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Life Stress and the Course Of Early-Onset Bipolar Disorder

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Abstract

Background—Studies of adult bipolar patients and adolescents with major depression indicate that life stress and mood symptoms are temporally and causally related to one another. This study examined whether levels of life stress predict levels of mood symptoms among bipolar adolescents participating in a treatment development study of family-focused psychoeducation and pharmacotherapy.

Methods—Bipolar adolescents (n=38) who reported a period of acute mood symptoms within the prior 3 months were recruited for a one-year study of life stress. Clinician-administered evaluations were completed with adolescents and parents at 3-month intervals for up to 12 months, using the UCLA Life Stress Interview and the K-SADS Mania and Depression Rating Scales.

Results—Chronic stress in family, romantic and peer relationships was associated with less improvement in mood symptoms over the study year. The frequency of severe, independent life events also predicted less improvement in mood symptoms. Higher levels of chronic stress in family and romantic relationships, and higher severity of independent events, were more strongly associated with mood symptoms among older adolescents. Results were independent of adolescents' psychosocial treatment regimens.

Limitations—The majority of adolescents received family-focused psychoeducational treatment and all were being treated with psychotropic medication. The influence of life stress on mood symptoms may have been attenuated by intensive intervention.

Conclusions—Stress is linked to changes in mood symptoms among bipolar adolescents, although correlations between life events and symptoms vary with age. Chronic stress in family, romantic, and peer relationships are important targets for psychosocial intervention.

Keywords

bipolar disorder; stress; adolescence

Introduction

Adolescence is characterized by marked physical, psychological, and social changes that rapidly expose a young person to a wide range of new stressors. For youths who concurrently struggle with early-onset bipolar disorder, the adolescent years represent an especially challenging and vulnerable phase of development. Although cross-sectional and prospective studies indicate strong relationships between levels of stress and childhood psychopathology

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(Compas, et al., 1994; Nolen-Hoeksema, et al., 1986; Williamson, et al., 1998), findings regarding psychosocial variables that predict the course of early-onset bipolar illnesses are limited. Among prepubertal and early-adolescent youths with bipolar disorder, low maternal warmth has been associated with more rapid recurrences after recovery from mania (Geller, et al., 2004), whereas living in an intact family has been associated with faster rates of recovery (Geller et al., 2002). A cross-sectional study found that bipolar youths experienced more stressful life events than youths with attention-deficit hyperactivity disorder (ADHD) and normal controls (Tillman et al., 2003). However, findings that implicate life stress as a significant prognostic factor come primarily from studies of bipolar disorder in adulthood. Longitudinal, prospective studies of adults with bipolar illness indicate that life stress may contribute to initial illness onset, relapse, and time to recovery (Hammen & Gitlin, 1997; Johnson, et al., 2000; Johnson & Miller, 1997; Johnson & Roberts, 1995).

However, differences in the phenomenology and course of illness between adult-onset and childhood-onset bipolar disorder preclude the automatic extension to children of findings on stress from adult populations. Adolescent bipolar disorder is associated with a higher familial loading for major affective disorder (Strober et al., 1988; Todd, et al., 1993). Furthermore, children and adolescents with bipolar disorder often show non-episodic, chronic courses and continuous rapid cycling patterns (Geller & Luby, 1997), unlike the majority of bipolar adults who show more discrete periods of mania or depression with improved functioning between episodes (McGlashan, 1988; Kalbag et al., 1999).

This study explored the role of life stress among 38 adolescents who were followed for up to 12 months during their participation in a study of family-focused psychoeducation for early-onset bipolar disorder. We examined: 1) whether higher levels of stress were associated with less improvement in mood symptom severity at each follow-up point, and 2) whether stress-symptom relationships varied as a function of age and sex. In contrast to prior investigations which have focused almost exclusively on episodic stressors (Hammen, 2004), the study examined both chronic and episodic life stress. The study also explored the role of independent and dependent events separately.

