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Mood regulation in euthymic patients with a history of antidepressant-induced mania

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Abstract

Introduction: The use of antidepressants in bipolar disorder (BD) remains contentious, in part due to the risk of antidepressant-induced mania (AIM). However, there is no information on the architecture of mood regulation in patients who have experienced AIM. We compared the architecture of mood regulation in euthymic patients with and without a history of AIM.

Methods: Eighty-four euthymic participants were included. Participants rated their mood, anxiety and energy levels daily using an electronic (e-) visual analog scale, for a mean (SD) of 280.8(151.4) days. We analyzed their multivariate time series by computing each variable's auto-correlation, inter-variable cross-correlation, and composite multiscale entropy of mood, anxiety, and energy. Then, we compared the data features of participants with a history of AIM and those without AIM, using analysis of covariance, controlling for age, sex, and current treatment.

Results: Based on 18,103 daily observations, participants with AIM showed significantly stronger day-to-day auto-correlation and cross-correlation for mood, anxiety, and energy than those without AIM. The highest cross-correlation in participants with AIM was between mood and energy within the same day (median (IQR), 0.58 (0.27)). The strongest negative cross-correlation in participants with AIM was between mood and anxiety series within the same day (median (IQR), −0.52 (0.34)).

Conclusion: Patients with a history of AIM have a different underlying mood architecture compared to those without AIM. Their mood, anxiety and energy stay the same from day-to-day; and their anxiety is negatively correlated with their mood.

KEYWORDS
antidepressant-induced mania (AIM), auto-correlation, bipolar disorder, cross-correlation, euthymia, mood regulation, time series analysis

1 | INTRODUCTION

Bipolar Disorder (BD) is a mood disorder marked by episodes of depression, (hypo)mania, and mixed episodes with interspersed subsyndromal symptoms in between episodes.[1] BD remains a prominent cause of disability, a root source of the economic burden of mental health disorders,[2] and a major risk factor for suicide.[3,4] As depressive episodes in BD are more prevalent, longer lasting, and have a greater negative impact on social functioning compared to (hypo)manic episodes,[5,6] up to 40% of BD patients are treated with antidepressants in the maintenance phase. Yet, treatment for the depressive phase of BD has received less attention in clinical practice[7–9] and the support for antidepressants in maintenance treatment remains limited.[9,10]

The use of antidepressants to treat acute depressive episodes in BD has been a subject of intense debate,[11–13] as studies have raised significant concerns about the efficacy and tolerability of antidepressants in this population.[10,13–16] One of these concerns is antidepressant-induced mania (AIM), a phenomenon reported across various classes of antidepressants, with an estimated rate of 11.8–30.9%.[17] While there is not a formal operational definition of AIM,[18] it has been defined as the emergence of (hypo)manic episodes within 8 weeks following the most recent change in the causal antidepressant treatment.[11,18] However, not all patients diagnosed with BD who are treated with antidepressants experience AIM.[1,19–21] Evidence indicates AIM is more frequent among those patients with a previous history of AIM,[22] a family history of BD[17] and exposure to multiple trials of antidepressants.[23,24]

In this context, like many other instances of clinical heterogeneity in BD,[1,19–21] treatment response to antidepressants (and susceptibility to AIM) in BD patients is heterogeneous, but the reasons as to why are unclear.[25,26] Potential mediating factors include polymorphisms in several gene candidates, including serotonin transporter gene promoter (*5HTTLPR*)[27–29]; *CYP2D6*,[30] brain-derived neurotrophic factor (BDNF)[31]; but not all studies have supported these findings.[32–34] However, differences in the underlying architecture of mood regulation in patients with and without a history of AIM have not been explored. Mood regulation in BD has been increasingly recognized as an important variable with possible genetic influences,[35] and specific patterns of mood regulation may be associated with individual responses to treatment and/or higher proclivity for specific side effects.

Mood regulation is a complex, "buffer" system that regulates responses to changing, unpredictable day-to-day events.[36] Healthy persons show different dynamics (i.e., more variability) compared with patients diagnosed with BD, whose mood regulation is characterized by a more rigid (i.e., less variable) system.[36–39] This is also consistent with other data patterns in biology, in which an increased degree of organization (i.e., less adaptability to changes in the environment) is indicative of pathology.[40–42] Studies have also indicated that this pathology becomes evident in longitudinal patterns of variability far in advance than changes in average values.[43,44]

To our knowledge, there have been no studies comparing mood regulation in patients who have and have not experienced AIM. Therefore, we analyzed the underlying architecture of mood regulation in euthymic patients with and without a history of AIM using time series analysis. We hypothesized that mood regulation would differ in patients with and without a history of AIM.

