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Prospective Predictors of Mood Episodes in Bipolar Disorder

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Abstract

Background—Bipolar disorder (BD) is associated with alterations in mood, personality, cognition and event-related potential (ERP) measures. The relationship between these multidimensional measures of state and subsequent course of the illness is not well understood. Therefore, this study aimed to prospectively identify factors that predicted the course of mood episodes.

Methods—Sixty-five participants with BD were administered the auditory P300 oddball task, clinical assessment instruments and cognitive tests at baseline, and were subsequently administered the SCID interview once a month by telephone for 12 months.

Results—Hierarchical regression analyses indicated that the Montgomery-Asberg Depression Rating Scale (MADRS) predicted the number of months spent in a depressed state ($p < .001$) and in a mixed state ($p = .001$), while both the MADRS ($p < .001$) and time to complete Trails A ($p = .033$) predicted total number of months in a mood episode (across all mood states). Among euthymic patients at entry, Cox regression analyses indicated that higher ratings on both the MADRS ($p = .017$) and Hypomania Personality Scale (HPS; $p < .001$) were associated with both increased likelihood of a mood episode and less time until the onset of a mood episode.

Limitations—The sample size is relatively small, not all participants completed 12 months, and follow-up assessments were conducted via telephone.

Conclusions—Our results suggest that affective and cognitive measures, and personality factors, especially the MADRS and HPS, serve as important predictors of the course of mood episodes or relapse in BD patients. These prospective markers of acute mood states may be used to guide treatment decisions.

Keywords

bipolar disorder; mood episode; prospective predictors; cognition; auditory evoked potentials; MADRS

Bipolar disorder (BD) is a chronic illness characterized by recurring mood episodes of depression, mania, or mixed states, which often lead to debilitating clinical and functional

outcomes. 30 - 60% of patients experience occupational impairment and social dysfunction even during inter-episode euthymic states (MacQueen et al., 2001). This functional impairment during euthymia may be a result of the progressive nature of the disorder, as the number of mood episodes has been linked to cognitive decline (Clark et al., 2002) and structural abnormalities in the prefrontal cortex and cerebellar vermis (see Strakowski et al., 2005 for a review). A recent study also documented progressive decreases in cerebellar and temporal lobe gray matter that were correlated with number of mood episodes and with declines in cognitive function (Moorhead et al., 2007). Given the repercussions associated with recurrent mood episodes, it is important to accurately predict the onset of acute mood episodes in BD so that prophylactic measures may be employed. As such, this study aimed at identifying those variables that predict the general course of illness and the onset of a mood episode.

Much of the current literature regarding prognosis in BD has focused on symptom and psychosocial markers to predict functional outcome and either symptomatic or syndromal recovery. Symptomatic recovery generally refers to substantial improvement in symptoms of the illness as indexed by symptom ratings scales, whereas syndromal recovery is typically defined as not meeting criteria for a DSM illness episode. Thus far, research indicates that female gender, shorter initial hospitalization and lower initial depression ratings predicted shorter time to syndromal recovery, while lower socioeconomic status and medication noncompliance were associated with poorer syndromal recovery (Delbello et al., 2007; Keck et al., 1998; Treuer & Tohen, 2010). Alternatively, older age of onset, higher socioeconomic status and shorter initial hospitalizations were associated with greater functional recovery (Keck et al., 1998; Post et al., 2010; Treuer & Tohen, 2010). Further, there seems to be a robust reciprocal relationship between depressive symptoms and functional impairment. For example, studies have shown that functional impairment at baseline was predictive of subsequent depressive symptoms during follow-up; as well, relatively minor changes in depressive (but not manic) symptoms had a significant impact on functional impairment. This suggests that more severe or persistent depressive symptoms are associated with a more severe course and functional impairment. Supporting this, the presence of depressive symptoms during a euthymic state has been associated with a shorter time to the onset of a mood episode (Simon et al., 2007; Treuer & Tohen, 2010; Weinstock et al., 2008). These findings, along with reports that patients with BD spend the majority of time in a depressive episode relative to other mood episodes (Judd et al., 2002), highlight that full depressive episodes and subsyndromal depressive symptoms are associated with a worse general course of illness in BD.