Methods

Participants

A total of 38 bipolar adolescents were recruited for a one-year study of stress and bipolar disorder. All participants were taking part in a treatment development study of family-focused psychoeducation (FFT) for early-onset bipolar disorder (NIMH R21-MH62555; Miklowitz et al., 2004). Youths and their families received a 9-month, 21-session manual-based family intervention in an open trial at the University of Colorado, Boulder (N=12) or participated in a subsequent, randomized pilot efficacy trial of FFT versus a brief (3-session) psychoeducational treatment called enhanced care (N=26). Of the 38 adolescents participating in this study of stress and bipolar disorder, 12 received FFT as part of the open trial, 14 received FFT as part of the randomized trial, and 12 received the three enhanced care family educational sessions.

All participants received medication management by a study psychiatrist throughout their participation in the study. At entry into the study, the majority were being treated with psychotropic medication, including lithium (n=10), divalproex (n=10), oxcarbazepine (n=11), and atypical antipsychotics (n=17). A total of 7 adolescents were not being treated with psychotropic medication at the time they entered the study. These patients were prescribed mood stabilizers (n=5) or other medications for bipolar disorder or comorbid conditions (n=2) upon study entry.

Patients were recruited through referral from community psychiatrists, and the Denver Children's Hospital Child and Adolescent Psychiatric Services. Requirements for participation included: 1) age between 13–17 years; 2) DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; American Psychiatric Association, 1994) diagnosis of bipolar disorder, type I, II, or not otherwise specified (NOS) based on the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997); 3) a manic, mixed, hypomanic, or depressive episode within the last 3 months; and 4) no active DSM-IV substance or alcohol abuse disorders in the prior 3 months. The study was approved by the University of Colorado, Boulder's Human Research Committee.

Patients consisted of 18 boys and 20 girls with a mean age of 15.03 ± 1.43 and index diagnoses of bipolar I ($n=27$), bipolar II ($n=4$), or bipolar NOS ($n=7$). Criteria for the diagnosis of bipolar NOS consisted of those established by the NIMH Course and Outcome of Bipolar Youth study (COBY; MH-59929; Birmaher et al., 2006). Comorbid diagnoses included attention deficit hyperactivity disorder ($n=18$; 47%), oppositional defiant disorder ($n=22$; 58%), anxiety disorders ($n=18$; 47%) and prior history of alcohol/substance abuse or dependence that was currently in remission ($n=12$; 32%).

Measures

At intake into the larger study of FFT, the K-SADS-PL was administered to obtain DSM-IV diagnoses and the K-SADS Depression and Mania Rating Scales (DRS and MRS) were administered to obtain dimensional ratings of mood symptom severity (Axelson et al., 1999; Chambers et al., 1985). The FFT study was underway when the study of stress and bipolar disorder was initiated, at which point the UCLA Life Stress Interview (Hammen 1989; 2003; 2004) was added to the intake battery. Intake evaluations of life stress were not available for 8 participants who were enrolled after at least three months of participation in the FFT study (and were therefore followed in the life stress study for less than 12 months). These 8 patients were followed in the life stress study for a mean of 6.38 ± 2.97 months. Follow-up sessions included administration of the UCLA Life Stress Interview and the K-SADS Depression and Mania Rating Scales, conducted with parents and adolescents separately.

Of the 38 participants, 30 completed an assessment of stress at intake into the treatment study (see above). A total of 30 (79%) participants completed a 3-month reassessment of life stress, 21 (55%) completed a 6-month reassessment, 22 (58%) completed a 9-month reassessment, and 24 (63%) completed a 12-month reassessment. On average, patients completed 40.89 ± 20.70 weeks of follow-up and 3.34 ± 1.51 life stress assessments. A total of 13 participants completed all follow-up assessments (i.e., had no missing data points). To account for any delays in follow-up (e.g., a 3-month follow-up occurring in the fourth month), the exact number of weeks between intake and follow-up was used in statistical analyses to represent the effects of time.

K-SADS Diagnoses—Research staff members who had received training in the KSADS-PL interviewed patients and at least one parent at intake. Separate K-SADS-PL ratings were made for current versus lifetime symptoms. Interrater reliability coefficients (kappas based on ratings of videotaped interviews) among diagnosticians for K-SADS-PL depression items averaged 0.71; for mania items, 0.84; and for other items (e.g., ADHD, conduct disorder), 0.70.