2 | MATERIALS AND METHODS

2.1 | Subject recruitment

All the participants included in the analyses are enrolled in an ongoing study, and its details have been reported previously.[45] Briefly, the study takes place in two academic hospitals in Canada: the Centre for Addiction and Mental Health, in Toronto (CAMH), Toronto, Ontario, and the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia. Participants in this study were recruited between April 2021 and June 2023. We recruited 135 patients diagnosed with BD I or II. All patients were assessed and received treatment by a psychiatrist as per standard practice.

2.2 | Measurements

After providing informed consent, participants completed two clinician-administered scales, the Young Mania Rating Scale (YMRS)[46] and the Montgomery-Asberg Depression Ration Scale (MADRS)[47] used to assess their polarity upon entrance to the study and the severity of symptoms, if applicable. A score of 10 or less for at least 60 days on both scales was defined as euthymia.

As per our prior work on mood regulation,[36,48] participants were required to fill out a visual analog scale (VAS) that measures mood, anxiety, and energy levels. The scale ranges from 1 to 9, with 5 being the participant's baseline score or "usual" self.[49,50] Each day, participants were asked to rate their mood, anxiety, and energy level daily using the REDCap electronic data capture tools hosted at CAMH and Queen Elizabeth II Health Sciences Centre.[51,52] This scale changes by an interval of 0.1, allowing us to generate continuous, fine-grained data. Participants had to complete all ratings of mood, anxiety, and energy levels to submit the e-VAS. We contacted participants by email to remind them to complete the scale when it was missing for three consecutive days.

History of antidepressant-induced mania was defined as at least one full manic or hypomanic episode that emerged during antidepressant treatment, and persisted at a fully syndromal level beyond the physiological effect of that treatment.[1] Although there is no consensus definition in terms of time frame for reasonably attributing emergent (hypo)manias to antidepressant use, we used a cutoff of 8 weeks as per existing literature.[53]

2.3 | Assumptions

The analyses performed relied on two assumptions: The first assumption involves finding the right model for our data. Since our data

contains noise, we were satisfied with a simple model that accounts for basic patterns – e.g., autoregressive process AR (1), which looks at how one data point relates to the one just before it. The second assumption involves the stability of our data over time. While ideal data would remain completely consistent throughout, our real-world data is subject to fluctuations. Therefore, we relaxed this criterion and aimed for weak stationarity, where we only needed the first two moments of the data (e.g., the average and the spread) to stay roughly the same over time. This concept allowed us to work with the inherent variability of our data while still maintaining a level of stability suitable for analysis. We used the Augmented Dickey-Fuller test to assess whether our data met the criteria for stationarity.[54]

2.4 | Data selection and preprocessing

As per our previous study showing that self-reported e-VAS is missing not at random (MNAR),[55] we used the K-Nearest Neighbors (KNN) method for missing scale observation imputation.[56] KNN imputation identifies the k-nearest neighbors to each missing data point based on a distance metric and imputes the missing value using the median of these neighbors. This method leverages the information from similar observations, making it suitable for handling data MNAR.[55] A minimum data length of 50 data observations (i.e., 50 days of valid self-reported scales) was imposed as recommended to fit an autoregressive integrated moving average (ARIMA) model to control for seasonal effects. We excluded the data of 51 participants who did not satisfy the following three criteria: (a) less than 20% missing data ratio; (b) at least 50 days of data points provided; (c) euthymic for at least 60 days throughout the observational period. See Figure 1 for details on study design.

