to this complex disease (Huang et al, 2010; Smith et al., 2009) and more specifically, in linkage and association to the 5-HTTLPR (SERT) polymorphism (Bellivier, 1998; Collier, 1996; Sun, 2004), which has become the most investigated genetic variant in psychiatry and neuroscience.

However, the monozygotic and dizygotic twin concordance rates as well as studies that do not support the association of SERT with bipolar disorder (Ewald et al., 1998; Neves et al, 2008), raise the possibility that variability in the onset and expression of bipolar disorder is not entirely dependent on susceptibility genes or biology and that other factors are involved in its manifestation.

Drawing from the perspective of psychosocial impact, life stress has been one such key factor investigated in association to bipolar disorder with findings clearly establishing its precipitative, maintaining and kindling role (Ambelas, 1987; Ellicott, 1990; S. Johnson, 2005; S. Johnson, Cueller, A.K., Ruggero, C., Winett-Perlman, C., Goodnick, P., White, R., Miller, I., 2008; S. Johnson, Miller, I., 1997; S. Johnson, Sandrow, D., Meyer, B., Winters, R., Miller, I., Solomon, D., Keitner, G., 2000; McPherson, 1993; Sylvia, 2009).

While genetic and psychosocial components are undoubtedly important in the etiology and maintenance of bipolar disorder, neither aspect investigated in separation from the other has been sufficient in explaining the variability of the disorder in its multiple stages. Over the past decade, work in gene x environment interactions has greatly contributed to this gap (Caspi, 2003; Mandelli, 2007). The diathesis-stress model provides a solid framework from which to examine whether the variance in bipolar disorder symptomatology is increased by interactions between the SERT polymorphism and life stress.

The purpose of this study was to add to the body of information on the subject, to assess whether variability in the SERT polymorphism moderates the role of life stress in predicting bipolar disorder symptomatology at the baseline of lithium prophylactic

therapy, and to promote understanding of the role of life stress dimensions in the precipitation of depressive and manic symptoms. The following sections will present evidence for serotonergic associations to psychopathology, life stress associations to psychopathology, and current evidence from the combined gene x environment perspective, which informs this study. This will be followed by a description of the specific hypothesis, the study sample, the measures, data analysis, and the methods used to test the hypotheses. Finally, results and interpretations of those findings will be presented.

B. Serotonergic System Abnormalities in Psychopathology

Research has helped identify genetic contributions to the development of psychopathology. For instance, family, twin and adoption studies suggest high concordance and heritability rates for obsessive compulsive disorder, panic disorder, major depression, bipolar disorder and schizophrenia (Shih, Belmonte & Zandi, 2004). Moreover, there is evidence that much of the variance in genetic susceptibility for bipolar disorder, schizophrenia and schizoaffective disorder is shared (Cardno et al., 2002). Recent advances in molecular psychiatry have identified one particularly promising avenue focused on understanding the impact of the genetically driven variation in the serotonin (5-hydroxytryptamine; 5-HTT) function on the development of neural systems and emotional behaviors present in psychopathology. For instance, variability in the 5-HTT region has been associated to a number of conditions, such as anxiety related traits in normals and in depressed patients, seasonal affective disorder, autism, obsessive-compulsive disorder, severe alcoholism, suicidal behavior, schizophrenia and bipolar

disorder, though associations exist in both the positive and negative directions and thus leave room for interpretation (Bellivier et al., 2000; Hranilovic et al., 2000; Hu et al., 2006; Klauck et al., 1997; Lesch et al., 1996; Rosenthal et al., 1998; Serretti et al., 1999, 2002; Sander et al., 1997).

C. 5-HTTLPR Location, Function, and Association to Psychopathology

The human HTT gene is encoded on chromosome 17q11.1-q12 (Ramamorthy et al., 1993) and has a polymorphism in the 5'-flanking promoter region designated HTTLPR (Heils et al., 1991). This polymorphism has been described as two allelic forms regulating the 5-HTT promoter activity; the "long", *l*, variant has about three-fold higher transcriptional activity than the "short", *s*, variant (Heils et al., 1996). The "short" variant results in decreased 5-HTT expression and 5-HTT uptake in lymphoblasts, compared to the "long" variant (Lesch et al., 1996).

Variation in 5-HTT polymorphic function has been linked to a range of psychopathological disorders and traits, such as anxious personality traits (Lesch et al., 1996), suicide (Bondy, Buettner & Zill, 2006), anxiety disorders (Chabane et al., 2004; Walitza et al., 2004), mood disorders (Collier et al., 1996; Lotrich & Pollock, 2004), and addiction disorders (Gerra et al., 2005; Roiser et al., 2005; Szilagyi et al., 2005), though these associations have not been consistently replicated across studies (Serretti et al., 2002). For instance, in a population of anxiety-related personality, those with an *s* variant exhibited higher neuroticism scores as opposed to those carrying the *l* variant (Lesch et al., 1996). The variation has been linked to a greater likelihood in the presence of familial mood symptoms. For instance, one study found those homozygous for the *s* variant were

significantly more likely to have two or more first-degree relatives with a history of depression (Joiner, Jr. et al., 2003). However, in a study on compulsive buying, no significant differences were observed (Devor et al., 1999) and no association of either polymorphism was found in later suicide replication studies

When bipolar disorder is treated as a categorical diagnostic entity, there is less compelling evidence for the direction of the association with 5-HTTLPR polymorphisms. Some literature suggests that the presence of at least one *s* variant is associated with early onset and with greater severity of the illness. Bellivier and colleagues (1998) reported that in individuals with bipolar disorder, the frequency for the *s* homozygous variant was higher than in controls, controlling for allele distribution, which suggests a dominance effect for the *s* allele. Similarly, in a 2002 report Bellivier and colleagues found that those homozygous for the *s* variant were at higher probability for early illness onset. Other research presents findings inconsistent with the previous literature. A meta-analysis by Lotrich and Pollock (2004) found a trend for the s/s genotype to be associated with bipolar disorder, though results did not reach statistical significance. Another study found a significant association with the *l* variant in relation to rapid cycling individuals (Cusin et al., 2001) while another found the *s* variant to be associated with lifetime history of rapid cycling (Rousseva et al., 2003).

Clearly, the role of 5-HTTLPR in bipolar disorder is still unclear. One possible reason for this ambiguity is lack of understanding of the role life stress plays in the onset and course of bipolar disorder.

D. Life Stress Influences in Psychopathology and Bipolar Disorder

Aside from genetic influences on psychopathology, the onset, recurrence and/or clinical course of psychiatric illnesses is also influenced by the experience of life stress (Ginsberg & Brown, 1982; McQuaid et al., 2000). In terms of stress characteristics, the literature on prospective measurements of life events in the bipolar population indicates that uncontrolled and unanticipated events (Hall et al., 1977) and employment events (Joffe et al., 1989) tend to precede bipolar episodes. In a study by Ellicot and colleagues (1990) it was found that severe, independent, and negative life events predicted a fourfold increase in risk of relapse and Johnson and Miller (1997) reported a threefold increase in the time until recovery for the same type of events and similar findings were reported by Hunt, Bruce-Jones and Silverstone (1992). The experience of severe life events is also thought to contribute to increased suicidality among bipolar patients (Johnson et al., 2000; Pettit et al., 2006). When examining another life stress characteristic, goal-attainment, the evidence points toward an increase in manic symptoms. Events such as acceptance into graduate schools, passing a very difficult career hurdle, or winning recognition for personal creativity predicted an increase in manic symptoms over a 3-month period (Johnson et al., 2000; Johnson et al., 2004).

In addition, while not definitively conclusive, research suggests that the predictors of mania and depression may differ, but that this difference becomes significant when accounting for individual characteristics, such as cognitive style. For instance, longitudinal studies suggest that bipolar participants exhibiting negative cognitive styles and reporting a high number of intervening negative events experience increases in manic, and opposed to depressive, symptoms (Alloy et al., 1999; Reilly-Harrington et al., 1999).

However, the inconsistent findings from the small literature on life events and bipolar relapse are easily explained by methodological differences. Different diagnostic criteria have been used, different time periods studied, and while some authors cluster all relapses together, others separate manic relapses from depressions or study manic episodes only (Dunner et al, 1979; Glassner & Haldipur, 1983; Bidzinska, 1984; Ambelas, 1987; Sclare & Creed, 1990). Some studies have small numbers, raising questions of statistical power (Chung et al, 1986 (n = 14); Lieberman & Strauss, 1984 (n = 3)). Many studies fail to separate dependent events, that is, those likely to have occurred as a consequence of the patient's illness, from independent events (Hall et al, 1977; Glassner & Haldipur, 1983; Bidzinska, 1984; Ellicott et al, 1990).

E. Methodological Issues in Life Event Research

The measurement of life events is essential to research into psychosocial factors of psychopathology and thus important to address prior to reviewing relevant findings. The two primary methods employed in measuring life stress have been interview-based (e.g., Bedford College Life Event Difficulties Schedule (LEDS; Brown and Harris, 1989)) and self-report checklists. There are advantages and disadvantages in choosing either method. The advantages to choosing self-report checklists include low expense, capturing of events that may be embarrassing to report to an interviewer, ease of administration and modification depending on the research project or target population. The disadvantages to choosing the self-report checklist method include lack of differentiation of the magnitude of the severity of the event, inability to distinguish events that are caused inherently by the patient's illness (Brown, 1989; B. P. Dohrenwend, Link, B.G., Kern, R., Shrout, P.E., Markowitz, J., 1987; B. P. Dohrenwend, Raphael, K.G.,

Schwartz, S., Stueve, A., Skodol, A., 1993), poor test-retest reliability, lack of possibility for assessing complex events related to each other (Jenkins, 1979; McQuaid, 1992), and confounding of stressors with manifestation of symptoms (e.g., "changes in social rhythm, inclusive of sleep and social activity patterns" might be symptoms as opposed to life events.)

Self-report checklists are also limited in the way their construction manufactures idiosyncratic interpretations of the items, allowing respondents to subjectively determine the threshold of their stress responses. In turn, this increases error variance and inaccuracy while decreasing the reliability of stress reporting. For instance, for a range of reasons, personality traits of the responder included, one may over-report the severity of a fairly minor event, such as lightly spraining an ankle, because he/she may feel compelled to endorse at least a few items on the checklist having been presented with the possibility of doing so. Alternatively, one may choose to omit reporting a fairly severe event, such as the diagnosis of cancer in a relative, if it occurred long ago enough to invite the possibility of subjective interpretation as to the relevance of the event (McQuaid, 1992). These limitations are averted by interviewer-based life stress measures, which pose contextual questions with the aim of differentiating across event severity and allow independent raters to arrive at a consensus regarding said severity.

Additionally, McQuaid and colleagues (1992) demonstrated the two methods as inconsistent to each other in a number of ways, where the interview-based approach captured a more accurate and representative occurrence of life events than the self-report checklists. For instance, self-report checklists tended to over-report events not otherwise reaching criteria for severity as determined by the interview-based method, incorrectly

grouped the type of events reported (i.e., single events vs. ongoing difficulties), underreported event occurrence, misrepresented events having occurred outside of the time frame of interest as having occurred within, over-reported events by way of presenting with the possibility of endorsing two otherwise mutually exclusive categories, and omitted events by way of not presenting with endorsable categories (Zimmerman et al, 1986). Determining the severity of stress is a key component of psychosocial research. Brown and Harris (1978) demonstrated that affective disorder symptoms, specifically, symptoms of depression were predicted only by severe events and difficulties. A review by Brown and Harris (1986) captures the singularity of this finding to hold up across numerous longitudinal studies of small and large samples assessing ranges of life event severity using the LEDS.

The disadvantages to using the LEDS include administration and consensus meeting time requirements as well as the necessity to train a team of raters with at least two reliable raters as established by the Kappa coefficient of reliability prior to event rating (McQuaid et al, 1992; Tennant, 1981).

The LEDS addresses most of the limitations posed by the self-report checklist. It also has several advantages over self-report checklists, such as facilitating more accurate dating of events, using recall-enhancing strategies, and its ability to distinguish between types of events. It reduces subjectivity on the part of the interviewee, as the raters are trained to ignore self-reports of the subjects' feelings or judgments and to look for behavioral evidence about event occurrence. In addition, there is a manual of precedent examples to use for the ratings and consensus meetings (with raters blind to subjective reports or diagnoses) held to discuss final ratings. The LEDS is designed to measure both

acute events and chronic difficulties using a contextual method of rating. Contextual ratings are based on "what most people in that circumstance would feel about the event given the plans and purposes of the person as well as biographical circumstances." Events are rated on a four-point scale (1-severe, 2-moderate [including the subcategory of A-short term threat, B-long term threat], 3-mild, 4-little/none). Severe events (or provoking agents) are defined as those events rated at a "1" or "2" level. Difficulties are defined as chronic problematic situations, regardless of severity, that last a minimum of four weeks. Difficulties are rated on a six-point scale and the ratings can change (up or down) depending on changing circumstances. See Appendix A for the rating scale, Appendix B for examples of typical events and difficulties and Appendix C for examples of rating dimensions of life stress.

Considering many of the advantages of the interview-based methodology over self-report checklists, this study employed the former method in assessing life stress in bipolar patients.

F. Diathesis-Stress Model in Psychopathology - Moderation of Life Stress by 5-HTTLPR in Bipolar Disorder

This diathesis-stress model hypothesizes that psychopathology develops in individuals biologically susceptible to an illness, but only in the presence of noxious environmental influences. The evidence for the influence of genetics and life stress on the development of psychopathology and specifically in affective disorders is abundant. However, research also points toward wide individual variability in response to stress,

genetic predictors to psychiatric illnesses, and the outcomes of their interaction (Kendler, Kuhn & Prescott, 2004).

In a sample of adolescents with major depression, those with at least one *s* 5-HTTLPR allele copy were more sensitive than those homozygous for the *l* allele to the influence of life stress as evidenced in higher depressive symptoms, diagnosable depression and suicidality (Caspi et al., 2003). The same results were replicated in a sample of depressed adult twins where *s* homozygosity predicted a higher vulnerability to the depressogenic effects of life stress (Kendler et al., 2005). A number of studies have reported replications of the Caspi study (Cervilla et al., 2007; Taylor et al, 2006), partial replications (Eley et al., 2004; Grabe et al., 2005; Scheid et al., 2007; Sjoberg et al., 2006; Zalsman et al., 2006), and others have failed to replicate results altogether (Coventry et al., 2010; Gillespie et al., 2005.) This source of variation is best explained by two overarching possibilities. The first possibility is the issue of methodological and operationalizational idiosyncrasies in life stress measurement (Monroe & Reid, 2008.) Of importance is the fact that the original gene x environment Caspi study demonstrated the G x E effect when accounting for childhood adversity and the stress measure employed a life-history calendar including fourteen events. The rest of the studies have employed discrepant life stress measurements (e.g., multi-information assessment of childhood maltreatment, negative family stressors, Social Problems Questionnaire, list of chronic diseases, among many other similar discrepant measures.) Additionally, the final stress index used in the analysis has been operationalized in idiosyncratic ways (e.g., total number of life events, probability of childhood maltreatment, dichotomized numeric stressor, presence or absence of events); the method to acquire this information has

ranged from interview, to questionnaire, to an unknown form of assessment; the stress dimensions studied have ranged from severe, to negative, to undesirable, to loss; and the temporal constriction of event measurement has ranged from within the last six months, to within the last year, to early childhood adversity.

The second explanation is related to the challenges inherent in conducting gene x environment research from a diathesis-stress perspective. Some of these challenges include the difficulty in removing the effect of gene-environment correlations and genetic control of exposure to the environment from the observable effect sizes (Kendler, 1998; Plomin et al., 2003)

No studies to date have investigated the 5-HTTLPR genotypic variant in relation to life stress as measured by the LEDS in predicting symptoms of bipolar disorder. This study attempts to do so.

To summarize, research has demonstrated the main effect of both, life stress and genotype in influencing the onset, course, and recovery of affective disorders. Further, diathesis-stress interaction research examining the moderating effect of genotype on the role of life stress has demonstrated that specific predictive power in illness course is increased in light of such interaction. However, the idiosyncratic findings of the current state of research make it imperative to explore the independent and interactive effect of life stress and genotype in the symptomatology of bipolar disorder. Most importantly, this research, keeping with the framework of the diathesis-stress model, will explore whether life stress is moderated by genetic variation coding for differential serotonin promotion and transcription rates.

G. Specific Aims and Hypothesis

Primary Aim 1: To examine the interaction of genotype and life stress in predicting the course of bipolar disorder symptomatology in response to lithium treatment.

Hypothesis 1 – The presence of genotype will moderate the influence of severe life events such that participants with the *s/s* or *s/l* genotype are expected to experience more depressive and manic symptoms than *l/l* participants; in the absence of severe life events, no such difference is expected.

Secondary Aim 2: To examine the role dimensions of life stress – rated on presence vs. absence of loss events, goal-attainment events and events independent from vs. dependent on illness - play on bipolar symptomatology at the baseline of lithium monotherapy initiation.

Hypothesis 2A – Presence vs. absence of loss events in the four months prior to treatment will predict higher severity of manic and depressive symptoms at baseline.

Hypothesis 2B – Presence vs. absence of disorder-dependent life events will predict higher severity of manic and depressive symptoms at baseline.

Hypothesis 2C – Presence vs. absence of goal-attainment events will predict higher severity of manic and depressive symptoms at baseline.

