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Making Waves: Dynamic Modeling of Bipolar Disorder

A dissertation submitted in partial satisfaction of the

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Elliot Gavin Keenan

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ABSTRACT OF THE DISSERTATION

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Professor Jeffrey J. Wood, Chair

Bipolar disorder affects about 1% of the world population and presents a serious problem for affected individuals in their attainment of educational and other societal goals. Although there has been some investigation into bipolar disorder's mathematical structure using damped oscillator models, so far there has been little attempt to use this mathematical structure to inform individuals of their mood states and predict mood into the future, much as one may forecast the weather. Methodologies that have been tried for these purposes have been prohibitively expensive and/or invasive and subjectively unacceptable to individuals with bipolar disorder, thus hindering their use in a variety of real-world settings such as schools and clinics. For this dissertation an app was developed called Shiny Mood App that allowed 13 participants to log various facets of their mood state (such as energy levels, sleep, and motivation) each day for 12 weeks and outputted a classification of their mood as manic or not manic, and depressed or not depressed using a form of latent class analysis. Weekly questionnaires were also completed by participants, which included standardized measures of mania and depression. Correlations between classifications and questionnaires were assessed; for the initial model, mania

classifications were significantly predictive of mania questionnaire scores when compared using a t-test ($p = .001$), but depression classifications did not predict depression questionnaire scores ($p = .42$). Additionally, the mean mania classification across weeks (proportion of time spent manic) was a significant predictor of mania severity as measured by questionnaire score (ASRM; $\beta = .21$; $R^2 = .042$; $p < .001$). A regression approach was used to fit sinusoidal waves to mania and depression classification probabilities. Although these findings are interesting, this study was limited by participant burnout and subsequent low participation from some individuals. Further research is needed to establish the feasibility of using an app-based approach.

The dissertation of Elliot Gavin Keenan is approved.

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Journal Publications

Keenan, E.G., Mahaffey, B., Kappenberg, C.F., & Lerner, M.D. (2023). Leveling Up Dialectical Behavior Therapy for Autistic Individuals with Emotion Dysregulation: Clinical and Personal Insights. *Autism in Adulthood.*

Libsack, E.J., **Keenan, E.G.**, Freden, C.E., Mirmina, J., Iskhakov, N., Krishnathasan, D., & Lerner, M.D. (2021). A systematic review of passing as non-autistic in autism spectrum disorder. *Clinical Child and Family Psychology Review*.

Keenan, E.G., Gotham, K., & Lerner, M.D. (2018). Hooked on a feeling: repetitive cognition and internalizing symptomatology in relation to autism spectrum symptomatology. *Autism*.

Introduction

Bipolar disorder is an episodic disturbance of mood including both extreme lows (depression) and extreme highs (mania) which typically alternate in a predictable fashion (Koukopoulos et al., 2013). Bipolar disorder presents a difficult-to-manage condition (Ortiz et al., 2018), which affects about 1% of the world population, along with the 2.4% of the world population who are on the "bipolar spectrum" with symptoms that fall below the threshold of Bipolar 1 or Bipolar 2 disorder (Merikangas et al., 2011). A variety of non-affective cognitive problems can be caused by bipolar disorder, including deficits in declarative memory (Bearden et al., 2006), non-verbal memory encoding (Deckersbach et al., 2004), episodic memory both during and outside of manic episodes (King et al., 2013; Shimizu et al., 2009), and executive functioning (Ibanez et al., 2012; Mur et al., 2007). Another cognitive problem common in bipolar disorder is lack of insight or awareness into one's own symptoms (Látalová, 2012). Lack of insight is most pronounced during periods of illness, especially mania, and this leaves a valuable target for study using quantitative methods. Impaired insight is associated with impaired memory and impaired executive functioning (Látalová, 2012). This dissertation seeks to address lack of insight in patients with bipolar disorder by means of a digital intervention so patients can have assistance in recognizing when they are experiencing onset of a manic state or depressive state and seek support accordingly. The main purpose of this dissertation is to identify and predict, using machine learning, mood episodes in bipolar disorder.

It is notable that there is reduced educational attainment among people with bipolar disorder (Glahn et al., 2006) and interventions that can be used in educational settings could narrow this divide. Previous attempts at predicting mood in bipolar disorder have been unacceptable to patients due to their invasiveness (Grünerbl et al., 2015) or have required

expensive specialized technology (wearable sensor t-shirts) that can't be applied today to a wide variety of real-world settings (Valenza et al., 2013). A common goal in clinical research on bipolar disorder is predicting mood by giving a mood forecast. Just as a weather forecast warns of a chance of rain, accurate mood prediction may forecast mood episodes that could be addressed or managed appropriately before they progress into severe symptomatology such as psychosis or catatonia or severe consequences such as attempted and completed suicide.

In the field of psychiatry, where underlying processes are rarely observable, accurate conceptual models can provide valuable insight into the mechanisms of illness (Bonsall et al., 2015; Rosenzweig, 1977). A mathematical conceptualization of bipolar disorder stands in contrast to the approach of the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, 2013), which relies upon uniform symptom checklists to categorize mood, and pays no heed to cyclical patterns or mechanisms. This approach is inherently flawed, considering that mood is always relative to an individual's baseline, and at times the presentation of a mood episode can be idiosyncratic (Bonsall et al., 2012; Lam & Wong, 2005; Perugi et al., 2001; Rybakowski et al., 2013; Vázquez et al., 2010).

One of the earliest conceptual models of bipolar disorder (then called manic-depressive insanity) comes from German psychiatrist Emil Kraepelin (Zivanovic & Nedic, 2012). In 1913, Kraepelin described bipolar disorder as a "periodic and circular" disturbance of mood which could form a gradient of severity that blends into non-pathological individual differences in temperament (Zivanovic & Nedic, 2012). Yet he maintained that one etiology accounted for the continuous array of mood symptoms he observed.

Kraepelin believed that delineating bipolar disorder based on the severity or duration of individual episodes was of limited utility, but that a delineation based on the frequency of episodes would be more useful (Kraepelin, 1921). Further, he documented the multifaceted presentations of mixed episodes, which blend symptoms of depression and mania in a variety of ways; in order to explain this phenomenon, he developed a three-component model consisting of disturbances in emotion, volition, and intellect. He saw each of these components as a harmonic wave (a wave that moves like a sine wave), and if the three waves were to come out of phase, mixed episodes could result.

There is also contemporary interest in the dynamics of bipolar disorder. One study reviewed the medical charts of 855 outpatients with bipolar disorder, and classified them based on the sequential pattern of mood episodes (Koukopoulos et al., 2013); of these patients, 57% were established as consistently having mania before depression, or as consistently having depression before mania. Further, 26% had cycling that was sufficiently rapid or chronic such that an apparent sequential pattern could not be discerned over the course of the study. Only 17% were determined to have an irregular pattern. The tendency for mood episodes to occur in a patterned fashion (noted by Kukopolis et al.; Kukopulos et al., 1975) suggests that there is an organized component to the dynamics of bipolar disorder that could be modeled.

In the first part of this dissertation, mathematical models of bipolar disorder and the argument for their usefulness will be reviewed; then, one simplified approach to building a dynamical theoretical model of bipolar disorder will be described; and then, using real-world data, an example model will be fit to daily mood data. This dissertation aims to introduce a potentially novel way of using longitudinal mood logging data (which can be collected using everyday tools such as several popular mobile apps) to enhance the classification and treatment

of bipolar disorder. Moreover, clarifying the mechanisms governing mood and cognition in bipolar disorder may illuminate lower-order mechanisms (for example, at the cellular level; M.B. Bonsall, Geddes, Goodwin, & Holmes, 2015). This "mechacognitive approach" goes beyond describing patterns and facilitates the development of testable hypotheses.

Background

A number of scholars since Kraepelin's time have evaluated cyclical modeling to explain the dynamics of bipolar disorder. This is a topic of interest because being able to predict severe psychopathology (i.e., psychosis and suicidality) that pose a risk to oneself and others, as well as to stop or slow the neuroprogression of bipolar disorder (Berk et al., 2011), by providing timely intervention would save many years of people's lives. Research has shown that even with contemporary standards of treatment, individuals with bipolar disorder die about 10 years earlier than non-bipolar peers (Kessing et al., 2015).

A literature search was conducted on Google Scholar using "models" and "bipolar disorder" as search terms along with "mathematical", "cyclic", and "harmonic".

A study using daily mood logs of 43 patients with bipolar disorder (for time periods ranging from 1 to 2.5 years) found that mood episodes in bipolar patients with rapid cycling did not behave in a periodic fashion over extended periods of time, although they appeared periodic over brief intervals (Gottschalk et al., 1995). Mood in the bipolar subjects was significantly more organized than in the control subjects, similar in concept to the increased organization of activity seen on an electroencephalogram (EEG) recording during an epileptic seizure (Gottschalk et al., 1995). The level of organization seemed to increase more with more severe courses of illness. Through a variety of mathematical examinations (including power spectra, time-delay

embedding, estimation of the correlation dimension, phase space reconstruction, and recurrence plots) it was found that bipolar mood reflected a low-dimensional chaotic system. Chaotic systems can appear random, but are actually generated in a deterministic fashion. In contrast with a periodic system, in a chaotic system each cycle is not identical to the one that preceded it (see Table 1 for a glossary of mathematical terms).

Low-dimensional chaotic behavior can be created by the interaction of relatively simple mathematical systems. The interaction of two or more harmonic oscillators is capable of producing chaotic dynamics: the authors speculate that an altered relationship between endogenous rhythms (such as circadian rhythm) and exogenous rhythms (such as light-dark cycles) could be responsible for the complex variations seen in bipolar disorder (Gottschalk et al., 1995). The reported success of "virtual darkness" therapy using amber-tinted glasses to block blue light would seem to substantiate this hypothesis (Phelps, 2008); virtual darkness therapy has been shown to rapidly improve mood and sleep disturbances, leading some authors to suggest that it may be targeting a central mechanism in bipolar disorder (Henriksen et al., 2014). Another study looking at daily mood ratings from 42 individuals with bipolar disorder found that bipolar depression was best modeled by two relaxation oscillators in the presence of noise (Bonsall et al., 2015). It was determined that these two oscillators were independent rather than deterministically coupled, and that in the presence of noise they exhibited increased synchrony (Bonsall et al., 2015). When two harmonic oscillators interact — exhibiting varying levels of synchrony — they can create self-sustaining motion dynamics, such as the case of parametric oscillators. An example of a parametric oscillator is a child moving a playground swing without the external force of being "pushed", by bringing their body into synchrony with the oscillations of the swing.

Chaotic systems, while not predictable in the long-term, are predictable within a certain timeframe (which varies by system) called the Lyapunov time. An example of this is weather forecasting, which is fairly predictable in the short-term, but appears random in the long-term. Thus, bipolar disorder may be predictable over short time periods, but likely not over months or years. This aligns with the finding of mood in bipolar disorder to have a "short memory", as in, it is predictable only over short time periods or appears reactive to recent events but not to distant events (Ortiz et al., 2015) . Factors that predict the imminent onset of mood episodes have been identified; for example, decreased sleep duration is well-known to precede mania (Leibenluft et al., 1996), and in one study the majority of bipolar patients identified sleep disturbance as a prodrome of their manic episodes (Harvey, 2008). Increased sleep duration also predicts depression, and in a study of 59 outpatients, 41% exhibited an inverse relationship between mood changes and changes in sleep plus bedrest the previous night (Bauer et al., 2006). Furthermore, degree of sleep disturbance has been found to be associated with mood symptom severity (Murray & Harvey, 2010). These findings suggest that sleep systems interact with mood systems, perhaps producing chaotic dynamics.

One study used limit-cycle oscillators (machines or mathematical simulations of machines that generate waves under different conditions; see Table 1) to gain insight into the complex dynamics of bipolar disorder (Daugherty et al., 2009). The authors note that their work is qualitative and theoretical rather than empirical in nature, but their use of mathematical equations is novel and has some advantages over statistical approaches. Several other possible mathematical approaches are mentioned, including trigonometric functions. Empirical studies are needed to validate such models. This study provides an interesting look into the dynamics of bipolar disorder worsening over time and becoming more stable in response to treatment.

However, the authors assert that their model does not need to account for mixed episodes because they are modeling Bipolar 2 disorder; this defies clinical knowledge that mixed states do occur in Bipolar 2 (Benazzi et al., 2004) and also ignores the conceptualization of bipolar disorders as a continuous spectrum with a single etiology.

Another theoretical model was constructed by Goldbeter (Goldbeter, 2011), which posits that mania and depression inhibit each other; thus, that they are diametrically opposed and mutually exclusive. This creates bistability, which features abrupt switches between two steady states. Mechanisms are discussed that could transform bistability into oscillatory behavior. However, this paper also does not account for the existence and clinical significance of mixed episodes. As Kraepelin attested, mixed episodes are common; a combination of mixed and depressive episodes is the most common presentation of Bipolar 1 disorder (32%), followed by the combination of manic and depressive episodes (30%; Grant et al., 2005). Mixed depression is also common in Bipolar 2 disorder (Benazzi et al., 2004). A more comprehensive model of the dynamics of mood in bipolar disorder must include mood mixing.