2.5 | Data analysis

Upon confirmation that the series were stationary, and upon removal of illusory time series inter-dependencies via pre-whitening using the Augmented Dickey-Fuller (ADF) test,[57] we conducted a two-dimensional correlation analysis: (i) Autocorrelation Function (ACF) to examine temporal dependencies within each e-VAS variable at lags 1 to 7 (e.g., mood today vs mood yesterday) across groups; and (ii) Cross-Correlation Function (CCF) to assess pairwise temporal dependencies between e-VAS variables at lags −7 to 7 (e.g., mood today vs energy tomorrow) across groups. To interpret the ACF, higher values at lags 1 to 7 indicate that the series is more self-similar, meaning each observation is highly correlated with observations at those specific lags (e.g., ACF at lag 1 assesses self-similarity between adjacent time series observations). Similarly, to interpret the CCF, higher values at a specific lag indicate that two series are more similar, meaning each observation of one variable is highly correlated with observations of the other variable at those specific lags (e.g., CCF at lag 1 assesses similarity between adjacent observations of two time series). Then, to quantify the complexity and dynamics of the daily reported mood, energy, and anxiety ratings, we employed Composite Multiscale Entropy (CMSE),[58] an extension of Multiscale Entropy

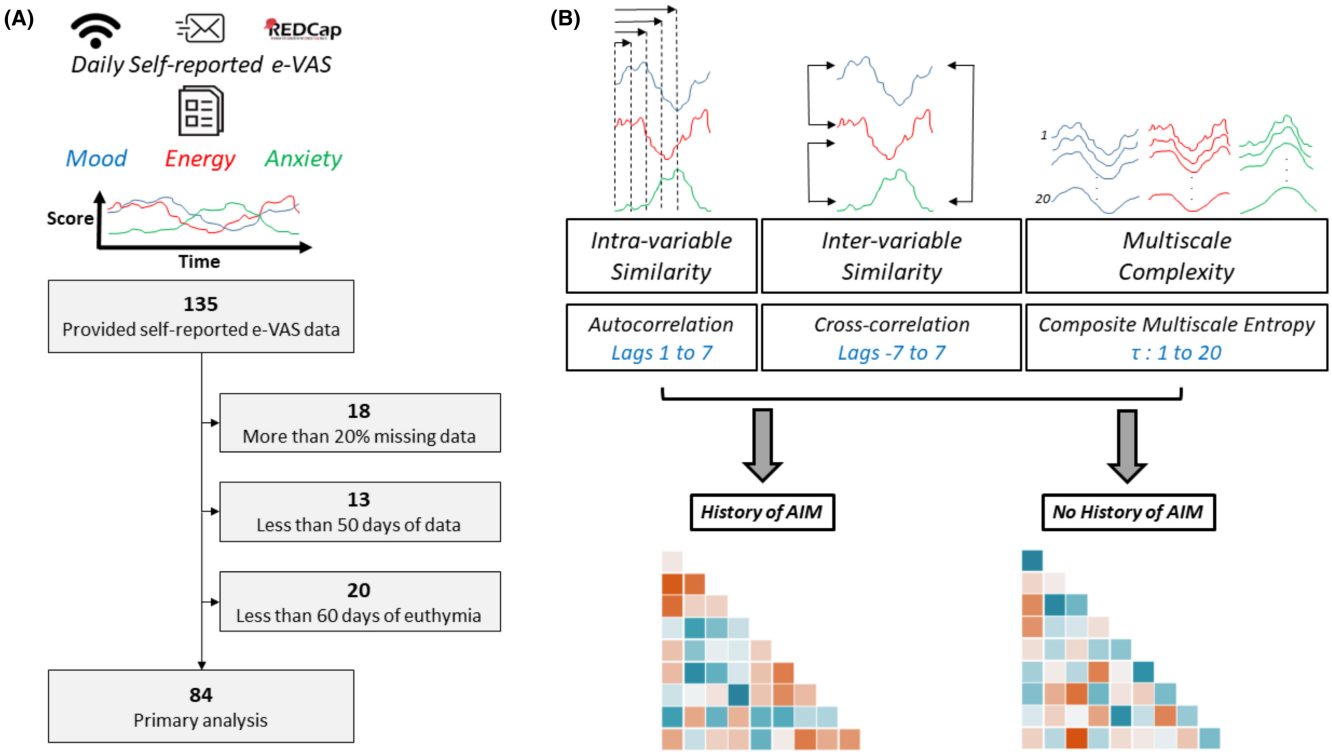

FIGURE 1 Study design (A) and data analysis pipeline (B).

that combines sample entropy calculations from multiple coarse-grained time series. CMSE is well suited for multivariate, non-stationary time series data, making it appropriate for analyzing complex patterns and interactions between the self-reported measures across multiple temporal scales. The analysis used an embedding dimension $m=2$, tolerance $r=0.2\times SD$ (data), and scale factors $\tau=1$ to 20. At each scale, CMSE was calculated by averaging the sample entropy values across mood, energy, and anxiety, providing a composite measure of complexity. This approach captures the intricate dynamics of the self-reported measures, while being robust to noise and non-stationarities common in such data. Finally, we controlled for seasonal effects by using frequency-determined filter procedures.