II. METHOD

A. Overview

The current project examined whether the interaction of stress and genotype was associated with current symptoms of bipolar disorder. The study used a single-group, multivariate, cross-sectional cohort 2 x 2 design with two between-subjects factors (genotype: two nominal levels [*s/s* and *s/l* vs. *l/l*]; stress: two types of nominal levels [presence of severe LE, absence of severe LE; presence of loss LE, absence of loss LE; presence of dependent LE, absence of dependent LE; presence of goal-attainment LE, absence of goal-attainment LE]) predicting dependent variables of bipolar disorder symptomatology (mania, depression) assessed at the baseline of a lithium monotherapy study.

Life stress was assessed for the four months predating baseline used the LEDS. Symptoms were assessed at baseline using the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS), and Clinical Global Inventory – Severity scale (CGI-S). Outcome variables were manic and depressive symptoms at baseline.

The goal of the overall study, Dr. Kelsoe's major funding project, of which this study was a subset, was to identify genetic predictors of lithium monotherapy response. Once individuals gave consent to participate, they were tapered off their previous medications (other than lithium) to receive lithium monotherapy over a month-long period of stabilization, 4-month long period observation, and 2-year period of maintenance. Dr. Kelsoe's protocol provided that if there was evidence patients were not

responding well to lithium, dosage would be reviewed by the psychiatrist with the needed increase or decrease.

B. Participants

Forty-two participants of either gender, aged 31 to 70 years, were recruited from the veteran population of the La Jolla VA in San Diego. Sample demographics are described in Table 1.

Inclusion and Exclusion Criteria: Participants were recruited if they met a lifetime diagnosis of a bipolar depressive episode according to the DSM-IV (1994) SCID-I criteria, were willing to commence lithium monotherapy involving tapering off any previous medications, lived within 50 miles of the VASDHS and identified a resource person who can aid in contact for assessments. Participants did not qualify if they had met a lifetime diagnosis of major depression, only, had current substance dependence/abuse (6-month minimum of being clean and sober), current psychotic symptoms, or a diagnosis of a psychotic disorder (previous psychosis in the context of mania will not be excluded), PTSD, physical disorders that may interfere with continuous treatment participation (e.g., cystic fibrosis; fibromyalgia), cognitive impairments, such as Alzheimer's or HIV induced dementia (measured by the MMSE), an unstable medical condition or medical condition that would contraindicate treatment with lithium treatment, acute suicidality (current plans and clearly stated intention toward suicide).

Recruitment: Recruitment occurred at the VASDHS Special Treatment and Evaluation (STEP) clinic. The STEP clinic is a research clinic designed specifically for

clinical studies of mood disorders. During the period of the study the STEP clinic received between 30 and 40 requests for services per month from providers in the VA.

At the STEP Clinic, referred patients received an appointment schedule by letter, and approximately 25 per month attended screening appointments (71% of those initially referred). Of these, approximately 65% had a bipolar disorder diagnosis. All clinic patients were invited to participate in research. In the 6 months prior to the study 45% of those with bipolar disorder patients agreed to participate in the lithium research study. Recruitment procedures in the clinic were facilitated by a research clinician who called all patients referred to the clinic to schedule appointments and problem-solved any obstacles to attending the appointment. Participants were paid $30 for their initial visit and another $20 for participation in the LEDS interview.

C. Procedures

Assessment Procedure: a) La Jolla VA STEP clinic: all patients who attended the orientation meeting were informed about the current study by a STEP program clinician as part of the initial clinic procedures. Clinicians informed patients of the study and asked whether the patients were interested in participating given the requirements of the study. A research assistant was available after the patient completed the STEP program orientation to consent the participant and enroll him or her in treatment.

All data from the initial assessment were reviewed by the investigators in a weekly staff meeting to determine whether participants were candidates for the rest of the study based on the established inclusion and exclusion criteria. If the participant was

appropriate for the study, he/she was placed in the lithium monotherapy study and was scheduled for his/her first baseline assessment. If the participant was not appropriate for the study, he/she was treated through the STEP clinic as appropriate but was not monitored according to this research protocol.

Written informed consent was obtained according to IRB approved procedures. Consent was reviewed with participants. The research assistant first read the consent form and provided a paper copy to the patient to review. This consent form included information (1) about lithium treatment and side effects (2) course of treatment, (3) all assessment procedures, including interviews, questionnaires and genotyping, and (4) payment for participation. Additionally, the consent form explained the Release of Information form from the patient's provider procedures. The research assistant then asked the patient a series of questions to assure that the patient adequately understood the consent. Critical responses that indicated sufficient understanding of consent included (1) the fact that the participant would receive lithium treatment, (2) the length of time of the study, (3) the assessment times and the nature of the assessments, (4) the amount of payments, frequency, and requirements to receive each payment and (5) reasons the participant would be excluded from the study.

Upon completion of the consent, participants then completed a full medical history prior to initiation of lithium treatment. Patients had laboratory studies that include baseline renal function tests (BUN, creatinine levels), thyroid function tests, and an electrocardiogram for those aged over 40 years (APA Practice Guidelines, 2002). Within the first week of their medical history, patients completed a psychiatric intake and within this week, participants had their blood drawn and completed an initial battery containing

the SCID, LEDS, HAM-D, BDI-I, YMSR. The research assistant then paid the participant $30 for the initial assessment battery.

The participant was scheduled for a blood draw at the time of baseline, which was at the time of the patient's visit with their psychiatrist. At this time, the SCID interview was administered as well as the questionnaires including the YMRS, HAM-D, and BDI to assess current bipolar symptoms. Within a week of the patient's intake, patients were scheduled for a LEDS interview. The initial assessment took approximately 5 to 7 hours over the course of the first week.

Baseline Interview Content:

1. Life-Stress Measurement: The Life Events and Difficulties Schedule (LEDS; Bifulco & Harris, 1989) is a two-stage life stress assessment technique. First, a research assistant conducts a semi-structured clinical interview, assessing life experiences in the prior specified time frame (for this study, 4 months). Emphasis is placed on gathering objective, measurable information about these experiences (e.g., financial and time costs, changes in amount of contact with supportive relationships), as well as the context in which they occur (e.g., ongoing financial stress, housing difficulties, health limitations). In the second stage, a trained research assistant reviews the audiotape and presents the data gathered in the interview to a panel of at least 3 trained raters, blind to the hypotheses of the study. Those raters use a standardized set of rules and criteria set forth in the LEDS manual for rating the objective information for each stressor to determine the type of stressor (acute events or long-term difficulties), and a variety of stressor dimensions (i.e., severity; loss; valence; dependence vs. independence; focus). Onset

dates and end dates (when appropriate) are established for each stressor, allowing examination of temporal relationships to other variables.

Stressors are also rated on their dependence vs. independence due to disorder; stress that is clearly not due to depressed or manic mood is defined as independent (rated 1 and 2), events that are potentially, but not definitely due to depressed or manic mood are defined as possibly independent (rated 3 through 11), and events clearly due to depressed or manic mood are defined as dependent (rated 12). Because Brown and Harris found that collapsing the independent and possibly independent events bore no difference in the prediction of symptoms, a dichotomous variable for independent events collapsing events rated 1 through 11 and dependent events rated 12 was created.

Severity of loss was rated on a four-point scale (1 = severe; 2 = moderate; 3 = mild; 4 = little or none). In the rating the degree of severity of loss associated with each event, the raters looked for evidence of four general categories of loss:

a. The loss of death or by separation of a valued person.

b. The loss of the person's own physical and psychological health.

c. The loss of a job, career opportunities, or material possessions.

d. The loss of a cherished idea (e.g., the discovery of a husband's infidelity could be rated under the appropriate circumstances as the loss of the notion of a happy marriage.)

Goal-attainment was rated on a four-point scale (1 = maximum accomplishment and/or effort; 2 = moderate amount of accomplishment and/or effort; 3 = minor accomplishment and/or effort; 4 = no accomplishment and/or effort) system which has been used in previous research on recovery from unipolar depression and anxiety

(Leenstra, 1995) Raters considered the degree to which a desired goal was achieved and the participant's amount of commitment or striving toward that goal.

Life event severity was scored using LEDS guidelines where a threat is considered more severe than a difficulty and has a clear start/end point. Two types of severe events were included in the analysis: short- and long-term threat (up to 2 weeks). For each category, a rating of 1=Severe and 2=Moderate was given and for the long-term threat, the Moderate category was further broken into 2a=more severe and 2b=less severe.

Raters training. Research on the effect of life stress on psychopathology and training on the Bedford College LEDS system has been undergoing at UCSD for approximately fourteen years under the supervision of Dr. John McQuaid. Training consisted of watching a series of videotapes where Dr. McQuaid describes the principles of the Bedford College LEDS system, reading pertinent articles and sitting in rating meetings with experienced raters. After several times the prospective raters have sat in these meetings they record their ratings to assess their reliability. Once the raters reached adequate agreement with experienced raters (Kappa > 0.80) they were allowed to provide input into deciding the final ratings of life stress of the panel while using the LEDS "dictionary" that contains over 5,000 case vignettes to provide anchoring examples and standardization. All prospective raters became reliable within a few months from starting the training. Raters were blind to participants' symptom severity. The LEDS interview covered events that occurred during the four months prior to admission into the study.

Summary of constructed stress variables: This study examined four different stress variables: a) the presence vs. absence of severe events, b) the presence vs. absence

of loss events, c) the presence vs. absence of disorder-dependent events, and d) the presence vs. absence of goal-attainment events.

2. Bipolar Disorder Diagnosis: Structured Clinical Interview for DSM-IV: (SCID; Spitzer et al., 1992). The SCID is a standardized semi-structured interview designed to assess psychiatric diagnosis, demographic and social information, and other pertinent diagnostic information. The SCID has well-documented reliability and validity. Interviewers at the STEP Clinic undergo an initial 8-hour training course including observing interviews. Diagnoses are made by consensus of a panel of clinicians who review the interview and medical records for a best estimate diagnosis. Reliability is periodically assessed by co-scoring of videotaped interviews and is consistently high.

3. Genotyping Procedures: After obtaining written informed consent from participants 40 mls of blood was obtained by venipuncture for the immortalization of lymphoblastoid cell lines. Lymphocytes were infected with EBV and transformed to immortalized lymphoblastoid cell lines. Dr. Kelsoe's lab has transformed over 2,000 cell lines with a > 97% success rate. DNA was isolated using the Qiagen column based non-organic methods and was prepared using standard phenol/chloroform extraction.

a. DNA extraction: QIAamp DNA Blood Kits used provided silica-membrane-based DNA purification. Optimized buffers lysed samples, stabilized nucleic acids, and enhanced selective DNA absorption to the QIAamp membrane. Alcohol was added and lysates loaded onto the QIAamp spin column. Wash buffers were used to remove impurities and pure, ready-to-use DNA was then eluted in water or low-salt buffer.

b. 5-HTT Polymorphism Genotyping: The polymorphism to be genotyped in the serotonin transporter gene (HTT) is a 40 bp tandem repeat in the promoter that has been widely studied and designated as HTTLPR. This polymorphism is characterized by the presence (long, or *l*) or absence (short, or *s*) and influences expression of the 5-HTT such that individuals of the *s/s* or *l/s* genotypes (~68% of the population) expression lower levels of 5-HTT than those with the *l/l* genotype (Heils et al., 1996.) 100 ng of DNA were PCR amplified using a sense primer from -1416 to -1397 (5' GGCGTTGCCGCTCTGAATGC) and an antisense primer from -888 to -910 (5' GAGGGACTGAGCTGGACAACCAC), relative to the transcriptional start site. The amplification conditions consisted of 2.5mM dNTPs and 7-dieza-dGTp, 5 μM of each primer, 1.5mM $MgCl_2$, 1 U TaqGold polymerase, 10X ABI Buffer without Mg, 5% DMSO. The cycling conditions were 61° C annealing for 30 seconds, 95° denaturing for 30 seconds, 72° C extension for 1 minute, and the final 72° C extension for 10 minutes. One primer was fluorescently labeled and the PCR product electrophoretically separated and detected on an ABI 3730 DNA Analyzer and GeneMapper 4.0 software. Each sample was run with an internal standard with a different color fluor enabling very precise sizing. The *s* allele was identified by the presence of 477bp band/peak and the *l* allele was identified by the presence of 521 band/peak. Genotypes were read visually by two different readers provided by Dr. Kelsoe's laboratory resources. Data was entered into a custom database that can output data in a variety of formats suitable for various statistical analysis packages. The Kelsoe lab has run several hundred subjects using this marker with very high success.

4. Bipolar Symptomatology: Young Mania Rating Scale; Hamilton Rating Scale for Depression; Beck Depression Inventory; Clinical Global Impression Scale-S: [(Y-MRS; Young et al., 1978); (HAM-D; Hamilton, 1960); BDI; Beck et al., 1961); ([CGI-S; Guy, 1976]). The YMRS is an 11-item, clinician-administered interview scale designed to quantify the severity of mania over the past 48 hours. Scores range from 0 to 60. Studies have demonstrated internal consistency ($\alpha = .80$), convergent validity ($r = .83$, $p < .0001$), divergent validity (no significant correlations with depression and hyperactivity ratings) and interrater reliability with a correlation of .93 between raters (Young et al., 1978). Patients are considered to be at minimal and subsyndromal symptom severity at <12 YMRS, at moderate syndromal symptom severity with 13-26 YMRS, at maximum syndromal severity with >26 YMRS.

The HAM-D is an interview assessment of depressive symptomatology. The 25-item version (which adds several cognitive symptoms to the scale over the BDI) was administered. Previous studies have demonstrated internal consistency reliability coefficients ranging from .83-.94, and inter-rater reliability was above .85 in 7 of 8 studies (Rabkin & Klein, 1987). Patients are considered to be at minimal and subsyndromal symptom severity at ≤22 HAM-D, at moderate syndromal symptom severity with 22-27 HAM-D, and at maximum syndromal severity with >27 HAM-D.

The BDI is a self-report rating inventory measuring characteristic attitudes and symptoms of depression. Internal consistency for the BDI ranges from .73 to .92 with a mean of .86. (Beck, Steer, & Garbin, 1988). The BDI has a split-half reliability co-efficient of .93. Groth-Marnat (1990) reported that re-test reliabilities ranged from .48 to .86, depending on the interval between re-testing and type of population. A meta-analyses

of studies on the revised BDI's psychometric properties by Richter, Werner, Heerlim, Kraus, & Sauer (1998) report advantages with the revised BDI's high content validity, and validity in differentiating between depressed and non-depressed people. Beck, Steer and Garbin (1988) reported that the revised BDI has been found to include three to seven factors, depending on the method of factor extraction. These include factors that reflect negative attitudes towards self, performance impairment and somatic disturbances, as well as a general factor of depression (Brown, Schulberg & Madonia 1995). Total scores ranging 0-13 indicate minimal levels of depression, scores ranging 14 to 19 indicate mild levels depression, scores ranging 20-28 indicate moderate levels of depression and scores ranging 29-63 indicate severe levels of depression.

The CGI-S is a subcomponent of the Clinical Global Scale, which has been in use for nearly 3 decades and used to assess treatment response. This module is rated on a seven-point scale (1=normal to 7=extremely ill); The Severity of Illness item requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating according to: normal (not at all ill); borderline mentally ill; mildly ill; moderately ill; markedly ill; severely ill; or extremely ill.

5. Lithium Presence: Because lithium levels may influence the primary and secondary aims of this study, an assessment of its presence and levels were derived from subjective interviews with patients and laboratory blood lithium levels.

6. Lifetime Illness Severity: Because lifetime illness severity may influence baseline symptomatology, this was assessed using SCID-IV Bipolar Module question, "How

many total episodes of depression, mania, and mixed episodes have you experienced?" Participants are asked when their first episode, depression and/or mania and/or mixed occurred. Lifetime illness severity is then determined by dividing total number of months since first affective episode by number of episodes reported yielding a coefficient that should be interpreted as *x* number of months per episode, where lower values represent a more severe lifetime illness course. For example, a participant with a coefficient of .5 may experience one bipolar episode every two weeks, whereas another with a coefficient of .25 may experience one bipolar episode per week. To reiterate, on an axis, lower scores represent higher illness severity (e.g., 0.1 represents higher illness severity than a score of 0.2.) Episode frequency as opposed to length of episode or number of years ill was chosen as the standard by which to assess illness severity as this captures the recurrent nature of the disorder, which is associated with higher scores of depression and mania at the index assessment (Valenti, 2011).

D. Data Analyses

Descriptive data analyses assessed normality, homogeneity of variance and outliers for all continuous variables. Analyses of frequencies were conducted to determine the proportion in the sample of participants reporting the presence of each stressor category, including severe events, loss events, dependent vs. independent events and goal-attainment events.

Data analysis addressed the aims of the study through the use of General Linear Model (GLM) multivariate analysis of variance (MANOVA). MANOVA was selected over ANOVA, given that there were four related primary outcome measures of interest,

and MANOVA controls for the relationships between dependent variables. Additionally, MANOVA is robust to violations of normal distributions and given the naturalistic character of this study, it allows for examination of a non-normal distribution in the independent variables of stress and genotype. Because MANOVA is sensitive to outliers, univariate and multivariate outliers were examined using the Mahalanobis distance, which was then compared to the chi-square critical value. Transformations were not conducted as the data did not contain many outliers. Multicollinearity between dependent variables was tested, with reason for concern if correlations reach .9 value. For each hypothesis, GLM was used with an outcome of depressive and manic symptomatology as measured by HAM-D, BDI, YMRS, and CGI-S, which were the four multiple continuous dependent variables for the MANOVA procedures. Main effects were tested for the effect of the 5-HTT allele (*s/s* and *s/l* vs. *l/l*), and stress (presence vs. absence of severe events), as well as interaction between genotype and stress.