With the exception of Kraepelin's harmonic model, these models view mood in bipolar disorder as one-dimensional, two ends of one continuum. This makes the inclusion of mixed mood in these models difficult. Still other studies posit that mania and depression are dissociated factors (Alloy et al., 2008), yet these conceptualizations fail to account for the non-random occurrence and sequence of manic and depressive episodes, which suggests an intrinsic link. A study evaluating personality traits as vulnerabilities to mania and depression in healthy controls suggested that a two-dimensional model, viewing mania and depression as separable but correlated dimensions, provides greater heuristic power (Murray et al., 2007). An accurate model must encompass the multi-dimensional complexity of bipolar disorder.

Chang and Chou (2018) created a model based on mood sensitivity, which is the reactivity of mood to positive or negative events; they found that when mood sensitivity exceeded a particular threshold, the system exhibited limit-cycle oscillatory behavior. Higher mood sensitivity resulted in a less damped mood response (the oscillations took longer to return to a baseline, non-oscillatory state). The authors also examined asymmetry in mood sensitivity (a differential response to positive or negative events) and found that atypical sensitivity to either positive or negative events was sufficient to trigger bipolar system behavior with the introduction of a large event. This provides further evidence of a partial dissociation between mania and depression.

Understanding the dynamics that interact with a bipolar mood system is essential to building a tool accurate enough to capture those dynamics.

Mood-Altering Rhythms

Circadian cycles are roughly periodic biological events that recur approximately every 24 hours (Murray & Harvey, 2010; Waterhouse et al., 2012). People with bipolar disorder are prone to alterations of the circadian cycle and the sleep-wake cycle, and these alterations can precede strong changes in mood (Bauer et al., 2006). Output of the circadian system (such as body temperature and melatonin secretion) has been found to be altered during mood episodes in bipolar disorder (Murray & Harvey, 2010). Circadian rhythms are generated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which contains cells exhibiting periodic activity; the interaction of these periodic cells creates a nonlinear dynamic system which determines the output of the SCN, not unlike the interaction of oscillators to create mood dynamics (Goldbeter, 2011).

In one study, 19 individuals with the bipolar phenotype showed greater activity during sleep and had a decreased amplitude of the circadian cycle relative to controls (Rock et al., 2014). Sleep-wake cycles are usually in synchrony with circadian cycles, but they can be disturbed to produce a non-24-hour sleep-wake cycle (Murray & Harvey, 2010). Models have been created which explain the sleep-wake cycle in terms of two interacting curves, the circadian cycle and the sleep homeostat, which increases the drive to sleep proportional to time awake and then decreases during sleep (Waterhouse et al., 2012); if the amplitude of the circadian cycle is decreased, changes in the sleep homeostat curves will have exaggerated effects on the sleep-wake system, producing increased sleep-wake variability. Further, if the slope of sleep homeostat curves are altered, it can alter the drive to sleep. If sleep homeostat activity increases less relative to the time spent awake, sleep drive will be delayed (consistent with mania), while if it decreases less during sleep, sleep will last longer and be less restorative (consistent with both depression and euthymia; Waterhouse et al., 2012). A combination of reduced circadian cycle amplitude and dampened activity of the sleep homeostat could thus produce dramatic changes in sleep-wake cycling. These changes are likely attributable to genetics (Waterhouse et al., 2012).

Sleep-wake cycle disturbance has negative implications for quality of life, relapse risk, emotion regulation, cognitive functioning, physical health, and impulsivity (Harvey et al., 2009). Instability of circadian rhythms and a hypersensitivity of the circadian system to the input of light are thought to be trait-like vulnerabilities to bipolar disorder (Murray & Harvey, 2010). For example, it seems that bright light administered in the morning can trigger mixed episodes, but when administered at mid-day it is well-tolerated (Sit et al., 2007). Yet it is notable that there is little evidence of systematic seasonal variation in bipolar mood (Murray et al., 2011). These findings suggest that vulnerabilities to changes in light occur on a particular temporal scale; thus,

the rhythms disturbed by light are likely to be rhythms with a high frequency (changes through the day), such as the circadian rhythm.

One paper formulated a cognitive pathway between circadian disruption and multilevel models of emotion that could lead to affective symptoms in bipolar disorder and downstream to behaviors (Jones, 2001). However, alterations to the circadian cycle may affect the internal cycle of bipolar moods more directly. Dopaminergic and serotonergic pathways connect sleep-wake and affective dynamics, and both are implicated in the mechanism of bipolar disorder (Berk et al., 2007; Mahmood & Silverstone, 2001; Murray & Harvey, 2010). In particular, dopaminergic dysfunction in bipolar disorder is posited to be a cyclical process contributing to the cyclical system of mood disturbance (Berk et al., 2007). Moreover, these neurotransmitters are targets for pharmacological intervention. Lithium lengthens the circadian cycle (Harvey, 2008), which could compensate for dampened activity of the sleep homeostat, albeit producing longer sleep times.

Considering the inverse relationship between mood and sleep duration, and the findings that changes in sleep duration precede changes in mood, altering sleep-wake cycles may alter mood cycling (perhaps introducing chaotic dynamics). A downstream effect of slon mood is further suggested by the persistence of some sleep disturbances even in euthymic states: interepisode bipolar individuals have poorer subjective sleep quality (Rocha et al., 2013), longer time to sleep onset, more frequent awakenings, and greater variability in sleep-wake cycles (Ng et al., 2015). However, changes in mood may form a feedback loop that further worsens sleep, which in turn leads to a magnified disturbance in mood (Harvey, 2008). It is therefore difficult to determine if mood cycles exert a reciprocal influence on sleep cycles. Further, energy (particularly in the evenings) — which would seem to exist in the space in between mood

cycling and sleep cycling — has been found to be the superior predictor (compared to mood and sleep) of bipolar mood episodes (Ortiz et al., 2018).

Other biological cycles may be implicated in altering the course of bipolar moods. Among them is the cycle of inflammation and counter-inflammation in the brain, which is thought to be perturbed in bipolar disorder and possibly a pathway to neuroprogression, in which the illness becomes more severe over time (Berk et al., 2011). This is reminiscent of Daugherty et al.'s conceptual model (2009) which modelled a progression over time using limit-cycle oscillators.

How Mood Changes Over Time

Mood cycling seems to be governed by a system where the occurrence of mania and depression is organized but changes nonlinearly over time (Bonsall et al., 2012). External input (such as light) and internal input (such as circadian instability) may interact with the mood system on a fundamental level, and identifying these interactive factors provides valuable insight into targets for intervention to correct dysfunction of the mood system. The question remains, however, of how the mood system functions. Although there are surely neurobiological explanations for these interactions, a complete understanding of neurobiology is not necessarily prerequisite to understanding the dynamics and interactive mechanisms that may drive change in mood.

Dynamical systems modeling simulates nonlinear change of a system over time using mathematical equations to represent interacting forces (Boker & Nesselroade, 2002; McKee et al., 2018). When dynamical systems models are applied to research with human participants, they are fit at the individual level to simulate change within a single participant, while multilevel

modeling can provide some insight into interindividual differences (Boker et al., 2009; Maxwell, S. E., & Boker, 2007). Within-individual comparisons of mood is a valuable approach in the context of bipolar disorder as it accounts for the relativity of mood disturbance to an individual's baseline. For example, it has been recognized since Kraepelin's time that some people have a naturally hyperthymic temperament (Zivanovic & Nedic, 2012); yet, for people with a naturally dysthymic temperament, exhibiting the same behavior may be pathological.

Damped oscillator models have been found to simulate within-individual differences well in a variety of contexts, and the usefulness of such models includes the identification of parameters to manipulate to correct dysfunction in the system (Boker & Nesselroade, 2002). While some dynamical systems models are purely theoretical, they can increase understanding of the mechanics governing a disordered system and provide clinically relevant information. For example, dynamical systems modeling has been used to link affective cognition with neurobiological mechanisms (Lewis, 2005).

The basic structure of the mood system appears to be harmonic. This claim is based in the intrinsic coupling of mania and depressive states, which can occur in either direction as shown by the course sequencing research showing mania-before-depression and depression-before-mania are likely subtypes of bipolar disorder which are consistent within individuals (Koukopoulos et al., 2013). Harmonic regression has been used to predict economic and environmental oscillations, such as forecasting the weather (Bujosa et al., 2007). A minimalistic version of a dynamical systems model which uses harmonic regression to fit trigonometric functions to mood data across time, and then assesses these functions for change, is proposed. This approach is efficient and accessible because regression is familiar to many researchers. The

goal is to correctly categorize mood states and predict oncoming mood episodes, creating a tool which would have clinical utility.

In this model, mania and depression are measured over time as separate components which interact with each other. Conceptualized as sinusoidal waves, they may have differing frequencies, which change over time; thus the output of their interaction may appear chaotic. A concept map (Figure 1) theorizes several factors (primarily light input and sleep systems) that might affect change in frequency over time, especially for the mania component. These contributing factors are also dynamical systems in their own right, and their interaction with mood is surely too complex to capture with a minimalistic model. Nonetheless, the theoretical justification for how wave frequencies may change over time is essential to my explanation of the model.

Preliminary Application of the Conceptual Model

For a hypothetical example of how a model to predict mood states could work based on my conceptual model, a participant with rapid-cycling bipolar disorder could measure their mood symptoms (such as sleep times, and participant ratings of energy levels, emotions, motivation, and self-esteem) daily over an extended period of time. At the end of every week, an algorithm calculates probabilities of each day belonging to each latent class (manic and depressed) using a diagnostic classification modeling/cognitive diagnostic modeling approach (DCM; Ravand & Robitzsch, 2015), taking into consideration the previous 4 weeks. DCM is able to estimate the probability of any particular day belonging to either class (or both, or neither) based on individual items, such as responses to a questionnaire; it does so by creating the most possible separation or mathematical distance between belonging to a group (“mastery” or “endorsement” of an attribute) and not belonging to a group (“nonmastery” of an attribute). Possible attributes

(latent constructs one may have “mastery” or “endorsement” of) are always pre-defined by a matrix specified by the researcher. DCM has been used in educational contexts to study “mastery” or learning of particular constructs, and has also been used to study evaluation data in similar ways to Item Response Theory as well as a traditional Factor Analysis.

Thus, the proposed DCM would define each individual’s mania and depression (the attributes pre-specified by the researcher) based on particular days which stand out the most as measured by their distance from an individual’s other days (so that there is maximum distance between “mastery” and “nonmastery” days). “Mastery” days are classified as a 1 and “nonmastery” days are classified as a 0 for each attribute. Assuming the individual has a justified diagnosis of bipolar disorder, this approach should accurately capture distinct mood episodes relative to their baseline.

Then, best-fit sinusoidal waves are found for both mania and depression probabilities using harmonic regression (in this case, a linear combination of sine and cosine functions). Figure 2 shows an example of these waves using arbitrary values, for the purposes of illustrating what the components “mania” and “depression” might look like in relation to each other, but this is not empirically derived. An additional sinusoidal wave is computed by taking the average of probability values for mania and depression; this wave represents the probability that an episode of either mania or depression will be of a mixed type (this is only one basic approach for determining the mixed probability, and other approaches should certainly be tried — perhaps based on the interactions in Figure 1). Thus, a variety of real-world mood presentations can be accounted for by the model. Note that in the DCMs which will be used in this dissertation, the probability of a mixed episode is estimated directly in the case of days where both mania and

depression are classified as 1 (“mastery”); the aforementioned depiction is for illustrative purposes.

Each week’s iteration of the harmonic regression model is compared to the previous week’s iteration to ascertain change in frequency of the mania wave. In turn, a change in estimated wave frequency of mania from one week to the next is recorded. Finally, a single model is fit using all of the available data and considering changes in wave frequency from one week to the next of the individual models as a moderator. This model can be used to make predictions of mood states in the near future.

Either mania or depression could have been selected as the moderator wave, but several factors suggest that mania is the driving force behind change over time in the occurrence of mood episodes. Most mood stabilizing medications for bipolar disorder — with the notable exception of lamotrigine and valproate (Hahn et al., 2004; Smith et al., 2007) — are more antimanic than antidepressive. Antidepressants alone do not protect against manic or mixed episodes, rapid cycling, or suicidal behavior in bipolar disorder (Pacchiarotti et al., 2011) although they may be used in combination with antimanic drugs, such as olanzapine.

Moreover, lithium — while it has been classically thought of as an anti-manic drug — has limited antidepressant properties and confers a specific, non-mood-related protective effect against suicide (Alda, 2015; Manchia et al., 2013). Augmentation of antidepressants with lithium to treat unipolar depression is rare but effective (Valenstein et al., 2006). When lithium is used as an adjunct to antidepressant therapy, it seems that several specific factors (including a family history and a recurrent course of mood disturbance) which are somewhat suggestive of an underlying bipolar disorder are predictors of response (Jollant, 2015). Therefore, it seems that the core symptomatology of bipolar disorder (even in the absence of manic episodes) is responsive

to antimanic effects. This is further supported by the popularity of atypical antipsychotics as mood stabilizers, although some atypical antipsychotics (such as aripiprazole; Fountoulakis et al., 2011) may have antidepressant effects in addition to antimanic effects.

Further, virtual darkness therapy has been shown to have an antimanic effect and stabilizes mood (Phelps, 2008) while bright light therapy improves depression symptoms, but does not prevent manic or mixed episodes — in fact, it can induce them (Sit et al., 2007). Ultimately, however, the relationship between mania and depression may be reciprocal. More complex future models can assess this.