Life stress—At intake and at 3-month intervals, research staff members evaluated life stress using the UCLA Life Stress Interview, a 45-minute structured interview designed to evaluate episodic (e.g., stressful events) and chronic stress. In contrast to self-report measures, the UCLA Life Stress Interview allowed for distinctions between participants' subjective reactions and objective evaluations of events.

The first component of the interview, the chronic stress assessment, identified ongoing conditions for several key domains: romantic relationships, close friendships, social activities, family relationships, school performance, physical health, and the health of family members. Levels of chronic stress were rated on a 1 (extremely positive conditions) to 5 (extremely poor conditions) scale by the interviewer, based on information regarding patients' circumstances rather than patients' subjective feelings about how distressing they found these conditions. Agreement among 3 raters on chronic stress scores (27 ratings) was .90 (intraclass r , $p=.0005$).

The second component of the UCLA Life Stress Interview assessed episodic stressors based on the contextual threat methods of Brown & Harris (1978). Interviewers obtained detailed information regarding the circumstances surrounding each episodic stressor, then provided narrative accounts of each event to an independent rating team. Any information about the adolescents' subjective reactions to the stressors was omitted from the narrative accounts, enabling objective ratings of the impact of events on the participants' lives. The independent team rated the degree of impact that each event would have for a typical person under identical conditions, using a scale ranging from 1 (no impact) to 5 (extremely severe impact). The team also rated the extent to which each event was independent of the person's behavior on a scale ranging from 1 (entirely independent of the person) to 5 (entirely dependent on the person).

Mood symptoms—The severity of mood symptoms was evaluated at intake and at 3-month intervals using the K-SADS Depression and Mania Rating Scales. In contrast to the K-SADS-PL, which identifies symptoms as absent, subsyndromal, or present, the K-SADS DRS and MRS are semistructured interviews with Likert scaled items (i.e., 1–7 scales) that enable more subtle ratings of mood symptom severity, including those within the subsyndromal domain. The scales have good test-retest reliability ($r = 0.67$ – 0.81) and internal consistency (Cronbach alphas = 0.68 – 0.72 ; Chambers et al., 1985). Agreement on total KSADS-DRS and -MRS scores among 11 study raters (51 ratings) was 0.89 and 0.97, respectively (intraclass r 's, p 's < .0001).

Statistical Analyses

Overview—Hierarchical linear model (HLM) analyses using SAS (proc mixed) were conducted to examine the effects of stress on depression, mania, and combined (depression plus mania) mood symptoms over the 12-month study period. The effects of time, sex, treatment condition (FFT versus enhanced care), and illness subtype were included as covariates in all analyses. Our primary hypothesis was that higher stress ratings would be associated with less improvement in symptomatology at each follow-up assessment, after controlling for the effects of relevant covariates. Ratings of stress were entered as time-varying predictors, whereas the effects of covariates were entered as time-invariant (Singer & Willett, 2003). Individual intercepts and slopes that represented changes in mania, depression, and combined mood (mania plus depression) scores over time were used as dependent variables. Individual slopes were weighted according to the number of ratings available for each participant, allowing inclusion of symptom data from adolescents who did not complete all follow-up assessments. Ratings of depression and mania were significantly correlated ($r=.70$, $p<.0001$) but examined separately in order to identify polarity-specific associations with life stress. Effect sizes were evaluated by calculating standardized regression coefficients (β), which are reported for significant findings.

Factor analyses—Because chronic stress was assessed in eight domains (close friends, romantic relationships, social activities, family, academics, school behavior, health, and family health), we conducted a principal components analysis with a promax rotation to identify domains assessing common underlying factors, and to allow for data reduction in HLM analyses. Two primary factors were revealed: 1) peer relationships, which included the close friends and social activities items (eigenvalue = 2.89); and 2) intimate relationships, which

included the family and romantic relationship items (eigenvalue = 1.50). Ratings obtained for the close friends and social activities domains were averaged to represent chronic stress in peer relationships, and ratings obtained for the family and romantic relationship domains were averaged to represent chronic stress in intimate relationships. The remaining domains were each examined separately as predictors of mood symptoms.

Results

Chronic and Episodic Stress Ratings

As indicated in Table 1, the highest levels of chronic stress were associated with family relationships and academics, which were characterized by mixed (both positive and negative) conditions. The lowest levels of chronic stress were associated with adolescents' health and the health of family members, which were characterized by generally positive conditions.