For each stress variable, a separate analysis was conducted, with stress and genotype coded as dichotomous variables. In determining covariate inclusion, age, gender, marital status, employment status, ethnicity, presence of psychotropic medication at the start of study, number of self-reported lifetime episodes as an index of illness severity, and presence of lithium at baseline were examined. Only presence of lithium at baseline predicted significantly different levels of depression and mania at baseline (Table 12) and as such, was included as a covariate in all of the analyses.

E. Power Analyses

The study was originally powered for a number of 72 participants, however 42 participants were feasible to recruit. Based on the following assumptions (i.e., power of = .80, given an effect size of $f^2 = .25$ and a significant level of $p < .05$), 42 participants was a sufficient number of participants. Power was estimated using an effect size of $f^2 = .25$ as an estimate of a large effect size for multiple R^2 as described by Cohen (1988). An $f^2 = .25$ corresponds to an $R^2 = .13$ that is interpreted as 13% of the variance of the dependent variable explained by the independent variables. Cohen (1988) stated that an effect of 13% of the variance explained corresponds to a "medium" effect size.

III. RESULTS

A. Preliminary Analyses

All data were analyzed using PAWSStatistics 17.0. The main analysis technique used to test the hypotheses was the General Linear Model (GLM). Correlation analyses were used to examine the relationships between potentially confounding clinically descriptive variables (i.e., presence of lithium at baseline, illness severity, age, gender, ethnicity, employment status), the dependent variables of interest, and the independent variables. Pearson correlations were also used to examine the multi-collinearity of the dependent variables. All the variables were examined for violations of the normality of distribution and homogeneity of variance assumptions.

For each hypothesis, Multivariate GLM was used with an outcome of depressive symptomatology as measured by the HAM-D and BDI. The outcome for manic symptomatology was measured by the YMRS, and the outcome for illness severity as deemed by the clinician was measured by the CGI-S. Main effects were tested for the effect of the 5-HTTLPR alleles (*s/s* and *s/l* vs. *l/l*), life events (presence vs. absence of severe events, loss events, dependent on disorder events, and goal attainment events in the four months prior to study baseline), as well as interaction between genotype and stress. As the *s* allele confers reduced transcriptional efficiency, *s*-carriers are considered the low efficiency group and were thus grouped together (Heils et al., 1996), following convention in the literature (Caspi et al., 2003). Therefore, the 5-HTTLPR genotype was analyzed as a bivariate variable (*s/s* and *s/l* vs. *l/l*). Similarly, given the non-normal distribution and high degree of skewness of life events as measured by the LEDS, life events were analyzed in a dichotomous fashion where the absence or presence of the

event makes for the most parsimonious analytic approach. Events which were rated as dependent on the disorder were excluded from the analysis of hypothesis one in the effort to control for the high degree of correlation such events contribute to the outcome variables of symptomatology.

Based on the preliminary analyses presence or absence of lithium at baseline was included as a covariate.

B. Characteristics of the Sample

Demographics

Table 1 displays the demographic characteristics of the sample. The mean age was forty-six with a range from thirty-one years old to seventy years old and most participants were Caucasian (66.7%). The sample was comprised of a male majority (90.5%) and most participants were separated or divorced (47.6%) as opposed to participants who were never married (16.7%) or married (35.7%.) More participants were unemployed and or disabled (64.3%.)

Clinical characteristics

Table 2 displays the means, standard deviations, range, skewness and kurtosis of participants' clinical characteristics. Twenty-one participants (50%) were prescribed lithium at baseline and blood levels were within therapeutic levels (i.e., 0.8 to 1.2 mEq/L) with a mean level of 0.9 mEq/L. In addition, eighteen participants (42.9%) were also taking another psychotropic medication at study baseline. These participants were being tapered off from all other psychotropic medication for the purpose of starting the longitudinal lithium monotherapy research protocol. Lithium presence was not

significantly predictive of presence or absence of other psychotropic medications (p = 1.00). For participants with lithium at baseline, the reported mean length of time to have taken lithium was 71.10 weeks or 17.75 months. Patients recorded as 0 weeks on lithium were prescribed lithium within the week of starting the study and had their lithium levels measured prior to completing study questionnaires. One participant reported having taken lithium for approximately 18 years (866 weeks) and was thus the only outlier in the sample in terms of lithium length at baseline. Participants' age of first affective episode (i.e., depression, mania, hypomania, or mixed episode) was 21.07 years old and the sample spanned participants with experience of first affective episode from three years old to sixty years old. Participants reported an index of illness severity mean of 13.7, which is to say, participants reported an affective episode approximately once every 13.7 months. The range for illness severity was one affective disorder episode every four months to four episodes daily. The data suggests this sample included participants who experienced categorically finite and distinct mood episodes and participants who experienced rapid cycling and mixed types of bipolar disorder. One-way ANOVA revealed participants with the *s/s* and *s/l* genotype did not significantly differ from those with the *l/l* genotype in their illness severity index (p = .389.)

Descriptive analyses of outcome measures

Table 3 displays the means, standard deviations, range, skewness and kurtosis of the outcome measures. The sample at baseline scored in minimal to mild symptoms of depression and mania with a mean HAM-D score of 8.67, mean BDI score of 14.43, mean YMRS score of 5.31 and mean CGI-S score of 3.19.

Genotype and Life Event Cross-Tabulations

Table 4 displays observed and expected genotype frequency. An equal number of participants carried the genotypes *s/s* and *s/l* and those carrying the homozygous genotype (*l/l*). The population was not in Hardy-Weinberg equilibrium, $\chi^2 = 4.65$. In this Hardy-Weinberg test, the actual degrees of freedom were (n-2), because the observed numbers were used to generate the expected numbers (rather than using a theoretical expectation from other sources). Thus, variation in expected numbers is also somewhat constrained. The appropriate chi-square value is that with (n-2) or 1 degree of freedom, which is equal to 3.84. Because the χ^2 value (4.65), which measures the extent of variation in the data from expectations, is more than the χ^2 value (3.84), it is not possible to accept the null hypothesis that the population is in Hardy-Weinberg equilibrium.

Table 5 displays the cross-prevalence of life events with genotype. Chi-square tests between the independent variables (i.e., genotype and life event dimensions) showed that 5-HTTLPR genotype was significantly associated with goal attainment events ($\chi^2 = 6.15$, $p = .013$) so that *s* allele carriers had more goal-attainment events than those with the *l/l* genotype. No other significant associations were found between 5-HTTLPR and life event dimensions. Figure 1 displays the cross-prevalence of goal-attainment events by levels of 5-HTTLPR genotype.

Genotype by Lithium Presence Cross-Tabulation

Table 6 displays the distribution of genotypes across levels of lithium presence at baseline. Genotype was not significantly associated with lithium status at baseline ($\chi^2 = .00$, $p = 1.00$).

Life Event by Lithium Presence Cross-Tabulation

Table 7 displays the Chi-square and *p* values. Chi-square tests showed that loss life events were associated with lithium status ($\chi^2 = 3.63$, p = .05) and that there was a trend toward significance for dependent events to be associated with lithium status ($\chi^2 = 3.43$, p = .06). Specifically, there were significantly fewer loss events and a trend toward significance for fewer disorder-dependent events in the presence of lithium. No other significant associations were observed for loss or goal-attainment events.

C. Prevalence of stress

Table 8 summarizes the following.

Severe events. Thirteen (31%) participants experienced at least one severe event. Examples of severe events included filing bankruptcy, wife's suicide attempt, financial crime committed against participant, removal of parental rights, father's death, job loss, being investigated for child abuse. Out of the seventeen severe events reported, four (23.52%) were money and financial related, three (17.64%) were crime and legal related, three (17.64%) were health related, two (11.7%) were education related, two (11.7%) were work related, two (11.7%) were death related, and one (5.88%) was marital related.

Loss events. Twenty-six (61.9%) participants experienced at least one loss event. Examples of loss events included death of confidante, work demotion, bankruptcy filing, arguments with significant other, tax debt, receiving unfavorable health diagnoses, moving in with in-laws, and being charged with a crime. Out of the one hundred and ten loss events reported, forty-four (40%) were health related, twelve (10.9%) were education related, twelve (10.9 %) were other relationship related, eleven (10%) were money and possession related, nine (8.18%) were work related, eight (7.27%) were death and miscellaneous related, seven (6.36%) were crime and legal related, four (3.63%) were

relationship and marital related, two (1.8%) were housing related, and one (.9%) was reproduction related.

Dependent events. Twenty-two (52.4%) participants experienced at least one disorder-dependent event. Examples of disorder-dependent events included starting psychological treatment, arguments with friends and relatives, quitting one's job, receiving a mental illness diagnosis, and being psychiatrically hospitalized. Out of the thirty-two disorder-dependent events, twenty-four (72.72%) were health related (i.e., starting psychiatric treatment or receiving mental health diagnosis), two (6.06%) were work related, two (6.06%) were crime and legal related, two (6.06%) were marital and relationship related, and one (3.03%) was categorized as miscellaneous.

Goal-attainment events. Thirty-one (73.8%) participants experienced at least one goal-attainment event. Examples of goal attainment events included drawing out a car loan for a car purchase, receiving a check toward financial gain, moving residence, starting a new job, resolution of legal case, starting psychotherapy, starting a hobby, contacting lost relatives, and going on a vacation. Out of the sixty-seven goal-attainment events reported, twenty-three (34.32%) were health and treatment seeking related, twenty-two (32.83%) were education related, eleven (16.41%) were work related, five were (7.4%) money and possession related, two (2.98%) were relationship oriented, one (1.49%) was housing related, one (1.49%) was legally related, and one (1.49%) was marital related.

D. Correlations

Table 9 displays the correlations between potentially confounding clinically descriptive variables (i.e., presence of lithium at baseline, illness severity, age, gender, ethnicity, employment status) and the dependent variables. Point biserial values are presented for the dichotomous variables – presence of lithium at baseline, gender, employment status, and ethnicity – and zero-order Pearson correlations for the continuous variables – illness severity, age. Lithium presence at baseline was significantly associated with HAM-D, CGI-S, BDI, and YMRS scores. ANOVA's were run with lithium presence as IV and symptoms as DV. Table 10 and Figure 2 display the means and significant values of the outcome variables dependent on presence vs. absence of lithium at baseline. Lithium predicted CGI-S scores ($p = .009$), YMRS scores ($p = .014$), BDI scores ($p = .001$), and HAM-D scores ($p = .011$). Therefore, lithium presence at baseline was entered as a covariate in all hypotheses analyses. Illness severity was also significantly negatively correlated with CGI-S score indicating the higher the illness severity, the higher the CGI-S score (as lower numbers of illness severity on an axis represent higher illness severity) but was not entered into the overall analyses given its lack of association with the other outcome measures.

Table 11 summarizes the relationships between life events and genotype with potentially confounding variables. Chi-square analyses did not reveal any significant differences in marital or employment status or gender as a function of genotype or life event dimensions. The differences that arose are summarized in Table 12 and were as follows: Caucasian participants were more likely to engage in goal-attainment events (67%) than African-Americans (19%) or Hispanics (9.67%) ($\chi^2 = 14.84$, $p = .011$).

Finally, as depicted in Figure 3, participants who were not on lithium tended to experience more loss events ($\chi^2 = 3.63$, $p = .05$).

Neither did one-way analysis of variance (ANOVA) reveal any significant differences in age or illness severity according to genotype and life event dimensions.

Table 13 displays the bivariate zero-order correlations, which were used to examine the multi-collinearity between the dependent variables. All outcome measures were positively associated with each other, with the exception of no significant association between BDI and YMRS scores. YMRS and HAM-D scores were counter-intuitively positively associated with each other, which may indicate a sample presenting with mixed bipolar disorder features.

Following convention in the literature (Brown & Harris, 1979) and given the associations between disorder-dependent events with occurrence of severe, loss, and goal-attainment events, all disorder-dependent events were removed from the main analyses.

E. Hypothesis 1

Interaction between life event severity and 5-HTTLPR genotype. Table 14 displays the omnibus MANOVA's and the main effects of genotype, life event severity (ES), baseline lithium, genotype x life event severity interaction, baseline lithium and genotype interaction, and genotype x life event severity x lithium presence at baseline interactions in predicting depression symptoms as measured by the BDI and HAM-D, illness severity as measured by CGI-S and manic symptoms as measured by the YMRS. A two-way MANOVA did not reveal a significant main effect for 5-HTTLPR genotype,

Wilk's λ = .779, F (4,31) = 2.2, p = .09, partial eta squared = .221. Power to detect was .578. It did not reveal a significant interaction between event severity and 5-HTTLPR genotype, Wilk's λ = .795, F (4,31) = 2.0, p = .119, partial eta squared = .205. Power to detect was .533. The two-way MANOVA revealed a significant main effect for event severity, Wilk's λ = .714, F (4,31) = 3.10, p = .029, partial eta squared = .286. Power to detect was .748. It also revealed a significant main effect for lithium presence at baseline, Wilk's λ = .601, F (4,31) = 5.135, p = .003, partial eta squared = .399. Power to detect was .938. It revealed a trend toward significance for the 2-way interaction between event severity and lithium at baseline, Wilk's λ = .765, F(4,31) = 2.38, p = .073, partial eta squared = .235. Power to detect was .617. Finally, it revealed a significant interaction between event severity, 5-HTTLPR genotype and lithium presence at baseline, Wilk's λ = .367, F (4, 33) = 3.029 p = .031, partial eta squared = .269. Power to detect was .740. For the omnibus MANOVA, Box's M test was run. Box's M = 57.05, p = .087 which means that there are no significant differences among groups in the covariance matrices.

Table 15 displays the follow-up MANOVA results. Given the significance of the overall test, the main effects were examined against the adjusted p-value, .037. The adjusted p-value was obtained by taking the equivalent distance between an alpha level of .05 and an alpha level of .012, the latter of which takes into account the four multiple comparisons of the dependent variables. Levene's statistic revealed no unequal group variances in the dependent variables (CGI-S, F[3,38] = 1.45, p = .24; YMRS, F[3,38] = .37, p = .775; BDI, F[3,38] = 1.36, p = .269; HAM-D, F[3,38] = 1.19, p = .327).

No significant main effect was observed for 5-HTTLPR genotype predicting BDI, CGI-S, HAM-D or YMRS scores at baseline.

A significant main effect was observed for the event severity dimension predicting BDI scores ($F[1,34] = 9.76$, $p = .004$]), CGI-S scores ($F[1,34] = 5.32$, $p = .02$]), and HAM-D scores ($F[1,34] = 13.23$, $p = .001$]). Specifically, participants with a severe event reported higher BDI scores ($\mu = 20.23$, S.D. = 16.82), higher HAM-D scores ($\mu = 12.46$, S.D. = 9.39) and higher CGI-S scores ($\mu = 3.77$, S.D. = 1.3) than those without the presence of a severe event in the four months prior to baseline where BDI scores were ($\mu = 11.83$, S.D. = 10.9), HAM-D scores ($\mu = 6.96$, S.D. = 6.88) and CGI-S scores ($\mu = 2.93$, S.D. = 1.16). Table 16 and Figure 4 display the main effect means.

A significant main effect was observed for baseline lithium predicting BDI scores ($F[1,34] = 12.44$, $p = .001$]), YMRS scores ($F[1,34] = 6.66$, $p = .014$]), CGI-S scores ($F[1,34] = 7.77$, $p = .009$]), and HAM-D ($F[1,34] = 7.28$, $p = .011$]) scores. Specifically, participants without lithium at baseline reported higher BDI scores ($\mu = 20.38$, S.D. = 15.03), higher HAM-D scores ($\mu = 11.29$, S.D. = 8.84), higher YMRS scores ($\mu = 7.75$, S.D. = 6.9), and higher CGI-S scores ($\mu = 3.71$, S.D. = 1.1) than those with lithium at baseline where BDI scores were ($\mu = 8.48$, S.D. = 8.3), HAM-D scores ($\mu = 6.05$, S.D. = 6.3), YMRS scores ($\mu = 3.05$, S.D. = 4.7(, and CGI-S scores ($\mu = 2.67$, S.D. = 1.19).

No significant interaction was observed between 5-HTTLPR and event severity at baseline in predicting BDI, YMRS, CGI-S, and HAM-D scores.

Table 17 and Figures 5 and 6 display the means for the significant 2-way interaction observed between event severity and lithium, which predicted BDI, $F(1,34) = 4.77$, $p = .03$ and HAM-D scores, $F(1,34) = 8.50$, $p = .006$. Specifically, in the presence

of a severe event, participants not taking lithium scored the highest in their BDI scores (μ = 30.57, S. D. = 15.42) and in their HAM-D scores (μ = 19.00, S. D. = 7.50).