2.6 | Statistical analysis

Upon calculation of correlation metrics and nonlinear dynamics (i.e., ACF, CCF and CMSE), the output coefficients were subjected to an analysis of covariance (ANCOVA) to assess statistical differences between participants with a history of AIM and those without. We also controlled for sociodemographic and clinical covariates (e.g., age, sex, and current treatment)[59] and used the Benjamini-Hochberg method for *p*-value adjustment.[60] All analyses were performed using Python 3.11. The study design and analytical pipeline are presented in Figure 1.

3 | RESULTS

3.1 | Participants

Out of the 135 participants who were recruited to the study as of June 1st 2023, 84 participants were included in this analysis (see Methods and Figure 1). Sixteen (19.04%) participants had a history of AIM. No statistically significant differences across groups were found for demographic or clinical characteristics (see Table 1). Data included 18,103 valid data observation per e-VAS variable (i.e., mood, energy, and anxiety) with 2515 missing observations (87.8% compliance) throughout 280.8 ± 151.4 (mean $\pm$ SD) days: 3519 valid daily observations in each of the e-VAS variables for participants with history of AIM, and 14,508 valid observations for the non-AIM participants. There was no statistically significant difference between groups in terms of length of participation in the study per participant and data completeness (*duration*: $F=1.241$, $p=0.214$; *compliance*: $F=0.214$, $p=0.871$). The detailed description of the participants' sociodemographics and clinical features are presented in Table 1.

TABLE 1 Demographic and clinical characteristics.

Characteristic	Participants ($N=84$)
Age, mean (SD)	39.5 (12.1)
Sex assigned at birth, n (%)	
Male	31 (36.9)
Female	53 (63.1)
Gender, n (%)	
Man	29 (34.5)
Woman	44 (52.4)
Queer/gender non-conforming	3 (3.6)
Prefer not to disclose	8 (9.5)
Education, n (%)	
Completed high school or less	11 (13.1)
College/diploma	50 (59.5)
University education	23 (27.4)
Marital status, n (%)	
Single	40 (47.6)
Married	31 (36.9)
Divorced	12 (14.3)
Widowed	1 (1.2)
Socioeconomic status, n (%)	
Work full-time	52 (61.9)
Work part-time	7 (8.3)
Social assistance or disabled	8 (9.5)
Retired	3 (3.6)
Student	4 (4.8)
Unemployed and other	10 (11.9)
Primary Diagnosis, n (%)	
Bipolar Disorder I	59 (70.2)
Bipolar Disorder II	25 (29.8)
History of Antidepressant-Induced Mania, n (%)	16 (19.0)
Rapid cycling, n (%)	13 (15.5)
Clinical Status at study entry, n (%)	
Euthymic	59 (70.2)
In a depressive episode	25 (29.8)
Pharmacotherapy at the time of entry to the study	
On no treatment at the time of entry	1 (1.2)
Lithium monotherapy	3 (3.6)
Anticonvulsant monotherapy	8 (9.5)
Antipsychotic monotherapy	8 (9.5)
Combination treatment	59 (70.2)
Other	5 (6.0)

3.2 | Distribution of individual measures

No significant difference was found between ratings for mood ($F=0.54$; $p=0.46$), energy ($F=0.09$; $p=0.76$) or anxiety levels ($F=1.09$; $p=0.30$) between groups.

3.3 | Autocorrelation (lags 1–7)

For all e-VAS variables, the highest autocorrelation for participants with and without history of AIM was observed at lag 1 (e.g., today's mood was correlated with yesterday's mood). There were no