Example Using Real-World Data

One hundred and eighteen consecutive days (from summer to fall of 2018) of mood-logging data were available from an individual with rapid-cycling Bipolar 1 disorder (the author of this dissertation). At the time of data collection the individual was enrolled in a partial hospitalization day program. Each day was rated using the mood-logging app Daylio; for each entry, users can select one mood state and then select any of the "activities", which are yes-no questions about the day. Both moods and activities are user-defined. The participant's mood was rated on a 1 to 5 scale where 1=manic, 2=happy, 3=neutral, 4=depressed, and 5 could mean "very suicidal" or "mixed episode" (either of them warranting a score of 1, although they often co-occurred). "Activities" included items like "slept 13 hours or more", "slept 5 hours or less", "went shopping", "showered", "ate over 600 calories today", and "experienced hallucinations". These activities often represent either symptoms or self-care goals, and were thus personalized by the participant. Sleep and energy ("went shopping", "had social interactions", "showered") were both captured by the activities. Recently, there has been a renewed interest in the collection

of subjective data such as these, which can be captured using smartphones and other electronic devices (Ortiz & Grof, 2016).

Example Results

Figure 3 shows an example of mood ratings throughout July to November 2018. Note that mood cycles in this month appear nearly isometric, three consecutive repetitions of a pattern with two peaks and a drop. From month to month the range of responses varied, but in general a similar pattern was observed throughout; however, mood frequency dropped from three repetitions per month to one repetition per month by the end of mood logging. A DCM q-matrix was constructed using mood scores and activity responses. A q-matrix specifies what "items" evince "mastery" over what "attributes". For example, a test could measure both reading and mathematics, and with a q-matrix one can assign individual items to one or more of the latent attributes (reading or math ability in this example). Table 2 shows the mood scores and activities considered towards classification as manic or depressed (or both, or neither). A generalized deterministic inputs, noisy and gate (G-DINA) model was used (Ravand & Robitzsch, 2015). G-DINA is a specific type of DCM, which fall into three main categories: compensatory models (models in which "mastery" of one attribute can "compensate" for another, such as DINO); non-compensatory models (such as DINA); and generalized models, which allow for specification of either compensatory or non-compensatory relationships via the q-matrix. G-DINA is a generalized model.

The $\max(X^2)$ absolute goodness-of-fit statistic for the resulting model was 16.7 (p = .003).

Overall, 49.6% of days were classified as mania, while 65.2% of days were classified as depression. Classification was based on the probability of a classification of 1 ("mastery") exceeding .5. Only 4.4% of days were classified as having neither attribute, and 19.1% were classified as having both. Some items performed unexpectedly. Mood lability was seen in 100% of days classified as mixed, but also in 100% of days classified as neither manic nor depressed — suggesting perhaps that the psychometric properties of the collection instrument leave much to be desired. Though, when considered, these results make sense if shifted to a broad definition of "mood lability" which is inclusive of both the chaos of mixed episodes and the normal shifting of emotions people experience throughout the day, perhaps made a little more drastic by the cyclothymic temperaments which are common in bipolar disorder – but, not necessarily characteristic of strictly manic or depressed episodes. However, most items worked as expected: 87.1% of days classified as depression had a mood rating of 3-5 while 70.8% of days classified as mania had a mood rating of 1-2 or 5. Surely, this model could be adjusted and refined for future study. However, as an illustrative example, it has some utility.

Figure 4 shows harmonic regression lines fit to probabilities of classifications from the DCM, and whether or not the day was classified as possessing both attributes (or both attributes classified as a 1, "mastery" based upon having a probability exceeding .5 – a mixed day) is shown using plotted dots. A cycle length of 7 days was chosen based on qualitative visual inspection of the results. The oscillations change over time, appearing to have a higher frequency and growing closer together until they begin to overlap around day 85. Although it appears chaotic, perhaps it is this overlapping of the two waves that creates sequential mood episodes, one after the other — and their disentangling therefore might be indicative of a mixed episode with rapid or chronic cycling. The overlapping wave pattern first became evident (based on a

visual inspection of the graph – with lines clearly crossing over each other at peaks and troughs) around a cycle length of 4 days, peaked at a cycle length of 7 days, and disappeared at a cycle length of 10 days.

Qualitatively, the change over time of the waves maps on to the progress seen by the individual as the mood logging continued; this can also be seen by the sparseness of plotted points around the areas of overlap. By the end of the log, the individual was able to be discharged from the partial hospitalization program.

Dynamic systems modeling is a very promising approach for studying the low-dimensional chaotic dynamics of mood shifts in bipolar disorder. One simplistic version of a dynamic systems model applied to bipolar disorder is proposed. More complex models are needed to accurately estimate and predict the rhythm of bipolar moods, and future models should account for a variety of mixed mood presentations; further, empirical studies are needed to validate such models. These models may shed light on the underlying mechanisms of bipolar disorder (Bonsall et al., 2015). It may also be possible to use dynamic systems models, when properly developed, to predict mood episodes in advance of symptoms or even prodromal signs. Such an approach, using daily longitudinal data, has been shown to improve patient stability and has been proposed as the next major treatment advance for bipolar disorder (Holmes et al., 2016). The ability to predict mood episodes with reasonable accuracy could be very informative to treatment for this difficult-to-manage condition.

The purpose of this dissertation is to address the following research questions:

a) Can the mood state of a person with bipolar disorder be identified using machine learning?;

b) Is it feasible to use an app to gather information and make determinations about a participant's mood on a day-to-day level?; and,
c) Given a and b are sufficiently true, can a person's mood state in the future be predicted based on their mood up until now?

Methods

This study was approved by the UCLA North General IRB and was conducted by researchers trained in ethical conduct of research. An app, Shiny Mood App (Shiny Mood), was developed by the researcher to a) identify mood states and b) forecast future mood states. For this study, the focus was on the first goal of identifying the current mood state. The hypotheses were as follows: there will be moderate convergence between questionnaires and app-generated classifications; a refined algorithm will result in improved convergent validity; and, when modeled as a wave, higher frequency waves will be associated with more severe moods.

Participants

Twelve participants with rapid-cycling bipolar disorder (4 or more episodes per year) were recruited from the internet using social media platforms such as Twitter and Facebook. Table 3 shows some demographics; participants were mostly white, more female than male, and 33% identified as transgender (possibly evidencing a positive bias held by the participants as the researcher is transgender). The distribution of annual income was concentrated in the lower tail.

Measures

Shiny Mood was written in R script and uses the *shiny* package to generate an HTML interface. It is hosted on an Amazon Web Services EC2 instance, where it can be accessed from any internet-capable device. The app asks the user questions about their sleep, behavioral

inhibition and behavioral approach sensitivity, energy, valence of emotions, physical pain, motivation to do activities, self-confidence, speed of movement, and desire (or avoidance) of social interactions. It also asks the user if they have trouble concentrating, if they have been told by someone they trust that they seem different than usual, if they experienced thoughts that seemed to be on repeat, or if they had "unusual experiences". A button triggered a pop-up defining "unusual experiences" (see Figure 5) as experiences consistent with psychosis. Optimally, the user would input this data daily. See Figure 6 for the exact questions and layout of the app interface.

The app displays a series of questions, which can be seen in Figure 6. When the user presses the submit button, the app displays a "thinking" message while it performs a DCM analysis of that user's data and then displays today's prediction based on the data that was just entered. The Q-Matrix used, which specifies what signs of mania and depression are, remains constant. Each individual is compared only to themselves, and the DCM is created iteratively for each day logged in Shiny Mood (every day, a new DCM is run). The app tries to create groups with maximum separation between them ("manic" and "not manic" as well as "depressed" and "not depressed"). It then displays one of four possible outcomes: Manic (manic-not depressed), Depressed (not manic-depressed), Mixed (manic-depressed), and Euthymic or normal mood (not manic-not depressed).

The Functioning Assessment Short Test (FAST; Rosa et al., 2007) was used to measure global functioning broadly, across multiple areas of life. It is a brief interview that consists of 24 items that cover six domains of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Each item is rated from 0 to 3 by the interviewer (with 3 representing extreme difficulty). It was developed

specifically for the bipolar population and it is reported to have very high internal consistency with Cronbach's alpha of .91 (Rosa et al., 2007). Initial studies also found it to have good test-retest reliability. Euthymic patients had a lower FAST score than either manic or depressed patients. In our sample, pooling individuals and measured at the beginning of the study (as FAST was administered only once) Cronbach's alpha for the FAST was .64; it went up to .71 (acceptable) if item 7 was deleted, indicating some issues with individual item functioning.

Weekly questionnaires included the Altman Mania Self-Rating Scale (ASRM; Altman et al., 1997) to measure mania symptoms (for convergent validity) and the first 8 items of the Patient Health Questionnaire – 9 item version (PHQ-9; Kroenke et al., 2001) to measure depression, as well as asking the participant to rate their adherence to the daily logging and their perceived accuracy of the app's classifications on a scale from 1 to 10 (0% of the time to 90% of the time or more). Both the ASRM and the PHQ-9 are widely used in clinical settings; for the ASRM, Cronbach's alpha was reported for the three subscales and ranged from .79 to .65 (Altman et al., 1997). The ASRM is a self-report with 5 items rated on a 5-point Likert scale. In our sample, Cronbach's alpha was .87 (good). The PHQ-9 has 9 items (although only items 1-8 were administered) and is a self-report with a 0-3 response scale. It is reported to have a Cronbach's alpha between .86 and .89 (Kroenke et al., 2001b); in our sample, Cronbach's alpha was .95 (excellent).

At intake, baseline questionnaires were collected including the ASRM and the Patient Health Questionnaire – Somatic, Anxiety, and Depressive Symptoms (PHQ-SADS; Kurt Kroenke et al., 2010), which is a more comprehensive version of the PHQ-9 that also measures anxiety and somatization. Additionally, some demographic information was collected.

Procedures

We obtained IRB-approved consent from participants. For those who were eligible and consented, each participant was interviewed by phone to discuss eligibility. The FAST was administered via phone. Participants were asked to complete daily logs in Shiny Mood for 12 weeks, and completed all the weekly questionnaires, which were sent by email. Participants received daily reminders at a time of their choosing by text message to minimize missing responses.

Data Analysis

First, correlations at baseline will be assessed, including with demographic variables.

Since Shiny Mood gives daily classifications, a weekly classification was computed by taking the highest priority classification given by Shiny Mood that week, in the following order: mixed, manic, depressed, euthymic. Weekly classifications were compared to ASRM and PHQ-9 scores for convergent validity using bivariate correlations. Weekly participant ratings of Shiny Mood accuracy (based on the immediate feedback the app provided to participants after completing mood logs) were also examined at the weekly level — correlations with other factors were examined.

The algorithm of the Shiny Mood app will be revised (by adjusting its Q-Matrix; for example, if the correlational data suggests an over-identification of mania, the Q-Matrix for mania can be adjusted accordingly), and the model will be re-run with the goal of improving convergent validity with ASRM and PHQ-9 scores. Thus, a refined algorithm for identifying mood states will be presented.

Using the classifications generated by the refined Shiny Mood algorithm, regression analysis will be used to examine mania and depression classifications as sinusoidal waves. Wave frequency will be assessed for ability to predict mood several days into the future.

Results

Characteristics of Participants' Bipolar Disorder and Medications

Among the 13 rapid-cycling participants recruited for this pilot study (1 participant missing baseline data), I captured a range of bipolar disorder phenotypes: 1 participant reported a diagnosis of Cyclothymia, 6 reported Bipolar 2 Disorder, and 5 reported Bipolar 1 Disorder. Nine (75%) of participants were taking prescription medication for their bipolar disorder, while 2 were not and 1 did not report; all of the Bipolar 1 participants were taking medication, which suggests that those who did not take medication experienced less severe manic symptoms. Among those taking medication, the number of medications that had been tried was normally distributed across of a range of 1 to 8 medications, with a mean of 3.9 and a standard deviation of 2.1. Most participants felt their medication regimen was stable: one did not, 8 did, and 3 did not report or did not take medication. Eighty-three percent felt their medication regimen was stable, counting those who were not taking medication.

The types of medications participants had tried was also investigated (see Table 4). The most common pharmacological class of medications that participants had tried was anticonvulsants, with 92% of the sample reporting having been on such a medication, followed by atypical antipsychotics, with 75% reporting having been on one. Meanwhile, only 8% had tried a typical antipsychotic or neuroleptic medication. In light of the overwhelming evidence for lithium's effectiveness (Smith et al., 2007), it's potentially suggestive of prescriber bias that

lithium was one of the least common drugs with only 25% of the sample having tried it. Lithium as well as "other hypnotics" (such as Ambien) were only seen in participants who reported a diagnosis of Bipolar 1 Disorder.

Baseline Questionnaires

The mean FAST score was 32, with a standard deviation of 8.1, and a range from 18 to 45. Participants who had ever taken SSRIs had significantly higher FAST scores (indicating lower global functioning) than participants who had never taken SSRIs ($t = -2.9$, $p = .02$). There was no relationship between diagnosis (Bipolar 1 vs. Bipolar 2) and FAST score. Taken together, this suggests that in our sample, functional impairment was driven by depression rather than mania. While there was no correlation between baseline depression (as measured by the PHQ-9) and FAST score, there was a significant correlation between baseline somatization and FAST score ($r = .62$, $p = .03$).

The mean baseline depression score on the PHQ-9 indicated moderate depression at 10.8 (SD = 4.6). 58% of participants met the cutoff of 10 for moderate depression, but only 17% met the cutoff of 15 for moderate-to-severe depression.