Table 18 and Figure 7 display the trend toward significance for the 3-way interaction observed between HTTLPR genotype, event severity, and lithium status at baseline. These independent variables predicted HAM-D scores, $F(3,34) = 2.9$, $p = .04$, but did not predict BDI, YMRS, or CGI-S scores. Specifically, in the absence of severe events lithium appeared to have little effect on depressive symptoms where the mean HAM-D score for those on lithium was (μ = 7.79, S. D. = 8.8) and for those not on lithium, the mean HAM-D score was (μ = 7.23, S. D. = 6.87). However, in the presence of a severe event, the presence of lithium had a significant effect in reducing depressive symptoms (μ = 4.83, S. D. = 3.55) when compared to the absence of lithium (μ = 19.12, S. D. = 7.85). Furthermore, this trend toward significance in the 3-way relationship was dependent on 5-HTTLPR genotype so that lower HAM-D scores were evident in the presence of lithium and severe life events for participants with the *s/s* and *s/l* genotype (μ = 3.00, S. D. = 3.00) whereas in the absence of stress and presence of lithium, the direction was opposite so that higher HAM-D scores were found for the *s/s* and *s/l* genotypes (μ = 9.5, S. D. = 10.6).

F. Hypothesis 2A

Loss events predicting bipolar symptomatology at baseline. A multivariate analysis of variance (MANOVA) was performed to investigate symptom differences in bipolar disorder at baseline. Four dependent variables were used - HAM-D, CGI-S, YMRS, and BDI scores. The independent variable was stress (presence vs. absence of

loss life event) and the covariate was lithium presence at baseline as a dichotomous variable (presence vs. absence) with a model that specified the main effects of loss life events and lithium at baseline and their interaction.

Table 19 displays the omnibus MANOVA's. MANOVA revealed a significant main effect for loss events, Wilk's $\lambda = .711$, $F(1,40) = 3.56$, $p = .01$, partial eta squared = .28. Power to detect was .81. It also revealed a trend toward significance for the loss event by lithium interaction, Wilk's $\lambda = .804$, $F(1,40) = 2.13$, $p = .08$, partial eta squared = .19. Power to detect was .57. Box's M test was run. Box's M = 14.56, $p = .234$ indicated no significant differences among groups in the covariance matrices. Levene's statistic revealed no unequal group variances in the dependent variables (CGI-S, $F[1,40] = .00$, $p = .43$; YMRS, $F[1,40] = 1.14$, $p = .29$; BDI, $F[1,40] = 1.93$, $p = .17$; HAM-D, $F[1,40] = .62$, $p = .43$).

Follow-up MANOVA of the omnibus significant main effect of loss events and the trend toward significance for the loss event by lithium interaction did not reveal a significant main or interaction effect for loss events and lithium presence predicting HAM-D scores, CGI-S scores or BDI scores. However, a significant main effect was observed for loss events predicting YMRS scores ($F[1,38] = 4.15$, $p = .048$). Participants with the presence of a loss event had higher YMRS scores ($\mu = 5.35$, SD = 1.15) than those without a loss event ($\mu = 3.63$, SD = 1.54.) A significant interaction was found between baseline lithium and loss events ($F[1,38] = 4.91$, $p = .03$) in predicting symptoms of the YMRS. Specifically, lithium had little effect on YMRS scores in the absence of loss events. Participants on lithium had a mean YMRS score of 4.27, SD = 5.85 and those not on lithium had a mean YMRS score of 3, SD = 2.55. However, in the

presence of loss events, lithium absence resulted in significantly higher YMRS scores (mean = 9, SD = 7.36) and lithium presence resulted in significantly lower YMRS scores (mean = 1.70, SD = 2.83.)

Table 20 displays main effects of loss life event, baseline lithium, and baseline lithium x loss life event interaction. Table 21 and Figure 8 display the YMRS means as predicted by the interaction of loss events by lithium status at baseline.

G. Hypothesis 2B

Disorder-dependent vs. disorder-independent life events predict bipolar symptomatology at baseline. A multivariate analysis of variance (MANOVA) was performed to investigate symptom differences in bipolar disorder at baseline. Four dependent variables were used - HAM-D, CGI-S, YMRS, and BDI scores. The independent variable was stress (disorder-dependent vs. disorder-independent life events) and the covariate was lithium presence at baseline as a dichotomous variable (presence vs. absence) with a model that specified the main effects of loss life events and lithium at baseline and their interaction.

Table 19 displays the omnibus MANOVA's. MANOVA revealed no significant main effect for disorder-dependent events, Wilk's $\lambda = .905$, $F(1,40) = .922$, $p = .46$, partial eta squared = .09. Power to detect was .26. It revealed no significant interaction of disorder-dependent event by lithium, Wilk's $\lambda = .940$, $F(1,40) = .559$, $p = .69$. Therefore, no follow-up tests were conducted.

H. Hypothesis 2C

Goal-attainment life events predict bipolar symptomatology at baseline.

An analysis of variance (MANOVA) was performed to investigate symptom differences in bipolar disorder at baseline. Four dependent variables were used - HAM-D, CGI-S, YMRS, and BDI scores. The independent variable was stress (presence vs. absence of goal-attainment life event) and the covariate was lithium presence at baseline as a dichotomous variable (presence vs. absence) with a model that specified the main effects of goal-attainment life events and lithium at baseline and their interaction.

Table 19 displays the omnibus MANOVA's. MANOVA revealed a significant main effect for goal-attainment events, Wilk's $\lambda = .643$, $F(1,40) = 4.86$, $p = .003$, partial eta squared = .35. Power to detect was .92. It also revealed a significant interaction between goal-attainment events and lithium, Wilk's $\lambda = .664$, $F(1,40) = 4.4$, $p = .005$, partial eta squared = .33. Power to detect was .89. Box's M test was run. Box's M = 17.91, $p = .132$ indicated no significant differences among groups in the covariance matrices. Levene's statistic revealed no unequal group variances in the dependent variables (CGI-S, $F[1,40] = .301$, $p = .58$; YMRS, $F[1,40] = .24$, $p = .62$; BDI, $F[1,40] = .57$, $p = .45$; HAM-D, $F[1,40] = 3.34$, $p = .07$).

Table 22 and Figure 9 display the follow-up MANOVA for the significant main effect of goal-attainment events. The analysis revealed a main effect for goal-attainment events ($F[1,38] = 5.95$, $p = .01$) in predicting BDI symptoms at baseline. Participants with goal-attainment events had significantly lower BDI scores ($\mu = 12.52$, SD = 11.68) than participants who had no goal-attainment events ($\mu = 19.82$, SD = 16.91). No other significant main effect was observed for goal-attainment events in predicting symptoms

as measured by the YMRS, HAM –D or CGI-S scores. The omnibus interaction between goal-attainment events and lithium did not hold when explored by follow-up tests.

IV. DISCUSSION

A. Summary

The current study investigated whether the interaction between the 5-HTTLPR genotype and life events was associated with symptoms of bipolar disorder at the baseline of a lithium monotherapy study. The diathesis-stress model assumes that the inherited predisposition for bipolar disorder is expressed only under certain environmental conditions. Stress in the current study was defined as life events rated along several domains - severity, loss, disorder-dependent, and goal-attainment - and was analyzed as either absent or present. Additional secondary aims of the study were to evaluate the impact of loss, disorder-dependent, and goal-attainment events on bipolar disorder symptomatology at lithium monotherapy study baseline. The psychiatric diathesis was evaluated by identifying the participant-specific polymorphism of the serotonin transporter gene (5-HTTLPR), which contains a *short* and a *long* allele resulting in three distinct 5-HTTLPR genotypes, *s/s, s/l,* and *l/l.*

This study investigated the following hypotheses: 1) the presence of severe life events in the four months prior to study initiation will moderate the influence of genotype such that participants with the *s/s* or *s/l* genotype are expected to experience more depressive and manic symptoms than participants with the *l/l* genotype and no such differences will be observed in the absence of severe life events; 2) the presence vs. the absence of loss events in the four months prior to treatment will predict higher severity of depression and mania baseline symptoms; 3) the presence vs. the absence of dependent life events will predict higher severity of manic and depressive symptoms at baseline; 4) the presence vs. the absence of goal-attainment events will predict higher severity of

manic and depressive symptoms at baseline. The primary and secondary analyses were conducted using as dependent variables the BDI, YMRS, HAM-D, and CGI-S. All analyses controlled for lithium presence at baseline given the influence of lithium on baseline symptoms.

B. Hypothesis 1

5-HTTLPR and severe life event interaction. The omnibus MANOVA procedure revealed no significant main effect for genotype and no significant interaction between 5-HTTLPR and life event severity.

However, the omnibus MANOVA revealed a significant main effect for event severity and a significant main effect for lithium status at baseline. The presence of a severe event predicted more severe depressive symptomatology on both, the self-report (BDI) and clinician-administered ratings (HAM-D and CGI-S), than the absence of a severe event. There were no significant differences in manic symptoms as measured by the YMRS among the two groups. The presence vs. the absence of lithium at baseline predicted lower depressive and manic symptoms on both, self-report and clinician-administered measures.

Additionally, the omnibus MANOVA revealed a significant 3-way interaction between 5-HTTLPR, event severity, and lithium status at baseline predicting manic and depressive symptoms at lithium monotherapy study initiation. Upon follow-up analyses there was a trend toward significance for lower HAM-D scores. Specifically, in the absence of severe events lithium had little effect on depressive symptoms, whereas in the presence of a severe event there was a trend toward significance for lithium to reduce

depressive symptoms. Furthermore, this 3-way relationship was dependent on 5-HTTLPR genotype, so that lower HAM-D scores were evident in the presence of lithium for participants with the *s/s* and *s/l* genotype when severe events were present and higher when severe events were absent. This finding is discussed below.

While the primary goal of this project was to examine the relationship between stress, genetics and bipolar symptoms, the interaction of lithium with these variables is an intriguing finding. The evidence for the prophylactic effect of lithium on symptoms of bipolar disorder is robust and spans some seven decades (Cade, 1949; Schou, 1954) and the US Food and Drug Administration approved lithium as an intervention for mania in 1970 (Jefferson & Greist, 1977). Lepkifker and colleagues (2007) reported significant reductions on indices of frequency, severity, and duration of depressive and manic relapse during lithium therapy compared to before lithium treatment.

The prophylactic efficacy, however, unfolds in a spectrum that ranges from an "excellent" response with complete suppression of episodes to "resistance" with no change in frequency, severity, or duration of episodes (Abou-Saleh & Coppen, 1990). In depressive symptoms, mixed states, and rapid cycling, for instance, the therapeutic window for lithium's effectiveness narrows (Young et al., 2000). Given the variability in lithium prophylaxis identifying specific factors associated with and predictive of favorable prophylactic response has become especially relevant. Most research has focused on clinical variables, which will be discussed below. Recent studies have also focused on genetic predictors to lithium prophylaxis. Few studies have examined psychosocial factors. No studies have examined the relationship of gene by life event interactions to lithium response or patient symptomatic presentation according to lithium

presence vs. absence from the framework of gene and life event interactions. The current results although cross-sectional, suggest that the benefit of lithium in treatment is dependent on the interaction between environmental and genetic factors in a predictable manner, which implies both, that we can better predict who will likely respond to lithium, and that psychosocial interventions to manage environmental stress may be beneficial adjunctive treatments to pharmacotherapy.

A number of variables have been shown to predict lithium prophylaxis. Some of the clinical variables predictive of poor response to lithium have been identified as frequency of episodes (e.g., a history of more than 10 previous episodes (Swann et al., 1999); presence of dysphoria (Dilsaver et al., 1993); illness severity (episodic and rapid cycling pattern of mania-depression interval (Coryell et al., 2000); early age of first onset (Okuma, 1993); a high number of previous hospitalizations (Tondo et al., 2001); lack of a family history of bipolar disorder, and an order of episodes where depression is followed by mania (Grof, 2010).

However, only a few studies focus on psychosocial factors as factors in predicting lithium response. Yazici and colleagues (1999) found that being unmarried was associated with poor lithium response. A study by Kleindienst and colleagues (2005) found that high social status, satisfactory social support, and social dominance were protective against the recurrence of an episode under lithium. In contrast, the same study found that stress and unemployment were predictive of poor response to lithium. In terms of life events, a high number of life events have been identified as possible risk factors for poor response (Maj, Del Vecchio & Starace, 1984; Kulhara et al., 1999). This study found that when not on lithium, those with life stress of a severe nature and stress with

components of loss exhibit higher symptomatic distress relative to individuals with similar stressors but adherent to lithium treatment. The findings suggest that lithium is most protective in the presence of such life events, and that despite life events being predictors of poor response to lithium, adhering to lithium treatment may help buffer the depressogenic effects of life stress.

Gene Polymorphism Variables: Other predictors of lithium response have been identified in molecular psychiatry. 5-HTTLPR, one of the most promising and studied biological variables, has been found to predict response to antidepressants and anti-anxiety agents (Staddon et al., 2002). Despite lack of consistency, there is some evidence to suggest that in bipolar patients and when lithium is used as a treatment agent, *s* carriers show favorable response. For instance, Stamm and colleagues (2008) found that the *s*-allele carriers had a more favorable lithium response compared with patients carrying at least one *l* allele, though this finding was in a sample of depressed patients. In bipolar patients treated with an antidepressant, *s* carriers were more prone to experience manic and hypomanic episodes, suggesting the *s* allele confers a propensity toward greater reactivity (Ferreira et al., 2009; Masoliver et al., 2006). Del Zompo and colleagues (1999) found a trend of higher frequency of the *l* allele among lithium non-responders. Similarly, Serretti and colleagues (2004) reported that patients homozygous for the *l* allele were more likely to develop an illness episode within 3 years of prophylactic treatment with lithium and that those homozygous for the *s* allele did not necessarily exhibit a poor efficacy in response. In another study, Manchia and colleagues (2009) found no significant association between the 5-HTTLPR polymorphism and response to lithium whereas Serretti and colleagues (2001) reported the *s/s* variant as associated with a worse

lithium response compared to both *s/l* and *l/l* variants. These findings are inconsistent, though there is evidence to suggest that *s* allele carriers may be more reactive individuals, including reactivity to pharmacotherapy, which is a finding consistent with this study.

Currently, the role which the 5-HTTLPR polymorphism plays in lithium response in bipolar populations is not clear. Neither is there an understanding of the interactive effects of life events, genotype, and lithium absence vs. presence in predicting symptomatic presentation in patients with bipolar disorder. The overall finding of this study mirrors previous research suggesting that *s* allele carriers exhibit more favorable response to lithium treatment. Findings suggest this effect is especially pronounced in the presence of severe life events. In addition to lending support to the diathesis-stress model, these findings potentially imply the importance of the psychosocial context in the understanding of response to lithium treatment. Further, these findings suggest a diagnosis-medication-genotype specific effect. That is, it is possible that the *l* allele confers ability to respond to antidepressants in unipolar patients, whereas the *s* allele may potentiate unique benefits for patients with bipolar disorder and those treated with mood-stabilizers, particularly lithium. Finally, the trend findings of this study for lithium conferring benefit in the direction of depressive as opposed to manic symptoms was unexpected as lithium has been found to be most efficacious in the treatment of acute mania, as demonstrated by placebo-controlled trials (Bowden, Brugger & Swann, 1994) and appears at least as effective and better tolerated than older typical antipsychotic medication for mania (Segal, Berk & Brook, 1998; Maj, 2000). However, these findings are concentrated in a purely manic sample and cannot be generalizable to the sample of this study, which presented with a primary mixed clinical presentation. It is possible that

lithium confers benefits in depressive symptoms in populations of mixed episodes and specifically, in *s* allele carriers when exposed to severe life events. Finally, considering research that identifies a key advantage of lithium in preventing suicide (Baldessarini, Tondo & Viguera, 1999; Baldessarini et al., 2006; Cipriani et al., 2005; Tondo et al., 1998), and although the mechanism by which this is achieved is yet unclear, it is possible that the finding of less severe depressive symptoms in this study is a reflection of lithium's beneficial impact on depressive polarity.

The results of this study lend partial support to the diathesis-stress model. The findings suggest that the inherited diathesis in bipolar patients expresses itself as vulnerability to severe life events. Further, findings suggest this diathesis is most pronounced in the absence of effective treatment but only in patients carrying at least one *s* allele of the 5-HTTLPR polymorphism. Results of this need to be replicated, with the implication of improving matching of patients to treatment based on genetic profile and specificity of diagnosis.

C. Hypothesis 2A

Loss events and bipolar symptoms at baseline. ANOVA tests with lithium status at baseline as a covariate revealed no main or interaction effects for loss and lithium status predicting HAM-D, CGI-S or BDI scores. A significant main effect was observed for loss events predicting YMRS scores so that participants with a loss event had a higher mania score than those without a loss event. Furthermore, this relationship was dependent on lithium status so that in the absence of loss events, lithium status had little effect on manic symptoms. However, in the presence of loss events, lithium

presence resulted in significantly lower YMRS scores. This finding suggests bipolar individuals are more likely to respond to events containing loss with symptoms of mania rather than symptoms of depression. These results might equip clinicians and caretakers with the knowledge required to monitor and possibly buffer the impact loss events might have on patients with bipolar disorder. In addition, the finding that patients with events of loss fare particularly well while on lithium, speaks to the clinical utility of this intervention.

D. Hypothesis 2B

Disorder-dependent events and bipolar symptoms at baseline. ANOVA tests with lithium status at baseline as a covariate revealed no significant main effect for disorder-dependent events and no significant interaction between such events and lithium status at baseline.