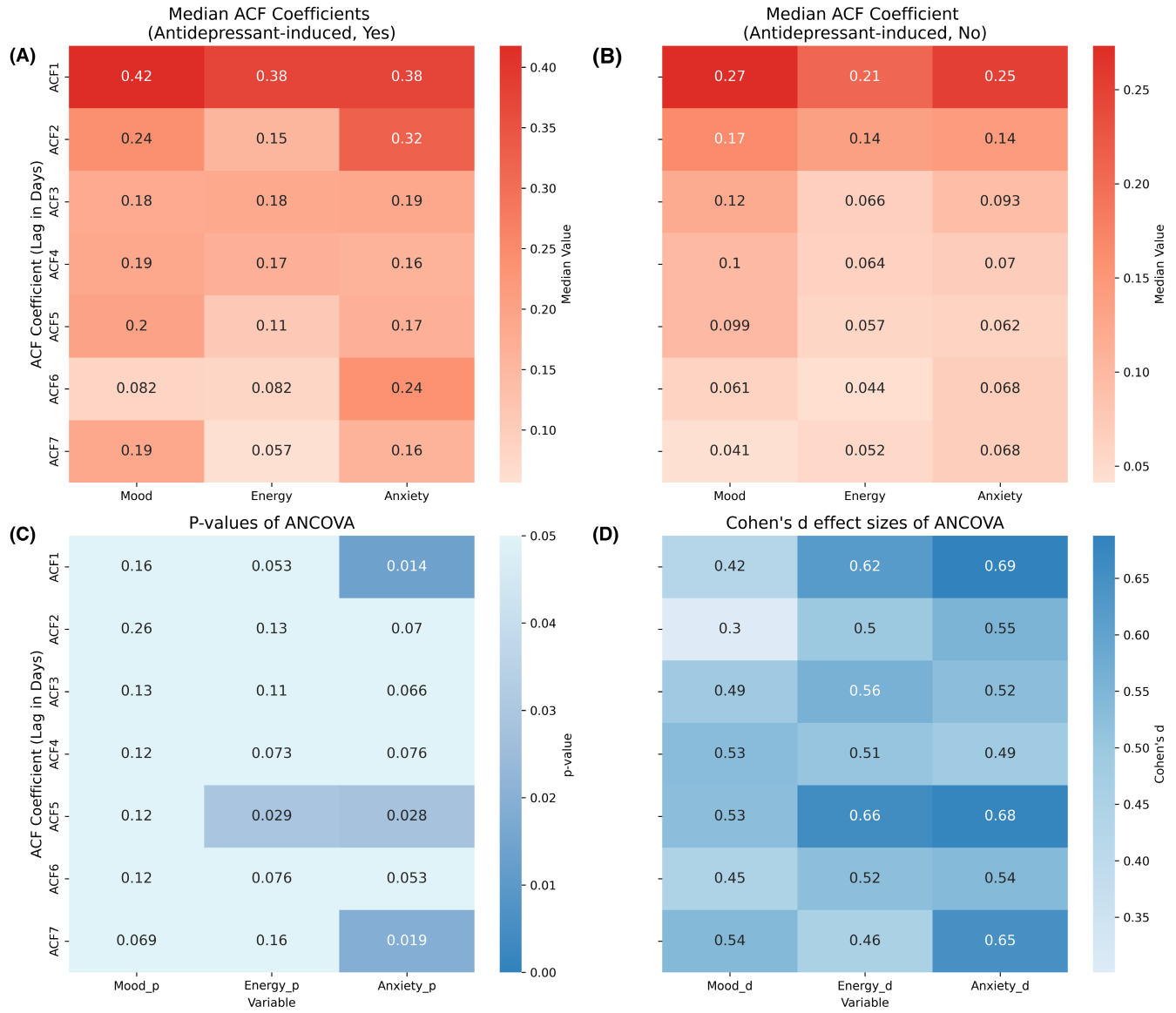

FIGURE 2 Mood, energy, and anxiety autocorrelation matrices for participants (A) with history of AIM and (B) those without history of AIM, (C) statistical significance of ANCOVA tests, and (D) the respective effective sizes.

statistically significant differences between the groups. See Figure 2 for the detailed representation of ACF coefficients across classes, along with the statistical significance and effect sizes.

3.4 | Cross-correlation between mood and energy (lags −7 to 7)

The highest cross-correlation for participants with a history of AIM (Figure 3A) was observed at lag 0 (i.e., between a participant's mood and energy on the same day); (median (IQR), 0.58 (0.27)). Similarly, for participants with no history of AIM, the highest cross-correlation was also at lag 0 (median (IQR), 0.42 (0.23)) ($p=0.065$, Cohen's $d=0.64$).

Although not significantly different across AIM groups, we also observed a strong positive cross-correlation at lag 1 (i.e., between mood on a certain day and energy the day after), which was higher in participants with AIM (median (IQR), 0.23 (0.34)) compared to participants with no history of AIM (median (IQR), 0.14 (0.17); $p=0.084$, Cohen's $d=0.60$). Cross-correlation coefficients between mood and energy beyond a single-day lag were negligible and not statistically different between groups.