Adolescents reported an average of .78 independent events and .72 dependent events during each 3-month assessment interval (covering the prior 3 months). Overall, severity ratings (mean=2.36±.65 and 2.42±.68 for independent and dependent events respectively) indicated that events were characterized by mild to moderate severity. As indicated in Table 1, events related to the family (e.g., parents separating; an argument or conflict with a parent) were reported most frequently, followed by events related to close friends, school, romantic relationships, other domains (e.g., car accidents, appearing in court), and social activities.

Chronic stress ratings and symptomatology at follow-up

After controlling for the effects of covariates (time, sex, treatment condition, and illness subtype), higher levels of chronic stress in intimate relationships significantly predicted less improvement in depression ($F(1,52)=9.86$, $p=.003$, $\beta=.21$), mania ($F(1,52)=10.37$, $p=.002$, $\beta=.22$) and combined mood symptoms ($F(1,52)=14.75$, $p=.0003$, $\beta=.24$; see Figure 1). A significant interaction between age and chronic stress in intimate relationships indicated that, with increases in age, chronic strains in intimate relationships became more closely associated with combined (manic plus depressed) mood symptoms ($F(1,51)=4.71$, $p=.03$, $\beta=.25$). Additionally, higher chronic stress in peer relationships significantly predicted less improvement in mania ($F(1,52)=6.50$, $p=.01$, $\beta=.20$), but did not predict changes in depression ($F(1,52)=.04$, $p=.85$) or combined mood symptoms ($F(1,52)=2.86$, $p=.10$). The remaining domains of chronic stress assessed by the UCLA Life Stress Interview (academics, school behavior, health, and family health) were not significantly associated with ratings of depression, mania, or combined mood symptoms (all $p's >.05$). Sex did not significantly interact with the various domains of chronic stress to predict mood symptoms.

Episodic stressors and symptomatology at follow-up

Independent and dependent life events were examined separately as predictors of mood symptoms by estimating 1) the mean severity of events reported at each follow-up assessment, 2) the total number of events reported at each follow-up (i.e., frequency of events), and 3) the number of events with moderate-severe impact reported at each follow-up. For both independent and dependent events, mean ratings of event severity and the total number of events were not associated with depression, mania or combined mood symptom scores (all $p's >.05$). However, an association between a higher frequency of severe, independent events and less improvement in mania ($F(1,55)=3.46$, $p=.06$, $\beta=.12$) and combined mood symptoms ($F(1,55)=3.65$, $p=.06$, $\beta=.12$) approached significance. The number of severe, independent events was not associated with depression symptoms ($F(1,55)=1.66$, $p=.20$).

An interaction between age and the severity of independent events indicated that, with increases in age, the severity of independent events became more closely associated with depression (F

(1,53)=4.54, $p=.04$, $\beta=.12$), mania ($F(1,53)=9.00$, $p=.004$, $\beta=.18$), and combined mood symptoms ($F(1,53)=8.24$, $p=.006$, $\beta=.30$). Because older age may be associated with greater severity of life events, correlations between age and life event ratings were examined. Although increases in age were modestly correlated with the frequency of dependent events (Pearson's $r=.39$, $p=.02$) and the severity of dependent events (Pearson's $r=.35$, $p=.05$), age was not correlated with the frequency (Pearson's $r=-.12$, $p=.46$) or severity of independent events (Pearson's $r=.18$, $p=.31$).

Additionally, an interaction between sex and the severity of independent events indicated that girls reported a stronger association between independent events and depression ($F(1,53)=4.08$, $p=.05$, $\beta=.11$) and combined mood symptoms ($F(1,53)=4.45$, $p=.04$, $\beta=.21$) than boys. However, this interaction between sex and the severity of independent events did not significantly predict mania symptoms ($F(1,53)=2.34$, $p=.13$).