Personality traits and temperament have also been implicated in predicting the course of illness. For example, harm avoidance was a significant predictor of depressed mood episodes (Farmer et al., 2009), as were trait depression and neuroticism (Christensen et al., 2006; Wilhelm et al., 1999). Further, Bipolar I patients who experienced mixed episodes were more likely to meet criteria for personality disorders and endorsed greater levels of depressive, cyclothymic, irritable and anxious temperament compared to those without mixed episodes (Röttig et al., 2007; although see Di Florio et al., 2010). Those with BD and co-morbid personality disorders were also less likely to reach syndromal recovery after hospitalization for a manic episode (Dunayevich et al., 2000). Likewise, individuals with a

hypomanic personality, as indexed by high scores on the Hypomanic Personality Scale (HPS), were more likely to experience mood episodes (Eckblad et al., 1986; Klein et al., 1996), specifically manic or hypomanic episodes (Meyer et al., 2003). As one of the only self-report mania scales, the HPS predicted BD at a 13-year follow-up of high-scoring college students (Kwapil et al., 2000). Taken together, these findings suggest that personality traits and temperament factors both influence the quality of acute mood states in those with BD. However, for the most part these results speak to the general course of illness and do not predict the onset of an individual, impending mood episode prior to its initiation.

Although bipolar disorder has been reliably associated with enduring cognitive deficits and neurophysiological abnormalities, these characteristics are not commonly used to predict the onset of a mood episode. For instance, cross-sectional studies using electrophysiological measures have reported increased latencies and reduced amplitudes of the P300 event-related potential (ERP) component in bipolar patients (Degabriele et al., 2009; Muir et al., 1991; O'Donnell et al., 2004; Souza et al., 1995). This indicates that they have disrupted context updating, a neural process indexed by P300 in which the current mental representation in working memory is updated upon detection of a new stimulus (Polich, 2007). In addition, bipolar patients display impaired neurocognitive performance compared to healthy controls, especially with regards to verbal memory and executive functions (Andersson et al., 2008; El-Badri et al., 2001; Ferrier et al., 1999; Malhi et al., 2005; Martinez-Aran et al., 2004; Treuer & Tohen, 2010). For example, Jabben and colleagues (2010) found that depressive, but not hypomanic, symptoms in euthymic patients were associated with worse verbal list learning. Importantly, some neuropsychological deficits such as working memory persist over time when assessed in a euthymic or symptomatic state (Hill et al., 2008; Mur et al., 2008), and cannot be attributed to medication status, substance abuse or residual symptoms (Torres et al., 2010a). This has been taken as evidence that impaired cognitive abilities are stable characteristics and do not vary as a function of mood state.

As a result of these enduring neuropsychological deficits in BD, several studies have investigated whether neuropsychological measures predict functional outcome. For example, Jaeger and colleagues (2007) found that attention and ideational fluency significantly predicted functional recovery after 12 months. Likewise, verbal learning and memory was predictive of functional outcome at 6-months (Torres et al., 2010a) and at 12-months (Martino et al., 2009). A composite neurocognitive score, including working memory, vigilance and visual-motor processing measurements, also predicted changes in functioning over a 1-year period (Tabares-Seisdedos et al., 2008). The majority of these prospective studies found that poorer performance on at least one cognitive domain predicts worse functioning in BD. Nonetheless, no studies to our knowledge have considered cognitive or electrophysiological measures as prospective predictors of individual mood episodes.

As reviewed above, many observational studies have used demographic, symptom and personality measures to help characterize the overall course of illness in those with BD. These studies have primarily focused on correlations between index variables and functional outcomes. Few have used a prospective design to predict the onset of an individual mood

episode, although cognitive styles rather than neurocognitive measures were previously used as potential predictors in these studies (Alloy et al., 2008; 2009). Despite the consistent findings of cognitive and electrophysiological deficits in cross-sectional studies of BD, no studies have used these variables as prospective predictors in a longitudinal design. Therefore the aims of the current study are to prospectively identify factors that predict not only the general course of illness (i.e. number of months spent ill) but also the onset of a mood episode (i.e. time to relapse) from an ensemble of cognitive and electrophysiological measures, in addition to clinical symptom ratings and personality indices in BD.

Patients and Methods

Participants

Sixty-five participants with DSM-IV diagnosed bipolar disorder took part in the study. Demographics information can be found in Table 1. The average age of the sample was 42 years, and 42 (65%) were female. Participants were outpatients at the time of testing. Six were unmedicated at baseline evaluation, and the medication status of another six were unknown due to participation in a double-blind drug trial. All others were taking medication (see **Table 1**). Participants were recruited by public advertisements and through physician referrals from Larue Carter Hospital in Indianapolis, Indiana, U.S.A. Exclusion criteria included serious head injury (with loss of consciousness > 5 minutes), neurological disorders, and intoxication (either drug or alcohol use as assessed via urine screen) at the time of testing. All participants provided written informed consent. This study was approved by the Indiana University Internal review board.