3.5 | Cross-correlation between anxiety and energy (lags −7 to 7)

The highest cross-correlation for participants with a history of AIM (Figure 3A) was observed at lag 0, i.e., between a participant's energy and anxiety on the same day (median (IQR), −0.45 (0.54)). Similarly, for participants with no history of AIM, the highest cross-correlation was also at lag 0 (median (IQR), −0.22 (0.18)), significantly

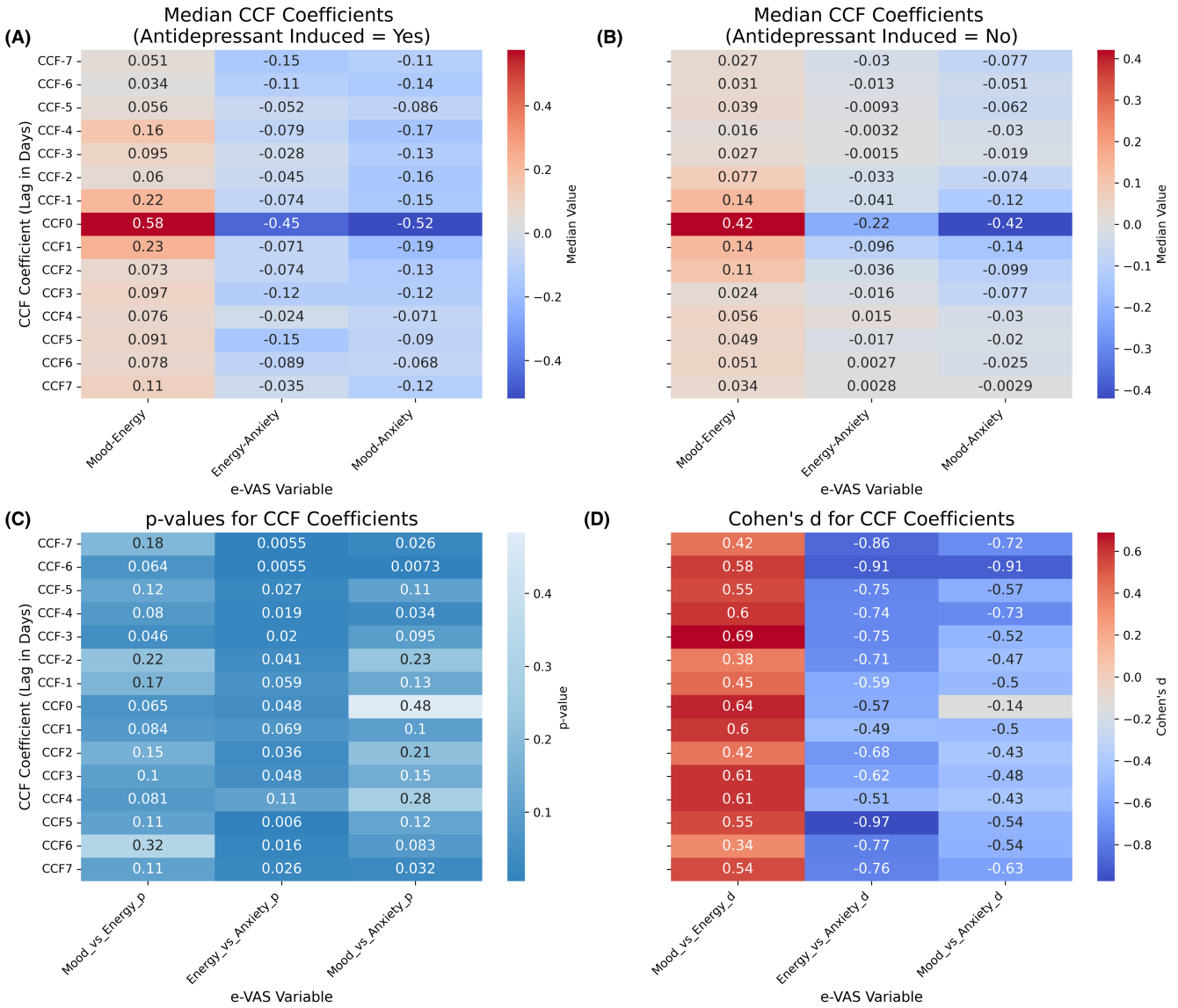

FIGURE 3 Mood, energy, and anxiety cross-correlation matrices for participants (A) with history of AIM and (B) those without history of AIM, (C) statistical significance of AIM inter-group ANCOVA tests, and (D) the respective effective sizes.

lower than that of participants with a history of AIM ($p=0.048$, Cohen's $d=-0.57$). Cross-correlation coefficients between anxiety and energy beyond lag 0 were negligible and not statistically different between groups.