Independent effects of covariates

In all HLM analyses examining stress as a predictor of mood symptom slopes, the main effect of time was significantly associated with decreases in depression, mania, and combined (depression plus mania) mood symptoms (all $p's < .05$). A diagnosis of bipolar I (versus bipolar II or NOS) was significantly associated with less improvement in depression, mania, and combined mood symptoms in all analyses (all $p's < .05$). Because a limited number of youths were diagnosed with bipolar II ($n=4$) or NOS ($n=7$), these youths were combined into a single group when covarying illness subtype. Examination of sex as an independent variable indicated that girls reported less improvement than boys in mood symptoms ($F(1,56)=3.80$, $p=.05$). Age was not directly associated with combined mood scores ($F(1,55)=1.99$, $p=.16$), and was therefore only included as a covariate in analyses examining interactions between age and stress variables (described above). The effects of stress on mood symptoms were independent of the effects of treatment condition (FFT versus enhanced care), which was included as a covariate in all HLM analyses. The independent effects of treatment condition on outcomes are not reported here because the randomized trial is not yet complete.

Discussion

This study examined life stress as a predictor of mood symptoms among adolescents who entered a treatment study following an acute episode of bipolar disorder. HLM analyses indicated that higher levels of chronic stress in intimate relationships (family and romantic) over a 12-month follow-up were associated with less improvement in depression, mania, and combined mood symptoms (depression plus mania).

Among the various domains of life stress that were assessed, family relationships were associated with the greatest frequency of stressful events and the highest levels of chronic stress. Because participants were recruited for a larger study in which family-focused psychoeducation was offered, it is possible that families with the most adverse home environments self-selected for the study. Naturalistic studies would further confirm whether family-related strains are the most prominent stressors for bipolar youths, whether these strains are associated with the severity of mood symptoms, and whether family-related stress has illness polarity-specific effects. However, the present study's findings are consistent with results from naturalistic studies showing that adverse circumstances in family relationships (e.g., low maternal warmth) are associated with shorter remission periods among prepubertal and early-adolescent youths with bipolar disorder (Geller et al., 2004).

Additionally, higher levels of chronic stress in peer relationships were associated with less improvement in mania symptoms. Given significant impairment in peer relationships among youths with bipolar disorder (Geller et al., 2000), particularly after onset of the illness

(Quackenbush et al., 1996), the association between chronic stress in peer relationships and mania symptoms is likely a recursive one in which the most impaired youths generate the highest levels of peer-related stress, which further exacerbates their mood symptomatology. However, the limited sample size prohibited causal modeling analyses that enable firmer conclusions about the directions of these relationships. Thus, the extent to which symptoms contributed to greater stress in peer relationships (as well as other life domains), and stress contributed to greater symptom severity remains unclear.

Although the overall severity and frequency of life events did not predict mood symptoms, separate examination of severe, independent events indicated that a higher frequency of severe events that were not attributable to patients' own actions may have exacerbated mania and combined mood symptoms. These results, although only approaching conventional levels of significance ($p = 0.06$), are consistent with findings from adults with bipolar disorder indicating that severe life events often precipitate the onset of mood episodes (Johnson & Roberts, 1995).

The influence of age on stress-symptom relationships was revealed for two dimensions of life stress: chronic strains in intimate relationships and the severity of independent life events. With increases in age, higher levels of stress in these domains became more closely associated with less improvement in mood symptoms. The findings are consistent with Post's hypotheses regarding stress-sensitization, which predict increased sensitivity to life stress as the illness progresses, until even minor amounts of stress precipitate mood symptoms. The present study's results are also consistent with two studies of adult bipolar patients, which have provided evidence for 1) increased sensitization to stress with increases in age (Hlastala et al., 2000), and 2) an increased likelihood of relapse after a stressful event among bipolar patients in later phases of the illness, compared to patients in earlier phases of the illness (Hammen & Gitlin, 1997).

Limitations

Overall, the effect sizes for significant predictors of mood symptoms ranged from small to medium (β 's = 0.12–0.30), with the majority of findings indicating medium effects. Various domains of chronic stress (academics, school behavior, health, and family health) were not associated with mood symptom severity. In evaluating the present findings, it is important to note that the majority of adolescents (68%) were participating in family-focused treatment and all were being treated with psychotropic medication during the follow-up period. Most of the adolescents experienced improvements in mood symptomatology over the 12-month follow-up. Possibly, participation in psychosocial intervention with appropriate medication management influenced adolescents' responses to chronically adverse circumstances, thereby attenuating the influence of life stress on mood symptoms. The influence of life events should be evaluated in future studies that examine stress-symptom relationships outside the context of intensive psychosocial and pharmacological treatment.