With a mean score of 10.8 (SD = 5.4), the average participant met the cutoff (10) on the GAD-7 (the anxiety portion of the PHQ-SADS) for a diagnosis of Generalized Anxiety Disorder. 75% of participants met the cutoff for anxiety. The somatization subscale also has a cutoff of 10 indicating medium somatic symptom severity, and in our sample the mean score was even higher at 12.3 (SD = 5.5). 67% of participants met the cutoff for somatization.

Likewise, the cutoff score for the ASRM is a 6; the mean score in this sample was an 8.5 (SD = 4.6) indicating likely hypomania (with 83% of the sample meeting cutoff at baseline), and the reported specificity of this measure in published samples for hypomania or mania was 87.3%.

Completion of Daily and Weekly Measures

Although data collection and text message reminders lasted for 12 weeks (84 days), the number of days logged by participants varied from 13 days to 93 days (one participant continued logging days after the end of 12 weeks). The mean number of days logged was 32 with a standard deviation of 21.8.

Twelve weekly surveys were sent to participants; the mean number of weekly surveys completed was 6 with a standard deviation of 3.5. A total of 105 weeks were recorded. Since the comparisons made by the algorithm are strictly within individuals and not between them, it does not pose a hindrance to analyze all participants, with the awareness that low levels of participation hinder the interpretation of those individuals in particular. Further, low participation severely limits the utility of the DCM approach. Several between-subjects analyses that follow were run with and without low-participation individuals; a comparison of the results is presented.

Participant-Rated Accuracy and Fidelity

On weekly questionnaires, participants were able to rate their perceived accuracy of Shiny Mood as well as their perceived fidelity to daily logging. Regarding the app's accuracy as perceived by users, looking over participants and over weeks, participants gave the app a mean rating of 4.3 (SD = 2.7) on a scale from 1 (Shiny Mood App was always wrong/0% accuracy) to 10 (Shiny Mood App was accurate over 90% of the time). Regarding their fidelity to creating daily logs, they gave a mean rating of 4.1 (SD = 1) on a scale from 1 (0% of the time) to 10 (over

90% of the time). According to one-sample t-tests, these ratings (accuracy and fidelity) did not significantly differ when individuals with less than 14 mood logs were filtered out (p = .69 and .61, respectively).

Revised Shiny Mood Algorithm

For the following analyses, a revised algorithm was used (different than what was originally shown to participants) which was determined by refining the Q-matrix (the "instructions" for latent variable modeling) to be more restrictive at the item level. For example, on the slider scale items which could be scored as -2 to 2, the initial model used all scores that deviated from 0; however, the revised model only counted the extremes of a slider (-2 and 2) as being indicative of a bipolar mood episode in either direction. Note that the -2 to 2 sliders were very similar to a 1 to 5 Likert scale, but differed because of the slider starting at the central point of 0 so that participants could drag it to the left or the right (see Figure 6). One attempt at revision was planned in advance.

Few significant associations between mood class and weekly mood questionnaires emerged in the initial model, suggesting convergent validity was not optimal. The vast majority of days were being classified as belonging to an atypical mood state (only 7.6% of recorded time was classified as euthymic, meaning neither manic nor depressed). Mania classifications were significantly predictive of mania questionnaire scores when compared using a t-test (p = .001), but depression classifications did not predict depression questionnaire scores (p = .42).

Based on these findings, the Shiny Mood App algorithm was made more restrictive (so that only scores of -2 and 2 on the slider questions were used as indicators in the algorithm's Q-matrix). In the revised model depression questionnaire scores, across weekly timepoints, were

predicted by both mania (p = .02) and depression (p = .02) classifications, but neither predicted mania questionnaire scores (p = .88 and p = .62, respectively).

With the revised (restricted) algorithm, convergent validity with the questionnaire measures based on regression analysis shifted from accuracy for mania to accuracy for depression, yet the algorithm did not clearly improve; nonetheless, this revised output was used for the remainder of the analyses.

Associations of Initial Model Scores with Questionnaires

I used Mplus to conduct a multi-level analysis, looking within individual participants and between days since a participant began the study. This allowed me to see my findings at the daily level within the context of time. For both mania and depression classifications, I used a logistic regression model where mania (or depression) classifications for each individual day predicted mania (or depression) questionnaire scores – the ASRM for mania, and the PHQ-9 for depression. Neither of these models were significant (see Table 5).

Aggregate Classifications for Mania and Depression

I examined the mean value per participant of mania (and depression) classifications (0 or 1) – that is, the proportion of days that were classified as having that attribute (mania or depression), for each individual that participated in the study. I then used a linear regression model to predict two things, treating each week as an independent observation:

1. Standardized weekly questionnaire scores
2. Functional impairment baseline interview (FAST scores)

Aggregate mania was a significant predictor of mania questionnaire score (ASRM; $\beta = .21$; $R^2 = .042$; $p < .001$), but not functional impairment as reported at the beginning of the study. Meanwhile, aggregate depression was not a significant predictor of depression questionnaire score (PHQ-9), but *was* a significant predictor of functional impairment (FAST; $\beta = -.08$; $R^2 = .01$; $p = .04$). Because FAST was phone-administered by the researcher instead of being administered by the internet, it was not repeated later in the study.

Aggregate Classifications in Individuals with Low Participation

To ensure that individuals with less than 14 daily mood logs did not bias results, the aforementioned between-subjects analyses were repeated with these low-participation individuals filtered out (n = 2). In comparing the results of aggregate mania and depression classifications and their associations with FAST and questionnaires for mania and depression, with and without low-participation individuals, the following was found.

For aggregate mania, the association with ASRM remained significant at the $p < .001$ level. The association with FAST remained nonsignificant. For aggregate depression, the association with FAST became nonsignificant ($p = .21$) and the association with PHQ-9 remained nonsignificant.

Predictions of Future Mood

There are two options for introducing the wave mechanics that may underlie mood changes in bipolar disorder. The first is similar to the analyses conducted in the self-collected pilot data already presented in this dissertation – a regression analysis using the shape of a sinusoidal wave, which could then be examined in an exploratory manner. For example, one could examine wave frequency and changes in wave frequency over time to predict outcomes such as aggregate mania

or aggregate depression within a specific time period. The downsides of this approach are its simplicity (though this is also an advantage—computationally, for example) and the necessity to choose a cycle length in order to use an unfussed regression model. Regression analysis is arguably the simplest form of machine learning; it can predict values beyond the range of the data. Another option, and certainly of interest, is to use more complex machine learning approaches to identify the optimal cycle length for each participant. It may be possible to use such approaches to follow what was done in the self-collected pilot data – to "visually" inspect and compare cycle lengths until an overlapping pattern emerges, suggesting the frequency picks up "natural meaning" for the participant's mood cycle.

The more complex option is to follow in the footsteps of many of the studies cited in the introduction (such as Bonsall et al., 2015) and use dampened harmonic oscillators to model bipolar mood. This approach has advantages in its own right, including a more complex model to capture the episodic disturbance and slow return to baseline experienced by many individuals with bipolar disorder.

For this dissertation, I chose to use the former approach (the trigonometric regression model). I used the harmonic function in the TSA (Time Series Analysis) package in R to model mania and depression classifications as two waves. Each participant had an individualized wave frequency estimated between 2 and 4 cycles – this reflects the natural variation in bipolar individuals, with some cycling much more rapidly than others (though all of our participants met the DSM criteria for rapid cycling). To determine this wave frequency, I visually inspected the graphs of the two waves and looked for wave definition. I then compared the graphs for all 13 participants and looked for similarities among them.

Figure 8 shows all 13 sets of waves produced from each participant's data. The frequency of these waves show mood cycling frequency – a result where waves are well defined means that the signal of that individual's mood cycling frequency is being captured. Ultimately, 4 of 13 graphs (31%) – 1, 2, 7, and 10 – produced an overlapping wave structure for mania and depression. The remaining graphs did not become significantly waveform, as they failed to produce a defined wave structure, or didn't show overlapping waves. There may be several reasons for this: one, limited participation may confound results. Like any form of machine learning, Shiny Mood App requires a "training set" to hone in on an individual's tendencies. For individuals who didn't participate as much (such as the two participants who logged less than 14 days) it's unsurprising if waveform patterns were not found. Two, creating these graphs requires the researcher to choose a period for the wave pattern. Only three periods were tried for each graph: 3 plus or minus 1. If someone had a very rapid cycling pattern with more than 4 repetitions of their cycle during the study period, it might not be captured here; the same could be said for individuals who were not as rapid cycling who went through less than 2 cycles. Finally, the algorithm for Shiny Mood App appears in some graphs to be overly "sticky" (see graphs 5 and 8). Once the algorithm had decided a certain individual exhibited manic or depressive tendencies, it didn't flip readily into the other state (not exhibiting those tendencies). This would prevent the graph from appearing waveform. Also, several graphs (4, 9, 11, 12, and 13) only display one attribute (depression). It appears from glancing at the data that in these graphs, the mania wave may be stuck at 0 (graph 4) or 1 (graphs 9, 11, 12, and 13).

Discussion

There remains much work to be done on the topic of mathematical and statistical modeling of bipolar disorder, and only the first scant glimpses of the potential of similar methodology to

make an impact in peoples' lives have yet been seen. Bipolar disorder is a common condition with similar prevalence rates around the world (Merikangas et al., 2011) and it is a serious condition with high morbidity (Post et al., 2003) yet few novel interventions exist to address key problems like lack of insight and treatment unacceptability (Baldessarini et al., 2008). This study examined an app called Shiny Mood and its uses for measuring mood at the daily level in people with rapid-cycling bipolar disorder.

My research was driven by three specific questions:

a) Can I use an app to tell what mood state a person with bipolar might be experiencing?
b) Is it feasible to use this kind of app in people's everyday lives?
c) Can I make an educated prediction about a person's future mood?

In this first attempt at identification of mood state, the evidence suggests there was poor convergence of daily-level mood classification with standardized weekly-level questionnaires for mania or depression. Participants rated the initial version of the app as having a mean accuracy rating of 4.3 (on a scale from 1 to 10). It is possible that the different levels of measurement confounded the convergence between Shiny Mood and questionnaires, since the questionnaires look at aggregates of time (for example, "within the past 2 weeks"); and, while I expected to see a modest convergence, certainly it is not surprising that there is not agreement between these metrics. If there was a strong convergence, that would suggest I am not capturing something uniquely different.

However, when looking at mania and depression mood classifications in aggregate – as a proportion of days per participant – interesting results emerge. Aggregate mania classifications were associated with higher mania questionnaire scores – which suggests more enduring and

more severe manic symptomatology overall, an important feature of bipolar disorder. This finding aligns with theories that mania exhibits a "kindling" effect similar to seizure disorders (Berk et al., 2011).

When I examined the wave structure of mania and depression classification probabilities, a few patterns emerged. Some of the graphs are similar – they have either mania or depression crowded at the ceiling. Among the graphs, which are shown in Figure 8, two are notable for being nearly identical copies of each other, but reversed on the vertical axis (see graphs 5 and 8) – one has depression clinging to the ceiling, and the other has mania. One interpretation of these graphs is that Shiny Mood App, in its current form, may be overly "sticky" – once a person has a tendency toward mania or depression, their classification did not flip readily enough from one to the other to reflect their true cycling. In other words, the algorithm may be somewhat perseverative. Or, perhaps, these graphs may reflect that people with bipolar disorder can have a consistent tendency towards mania or depression.

The recruitment for this study suggests recruiting rapid cycling bipolar participants is feasible (something several professionals doubted was seriously possible); people appeared to be eager to support the study, and to join and use the app if they were eligible to participate. However, I did see signs of participant burnout, particularly after the halfway mark. After this point, a handful of participants formally dropped out of the study, all of them offering kind words but expressing a feeling of overwhelm with things in their lives. It must be considered that using an app to monitor mood can only be effective if participants use the app, and they must do so with regularity. If participants become overwhelmed, they may discontinue use. That is an important limitation of our methodology.

Limitations

My research is ongoing, and has a number of limitations; for one, I recruited a sample that was mostly white, and future research would benefit from more diverse samples. My sample was 33% transgender, which is probably an overrepresentation based on the fact that I am transgender. This could have implications for generalizability to the larger population.

Measurement issues – namely, variability in the number of observations collected across individuals – also present a serious limitation to this work. Low participation by some individuals (especially the two individuals who made less than 14 daily logs) may confound the interpretability of these findings. The number of daily logs submitted ranged from 13 to 93.

Additionally, the methodology used may pose problems in the replication of this study due to challenges with participant recruitment and retention throughout the study. Burnout seemed to be a significant problem, and this suggests that while Shiny Mood App is not invasive like phone monitoring or expensive like wearable sensor t-shirts, there were still important issues regarding the feasibility of using the app with people with bipolar disorder.

Future Directions

The first, and possibly most notable, of the gaps left in the field by this research is that a great deal of foundational work still needs to be done in pursuit of our final aim – the use of wave modeling to predict future timepoints. I am still in the stage of validating Shiny Mood classifications, and this work remains ongoing towards the goal of elucidating the predictive power of my model.