E. Hypothesis 2C

Goal-attainment events and bipolar symptoms at baseline. ANOVA tests with lithium status at baseline as a covariate revealed a significant main effect for goal-attainment events predicting BDI symptoms at baseline so that participants with goal-attainment events had significantly lower BDI means than participants without such events. No other significant main effect on YMRS, CGI-S, or HAM-D was observed for goal-attainment events and neither was a significant interaction between lithium status at baseline and goal-attainment events.

F. Role of Life Events in Bipolar Disorder

1. Severe Events and Bipolar Symptomatology

The findings of this study suggest that life events are closely associated to the symptomatic presentation of bipolar disorder. They imply the impact that environmental factors might have on symptomatic presentation of an affective disorder with a biological base. However, this study is unable to speak to the causal nature of such relationships. These findings are consistent with previous research demonstrating the role of life events on bipolar disorder recovery and relapse, though most of research in the area has not specifically focused on life events as conceptualized along severe, loss, goal-attainment and disorder-dependent domains. Many of the studies focus on negative, as opposed to severe, life events and indicate that they predict increases in depression, that they are not common before manic episodes and that they do not predict increases in mania for most people with bipolar disorder (Johnson & Miller, 1997; Johnson et al., 2004; Johnson et al., 2008). Similarly, in a longitudinal study negative life events, as measured using the LEDS, predicted increases in depressive symptoms over several months even after controlling for baseline levels of depressive symptoms (Johnson et al., 2004).

The current findings are consistent with a report by Hall (1984), which found an excess of severe events prior to depressive swings in patients with bipolar disorder. Moreover, the finding that the presence of a severe event is associated with more severe depressive symptoms as opposed to manic symptoms correlates with six studies (Christensen et al., 2003; Kennedy et al., 1983; Malkoff-Schwartz et al., 2000; McPherson et al., 1993; Pardoen et al., 1996; Sclare & Creed, 1990). These studies found no difference between the number of severe negative events before and after a manic

episode suggesting that the presence of a negative event prior to mania is not causal toward mania development. Similar findings were reported in longitudinal studies examining severe negative life events in relation to increases in baseline levels of manic symptoms (Alloy et al., 1999; Reilly-Harrington et al., 1999).

Given the mixed presentation sample of this study and the role of severe events in predicting increases in depressive symptoms, it may be important to consider that the same risk variables for unipolar depression, such as maladaptive cognitive style, when present in individuals with a bipolar disorder with a history of depressive symptoms as opposed to those with unipolar mania, elevate the reactivity to negative and severe life events resulting in higher depressive symptoms at the time of assessment (Alloy at al., 1999.) In fact, given the mixed clinical presentation of this sample, the findings of this study support the proposal that patients with a history of bipolar depression become more depressed in the presence of severe life events.

2. Loss Events and the Manic Defense

The findings of this study suggesting that loss events were associated with higher mania scores might initially present an interpretive challenge. Intuitively, one would expect loss events not to predict euphoria, grandiosity and increased productivity, all symptoms characteristic of mania.

One of the most cited models to explain the link between the presence of loss events and the increase in mania has been the psychodynamic model of mania (Klein, 1948) which postulates a defense brought into play to protect the patient from the most destructive effects of depression. That is, in situations of loss, the manic response is conceptualized as a temporary shield or buffer of averting the potential of sequential

depression. Further research supports the idea that people with bipolar disorder have high levels of defensiveness against painful thoughts or experiences and may show more defensive behavior after a threat (Johnson, Ballister, & Joiner, 2005). For instance, Johnson and colleagues (2005) reported a discrepancy in response on overt measures of self-esteem compared to subtle measures with less potential for response bias. Patients with bipolar disorder denied that they saw themselves negatively, yet also said they blamed themselves when things went badly, suggesting that although, and perhaps because, people with bipolar disorder may actually perceive themselves negatively, they ward such thoughts off consciously with elevated mood, grandiosity and increased productivity. Additionally, though studies which investigate life events conceptualized as containing loss are few, those which explore the role of loss in the development and prevalence of bipolar disorder seem to lend support to the manic defense hypothesis. For instance, in terms of the frequency of loss life events prior to a manic episode, Hall (1984) reported that a higher number of such events occurred prior to a manic relapse. Similarly, parental loss in childhood has also been associated to bipolar disorder (Alciati et al., 2011; Horesh et al., 2011).

Finally, many published case reports of "funeral mania" exist, in which people demonstrate manic symptoms at an important funeral or death (Hollender & Goldin, 1978; Krishnan et al., 1984; Morgan, Beckett, & Zolese, 2001; Rickarby, 1977). Though the caveat with such reports is that they are not of an epidemiological nature and do not provide prevalence data, these case studies lend some support to the manic defense hypothesis and render the findings of increased manic symptoms in light of the presence of loss events more interpretable. In this sample, the majority of the loss events reported

(40%) were health related. The loss associated with diminishing personal health in a middle-aged population and its association to higher symptoms of mania may indicate a cognitive compensatory response, employed to alleviate the threatening implications of worsening health.

3. Goal-Attainment Events, Symptoms of Bipolar Disorder, and the Behavioral Inhibition/Behavioral Activation (BIS/BAS) System

Given the heterogeneous nature of bipolar disorder, one of the reasons to consider the influence of goal-attainment events on polar-specific symptoms is the importance of identifying the role of specific dimensions of life stress on polarities of the disorder. 25-33% of individuals from the bipolar disorder diagnosis pool are identified by epidemiological studies as unipolar manic (Karkowski & Kendler, 1997). This raises the need to consider the possibility that a different set of life stress characteristics contributes to the lack of depressive symptomatology and a consistent manic presentation in this subset. In fact, research suggests that the predictors of mania and depression differ. Specifically, Johnson and colleagues (2000) found that life events involving goal attainment were predictive of increases in manic symptoms, but not in depressive symptoms (Johnson et al., 2000). Similar results were obtained where life events predicted increases in manic symptoms over a 3-month period (Johnson et al., 2004). Urosevic and colleagues (2010) also reported that life events involving goal-attainment and goal-striving trigger hypomania/mania and that negative life events trigger bipolar depression. No support has been obtained for goal-attainment life events as triggers of depression (Johnson et al., 2000; Johnson, et al., 2004). The findings of such research provide support for the behavioral activation/behavioral approach system (BIS/BAS)

(Depue, Collins, & Luciana, 1996), which posits that in order to facilitate approach behavior, increases in positive affect, energy, goal pursuit and attention towards cues of become prominent. According to this model, individuals with bipolar disorder are expected to exhibit increased reactivity to reward. When asked to describe how much undergraduates experienced increases in positive affect, energy, and motivation in the presence of cues of incentives, vulnerability to mania was indeed correlated with high BAS Reward Responsiveness, which is a subscale of the self-report Behavioral Activation Reward Responsiveness Scale (BAS; Carver & White, 1994) (Meyer, Johnson, & Carver, 1999).

The findings of this study that the presence of goal-attainment events is associated with lower depressive symptoms is somewhat consistent with the BIS/BAS model. This suggests that the presence of goal-attainment events may buffer against depression. Interestingly, the majority of the goal-attainment events (34.32%) were related to health and treatment seeking goals. This may represent a sample already motivated and thus inherently less depressed. However, the frequency of health events is similarly matched by that of education related goal-attainment events (32.83%). The data suggest the clinical importance of monitoring patients with bipolar disorder for their engagement in treatment and providing opportunities for connection to social circles, often provided by the infrastructure of education. Finally, the lack of significant finding for goal-attainment events predicting higher manic symptoms may also be due to the lifetime diagnosis status of this sample, where the majority of the sample did not receive a clear Bipolar I diagnosis.

G. Clinical Implications

The major finding of this study, which suggests that in a sample of bipolar patients with a mixed presentation lithium affords protection against the depressogenic association of severe life events and does so especially for individuals with the *s/s* and *s/l* genotype, is of great clinical relevance.

First, the finding speaks to the utility of lithium treatment in patients with bipolar disorder, who present with mixed and with subthreshold symptoms. Though research has identified episodic, mixed, and cyclical types of bipolar disorders to be poor predictors of response to lithium, this study suggests that lithium may be of significant benefit in such populations, particularly when severe life events are present. Adherence to medications is a particular challenge in patients with bipolar disorder. Nonadherence reasons range from forgetting to side effects and disorganized home environments, concern over having to take medication long-term, and insufficient information concerning bipolar disorder (Sajatovic et al., 2011). Cognitively related reasons for nonadherence include patients' beliefs about the medications being unnecessary, lack of perceived daily benefit, perceived change in appearance for the worse, and perceived interference with life goals (Devulapalli et al., 2010). Given the prophylactic effect of lithium on symptoms, it is important for clinicians to work collaboratively with patients in monitoring lithium adherence in relation to patients' contextually relevant factors, such as the presence of "candidate stressors" and to provide patients with important information, such as state of the art research, regarding their diagnostic status and lithium benefit.

Second, the findings of this study suggest that life events contribute in undesirable ways to symptom severity in bipolar disorder. This makes pertinent work that might

ameliorate the impact of severe and loss-containing events on symptoms. Some of the most used psychotherapeutic models in the treatment of bipolar disorder are psychoeducation (Colom et al., 2005; Miklowitz, 2008), cognitive behavioral treatments (Scott, Colom & Vieta, 2007), family therapy (Miklowitz et al., 2003), and most notably interpersonal and social-rhythm therapy (Frank, Swartz & Kupfer, 2000). Interpersonal and social-rhythm therapy explores pathways to relapse, including disruptions to social and circadian patterns and stressful life events. The model suggests that positive and negative life events can adversely affect circadian rhythms, posing a risk of recurrence. It tackles these issues by establishing regular routines, exploring interpersonal conflict and addressing issues around social roles, and it seems to have promise in managing bipolar disorder (Frank, 2007). It might be particularly beneficial to patients these therapies apply similar strategies toward addressing the disruptive effect of severe and loss life events. Similarly, the finding that goal-attainment events are associated to less severe depressive symptoms, and in fact, in this mixed state population do not increase symptoms of mania, are suggestive to the aforementioned psychotherapeutic models for incorporating striving toward reasonable goals in the form of pleasant activities, or activity scheduling, in their formats.

The trend toward a significant interaction between lithium, life events, and genotype suggests that research should continue research in the area with the aim of replicating results. The potential clinical uses of this research would be to identify favorable genetic profiles that would be of clinical utility. Knowledge of contextual factors, such as the presence of specific types of life events (i.e., severe events and those

containing components of loss) would help the clinician in selecting an appropriate treatment, which would reduce treatment relapses and failures.

H. Limitations and Strengths

Limitations: The most critical limitation of the study was that it used a cross-sectional design. Therefore, establishing causal links from events to symptomatology is not possible. Further, despite LEDS raters rating events along the dimension of dependent vs. independent of the disorder, the study did not assess for symptoms four months prior to the assessment. Subthreshold symptomatology may have confounded the occurrence of life events in a subtle manner not entirely apparent to the LEDS rating team.

Sample size was also a limitation, and likely limited the ability to detect significant effects. Based on the effect sizes observed, it is likely a larger effect size would have detected a significant interaction for the primary gene x stress interaction. Using GPower 3.1 and assuming the observed Wilk's λ of .795, two predictors, four dependent variables, power specified as 0.80 and alpha of .05, 52 participants would be necessary to sufficiently test this hypothesis. The current study therefore provides both some intriguing findings involving the 3-way interaction, and useful pilot data for designing next steps to more effectively test the gene x stress interactions in patients with bipolar disorder.

The lack of equilibrium in 5-HTTLPR genotype frequency presented a challenge and limitation in the study. Where the 5-HTTLPR genotype is distributed as 32% *l/l*, 49% *s/l* and 19% *s/s* (Lesch et al., 1996), in this sample, the observed frequency was 33.3% across all genotypes. Therefore, lack of genetic impact on baseline symptoms as

investigated in the main hypothesis may reflect deviation from the expected genotype frequency. The absence of statistically significant findings in the primary hypothesis needs to be interpreted with caution in this case. The population's deviation from Hardy-Weinberg equilibrium in this study may be a byproduct of random sampling effect due to the small population size. In the future, this can be addressed by conducting an adequately powered study for genetic analyses. In fact, recent work in gene x environment research investigating gene polymorphisms has progressed from gene by gene linkage and association studies to genome-wide association studies, which recruit thousands of individuals in the investigation of complex psychiatric diseases. Additionally, it is important to note that the Hardy-Weinberg equilibrium is an ideal principle which will remain constant only when the principles of random mating, a large enough population size, lack of mutation, no natural selection, and no introduction of new alleles are introduced or lost, are met. It may be possible that apart from small sample size, lack of Hardy-Weinberg equilibrium in this population may reflect a number of deviations from the aforementioned equilibrium criteria. Specifically, the increased frequency of the *s* allele is consistent with its association with bipolar disorder (Bellivier et al., 2002; Lotrich & Pollock, 2004), which may be a possible explanation for the deviation from equilibrium. The study would benefit from a control sample composed of VA patients with medical, but no psychiatric problems. If Hardy-Weinberg equilibrium is observed in the control sample, then the deviation from equilibrium findings of this study may not reflect genotyping or veteran-related problems, but rather sampling error or an association to bipolar disorder.

Additionally, though life events assessed in this study were most etiologically pertinent to symptomatology as shown previously found by Brown and Harris (1979), the research on gene by environment interactions was inspired by investigations of childhood adversity (Caspi et al., 2003). Early life stress and recent life stress, though related constructs speak to unique environmental influences, each with its own unique impact on expressing biological susceptibility, the mechanisms of which are not yet fully understood. In fact, a systematic review of ninety-four articles by Cerda and colleagues (2010) found that childhood adversity was of a pivotal factor in the development of psychiatric morbidity. Therefore, though not specifically a limitation, the assessment of stress within the four months to study baseline does not provide a comparative standard to the original gene by environment interaction of the Caspi study.

The sample was also predominantly Caucasian male, with approximately half of the participants unemployed and not married or divorced, and representative of a middle-aged, U.S. veteran population. The findings may be applicable to other populations similar to the current sample with limited generalizability. For instance, research has found that although the prevalence rate of bipolar disorder is the same in women as in men, women tend to be at increased risk for bipolar II/hypomania (DiFlorio & Jones, 2010) and the extent to which specific life event domains, genotypic polymorphisms and their interaction influence such diagnostic expression in women is currently unclear. Research suggests that reproductive life events, particularly childbirth, are significantly impactful on women and on the expression of bipolar symptoms (Jones & Craddock, 2005; Jones et al., 2010). This study was not able to assess this life event domain in

relationship to symptomatology. In men, the extent to which this domain could be studied would be through the joint impact of childbirth.

Additionally, the extent to which these results would be applicable to populations of a non-Caucasian ethnicity is limited. In Asian populations, the frequency with which the 5-HTTLPR polymorphism is found is often reversed and findings appear similarly in a reversed direction. For example, Ng and colleagues (2006) reported via genomic analysis for the *l* and *s* allele variants that Caucasian subjects had a higher rate of *l/l* genotype while Chinese subjects had higher frequencies of *s/l* and *s/s* genotypes. Significant genotype frequency differences exist even within Caucasian groups and across gender (Noskova et al., 2008). This suggests that specific region of origin should be taken into account when studying 5-HTTLPR polymorphisms in relation to illness and to their interaction with life events.

Another limitation of this study was that the sample was of a predominantly mixed symptom presentation given the .322 correlation between the HAM-D and YMRS scores. The lithium findings are difficult to interpret reliably in this context given that most research concentrates on predictors to lithium response with patients with a mixed presentation responding poorly (Soares & Gershon, 1998; Swann et al., 1986), without focusing on symptomatic differences in patients with mixed presentations when dichotomized according to lithium presence vs. absence. However, this limitation supports the use of MANOVA including depression and manic symptoms in the model.

Additionally, this study did not assess for level of patient insight into illness and symptoms. Patients with bipolar disorder, as opposed to patients with unipolar or anxiety disorders, often lack insight into their illness, which results in under-reporting symptoms

of mania and depression, and which was reported as a qualitative description of the reporting sample by the interviewer who delivered the HAM-D (Amador et al., 1994; Dell'Osso et al., 2002; Dorz et al., 2004; Ghaemi, Boiman, & Goodwin, 2000). The challenge of unreliable reporting was addressed by using interviewer-based questionnaires, the HAM-D and the YMRS rating scale, in conjunction to the BDI. Interviewer-based questionnaires are known to yield larger effect sizes than self-report ones (Cuijpers et al., 2010). They also more accurately capture symptoms on which patients might not have insight, such as psychotic symptoms, which are often a component of bipolar disorder (Seemuller et al., 2011). However, given that patients with bipolar disorder, especially those with manic and mixed symptomatology score lowest on illness insight, it is possible that lack of significant gene by environment findings might be related to unreliable self-report data.

Ruling out participant-specific factors (e.g., defensiveness, lack of insight due to illness severity or other factors, personality variables) contributing to under- or over-reporting the number of events, contextual detail surrounding an event, and timing of an event remained a challenge despite interviewer efforts during the LEDS interview. In the future, this limitation may be addressed by test-retest reliability, keeping in mind that as much as 61% of the events may be underreported on the second interview, though no data exists regarding re-test validity reporting in a sample of bipolar patients (Dorz et al., 2004).

Finally, given that the principal investigator conducted all LEDS interviews, the possibility of investigator bias is present. However, the LEDS rating team was blind to the hypothesis, sample symptomatic presentation and allelic variation. Similarly, the

principal investigator was blind to genotype and pharmacotherapy status at time of interview.