3.6 | Cross-correlation between mood and anxiety series (lags −7 to 7)

The highest cross-correlation for participants with a history of AIM (Figure 3A) was observed at lag 0, i.e., between a participant's mood and anxiety on the same day (median (IQR), −0.52 (0.34)). Similarly, for participants with no history of AIM, the highest cross-correlation magnitude was also observed at lag 0 (median (IQR), −0.42 (0.27)). However, the differences in CCF at lag 0 were statistically non-significant ($p=0.48$, Cohen's $d=-0.14$). Cross-correlation coefficients between mood and anxiety beyond lag 0 were negligible and not statistically different between groups. See Figure 3 for a detailed representation of the cross-correlation analysis results and associated statistical test outputs.

3.6.1 | Composite multiscale entropy

There were no statistically significant differences between groups.

4 | DISCUSSION

In this study, we examined the temporal dynamics of mood, energy, and anxiety in euthymic participants diagnosed with BD, with and without a history of AIM. Our analysis revealed distinct patterns

within mood, energy, and anxiety time series, indicating that mood regulation is different in those participants who have had AIM compared to those who have not.

Specifically, our autocorrelation analysis showed that, in participants with a history of AIM, their mood series have a strong relationship between consecutive days (median (IQR), 0.42 (0.24)); while participants without history of AIM exhibited a slightly weaker autocorrelation (median (IQR), 0.27 (0.27); $p=0.061$, Cohen's $d=0.42$). Energy series followed a similar trend, with AIM participants showing higher autocorrelation at lag 1 (median (IQR), 0.38 (0.32)) compared to those with no history of AIM (median (IQR), 0.21 (0.26); $p=0.052$, Cohen's $d=0.62$). Moreover, for anxiety series, patients with a history of AIM showed higher autocorrelation at lag 1 (median (IQR), 0.38 (0.35)) than those without a history of AIM (median (IQR), 0.25 (0.24); $p=0.014$, Cohen's $d=0.69$). This suggests that individuals with a history of AIM may experience more consistent levels of anxiety from one day to the next. Overall, our results throughout the mood, energy, and anxiety time series showed a pronounced autocorrelation at lag 1 for AIM participants, suggesting an increased temporal stability in these series. This pattern implies that mood regulation is different in those with a history of AIM, with probably more extensive day-to-day "carryover effects" in their mood, energy, and anxiety levels.

Moreover, our cross-correlation analysis between mood and energy series revealed that participants with a history of AIM exhibited the highest cross-correlation at lag 0 (median (IQR), 0.58 (0.27)). This pattern (i.e., same-day) similarity between mood and energy levels suggests that fluctuations in mood and energy occur simultaneously for these individuals, potentially reflecting a heightened interdependence between these two series. Clinically, this could be reflected in the phenomena that increased energy levels, commonly seen as one of the earliest features in antidepressant treatment, can "tip over" the system, with the resulting mood changes (elation or irritability), seen in participants with AIM. Conversely, for participants without AIM history, the highest cross-correlation at lag 0 was lower (median (IQR), 0.42 (0.23)), but not significant ($p=0.065$, Cohen's $d=0.64$). Additionally, the strong positive cross-correlation at lag 1 for participants with a history of AIM (median (IQR), 0.23 (0.34)), implies that mood on Day 1 is predictive of energy levels the following day. This effect was less pronounced for non-AIM participants (median (IQR), 0.14 (0.17); $p=0.17$, Cohen's $d=0.55$). Overall, these findings indicate that the temporal dynamics of mood and energy are more tightly coupled in individuals with AIM history.