An additional future direction is the possibility of a parent or caregiver version of the Shiny Mood app, where caregivers are asked to complete surveys instead of people with bipolar disorder themselves. A caregiver might be more able to provide consistent feedback. Of course,

most adults with bipolar disorder do not have formal caregivers, and some may have nobody to play this role for them. Despite this drawback, making a caregiver version available may benefit some people, and it could even allow other individuals – for example, staff in hospitals, or teachers in schools – to use this type of methodology if it were accurate for these types of informants. There is interest in how a parent-report (or teacher-report) version of Shiny Mood for children with bipolar disorder would function psychometrically, and what might set it apart from the adult version.

In conclusion, future research should continue in the area of mood identification and prediction by use of statistical models. This line of research is still in its early stages, and there is much to be done. It is hoped this work will inspire further research that applies novel, ambitious, and even outlandish ideas to improve the lives

Table 1

Glossary of terms related to mathematical systems

Term	Meaning
Chaotic System	A nonlinear system that appears to be random, but actually reflects some combination of deterministic mechanisms (as opposed to stochastic, or random, influences). Weakly chaotic systems, also called low-dimensional chaos, may appear periodic (exhibiting a patterned recurrence), but their recurrences are not isometric (they are inexact copies of each other). Chaotic systems of equations such as the Lorenz Attractor have been described by mathematicians.
Harmonic Oscillator	An oscillator is a nonlinear mathematical object. The simplest oscillator would be similar to a trigonometric wave function (sine or cosine)—its motion is constant with respect to time. A "damped" oscillator changes over time, reducing amplitude until momentum is lost. "Coupled" oscillators interact and can become self-sustaining in motion, like using a playground swing.
Lyapunov Time	Chaotic systems have a particular timeframe in which the future the system's activity will be predictable. When predictions can no longer be made greater than chance, you're at the Lyapunov time.
Limit Cycles	Limit cycles are systems where the trajectory spirals into or out of some fixed point in space as time approaches infinity. A "limit cycle oscillator" is a type of damped oscillator.

Bistability	Describes a system characterized by two steady states which are abruptly switched between.
Dynamical Systems Modeling	An approach that uncovers the mechanics behind nonlinear change over time in a system using mathematical models.
Diagnostic Classification Model	Also known as "cognitive diagnostic model" and abbreviated as DCM. This is a type of latent class analysis that is used to sort individuals into "masters" or "nonmasters" of any particular latent attribute specified in the model; you can also think of this as "demonstrating" or "not demonstrating" a specified symptom. The decisions are made to produce maximum separation between the two possible classifications. It is often considered as an alternative to item response theory models.

Table 2

Moods and activities used in Diagnostic Classification Modeling Q-Matrix for preliminary study

Mania	Depression
Mood score 1-2 or 5	Mood score 3-4 or 5
Slept 5 hours or less the previous night	Slept 13 hours or more the previous night
Mood lability	Mood lability
Went shopping	Suicidal (7/10 or higher)
Had social interactions	Did not shower
Ate less than 600 calories	
Hallucinations	

Note. Mood scores were rated on a scale of 1 (manic) to 4 (severely depressed); ratings of 5 could indicate either mixed mood or intense suicidality, which often coincided with mixed mood.

Table 3

Demographic information of Shiny Mood App dissertation study

Variable	Frequency	Percent
Ethnicity		
White/Caucasian	10	83%
Hispanic/Latino	1	8%
Other/Not Reported	1	8%
Gender		
Female	**7**	58%
Male	1	8%
Other Gender	3	25%
Not Reported	1	8%
Transgender		
Yes	4	33%
No	7	58%
Not Reported	1	8%
Age		
18-25	3	25%
26-35	6	50%
36-45	3	25%
Income		
Under $20,000	3	25%
$20,000 to $34,999	5	42%
$35,000 to $49,999	1	8%
$50,000 to $74,999	1	8%
$75,000 to $99,999	1	8%
Over $100,000	1	8%

Table 4

Medications tried by participants by pharmacological class

Medication Class	Tried it	Haven't tried it
Atypical Antipsychotic	9 (75%)	3 (25%)
Neuroleptic	1 (8%)	11 (92%)
Anticonvulsant	11 (92%)	1 (8%)
SSRIs	7 (58%)	5 (42%)
Other Antidepressants	4 (33%)	8 (67%)
Other Hypnotics	3 (25%)	9 (75%)
Stimulants	3 (25%)	9 (75%)
Benzodiazepines	5 (42%)	7 (58%)
Lithium	3 (25%)	9 (75%)

Table 5

Model Parameters and Goodness of Fit for Mania and Depression Classifications Predicting Questionnaire Scores and Functional Impairment, Days Within Participants

Effect	Mania	Depression
Mood Class on Questionnaire Score	0.11	0.08
Standard Error	.07	.06
P-Value (Two-Tailed)	.12	.16
Model Fit (AIC)	6361.97	6049.91
Mood Class on Functional Impairment	0.00	0.01
Standard Error	.06	.06
P-Value (Two-Tailed)	.99	.85
Model Fit (AIC)	7160.35	6998.97

Note. Questionnaires used were the Altman Mania Self-Rating Scale and the Patient Health Questionnaire. The Functioning Assessment Short Test measured functional impairment.

Figure 1

Theoretical Components of Bipolar Mood as a Dynamic System

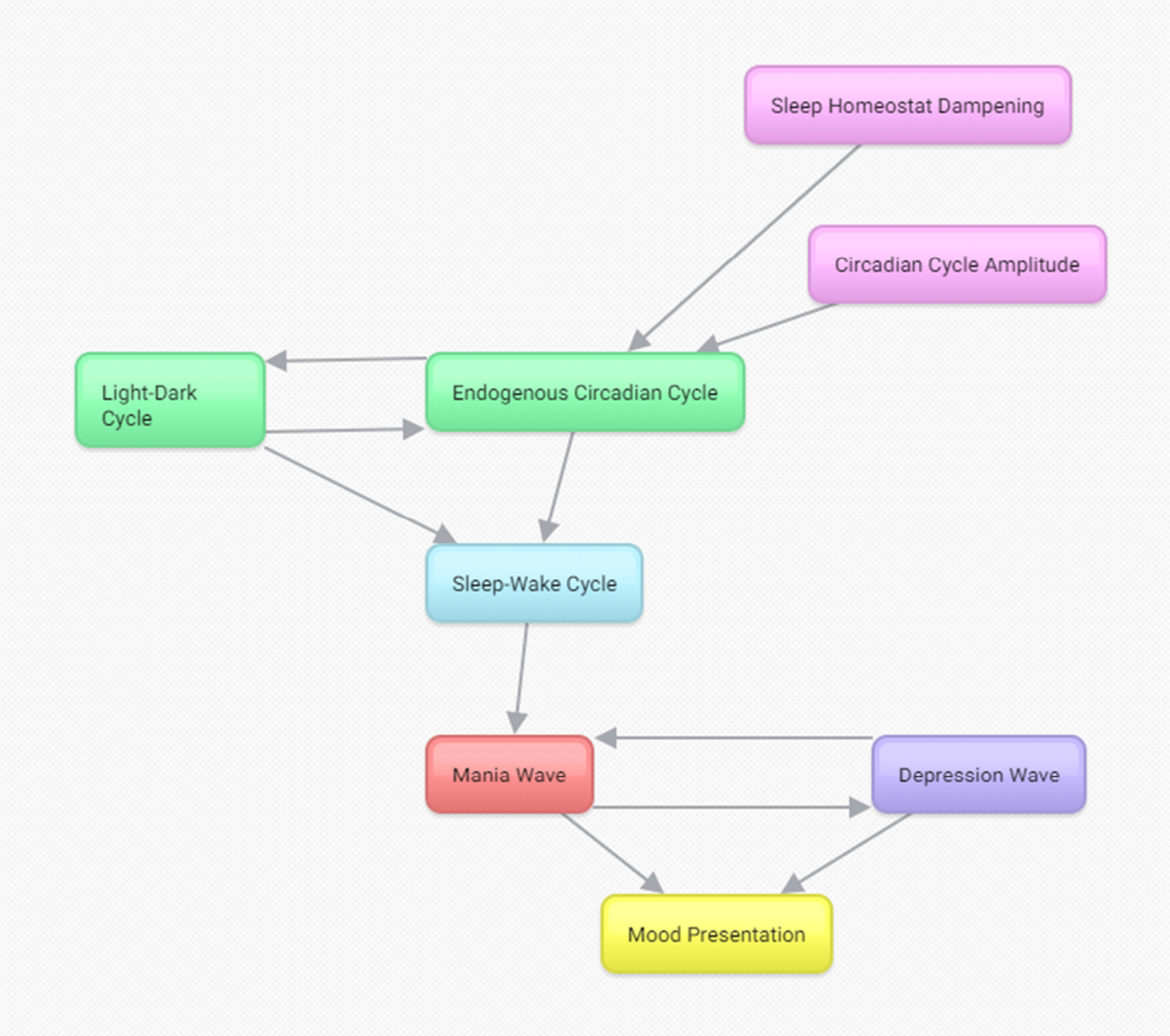
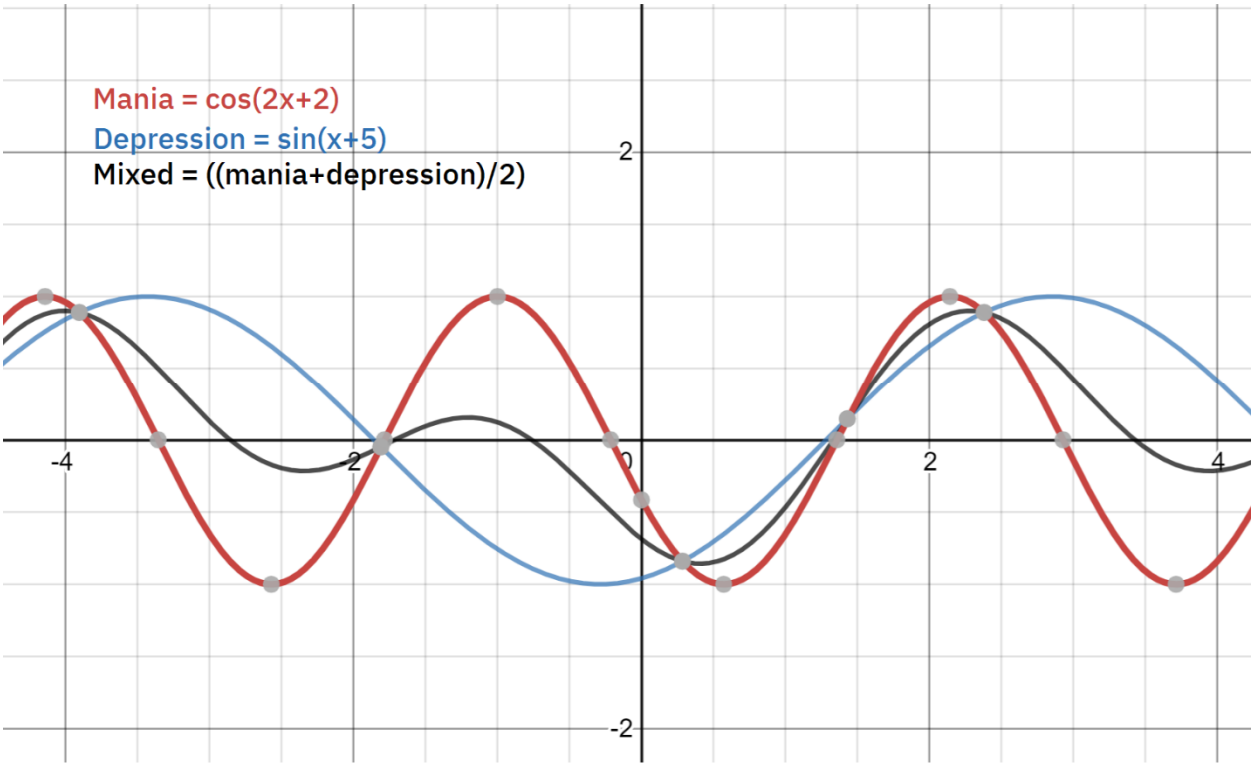


Figure 2

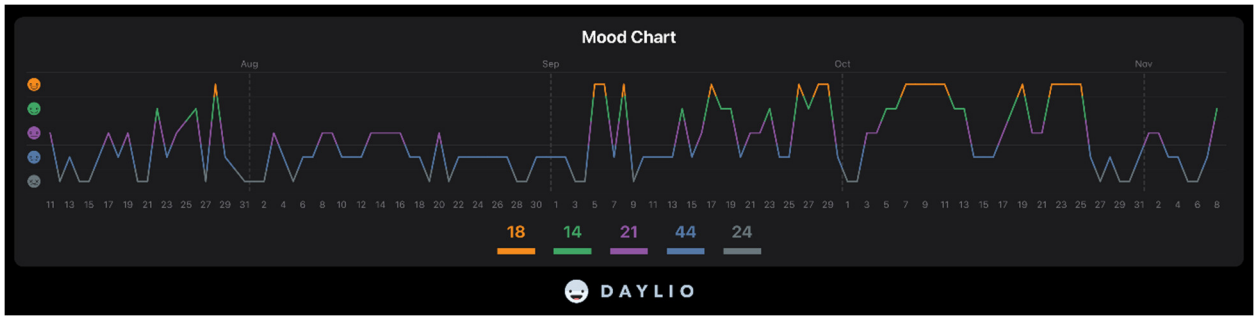
Theoretical Estimated Probability of Mood Episode by Type



Note. This figure show sinusoidal waves representing waves fitted to probabilities of class membership produced by diagnostic classification modeling. As this is a theoretical depiction of the model, arbitrary values were chosen for illustration.