Procedures

Participants were administered the auditory P300 task, clinical assessment instruments and cognitive tests at baseline (see **Table 1**). In the interim, the mood disorders section of the Structured Clinical Interview for DSM Disorders Research Edition (SCID-IP Module A) was administered once a month over the telephone. Forty participants completed all 12 months follow up.

Clinical Assessment

The research edition of the SCID, the Young Mania Rating Scale (YMRS) and the Montgomery-Asberg Depression Rating Scale (MADRS) were administered to each participant at the baseline and follow-up appointments by two of the authors (C.A.B. & A.R.B.) or a trained research assistant. Diagnoses of Bipolar I Disorder at baseline were made on the basis of the SCID, YMARS and MADRS interviews (YMRS 12-19=hypomania, YMRS>20 = mania, MADRS>20 = depression) in conjunction with medical records by doctoral level psychologists (C.A.B. and A.R.B.). A monthly SCID mood module was administered by phone interview to determine the mood symptoms and episodes in the previous month. In turn, the number of months was tallied according to whether subjects were depressed, manic, in a mixed state and the total number of months they were ill collapsed across mood types were calculated. At baseline 40 participants were euthymic, 5 were depressed, 13 were manic, and 7 were mixed (above threshold on both the YMRS and MADRS). All but two participants (due to experimenter error) also completed

the Hypomania Personality Scale, a 48-item questionnaire designed to measure a personality style characterized by euphoria, increased energy, and the experience of a hypomanic mood episode (Eckblad et al., 1986).

Neuropsychological Assessment

Five subtests from the WAIS-III-R were administered: Picture Completion (a test of visual object recognition), Digit Symbol Coding (a measure of memory and motor speed), Similarities (the ability to synthesize verbal relationships), Digit Span (verbal short term memory), and Vocabulary. In addition, the Trail Making Tests (A & B; a test of motor speed and executive function) as well as the Word List Memory, Recall and Recognition Test from the CERAD battery were given at baseline.

Electrophysiological Assessment

EEG was recorded from the scalp with Neuroscan SYNAMPS (Neuroscan, Inc., El Paso, TX, USA) using a 0.10 Hz high-pass filter and a 200 Hz low-pass filter and a nose reference. All impedances were below 10 k Ω . Participants were instructed to press a button in response to the rare tones that were randomly interspersed among the standard tones, all of which were presented binaurally at 86 dB SPL (50 ms duration) via Etymotic insert earphones. There were 600 tone pips presented, including frequent ($p = .85$) 1000 Hz non-target tones and rare ($p = .15$) 1500 Hz target tones. Raw waveforms were segmented (-100 to 800ms post-stimulus onset) and were filtered at 24 Hz. Activity that exceeded $\pm 100 \mu\text{V}$ was excluded from analysis and ocular correction procedures used the algorithm of Gratton et al. (1983). Baseline correction used the pre-stimulus interval (-100 ms) to correct for drift. P300 amplitude and latency were manually chosen at electrode site Pz in response to rare target tones.

Statistical Analysis

Hierarchical regression analyses require that all participants have the same amount of data. Therefore, only patients who completed all 12 follow-ups ($N=40$) were used in correlation analyses to determine which electrophysiological, clinical and cognitive measures were related to the total number of months subjects were depressed, manic, in a mixed state and the total number of months they were ill collapsed across mood type. Only variables associated with significant correlations (see **Table 2**) were considered as relevant independent variables in the subsequent regression analyses. We then examined whether commonly acknowledged predictors of disorder status, including age, gender, medication status (at baseline), presence of psychotic symptoms, and number of past hospitalizations (at baseline), were associated with our independent variables. Several independent variables displayed significant differences across gender and age only, therefore both gender and age were included in all hierarchical regression analyses as covariates. Four separate hierarchical regression analyses ('Enter' method) were conducted to predict variation in the total number of months in which a depressed, manic, or mixed episode occurred, and the total number of months in which a mood episode across mood types occurred. To control for age and gender, they were entered first in Model 1 of the regression equation, while the relevant independent variables were simultaneously included in Model 2 to determine whether they

accounted for variance in the dependent variables above and beyond the covariates (i.e. age and gender). Statistics associated with the covariates were reported only when they significantly predicted variance in the dependent variables.