Strengths: This study's strengths included: exploration of the diathesis-stress model in relation to symptom presentation in the context of medication status; focus on a veteran male population, generalizable to most U.S. male veteran populations; and, use of the LEDS. Use of the LEDS measurement allowed for specific focus on the most etiologically relevant life events (i.e., events of acute and distinct onset; very recent - temporally measured events that occurred in the four months prior to assessment; major – severe life events; primarily focused on the participant) (Brown & Harris, 1978) within a timeframe most etiologically relevant to symptom and illness development. Considering the investigation relied on participant self-report, the possibility of memory bias comes into play. However, data suggest that there is only a 6% fall-off in reporting with non-severe events, an effect that takes place approximately five months prior to index interview time (Brown & Harris, 1986). This study limited retrospective recall to four months prior to interview to account for event fall-off and therefore we would not expect even a 6% fall-off rate in event reporting. Finally, in the effort of improving reporting accuracy, the interviewer employed memory aides, such as use of a calendar and temporally orienting the participants according to major holidays.

I. Future Directions

The most important next step stemming from this research is to test these relationships in a longitudinal design to establish, as much as possible, the causal relationships between the stress by gene relationship, lithium response, and bipolar

symptoms. Given the recent technological progress and the statistical tools developed to explore such multifactorial relationships, future research can move beyond techniques which link specific exposures to specific outcomes toward life course principles and methods. For instance, time-sensitive modeling techniques, such as structural equation modeling, are able to incorporate multiple interacting factors across long periods of time. These methods will be critical in understanding the complexity of causal and influencing factors from early development to the end stages of life.

This study did not find a 5-HTTLPR by life event interaction to predict bipolar symptoms at baseline. Considering the small sample size of the study, future studies should recruit a large enough sample size which would reliably inform conclusions regarding the moderating influence of life events on genotype and vice versa. For sample size requirements in case-only designs to detect gene-environment interactions, it might be useful to refer to statistical methods developed by Yang, Khoury and Flanders (1997).

Because previous research has suggested that response to treatment depends on clinical co-morbidity (Bremer et al., 2007) and on heterogeneous diagnostic features (i.e., mixed mania, rapid cycling, cyclothymia) (Levine et al., 2002) and because this study did not consider these factors, future research investigating the variables of interest in this study should also take into account the aforementioned literature.

Future research might also consider alternative dimensions of life events (i.e., social-rhythm disruption, sleep disruptive events) and a range of psychosocial variables (i.e., social support, employment and marital status) in their interaction with genetic factors in influencing expression of bipolar heterogeneity.

This study did not study mechanisms by which specific types of events influence symptom severity and polarity. Future studies might test whether Beck's model of cognitive biases (Beck et al., 1979) and dysfunctional attitudes might be applicable to the mechanistic understanding of how severe events lead specifically to depressive symptoms, how loss events lead to increases in manic symptoms, and how goal-attainment events lead to decreases in depressive symptoms.

J. Conclusions

The findings of this study lend support to the diathesis-stress model in the context of medication presence. The study does not show a significant interaction between the 5-HTTLPR genotype and the presence vs. absence of severe life events, but follow-up univariate analyses on the dependent variables suggest that depressive symptoms are most improved when severe events are present in patients with the *s/s* or *s/l* genotype adherent to lithium. This study is the first to suggest the effect of lithium in the context of life stress in patients with bipolar disorder and to do so taking into account genetic variation in the 5-HTTLPR polymorphism.

Additionally, findings extend literature on assessment of life stress using the Life Events and Difficulties Schedule (LEDS). The LEDS format has been most extensively used in research on unipolar depression and patients with schizophrenia. Extending use of the LEDS in individuals with bipolar disorder helps improve understanding of convergent and divergent effects events of a particular dimension play in each disorder. For instance, while presence of severe events has been robustly associated to an increase in depressive symptoms in unipolar populations, given parallel findings of this study, it is now possible

to more confidently conclude that severe events impact patients with bipolar disorder in a similar fashion. However, whereas events of a loss component predict increases in depressive symptoms in unipolar patients, this effect does not hold in patients with bipolar disorder. Specifically, this study found high scores of manic symptoms in patients who had experienced a loss event in the four months prior to assessment. This finding is particularly important as it may help clinicians better monitor and respond to such events in their patients' lives.

The findings of this study do not lend support for the conceptualization of mania as a syndrome of non-specific etiology, which can be expressed in the context of a variety of noxious stimuli. In fact, in regards to the impact of life events, higher manic symptom severity is observed only in the presence of loss as opposed to events of a severe nature, those that are disorder-dependent or those that contain a component of goal-attainment. In the context of these findings, it may useful to refer to loss events as "candidate stressors" (Monroe & Reid, 2008), in a similar way as psychiatric genetics conceptualizes "candidate genes," although longitudinal studies are needed to adopt such vocabulary. Given the inconsistencies in the gene x environment literature in predicting psychiatric sequelae and response to treatment, the non-polyprocedural study of "candidate stressors" would allow researchers to more confidently draw conclusions from gene x environment findings.

K. Key Implications

The diathesis stress model predicts that symptoms will be dependent on both environment and genetics. The findings suggest that the diathesis-stress interaction is

critical to also understanding medication response, at least in bipolar disorder, and open up a range of research possibilities examining the role of stress in pharmacogenetics and other prophylactic treatments.

Additionally, the findings of this study suggest convergence and divergence in their association with affective disorder (i.e., unipolar, bipolar) symptoms. For example, it appears that severe life events are associated with depressogenic symptoms in patients with unipolar depression and in patients with bipolar disorder. However, loss events appear to associate with manic, as opposed to depressive symptoms in bipolar disorder, an association not found in individuals with unipolar depression. These findings suggest both, disorder-specific mechanisms and characteristics of stress that predict specific polarities in bipolar disorder.

All this compels investigation into the mechanisms by which biological susceptibilities and environmental impacts are conferred and expressed (e.g., longitudinal epigenetic research). It also highlights the importance of developing scientific methods and tools, which help match individuals to most effective treatment packages and ease the burden associated with bipolar illness.

APPENDIX A

LEDS RATING SCALES USED FOR STRESS MEASUREMENT

Event Rating Scale

1. Short Term Threat			1 = Severe 2 = Moderate 3 = Mild 4 = Little or none
2. Long Term Threat			1 = Severe 2 = Moderate 3 = Mild 4 = Little or none
3. Focus			1 = Self 2 = Joint (equally between self and other) 3 = Possession (including pets) 4 = Other person
4. Independence	Independent		1 = Totally independent 2 = Nearly totally independent 3 = Possible influence from subject but unlikely 4 = Independent, but involving physical illness
		Possibly	5 = Compliance with external situation
		Independent	6 = Intentional act by subject 7 = Probable negligence/carelessness 8 = Arguments/tension & end conflict 9 = End of contact, no argument 10 = Subject's love/sex events 11 = Partner's love/sex events 12 = Dependent on d/o

Goal-attainment rating scale

1 = maximum accomplishment and/or effort

2 = moderate amount of accomplishment and/or effor

3 = minor accomplishment and/or effort

4 = no accomplishment and/or effort

APPENDIX B

LEDS EVENTS VIGNETTES

Events rated as severe:

1. Thirty-nine year old participant with history of sex offense became homeless because his parole payment stopped the previous months. Had he stayed at a hotel, he would have violated his parole terms and would have had to be taken back to custody, facing 12 months in prison. Participant started living out of his car. He would have to move from place to place to avoid police tickets. At night, he would be stopped him six times in the early hours, he would be handcuffed, put on the curb and car searched. Participant was facing the possibility of imprisonment as he could not find an appropriate parking spot and was parking close to schools.
   Rated Short Term: 1; Long Term: 1.

2. Forty-five year old participant, laid off work and subsequently unemployed due to wife's fibromyalgia, with no children, was forced to file bankruptcy. Couple was living by skipping meals and rationing food, liquidated all credit cards, returned a new car just bought and foreclosed their home. Participant started withdrawing from retirement accounts to supplement disability income wife was receiving and his unemployment benefits. Reported he would be able to find a job in the near future with his particular skill set.
   Rated Short Tem: 2; Long Term: 2A.

Events not rated as severe:

3. Twenty-six year old participant was hospitalized for diverticulitis for 12 days after experiencing pain in the lower abdominal region and difficulty walking and moving around. There was some uncertainty as to the etiology of symptoms in the first few days of the hospitalization, necessitating a longer stay. This was the first diagnoses of diverticulitis he received. He received advice on changing his diet to a more diverticulitis friendly one. He was given morphine for his pain. He paid a $500 co-pay which he took out of his emergency fund and the rest of the cost was covered by his insurance.
   Rated Short Term: 2; Long Term: 3.

4. Thirty-seven year old participant, married and with three daughters living in a four bedroom house, learns his wife's sister who was living with his mother-in-law was arrested and would be in jail for approximately one year. Wife insisted mother come and live with her, participant and daughter. Participant's relationship with mother-in-law was good. He learned she would move in approximately one month and stay for one year. At the time of the news, mother-in-law was mobile and independently caring for herself, with own means of transportation.

Rated Short Term: 3; Long Term: 3.

5. Thirty-seven year old participant with history of severe sinusitis (19 surgeries and built up scare tissue) suffered from Gulf War and 100% service connected at the VA for the condition, gets travels from Southern California to the Southeast to see parents for a week's vacation. Experienced facial pain due to air travel. Did not require hospitalization as he occasionally would in the past, but was worried that allergies would flare up due to allergenic nature of the Southeast, which did not take place.
   Rated Short Term: 3; Long Term: 4.

6. Thirty-one year old participant was awarded temporary custody of both her children and placed on a 60-day trial period with them, during which she could see children only on weekends. For the two and a half years prior this, her children had been placed in a foster home.
   Rated Short Term: 4; Long Term: 4.

APPENDIX C

DIMENSIONS OF LIFE STRESS RATING EXAMPLES

1. Independence

   Events rated as independent of disorder:

   - 60 year old man's sister moved to Latvia for personal reasons. Rated = 1
   - 60 year old man started accidentally reconnected with high school love and started dating. Rated = 10.
   - 60 year old man has a major argument with sister-in-law when he attempts to invite his dating partner for a visit to his brother's house. Sister-in-law refuses to welcome her on grounds that participant's dating partner has had a relationship with her husband many years ago. Participant tries to persuade her, is unsuccessful and thus, leaves brother's house with dating partner to spend their vacation week at brother's other beach house. Rated = 8.

   Events rated as dependent on disorder:

   - 39 year old man receives a diagnosis of bipolar disorder and starts psychotherapy treatment. Rated = 12.
   - b. 39 year old man impulsively overdoses on his sister's sleeping pills while out shopping with his brother and sister. Participant reports passing out in the back seat of the car, being taken to the ER and being discharged after a few hours of re-gaining consciousness. Reports

brother locked away the gun he had at home for participant's self protection. Rated = 12.

2. Loss

- 41 year old man, self-employed handyman, making a living off equity of old houses he purchases, repairs, and re-sells. Reported being on a "shoestring budget," unable to save, incurring negative balances on his bank account, repaying $7,000 monthly bank loans. Suffered business failure and filed for bankruptcy when home he bought and remodeled extensively did not sell due to the crash in the housing market. Rated = 1
- 34 year old man, having lived in Latin America for the past two years, moved to the United States for better job opportunities at the referral of his friends to take a job as a foreclosure consultant. Two months into his work, he discovered through his own evaluation of company documents and finances that the company was a fraud. This prompted him to contact the FBI and was told the company had been under investigation for the last two years. The following day, FBI officers arrested most people in the company, but not the participant, as he had not been personally present on company grounds. Participant reported he lost his means to an income at the time, but decided to keep a few of his clients out of moral obligation. Rated = 3
- 36 year old male previously employed as a communications electronics technician, was searching online for other employment

when the business he shared with his girlfriend became so unprofitable, participant was just making ends meet between credit card and vehicle purchase debt, IRS payments, and child support. Reported he was called for an interview in similar line of work and of being told after the interview he would receive the job. Was contacted by Human Resources the following day, went through a background investigation and was made the official offer within the week. Rated = 4

3. Goal Attainment

    - 31 year old female, with children removed from custody and placed in foster care five years prior to assessment, would meet the Child and Protective Services (CPS) worker once every two weeks to ensure compliance CPS treatment recommendations with the goal of regaining custody of children. Participant would also attend court dates. Two years prior to assessment participant married man she had known for past ten years with aim of increasing chances of regaining custody of children. She ensured the CPS worker attended the ceremony, for which she had to save considerably in the context of her unemployment and habitation at homeless shelter. Two years prior to assessment, participant started individual therapy to increase chances of regaining custody of children. She gained temporary custody at the time with weekend visitation rights and a 60-day probation period. She gained full custody of children at time of assessment. Rated = 1

- 47 year old man, recently having moves from CO to CA to be closer to immediate family, unemployed, homeless (with repeated previous homelessness experiences), suffering illness due to homelessness, is able to enroll in a transitional housing and per-diem program where he lives in a room with ten other men. Was able to eat, sleep, shower, and receive counseling there for free and was aware the limit to stay there was 24 months. Rated = 2
- 49 year old man having coached Little League Baseball on and off for the past two years researched ways of becoming re-integrated and took a volunteer coaching position with a local team twice a week. Rated = 3
- 60-year old man's residence in which he lived with a roommate was accidentally hit by a car. This caused damage to the water pipes and bathtub necessitating repair work for the following two weeks. Repairs were paid by the landlord. Participant reported the repair work caused disruptions to his daily routine as he would not be able to cook in the house or be around the house much when repairmen were occupying the space. Rated = 4

Table 1. Demographic characteristics of the sample

Variables	n (%)	Mean (SD)	Range
Sociodemographic			
Age		46.21 (11.2)	31-70
Gender			
Male	38 (90.5)		
Female	4 (9.5)		
Marital Status			
Never married	7 (16.7)		
Separated/Divorced	20 (47.6)		
Married	15 (35.7)		
Ethnicity			
Caucasian	28 (66.7)		
African American	6 (14.3)		
Hispanic	3 (7.1)		
Asian	3 (7.1)		
Other	2 (4.8)		
Employment			
Unemployed/disabled	27 (64.3)		
Part time/full time	15 (35.7)		

Table 2. Mean, Standard Deviation, Range, Skewness and Kurtosis distribution of the Clinical Characteristics of Study Participants

Variable Name	n (%)	Mean	SD	Range	Skewness	Kurtosis
Length of Lithium Presence (weeks)		71.10	166.50	0-866	3.58	14.08
Age of First Affective Episode		21.07	11.63	3-60	1.11	1.92
Lifetime Illness Severity		13.70	21.06	.25-120	3.51	15.64
Number of Lifetime Episodes		125.12	202.15	2-768	2.38	4.59
Presence of Psychotropics						
Yes	18 (42.9)					
No	24 (57.1)					
Baseline Lithium Presence						
Yes	21 (50)					
No	21 (50)					

Table 3. Mean, Standard Deviation, Range, Skewness and Kurtosis distribution of Outcome Measures

Variable Name	Mean	SD	Range	Skewness	Kurtosis
Depressive symptoms					
Hamilton (HAMD) Total Score	8.67	8.05	0-31	.97	.08
Beck Depression (BDI) Inventory Total Score	14.43	13.42	0-59	1.41	2.31
Manic symptoms					
Young Mania Rating (YMRS) Scale Total Score	5.31	6.32	0-21	1.08	.06
Clinical Global Scale – S (CGI-S)	3.19	1.25	1-6	.167	-.15

Table 4. 5-HTTLPR Hardy-Weinberg Equilibrium

Genotype	Observed #	Frequency	Expected #	Expected Frequency
s/s	14	.33	10.5	.05
s/l	14	.33	21.0	.25
l/l	14	.33	10.5	.05

Table 5. 5-HTTLPR by Life Event Distribution

Genotype	Severe Events		χ^2	df	p-value
	Presence	Absence			
s/s, s/l	10	18	.89	1	.345
l/l	3	11			
Goal-Attainment Events					
s/s, s/l	24	4	6.15	1	.013*
l/l	7	7			
Loss Events					
s/s, s/l	17	11	.05	1	.822
l/l	9	5			
Disorder-Dependent Events					
s/s, s/l	15	13	.04	1	.827
l/l	7	7			

* indicates statistical significance

Table 6. Genotype by Lithium Presence Distribution

Genotype	Lithium presence		χ^2	df	p-value
	Presence	Absence			
s/s, s/l	14	14	.00	1	1.00
l/l	7	7			

Table 7. Life Events by Lithium Presence Distribution

Lithium Presence	Severe Events		χ^2	df	p-value
	Presence	Absence			
Absent	7	14	.111	1	.500
Present	6	15			
	Goal-Attainment Events				
Absent	16	5	.120	1	.720
Present	15	6			
	Loss Events				
Absent	16	5	3.630	1	.050*
Present	10	11			
	Dependent Events				
Absent	14	7	3.430	1	.060
Present	8	13			

* indicates statistical significance

Table 8. Prevalence of stress

Type of Stress	N[1] (%)	Total Events
Presence of Severe Events		
Yes	13 (31.0)	47
No	29 (69.0)	
Presence of Loss Events		
Yes	26 (61.9)	110
No	16 (38.1)	
Dependent Events		
Yes	22 (52.4)	29
No	20 (47.6)	
Goal-Attainment Events		
Yes	31 (73.8)	67
No	11 (26.2)	

Note: [1]=number of participants reporting stress.