Figure 3

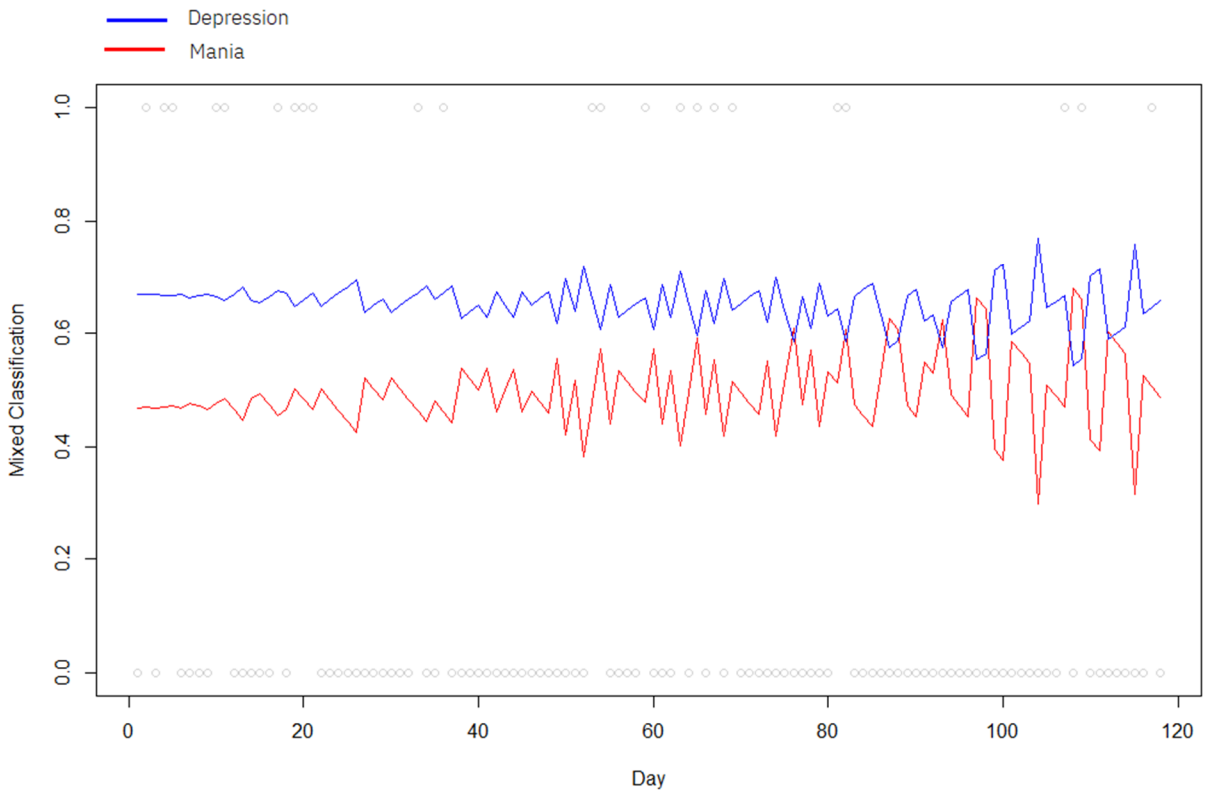
Real World Mood Ratings Of Preliminary Participant Throughout July to November 2018



Note. This figure generated by the Daylio app shows mood ratings of 1 (mania, orange) to 4 (depression, blue) and 5 (mixed episode or intensively suicidal, gray).

Figure 4

Harmonic Model of Class-Membership Probability Over 118 Days of Preliminary Participant



Note. Plotted with gray dots classifications for mixed episodes (both mania and depression classifications were made). A period of 7 days was chosen.

Figure 5.

Screenshot from Shiny Mood App of Unusual Experiences Explained

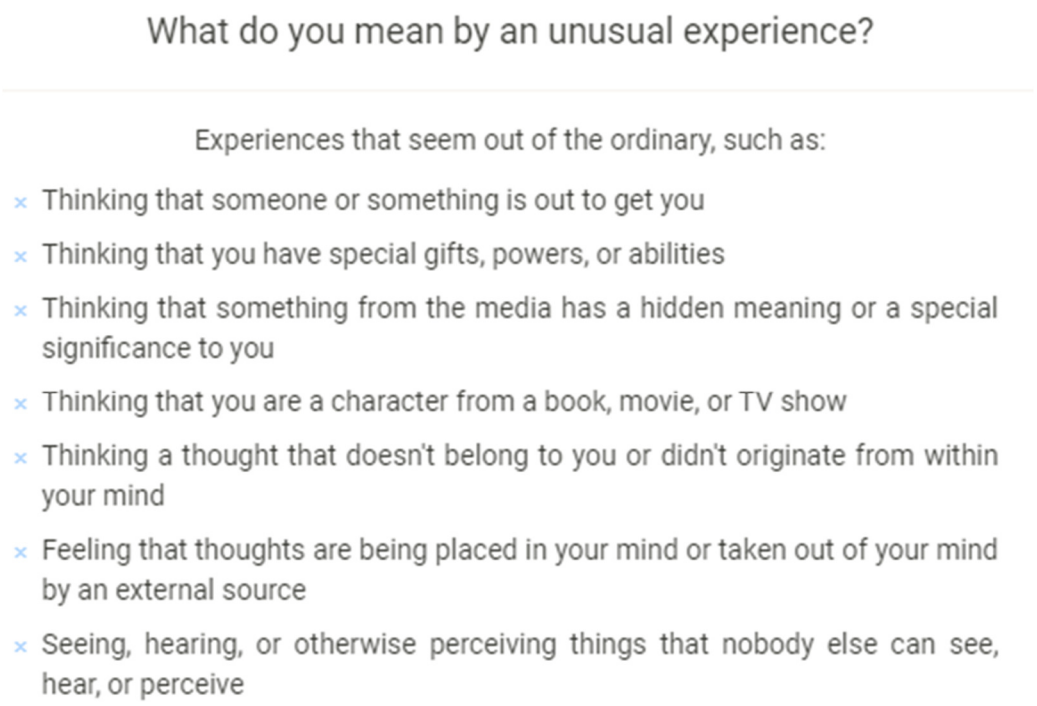
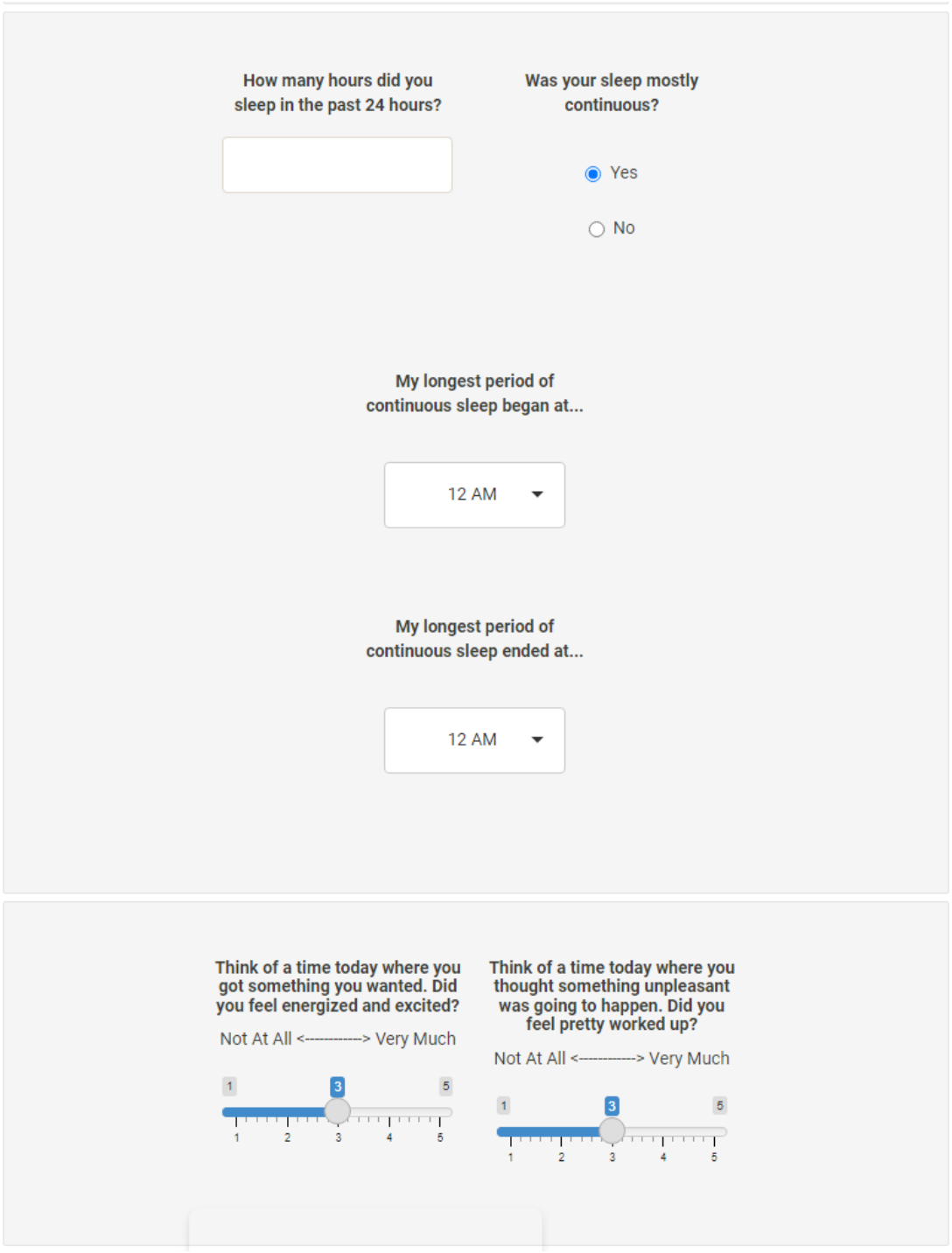


Figure 6.

Screenshot of Shiny Mood App Questions Layout

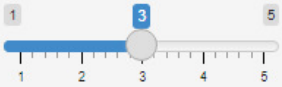


In the past day, I have...

No Energy (1)

↓

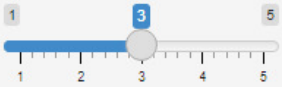
Very High Energy (5)



Mostly Negative Emotions (1)

↓

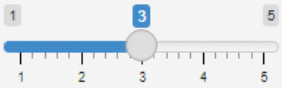
Mostly Positive Emotions (5)



More Physical Pain Than Usual (1)

↓

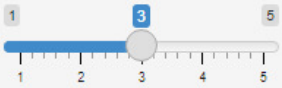
Feeling Better Than Ever (5)



Nothing I Want To Do (1)

↓

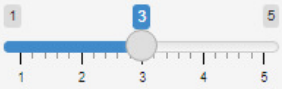
Want To Do Many Different Things (5)



Felt Very Inadequate (1)

↓

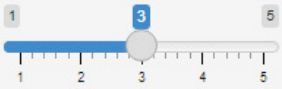
Felt Very Confident (5)



Moved Very Slowly (1)

↓

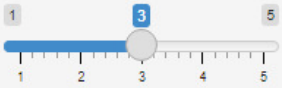
Moved Very Quickly (5)



Wanted To Be Alone (1)

↓

Wanted To Socialize (5)



Today, have you had...

Trouble concentrating?

- ◯ Yes
- ◯ No

Been told by someone you trust that you seem different than usual?

- ◯ Yes
- ◯ No

Experienced thoughts that seemed to be on repeat?

- ◯ Yes
- ◯ No

Had unusual experiences?

- ◯ Yes
- ◯ No

WHAT IS AN UNUSUAL EXPERIENCE?

SUBMIT DATA

Figure 7.