Patients who were euthymic at entry and had at least one follow up assessment were evaluated in a separate survival analysis ($N = 40$). The Cox model was used to determine which of the variables obtained at entry predicted time to relapse, defined as the occurrence of a mood episode. In order to reduce the number of variables in the Cox model, correlations were computed between candidate clinical, cognitive and P300 measures and time to relapse. Only variables associated with significant correlations were used in the subsequent Cox regression analyses ('Enter method'). 25 of these patients were the same individuals included in the hierarchical regression analyses. Both age and gender were included in the model, however neither of these variables alone significantly predicted the variation in time until relapse ($p > .16$). Therefore, statistics associated with age and gender were not reported. All statistical analyses were conducted with SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Hierarchical Regression Analyses

Number of months with a depressed episode—Only one clinical variable – total MADRS score – significantly accounted for variance in months with depression ($R^2 = 0.29$, $F(3,36) = 17.42$, $p = .000$) above and beyond age and gender. The total MADRS score, while holding constant age and gender, was significantly related to the number of months in which a depressed episode occurred ($t(36) = 4.17$, $p < .001$, $\beta = 0.546$). Table 3 summarizes the hierarchical regression analysis predicting frequency of depressed episodes.

Number of months with a manic episode—None of the electrophysiological, clinical nor cognitive variables were significantly correlated with the total number of months during which a manic episode occurred.

Number of months with a mixed episode—The total MADRS score accounted for 26% of unique variance ($R^2 = 0.26$, $F(3,36) = 13.38$, $p = .001$; see Table 3) above and beyond age and gender. Controlling for age and gender, there was a significant positive relationship between the total MADRS score and the number of months during which a mixed episode occurred ($t(36) = 3.66$, $p = .001$, $\beta = 0.517$).

Number of months with any mood episode—Two clinical and cognitive variables – the total MADRS score and time to complete Trails A – accounted for an additional 46% of variance ($R^2 = 0.46$, $F(4,34) = 20.80$, $p < .001$; see Table 3), beyond age and gender. Holding constant age, gender and time to complete Trails A, the total MADRS score was significantly related to the number of months during which any type of mood episode occurred ($t(34) = 5.71$, $p < .001$, $\beta = 0.608$). Similarly, time to complete Trails A was significantly associated with the number of months during which a mood episode occurred, while controlling for age, gender and total MADRS score ($t(34) = 2.22$, $p = .033$, $\beta = 0.252$). In model 1, both age and gender significantly accounted for 17% of variance ($F(2,36) =$

3.71, $p = .034$, $r^2_{\text{adj}} = .125$). Specifically, age while holding gender constant significantly predicted the number of months during which any type of mood episode occurred ($t(34) = 2.83$, $p = .008$, $\beta = 0.301$).¹

Prediction of Relapse in Euthymic Patients: Cox Regression Analysis and Kaplan Meier Survival Analysis—For patients who were euthymic at entry, two clinical variables predicted time to the onset of a mood episode after baseline assessment: the HPS and MADRS total scores. The entire model, including total HPS and MADRS scores along with age and gender, was significant ($-2LL = 146.01$, $\chi^2(4) = 20.51$, $p < .001$), suggesting the variables together significantly contributed to explaining variation in the time until the onset of a mood episode. Both the total HPS scores (hazard ratio = 1.03, $CI_{.95} = [1.01, 1.05]$, Wald $\chi^2(1) = 14.77$, $p < .001$) and total MADRS scores (hazard ratio = 1.10, $CI_{.95} = [1.02, 1.18]$, Wald $\chi^2(1) = 5.65$, $p = .017$) significantly predicted reduced time to the onset of a mood episode.

These predictors were then included in separate Kaplan-Meier survival analyses. A median split was used to divide the HPS (median = 23) and MADRS (median = 5) into high and low scorers when patients were euthymic at baseline. The survival curves of the high scorers and low scorers on the HPS are shown in **Figure 1**. These curves illustrate a marked difference in the survival rate between the two groups ($\chi^2(1) = 13.81$, $p < .001$). Specifically, the high scorers were more likely to experience a mood episode sooner than the low scorers.