Beyond a single-day lag, cross-correlation coefficients were negligible and did not significantly differ across AIM groups, highlighting the temporal architecture of mood regulation that has been described in both healthy controls and patients diagnosed with BD.[36]

Similarly, in the analysis of cross-correlation between energy and anxiety time series, we also found the highest inverse cross-correlation for AIM participants at lag 0 (median (IQR), −0.45 (0.54)), suggesting a significant inverse relationship between these variables on the same day. For participants with no history of AIM, the cross-correlation at lag 0 was weaker (median (IQR), −0.22 (0.18)), yet still indicative of a negative relationship ($p=0.048$, Cohen's $d=-0.57$). This suggests that higher energy levels are associated with simultaneously lower anxiety levels. The cross-correlation coefficients between energy and anxiety at other lags were negligible, indicating no meaningful relationship between energy on Day 1 and anxiety on subsequent or previous days. This pattern underscores the immediate impact of energy fluctuations on anxiety levels, with a more pronounced effect observed in those with a history of AIM.

Lastly, the cross-correlation between mood and anxiety time series revealed that the highest cross-correlation for AIM participants occurred at lag 0 (median (IQR), −0.52 (0.34)), indicating a negative simultaneous association. For non-AIM participants, the cross-correlation at lag 0 was also negative but less pronounced (median (IQR), −0.42 (0.27); $p=0.48$, Cohen's $d=-0.14$). These findings suggest that higher mood levels are associated with lower anxiety levels on the same day, with a stronger effect in AIM participants. Cross-correlation coefficients at other lags were negligible, indicating no significant relationship between mood and anxiety on different days. This finding highlights the importance of treating anxiety symptoms to improve mood, particularly in patients with no history of AIM.

Our study revealed no significant differences in the overall ratings for mood, energy, or anxiety levels between the two groups, nor did it reveal significant multiscale (i.e., short- and long-term) pattern complexity differences: Participants with history of AIM showed higher mood multiscale entropy (i.e., short-term and long-term dynamics complexity (median (IQR)): 1.02 (0.91) than those with no history of AIM (0.80 (1.08); $F_{ANCOVA}=0.6$, $p=0.45$). Conversely, their energy dynamics were less complex than those in participants with no history of AIM (mean (IQR): (0.90 (0.76) vs 1.60 (0.94); $F_{ANCOVA}=1.5$, $p=0.23$). The complexity of anxiety dynamics was nearly identical for participants with history of AIM (median (IQR), 1.06 (0.81)) and those with no history of AIM (median (IQR), 1.10 (0.97); $F_{ANCOVA}=0.2$, $p=0.68$).

Our results are consistent with the literature describing the prevalence of AIM at 11.8–30.9%[17] and emphasizing the role of lithium in particular, to prevent AIM.[61,62] In keeping with our previous findings in BD,[48] mood was considered a short-term memory process where the current values in the series are related to one previous point only. The pattern of mood regulation in patients diagnosed with BD with a history of AIM is different from the ones without a history of AIM, with our results showing significantly higher autocorrelation in the AIM group in the mood and anxiety series. This means that mood and anxiety levels in patients with AIM are closely "coupled" in time: their current mood and anxiety levels are more affected by their past mood and anxiety levels.

The main limitations of the study are the relatively small sample size and class imbalance between AIM and non-AIM groups. However, our time series analysis required the assumption of normality of the dataset, which was verified, and the effect of sample size and class imbalance were mitigated using permutation testing and bootstrapping techniques, while also controlling for clinically relevant covariates.

Future studies should continue to investigate the intricate temporal dynamics and interrelationships between mood, energy, and

anxiety. This could be achieved by leveraging larger, more diverse datasets and employing advanced statistical models that account for additional confounding variables (e.g., comorbid conditions, sleep quality, and levels of physical activity). Understanding these dynamics may ultimately contribute to the development of more tailored and effective interventions for BD.

5 | CONCLUSION

Our study uncovers distinct patterns of mood regulation in euthymic patients with a history of antidepressant-induced mania (AIM), compared to those without. By employing advanced time series analysis, we demonstrated that patients with AIM exhibit stronger autocorrelation and cross-correlation among mood, anxiety, and energy levels. This dynamic representation of mood regulation in BD highlights the potential for more personalized approaches in managing mood stability, particularly in those with a history of AIM.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to privacy considerations.

ETHICS STATEMENT

The study was approved by the Research Ethics Board (REB) at the Centre for Addictions and Mental Health (CAMH), Toronto, Ontario, Canada; and at the QEII Health Care Center, Halifax, Nova Scotia, Canada, in accordance with the Declaration of Helsinki. REB #: 059–2019. All participants consented in writing to participate in the study.

CODE AVAILABILITY

The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

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