Shiny Mood Mood By Week

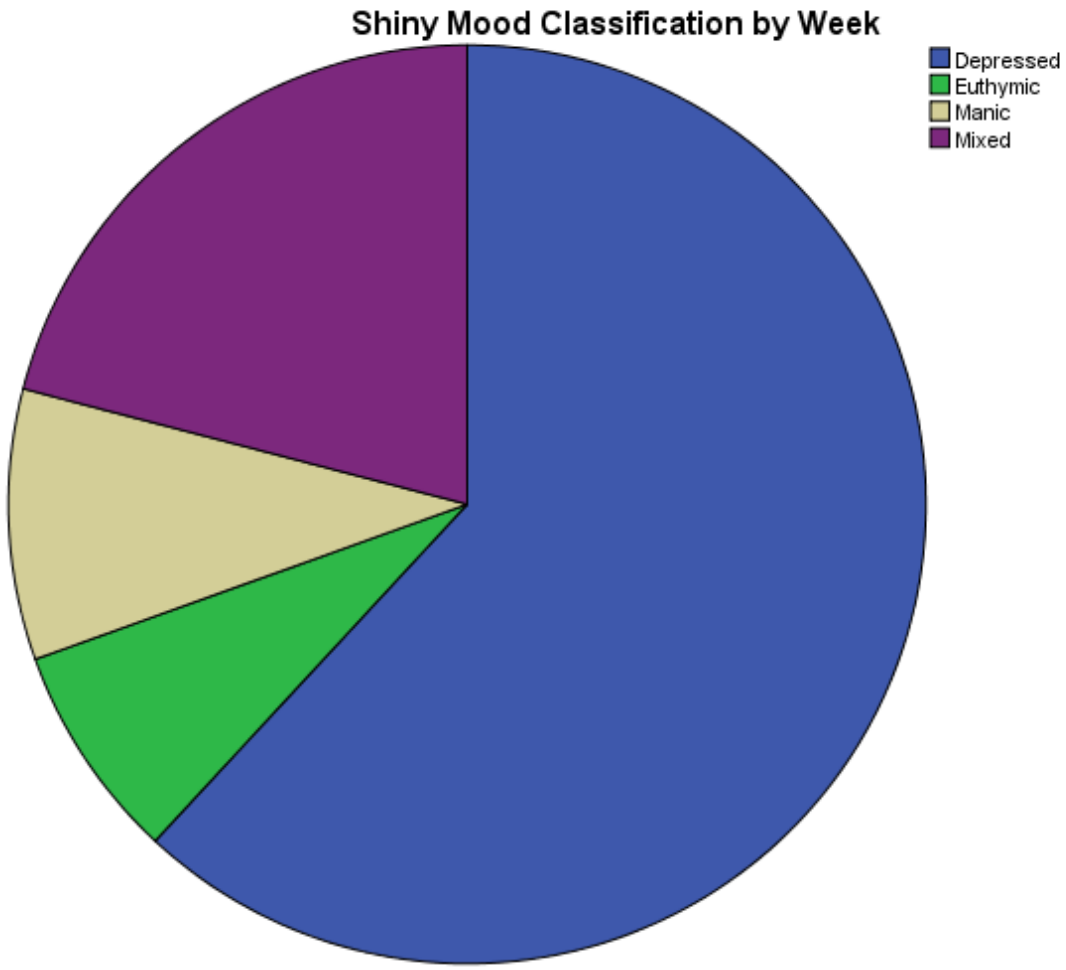
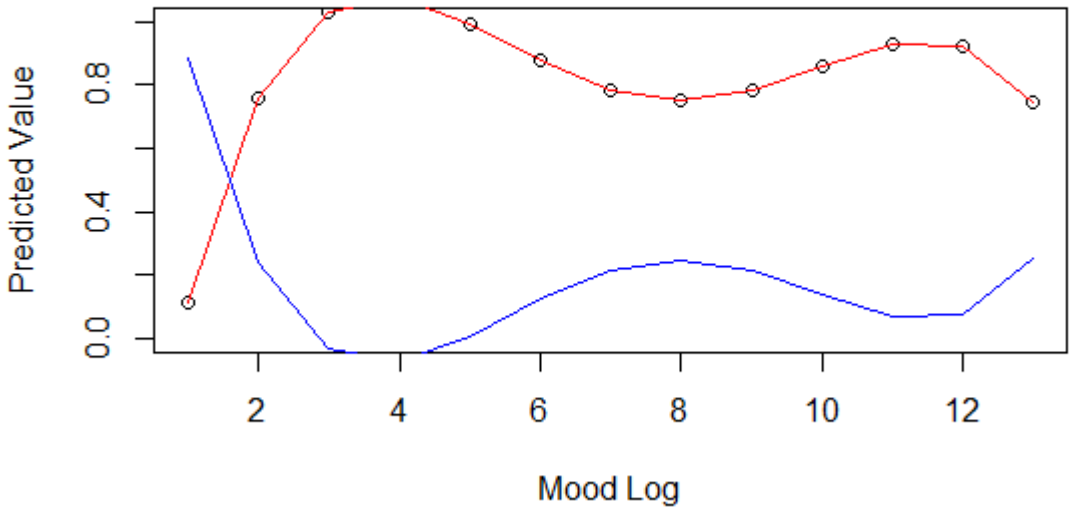


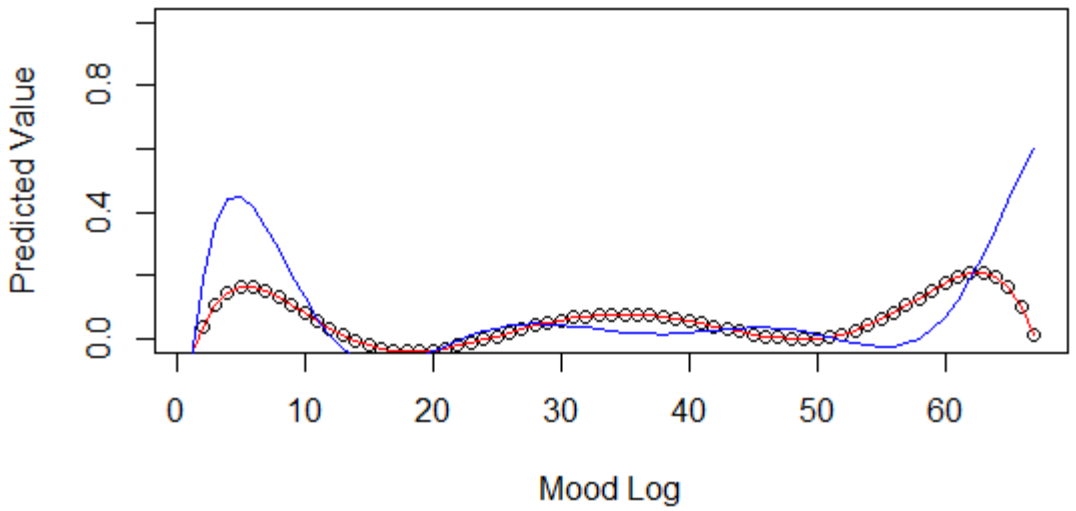
Figure 8.

Harmonic mood graphs for each participant in the Shiny Mood App study

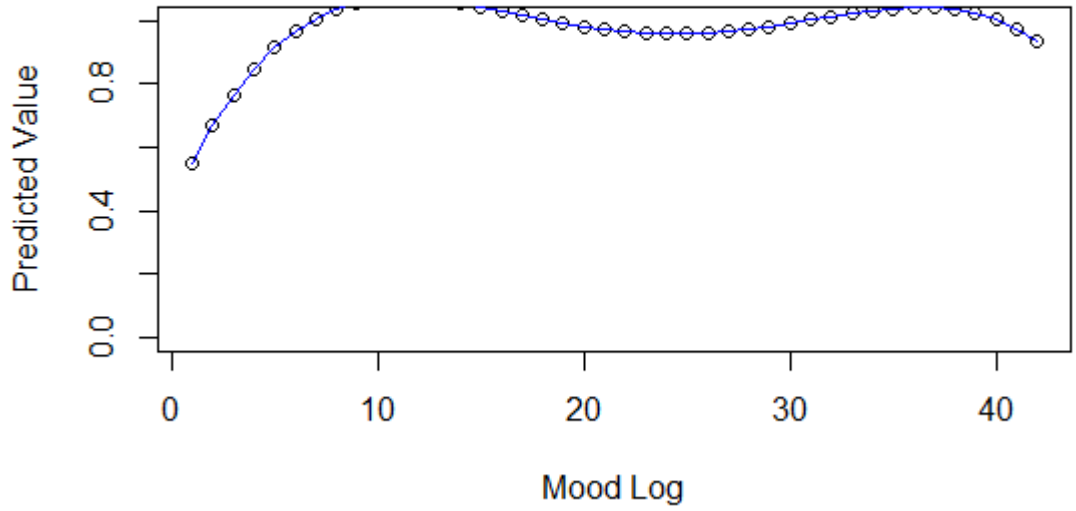
1.



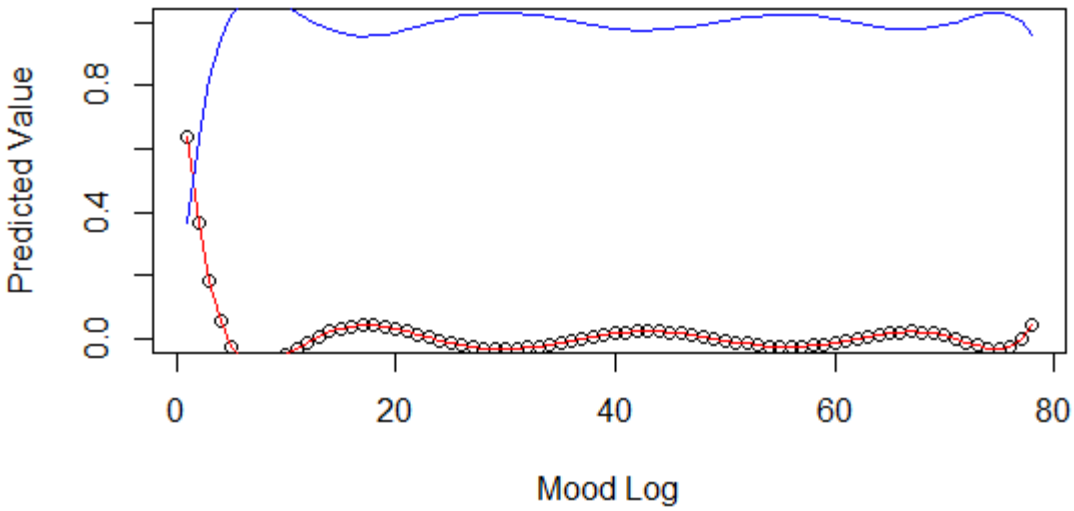
2.


Predicted Value
0.0
0.4
0.8
0
10
20
30
40
50
60
Mood Log

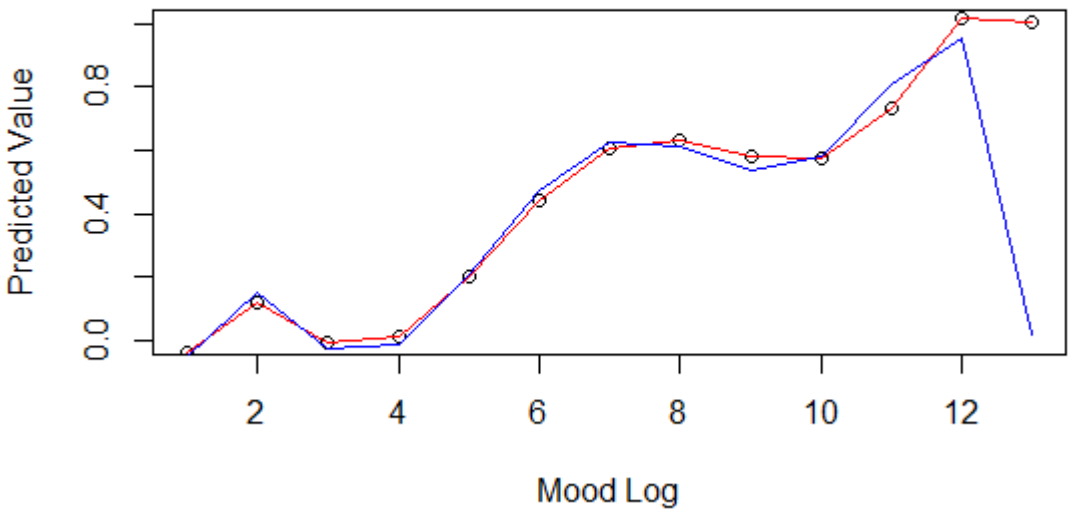
3.


Predicted Value
0.0
0.4
0.8
0
10
20
30
40
Mood Log

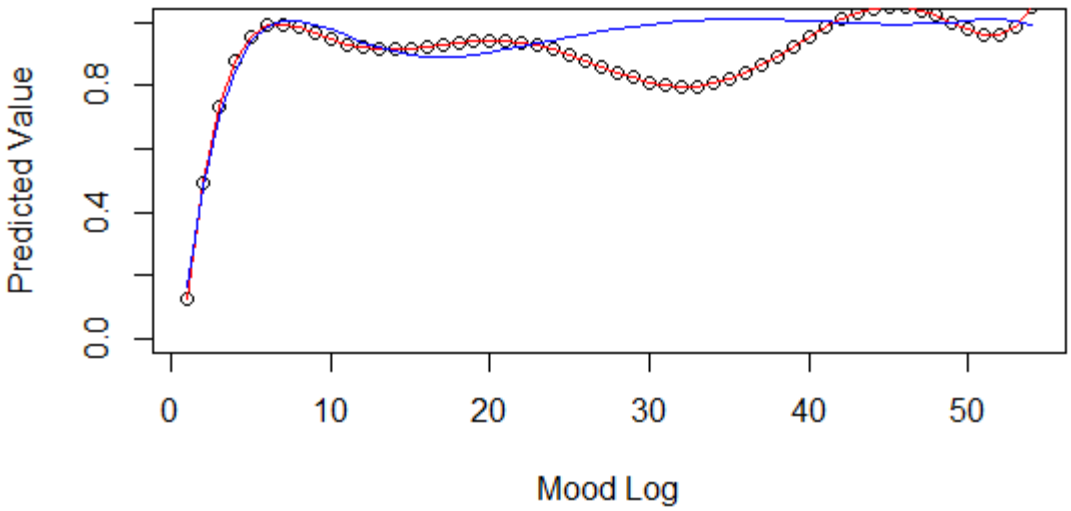
4.