Examination of the survival curves of the high and low scorers on MADRS in **Figure 2** reveals a similar pattern ($\chi^2(1) = 8.53$, $p = .003$).

Discussion

In this sample of participants with DSM-IV diagnosed Bipolar-I disorder who completed all 12 months of follow-up, the MADRS administered at baseline predicted the number of months patients spent in a depressed mood episode, the number of months spent in a mixed episode and, combined with Trails-A time-to-complete, predicted the time spent in any type of mood episode (manic, mixed and depressed combined) during the follow-up period. In addition, for those who were euthymic at baseline, MADRS and HPS total scores administered at baseline predicted the amount of time until the onset of a mood episode. These findings indicate that specific mood, personality and cognitive measures may serve as predictors of mood episodes in those with BD. The P300 ERP measure, in contrast, did not predict course or relapse in any of the analyses.

That the MADRS total score predicted most of the dependent measures may reflect the overall clinical nature of our sample. Specifically, even though only five of the 65 patients were in a depressed state at baseline, these patients spent more of their time ill during the 12-month follow-up (53%) than the 13 patients in a manic state (19%) and the 40 patients euthymic at baseline (24%). Similarly, the seven patients in a mixed state at baseline spent

¹In order to maximize generalizability of our findings, we conducted the same hierarchical regression analyses in subjects who had completed at least 6 follow-ups ($N=52$) and only examined data from the first 6 follow-ups. The pattern of data upholds for all of our analyses. The only exception lies in the unique variance in number of months with any mood episode accounted for by age ($p=.371$) and completion time in Trail A ($p = .067$), both of which were significant variables in the original analyses.

60% of their time ill during the follow-up period. The characteristics of our sample are consistent with others in that depressed and mixed states characterize the majority of time spent symptomatic in BD (Judd et al., 2002; 2003). Whether this is due to underlying mechanisms of the disorder or the lengthy wait for clinical effectiveness of anti-depressant medication is currently unknown. Nevertheless, given that the patients experiencing depression or a mixed state at baseline spent a considerable amount of time being ill during the follow-up period, this may explain the robust effect of the MADRS in predicting the total time patients spent in a depressed state, a mixed state, or in any mood state.

Interestingly, higher self-reported hypomanic personality style, and not clinician ratings of current manic symptoms, predicted a shorter time until the onset of a mood episode in those euthymic at baseline. There is some evidence that personality factors influence the onset of affective disorders (Christensen et al., 2006). In fact, Grilo and colleagues (2010) found that the presence of personality disorders at baseline predicted shorter time to relapse in those with major depressive disorder. While comorbid personality disorders are known to have detrimental effects on the course and treatment of bipolar disorder (see Krishnan et al., 2005 for a review), this is the first study to investigate the relationship between a personality style that is characteristically similar to an acute mood state and the onset of a mood episode in those with BD. Our data suggests that the questions on the HPS regarding the *usual* way individuals react to situations and regard themselves may provide more variability and therefore be a more sensitive measure in predicting the onset of a mood episode compared to the necessarily restricted-range of clinical ratings when assessing manic symptoms in euthymic patients (i.e. YMRS). Given our findings and the predictive power of HPS evident in a longitudinal study (Kwapil et al., 2000), this self-report instrument may have potential as an efficient screening tool.

Although patients with BD exhibit a variety of cognitive deficits, the only cognitive domain that predicted the onset of mood episodes in our study was processing speed as assessed by time-to-complete on Trails A. While processing speed impairments have been previously found in BD (Ferrier et al., 1999; Quraishi et al., 2002), not all studies show slowed completion time of Trails A in euthymic BD (Hawkins et al., 1997) and some have identified a relationship between medication use and slower processing speed (Bora et al., 2009). This association between medication status and time-to-complete Trails A, however, was not observed in our sample ($r = -0.002$, $p = .993$). Of interest to this study is that other measures of cognitive functioning that have previously been shown to differentiate BD, such as verbal memory, executive functioning, and P300 amplitude and latency did not predict overall course or the onset of an impending mood episode. It is possible that these cognitive and electrophysiological measures may reflect fairly stable traits, and therefore provide little information regarding dynamic changes in mood state over a relatively short interval.