Table 9. Pearson correlations between outcome variables and potential confounding variables

Potential Confounds	Dependent Variables			
	HAM-D	CGI-S	BDI	YMRS
Ethnicity$_a$	.145	-.042 .	.184	-.231
Employment$_a$	-.187	-.074	-.178	-.005
Gender$_a$	-.054	.050	-.081	.120
Marital$_a$	.053	.042	.450	-.161
Lithium Presence$_a$	-.329*	-.423**	-.449**	-.362**
Age$_b$	-.138	-.184	-.088	.074
Illness Severity$_b$	-.131	-.281*	-.130	.103

Note. * $p < .05$, **$p < .01$
Note. a. Represents point-biserial correlation values.
b. Represents Pearson *r* correlation values.

Table 10. Lithium Presence at Baseline Influences BP Symptomatology

Outcome Variable	Lithium		*p*-value	F
	Present (N = 21) Mean, (SD)	Absent (N = 21) Mean, (SD)		
CGI-S	2.67, (1.19)	3.71, (1.10)	.009	7.77
YMRS	3.05, (4.70)	7.75, (6.90)	.014	6.64
BDI	8.48, (8.30)	20.38, (15.03)	.001	12.44
HAM-D	6.05, (6.30)	11.29, (8.84)	.011	7.28

Table 11. Life events and 5-HTTLPR relationships with potentially confounding demographic and clinical variables

	F	χ^2	df	p-value
			Genotype	
Gender		.138	1	.71
Marital Status		.611	2	.61
Employment		.000	1	1.00
Ethnicity		6.530	5	.25
Lithium Presence		1.710	1	.19
Illness severity		.760	1	.38
Age		.142	1	.70
			Severe Life Event	
Gender		.073	1	.78
Marital Status		1.490	2	.47
Employment		1.130	1	.25
Ethnicity		6.400	5	.26
Lithium Presence		.111	1	.73
Illness severity	.508		1	.48
Age	1.730		1	.19
			Loss Life Event	
Gender		.266	1	.60
Marital Status		1.300	2	.52
Employment		.036	1	.85
Ethnicity		2.720	5	.74

Table 11 Continued. Life events and 5-HTTLPR relationships with potentially confounding demographic and clinical variables

Lithium Presence	3.630	1	.05*
Illness severity	.001	1	.96
Age	1.700	1	.19
		Dependent Life Event	
Gender	.010	1	.92
Marital Status	.315	2	.85
Employment	1.430	1	.23
Ethnicity	9.210	5	.10
Lithium Presence	3.430	1	.06
Illness severity	1.250	1	.27
Age	2.350	1	.13
		Goal-Attainment Life Event	
Gender	1.290	1	.25
Marital Status	2.100	2	.34
Employment	.616	1	.43
Ethnicity	14.840	5	.01*
Lithium Presence	.123	1	.72
Illness severity	1.108	1	.29
Age	2.104	1	.15

- Denotes statistical significance

Table 12. Ethnicity and Goal-Attainment Events

Ethnicity	Goal-Attainment Events	
	Absence	Presence
Caucasian	7	21
African-American	0	6
Hispanic	0	3
Asian	3	0
Native-American	0	1
Mixed	1	0

Table 13. Bivariate associations between outcome variables

	HAM-D	CGI-S	YMRS	BDI
HAM-D	1.000	.683**	.322*	.914**
CGI-S	-	1.000	.410*	.612**
YMRS	-	-	1.000	.287
BDI	-	-	-	1.000

Note. * $p < .05$, ** $p < .01$

Table 14. Hypothesis 1 – Omnibus MANOVA as a function of SERT, presence of severe stress (PSS), presence of lithium at baseline, and their interaction

Source	Wilk's λ	F	partial η^2	Observed Power	p
Intercept	.113	60.85	.887	1.000	.000
5-HTTLPR	.779	2.20	.221	.578	.092
Presence of Severe Stress (PSS)	.714	3.10	.286	.748	.029
Lithium Presence	.601	5.13	.399	.938	.003
PSS x 5-HTTLPR	.795	2.00	.205	.533	.119
5-HTTLPR x Lithium	.786	2.11	.214	.558	.103
PSS x Lithium	.765	2.38	.235	.617	.073
PSS x 5-HTTLPR x Lithium	.367	3.02	.269	.740	.031

Table 15. Hypothesis 1 - MANOVA of HAM-D, CGI, YMRS, and BDI as a function of SERT, presence of severe stress (PSS), presence of lithium at baseline, and their interaction

Source	Type III SS	df	F	p
Corrected Model				
BDI_a	3091.18	7	3.49	.00
$YMRS_b$	348.56	7	1.31	.27
$CGI - S_c$	21.82	7	3.11	.03
$HAM\text{-}D_d$	997.78	7	2.91	.01
Intercept				
BDI_a	9946.66	1	78.60	.00
$YMRS_b$	1134.00	1	29.83	.00
$CGI - S_c$	283.50	1	226.01	.00
$HAM\text{-}D_d$	3175.05	1	64.97	.00
5-HTTLPR				
BDI_a	139.33	1	1.10	.30
$YMRS_b$	23.14	1	.60	.44
$CGI - S_c$	.07	1	.05	.81
$HAM\text{-}D_d$	1.24	1	.02	.87
Presence of severe stress (PSS)				
BDI_a	1235.16	1	9.76	.004*
$YMRS_b$	41.14	1	1.08	.30
$CGI - S_c$	6.67	1	5.32	.02*
$HAM\text{-}D_d$	646.90	1	13.23	.001*
Baseline Lithium				
BDI_a	1572.96	1	12.44	.001*
$YMRS_c$	253.32	1	6.66	.014*
$CGI - S_b$	9.75	1	7.77	.009*
$HAM\text{-}D_d$	356.04	1	7.28	.011*
PSS x 5-HTTLPR				
BDI_a	297.16	1	2.35	.13
$YMRS_b$	10.28	1	.27	.60
$CGI - S_c$	1.34	1	1.06	.30
$HAM\text{-}D_d$	23.57	1	.48	.49
5-HTTLPR x Lithium				
BDI_a	163.39	1	1.29	.26

Table 15 Continued. Hypothesis 1 - MANOVA of HAM-D, CGI, YMRS, and BDI as a function of SERT, presence of severe stress (PSS), presence of lithium at baseline, and their interaction

$YMRS_b$	1.58	1	.04	.83
$CGI - S_c$	.00	1	.00	.94
$HAM\text{-}D_d$	.30	1	.93	.93
PSS x Lithium				
BDI_a	604.01	1	4.77	.03*
$YMRS_b$	27.74	1	.73	.39
$CGI - S_c$	2.47	1	1.97	.16
$HAM\text{-}D_d$	416.41	1	8.50	.006*
PSS x 5-HTTLPR x Baseline Lithium				
BDI_a	1016.78	3	2.68	.06
$YMRS_b$	32.97	3	.28	.83
$CGI - S_c$	3.15	3	.83	.48
$HAM\text{-}D_d$	430.96	3	2.90	.04*
Error				
BDI_a	4299.09	34		
$YMRS_b$	1292.41	34		
$CGI - S_c$	42.64	34		
$HAM\text{-}D_d$	1661.54	34		
Total				
BDI_a	16134.00	42		
$YMRS_b$	2825.00	42		
$CGI - S_c$	492.00	42		
$HAM\text{-}D_d$	5814.00	42		
Corrected Total				
BDI_a	7390.28	41		
$YMRS_b$	1640.97	41		
$CGI - S_c$	64.47	41		
$HAM\text{-}D_d$	2659.33	41		

Note.

a. $R^2 = .418$, Adjusted $R^2 = .299$
b. $R^2 = .212$ Adjusted $R^2 = .050$
b. $R^2 = .339$, Adjusted $R^2 = .202$
c. $R^2 = .375$, Adjusted $R^2 = .247$

*indicates statistical significance

Table 16. HAM-D, YMRS, CIG-S, and BDI Means for Main effect of Presence vs. Absence of Severe event

Severe Event	HAM-D	BDI	YMRS	CGI
		Mean, (SD)		
Presence (N =13)	12.46, (9.39)	20.23, (16.82)	5.85, (6.71)	3.77, (1.30)
Absence (N = 29)	6.97, (6.88)	11.83, (10.90)	5.07, (6.25)	2.93, (1.16)

Table 17. Hypothesis 1 - Means of 2-way interaction between absence vs. presence of severe event and lithium status

Severe Event	Lithium Presence	Lithium Absence
	Mean, (SD)	Mean, (SD)
Absent		
BDI	8.60, (8.59)	15.29, (12.41)
HAM-D	6.53, (7.18)	7.43, (6.80)
Present		
BDI	8.17, (8.32)	30.57, (15.42)
HAM-D	4.83, (3.81)	19.00, (7.50)

Table 18. Simple Effect Means for 3-Way Interaction of Lithium at Baseline by 5-HTTLPR Genotype in the Presence vs. the Absence of Severe Events in the Four Months Prior to Baseline

Genotype	Lithium Presence Mean, (SD)	Lithium Absence Mean, (SD)
	Presence of Severe Events	
s/s, s/l	3.00, (3.00)	20.00, (12.12)
l/l	6.67, (4.10)	18.25, (3.59)
	Absence of Severe Events	
s/s, s/l	9.50, (10.60)	8.63, (4.34)
l/l	6.08, (7.00)	5.83, (9.40)

Table 19. Hypothesis 2A, 2B, 2C – Omnibus MANOVA as a function of loss, dependent and goal-attainment event, presence of lithium at baseline, and their interaction

Source	Wilk's λ	F	partial η^2	Observed Power	*p*-value
Intercept	.166	43.98	.83	1.00	.00
Loss Event	.711	3.56	.28	.81	.01*
Loss Event X LP	.804	2.13	.19	.57	.08
Intercept	.140	53.73	.86	1.00	.00
Dependent Event	.905	.92	.09	.26	.46
Dependent Event x LP	.940	.55	.06	.16	.69
Intercept	.170	42.62	.83	1.00	.00
Goal-attainment Event	.643	4.86	.35	.92	.003*
Goal-attainment Event x LP	.665	4.40	.33	.89	.005*

Table 20. Hypothesis 2A – MANOVA's of HAM-D, CGI, YMRS, and BDI as a function of loss event, presence of lithium at baseline, and loss event x lithium presence interaction

Source	Type III SS	df	F	p
Corrected Model				
BDI_a	1826.79	3	4.15	.01
$YMRS_b$	386.69	3	3.90	.01
$CGI - S_c$	11.94	3	2.88	.04
$HAM\text{-}D_d$	421.31	3	2.38	.08
Intercept				
BDI_a	4889.26	1	33.39	.00
$YMRS_b$	548.57	1	16.62	.00
$CGI - S_c$	205.80	1	148.88	.00
$HAM\text{-}D_d$	1446.71	1	24.56	.00
Loss Event				
BDI_a	338.40	1	2.31	.13
$YMRS_b$	137.14	1	4.15	.04*
$CGI - S_c$	.08	1	.06	.80
$HAM\text{-}D_d$	132.04	1	2.24	.14
Baseline Lithium (BL)				
BDI_a	784.61	1	5.35	.02*
$YMRS_c$	80.12	1	2.42	.12
$CGI - S_b$	8.86	1	6.41	.01*
$HAM\text{-}D_d$	121.25	1	2.05	.16
BL x Loss Event				
BDI_a	186.21	1	186.21	.26
$YMRS_b$	162.08	1	4.91	.03*
$CGI - S_c$	.02	1	.01	.89
$HAM\text{-}D_d$	89.21	1	1.51	.22
Error				
BDI_a	5563.49	38	146.40	
$YMRS_b$	1254.28	38	33.00	
$CGI - S_c$	52.52	38	1.38	
$HAM\text{-}D_d$	2238.01	38	58.89	
Total				
BDI_a	16134.00	42		
$YMRS_b$	2825.00	42		

Table 20 Continued. Hypothesis 2A – MANOVA's of HAM-D, CGI, YMRS, and BDI as a function of loss event, presence of lithium at baseline, and loss event x lithium presence interaction

CGI – S_c	492.00	42
HAM-D_d	5814.00	42
Corrected Total		
BDI_a	7390.28	41
$YMRS_b$	1640.97	41
CGI – S_c	64.47	41
HAM-D_d	2659.33	41

Note.

c. $R^2 = .247$, Adjusted $R^2 = .188$
d. $R^2 = .236$ Adjusted $R^2 = .175$
d. $R^2 = .185$, Adjusted $R^2 = .121$
e. $R^2 = .158$, Adjusted $R^2 = .092$

*indicates statistical significance

Table 21. Hypothesis 2A - YMRS Means as predicted by the interaction of loss events by lithium presence at baseline

Loss Life Event	Lithium Absence Mean, (SD)	Lithium Presence Mean, (SD)
Absence	3, (2.55)	4.27, (5.85)
Presence	9, (7.36)	1.70, (2.83)

Table 22. Hypothesis 2C – MANOVA's of HAM-D, CGI, YMRS, and BDI as a function of goal-attainment event, presence of lithium at baseline, and goal-attainment event x lithium presence interaction

Source	Type III SS	df	F	p
Corrected Model				
BDI_a	2308.91	3	5.75	.00
$YMRS_b$	229.74	3	2.06	.12
$CGI – S_c$	15.36	3	3.96	.01
$HAM\text{-}D_d$	443.81	3	147.93	.07
Intercept				
BDI_a	8901.00	1	66.56	.00
$YMRS_b$	768.15	1	20.68	.00
$CGI – S_c$	190.68	1	147.52	.00
$HAM\text{-}D_d$	2404.82	1	41.24	.00
Goal-attainment Event (GA)				
BDI_a	796.81	1	5.95	.01*
$YMRS_b$	12.34	1	.33	.56
$CGI – S_c$	1.73	1	1.34	.25
$HAM\text{-}D_d$	90.53	1	1.55	.22
Baseline Lithium (BL)				
BDI_a	1860.27	1	13.91	.00
$YMRS_c$	143.43	1	3.86	.05
$CGI – S_b$	4.19	1	3.24	.08
$HAM\text{-}D_d$	260.19	1	4.46	.04
BL x GA				
BDI_a	295.07	1	295.07	.14
$YMRS_b$	2.15	1	.05	.81
$CGI – S_c$	3.81	1	2.95	.09
$HAM\text{-}D_d$	1.91	1	.03	.85
Error				
BDI_a	5081.37	38	133.72	
$YMRS_b$	1411.23	38	37.13	
$CGI – S_c$	49.11	38	1.20	
$HAM\text{-}D_d$	2215.51	38	58.30	
Total				
BDI_a	16134.00	42		
$YMRS_b$	2825.00	42		

Table 22 Continued. Hypothesis 2C – MANOVA's of HAM-D, CGI, YMRS, and BDI as a function of goal-attainment event, presence of lithium at baseline, and goal-attainment event x lithium presence interaction

CGI – S_c	492.00	42
HAM-D_d	5814.00	42
Corrected Total		
BDI_a	7390.28	41
$YMRS_b$	1640.97	41
CGI – S_c	64.47	41
HAM-D_d	2659.33	41

Note.

e. $R^2 = .312$, Adjusted $R^2 = .258$
f. $R^2 = .140$, Adjusted $R^2 = .072$
f. $R^2 = .238$, Adjusted $R^2 = .178$
g. $R^2 = .167$, Adjusted $R^2 = .101$