Predicted Value
0.0
0.4
0.8
0
20
40
60
80
Mood Log

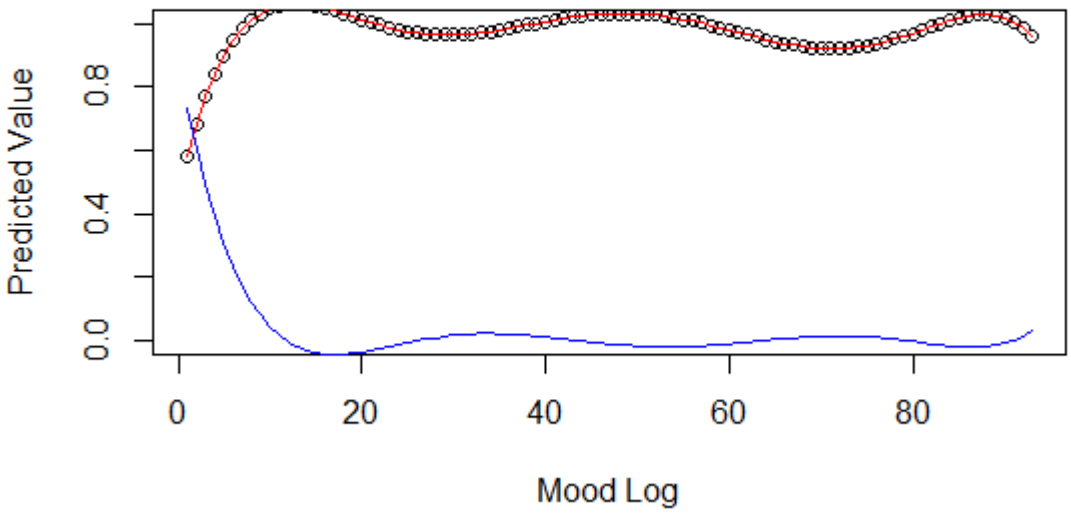
5.


Predicted Value
0.0
0.4
0.8
2
4
6
8
10
12
Mood Log

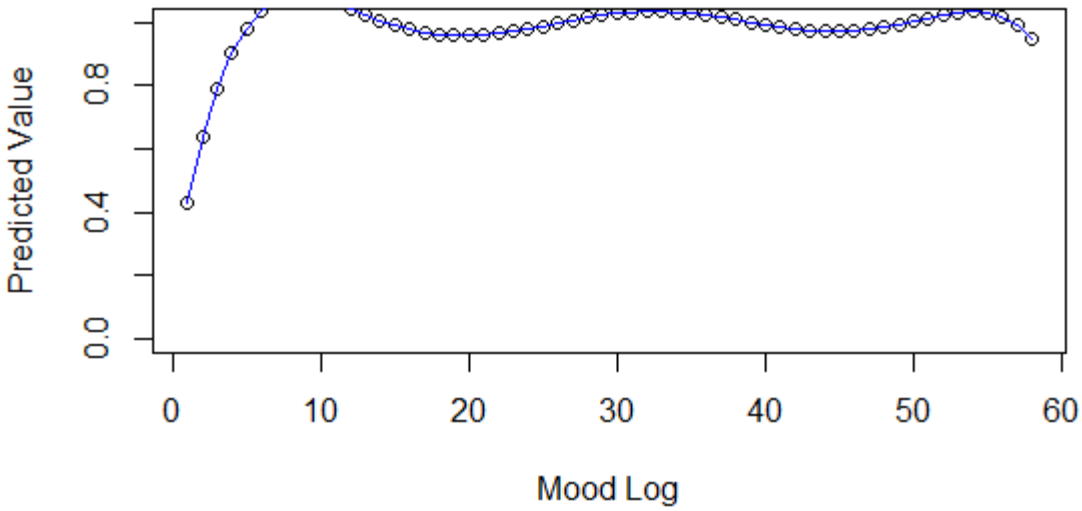
6.


Predicted Value
0.0
0.4
0.8
0
10
20
30
40
50
Mood Log

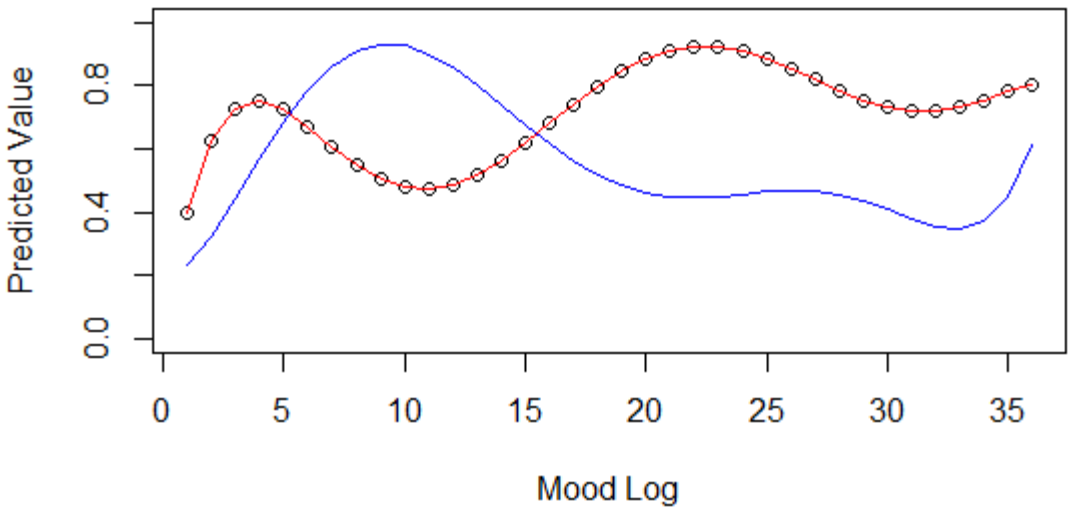
7.


Predicted Value
0.0
0.4
0.8
0
20
40
60
80
Mood Log

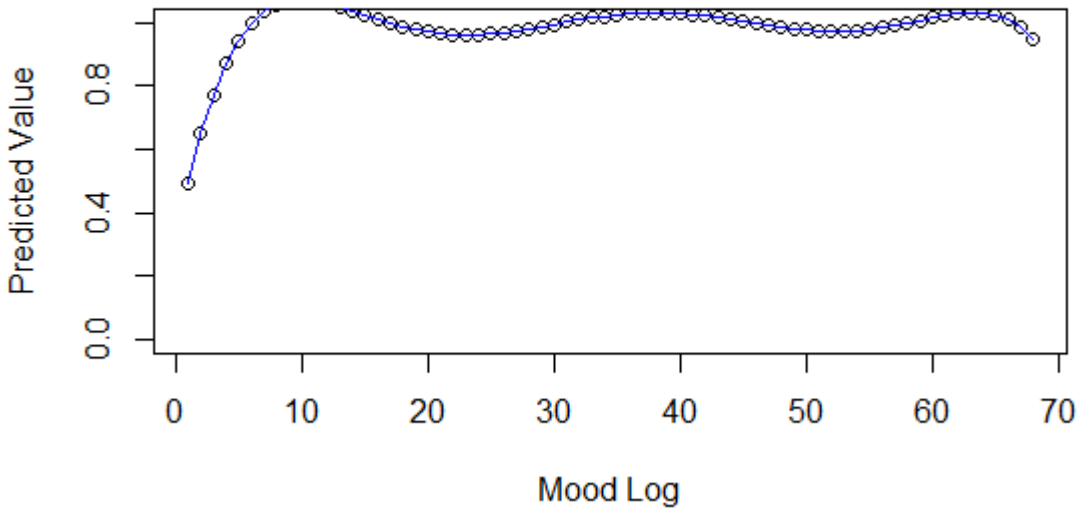
8.



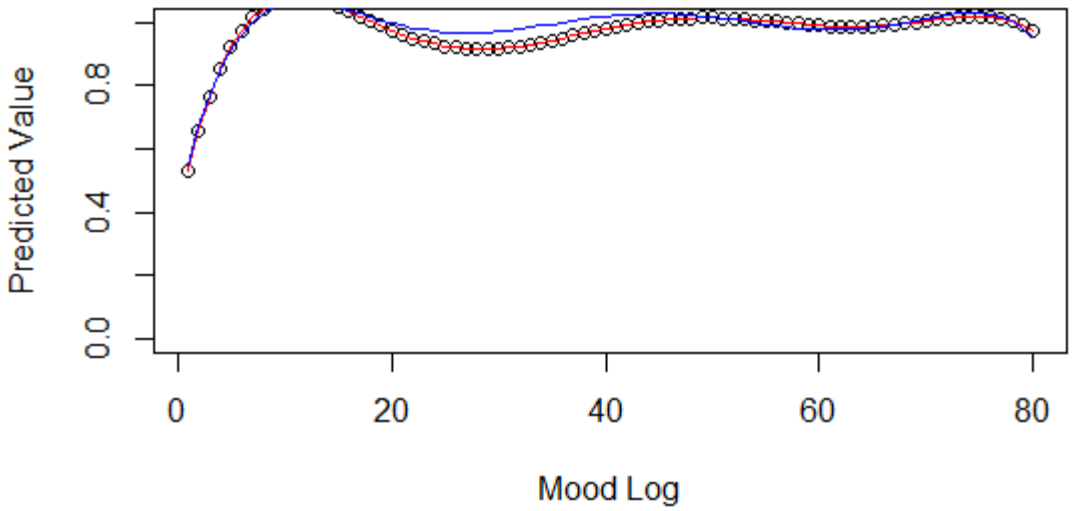
9.


Predicted Value
0.0
0.4
0.8
0
5
10
15
20
25
30
35
Mood Log

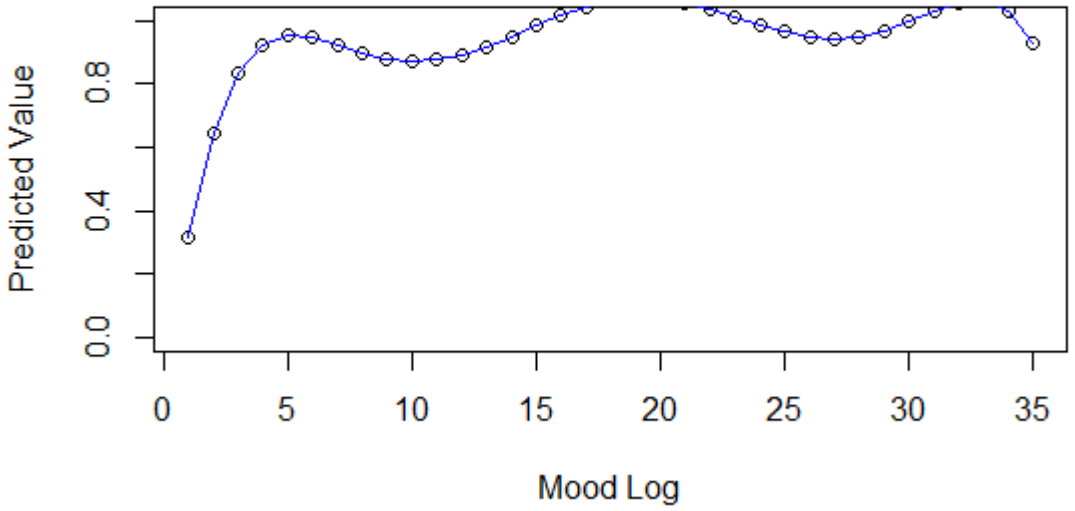
10.


Predicted Value
0.0
0.4
0.8
0
10
20
30
40
50
60
70
Mood Log

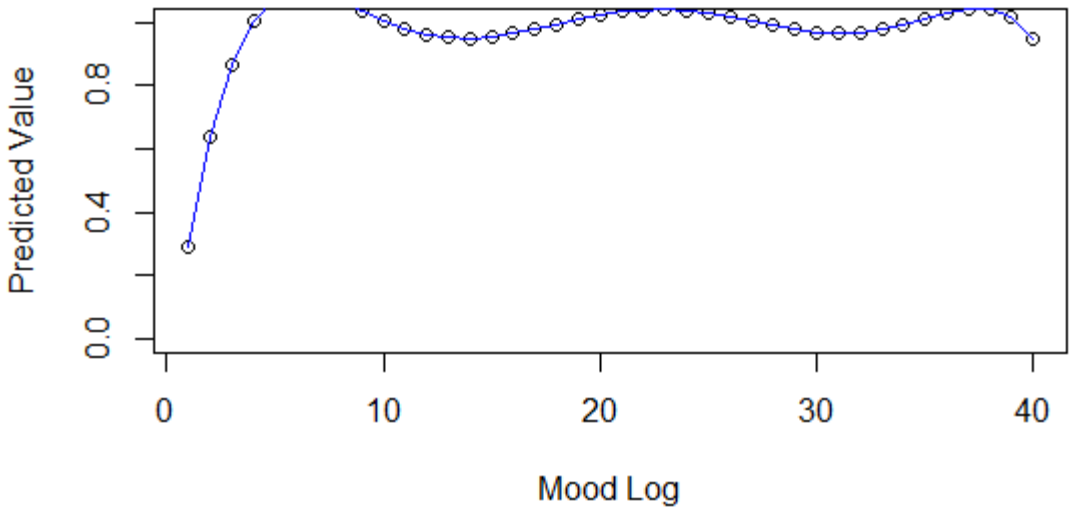
11.


Predicted Value
0.0
0.4
0.8
0
20
40
60
80
Mood Log

12.


Predicted Value
0.0
0.4
0.8
0
5
10
15
20
25
30
35
Mood Log

13.



Note. The red wave indicates mania. The blue wave indicates depression.

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