In summary, our findings indicate that clinical and personality factors, especially the MADRS and HPS, serve as predictors of mood episodes in BD patients. In comparison, cognitive function and ERP measures did not predict the onset of mood episodes in our sample. However, several limitations should be considered when interpreting the results of our study. First, we administered monthly follow-ups via telephone. Face-to-face interviews may elicit a more detailed and accurate account of the patients' mood symptoms. Second,

although we followed up with the patients for 12 months, other studies have followed patients over much longer time periods (Farmer et al., 2009; Wilhelm et al., 1999), which may allow one to better understand the long term predictability of these clinical factors. Third, our sample size is relatively small and all patients were in an outpatient setting, which may limit the generalizability of our findings. This methodological issue also limits our ability to thoroughly examine the subgroup of patients in different mood states at baseline. Despite these limitations however, our results provide evidence that specific clinical and personality measures may be particularly informative regarding future course of BD. Importantly, we employed a novel approach of prospectively predicting the onset of individual mood episodes in this disorder. As an extension of this approach, future studies should consider including a broader array of candidate biomarkers (e.g. cognitive and ERP measures). The addition of neuroimaging techniques in longitudinal studies would also help reveal abnormal functional and structural activation in the brain associated with behavioral performance and clinical symptoms. Lastly, future studies with a larger sample sizes and longer follow-up durations are necessary to confirm the predictive validity of these measures and for the implementation of these methods in prophylactic treatment studies.

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HPS Scores of Patients Euthymic at Baseline

Figure 1.

Kaplan-Meier survival curves of first mood episode recurrence subsequent to study entry comparing HPS low-scorers and high-scorers among patients who were euthymic at baseline.

MADRS Scores of Patients Euthymic at Baseline

Figure 2.

Kaplan-Meier survival curves of first mood episode recurrence subsequent to study entry comparing MADRS low-scorers and high-scorers among patients who were euthymic at baseline.

Table 1

Demographic, clinical, neuropsychological, and illness characteristics of bipolar disorder patients.

	Mean	SD
Female gender (N, %)	42 (65)	
Age	42	11.23
Years of education	14	2.50
Months of follow-up	10	3.65
Months in any mood episodes during follow-up (%)	/0) 26.72	27.46
Frequency of hospitalizations	3.05	2.28
Presence of psychotic disorder (N, %)	23 (39)	
Clinical Measures		
YMRS	11.97	11.27
MADRS	10.98	11.14
HPS	33.73	24.76
Neuropsychological Measures		
WAIS-III-R – Picture Completion	8.19	3.19
WAIS-III-R – Digit Symbol Coding	8.12	3.07
WAIS-III-R – Similarities	9.54	2.73
WAIS-III-R – Digit Span	9.50	3.48
WAIS-III-R – Vocabulary (t-scores)	49.62	12.00
Trail A time-to-complete	39.54	26.08
Trail A errors	0.41	0.91
Trail B time-to-complete	86.23	40.26
Trail B errors	0.68	1.03
CERAD total score	21.35	3.68
Electrophysiological Measures (for oddballs, in amplitude)		
Fz	4.51	6.24
FCz	5.89	6.96
Cz	7.87	7.51
CPz	10.23	7.29
Pz	11.43	6.56
Current Medications		
	N	%
Mood Stabilizers	30	46
Anticonvulsants	14	22
Antipsychotics	39	60
Patients who relapsed during follow-up period	43	66

Table 2

Significant correlations between clinical, neuropsychological, and electrophysiological variables and dependent variables.

	r	p
Total months spent in a depressed episode MADRS	.586	<.0001
Total months spent in a mixed episode MADRS	.521	.001
Total months spent in any mood episode MADRS	.694	<.0001
Trails A time-to-complete	.322	.046
Time to first mood episode following baseline MADRS	-.418	.001
HPS	-.413	.001

Table 3

Hierarchical regression analyses of the relationship between clinical and cognitive variables and frequency of mood episodes.

Dependent Measure	Model	Predictor Variable	Adjusted R ² of model	β	t	P
Total months spent in a depressed episode	1	Age	0.062	.181	1.39	.173
		Gender		.160	1.23	.226
	2	MADRS	0.351	.546	4.17	< .001
Total months spent in a mixed episode	1	Age	0.043	.110	0.78	.440
		Gender		-.132	-0.95	.351
	2	MADRS	0.243	.517	3.66	.001
Total months spent in any mood episode	1	Age	0.125	.301	2.83	.008
		Gender		.136	1.21	.234
	2	MADRS	0.583	.608	5.71	<.001
		Trails A time-to-complete		.252	2.22	.033