Moderators of stress-symptom relationships to be explored in future studies include sex and comorbid conditions. Despite greater improvement in mood symptoms among boys, only one sex difference was revealed with respect to the relationship between stress and mood: a stronger association between the severity of independent events and mood symptoms in girls. Questions regarding differences in the types of events that are reported by boys and girls (e.g., relationship versus achievement) and the differential impact of these events on illness outcome remain to be addressed in studies designed to answer questions about sex moderation.

Conclusions

In summary, the present study suggests that various domains of life stress are correlated with the severity of mood symptoms over time, even among adolescents receiving psychotropic and psychosocial interventions. Chronic stress in family, romantic, and peer relationships may represent especially important targets for psychosocial intervention. Early psychosocial interventions may attenuate the influence of life stress on the course of illness by teaching effective strategies for coping with stressful circumstances, educating bipolar youths about the reciprocal nature of stress-symptoms relationships (i.e., the impact of stress on mood symptoms and the generation of stress as a result of mood symptoms), and providing developmentally-appropriate intervention strategies for reducing stress as the child ages. Development of age-appropriate interventions is dependent on a thorough understanding of the various pathways between stressors and the course of early-onset bipolar disorder across various phases of development.

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Figure 1.

*Chronic stress in family and romantic relationships as a predictor of depression+mania symptoms over 12 months.

Table 1

Chronic Stress Ratings Across 12-months of Follow-up: (N = 38; mean age=15.03±1.43)

Domain	Mean rating ± SD (across all time points) [*]	Range
Family	3.06±0.85	1.5–5.0
Academics	3.08±1.09	1.0–5.0
Social activities	2.85±0.81	1.5–5.0
Close Friends	2.78±0.99	1.5–5.0
Romantic relationships	2.76±0.86	1.5–5.0
School Behavior	2.47±0.82	1.0–5.0
Family Health	2.31±0.45	2.0–3.5
Health	2.20±0.45	1.5–3.0
Frequency and Severity of Episodic Stressors Across 12-months of Follow-up		
Domain	Number of events across all time points (Percentage of all events reported across all time points)	Mean severity ± SD (across all time points) [*]
Family	64 (33%)	2.59±0.68
Close Friends	43 (22%)	2.25 ±0.59
School	28 (14%)	2.11±0.51
Romantic relationships	25 (13%)	2.29±0.47
Other	26 (13%)	2.40±0.86
Social Activities	10 (5%)	2.20±0.54

* 1=exceptionally good conditions; 2=good, stress-free conditions; 3=average or mixed conditions; 4=poor conditions; 5=severely adverse conditions

* 1=no impact; 2=mild impact; 3=moderate impact, 4=marked impact, 5=severe impact

Table 2

Significant predictors of depression, mania, and combined mood symptoms over 12 months (N=38)

Independent Variables	Dependent Variables (F, p, and β values)		
	K-SADS Depression Rating Scale scores	K-SADS Mania Rating Scale scores	Combined mood symptoms (K-SADS Depression + Mania Scores)
Chronic stress – intimate relationships	F=9.86, p=.003, β =.21**	F=10.37, p=.002, β =.22**	F=14.75, p=.0003, β =.24**
Chronic stress – peer relationships	F=.04, p=.85, β =.02	F=6.50, p=.01, β =.20**	F=2.86, p=.10, β =.13 [†]
Number of severe, independent events	F=1.66, p=.20, β =.08	F=3.46, p=.06, β =.12 [†]	F=3.65, p=.06, β =.12 [†]
Interaction: age x chronic stress - intimate relationships	F=2.92, p=.09, β =.11 [†]	F=2.92, p=.09, β =.11 [†]	F=4.71, p=.03, β =.25*
Interaction: age x severity of independent events	F=4.54, p=.04, β =.12*	F=8.88, p=.004, β =.18**	F=8.24, p=.006, β =.30**
Interaction: sex x severity of independent events	F=4.08, p=.05, β =.11*	F=2.34, p=.13, β =.09	F=4.45, p=.04, β =.21*

[†] p<.10,

* p<.05,

** p<.01