*indicates statistical significance

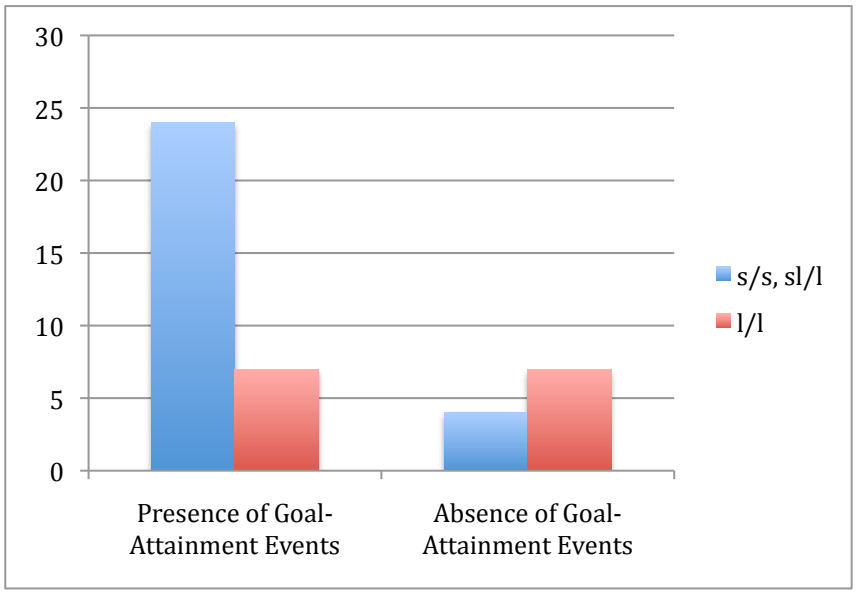


Figure 1. 5-HTTLPR by Goal-Attainment Event Distribution

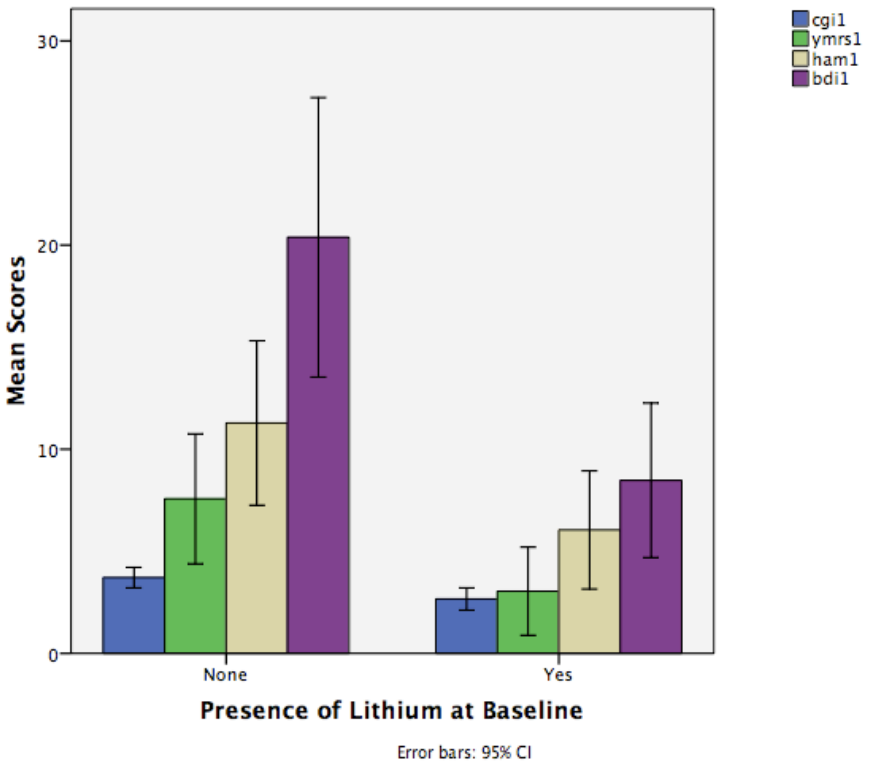


Figure 2. Lithium Presence at Baseline Influences BP Symptomatology

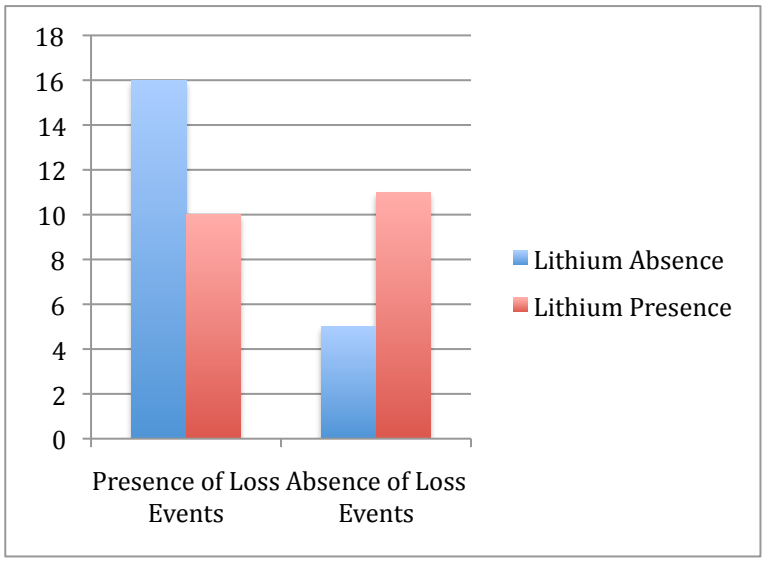


Figure 3. Loss Life Events by Lithium Presence Distribution

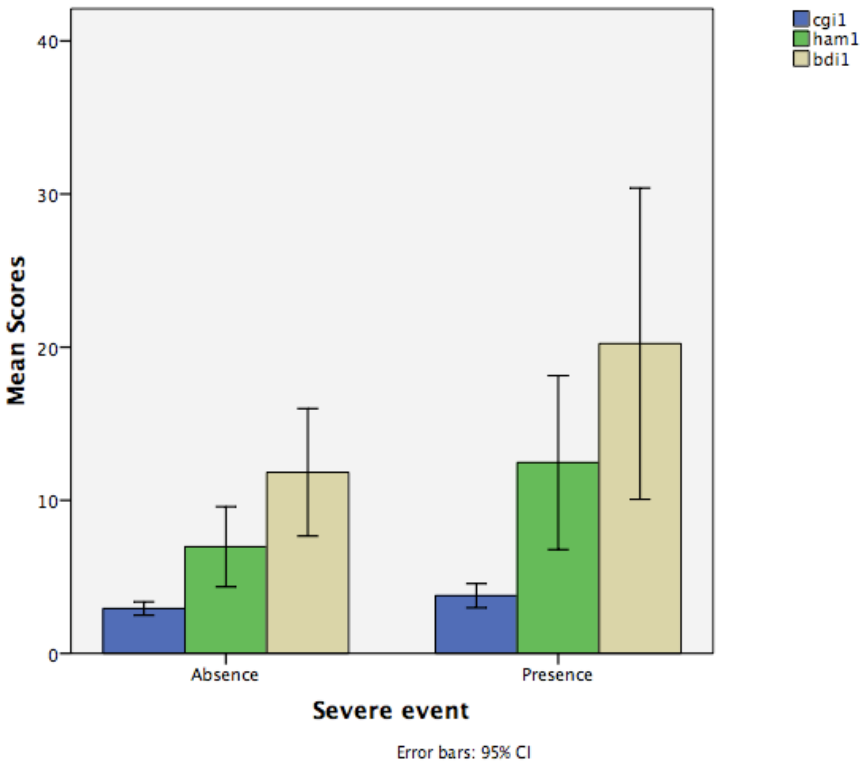


Figure 4. Presence of Severe Event Predicts Higher Baseline CGI-S, HAM-D, and BDI Mean Scores

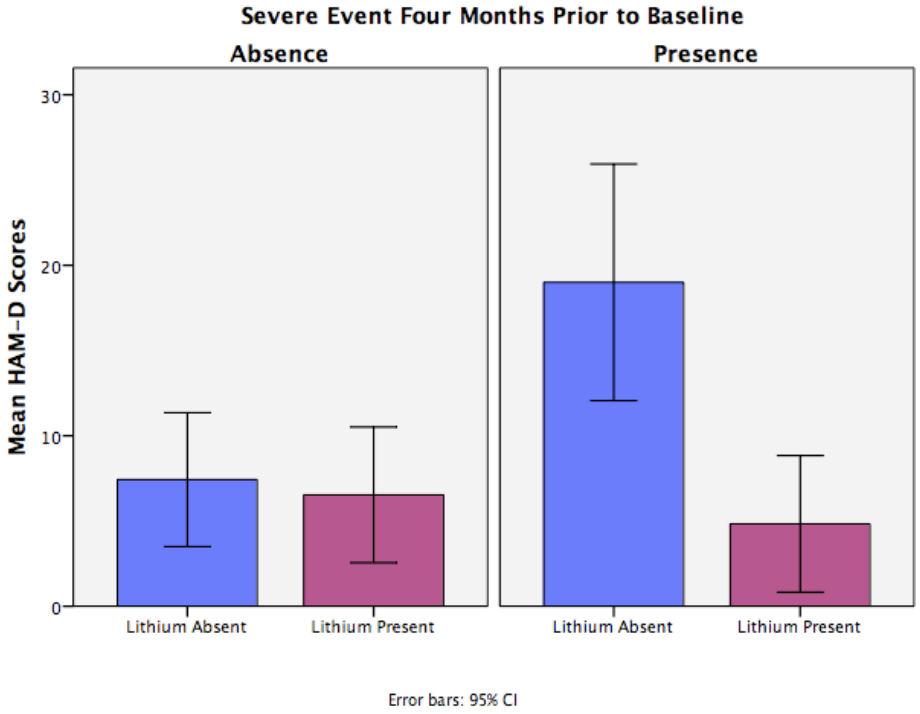


Figure 5. Hypothesis 1 – HAM-D Scores at Baseline as a Function of Presence vs. Absence of Severe Event and Lithium Status

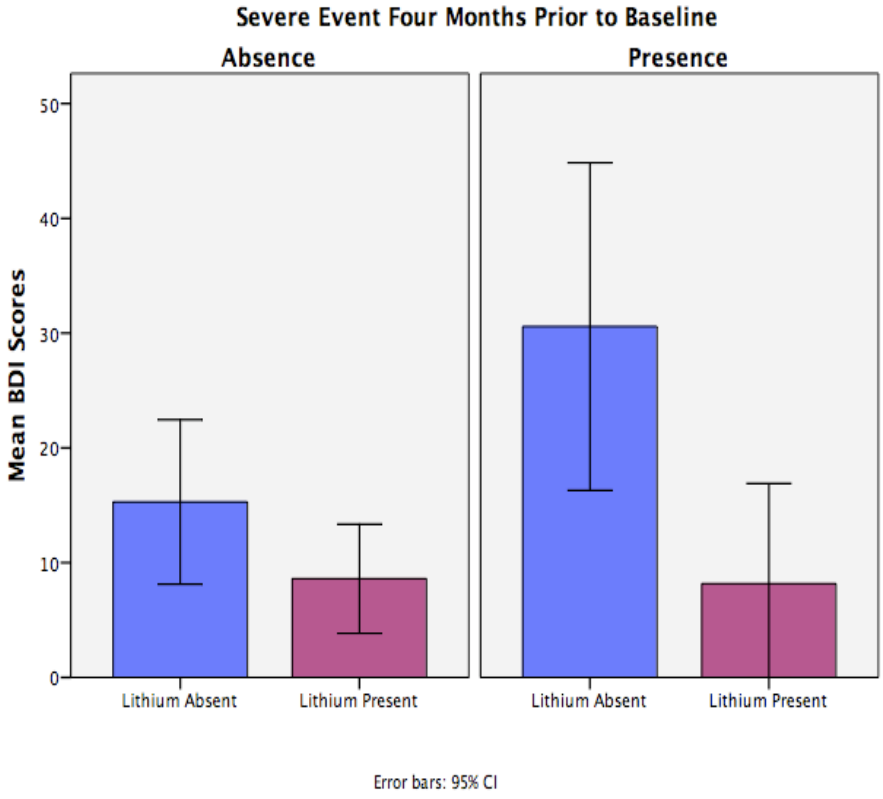
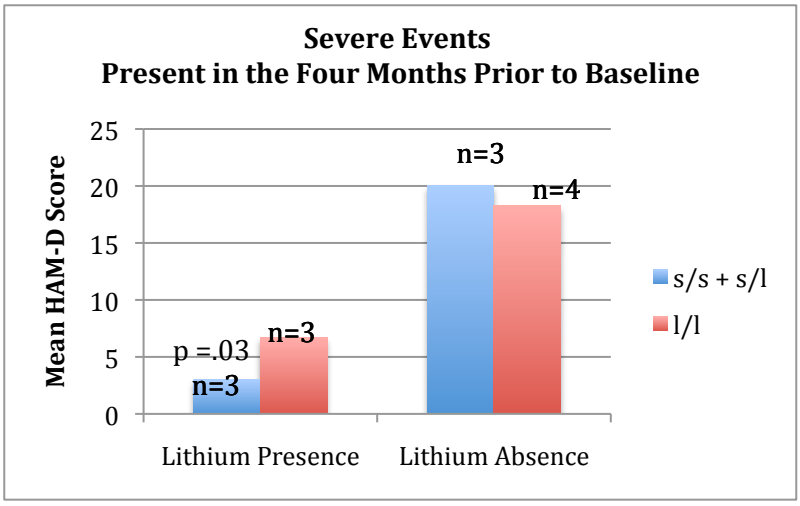


Figure 6. BDI Scores at Baseline as a Function of Presence vs. Absence of Severe Event and Lithium Status



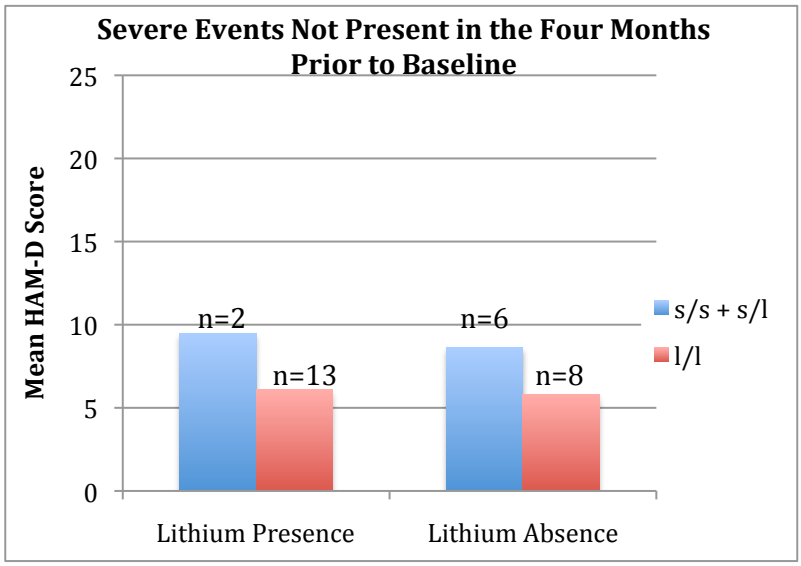


Figure 7. Simple Effect Means for 3-Way Interaction of Lithium at Baseline by 5-HTTLPR Genotype in the Presence of Severe Events in the Four Months Prior to Baseline

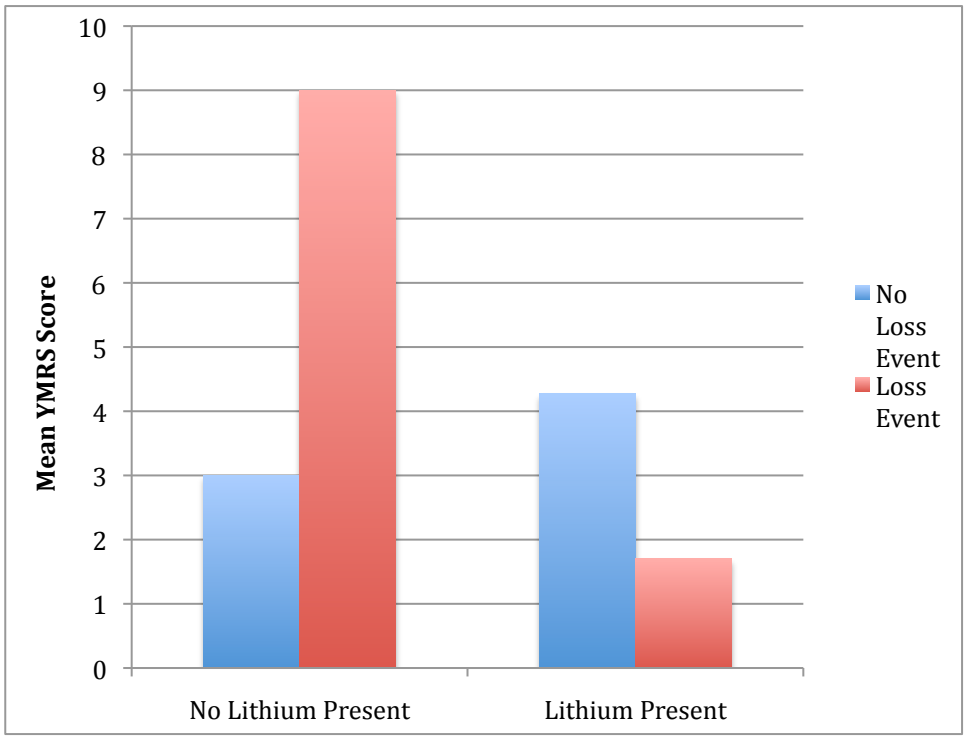


Figure 8. YMRS Marginal Means for Interaction of Loss Events and Lithium Presence

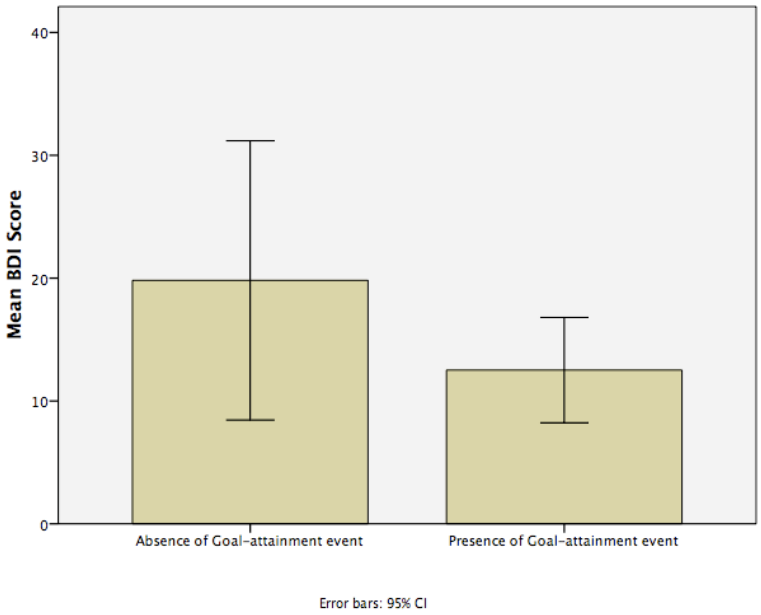


Figure 9. Hypothesis 2 C – BDI Scores at Baseline as Predicted by Goal-Attainment Events

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