Daily dynamics of negative affect: indicators of rate of response to treatment and remission from depression?

Marieke A. Helmich^{a*}, Marieke Wichers^a, Frenk Peeters^b and Evelien Snippe^a

^aUniversity of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation, Groningen, the Netherlands; ^bDepartment of Clinical Psychological Science, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

*Corresponding author: Marieke A. Helmich, e-mail address: marieke.a.helmich@gmail.com
University Medical Center Groningen, P.O. Box 30.001 (CC72), 9700 RB Groningen, the Netherlands

Data Availability Statement

Due to the privacy-sensitive nature of psychiatric patient information, it is not possible to share this dataset publicly.

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More instability (MSSD) and variability (SD) of negative affect (NA) have been related to current and future depressive symptoms. We investigated whether NA instability and variability were predictive of the rate of symptom improvement during treatment and of reaching remission status. Forty-six individuals with major depressive disorder completed six days of ecological momentary assessments (10 beeps/day) before starting a combination of pharmacotherapy and supportive therapy. During and after treatment, the Hamilton Depression Rating Scale (HDRS) diagnostic interview was performed monthly for 18 months. The rate of change in HDRS scores over five months (during treatment) and remission status (HDRS ≤ 7) over eighteen months were predicted by the SD, MSSD and Mean of NA, and relevant baseline predictors. Higher Mean NA and baseline symptom severity, but not NA variability or instability, predicted stronger depressive symptom reduction during treatment. Higher odds of remitting were only associated with lower Mean NA. Higher mean NA may indicate more room for improvement and thus for a steeper rate of symptom change, while lower mean NA levels may imply that remission status is more readily reached. To resolve the inconclusive findings for instability and variability as predictors of symptom improvement replication in larger samples is required.

Keywords: symptom improvement; emotion dynamics; treatment response; experience sampling method; destabilization

Introduction

The likelihood that a patient responds to treatment for depression is hard to predict. The process of remission is heterogeneous and even those patients that respond during therapy may not maintain the symptom improvements over the long term (Gelo & Salvatore, 2016). A more unfavourable course of depression is often characterized by symptom instability and recurrences of symptoms (Wichers et al., 2010). Because such an unstable course is debilitating, it is important to identify predictors of treatment response and change in depressive symptoms at an early stage.

Drawing on dynamical systems theory, potential candidates for determining the likelihood of treatment response and long-term presence of depressive symptoms may be found in the dynamics of moment-to-moment negative affect (NA). In a complex dynamical system, large state changes are often preceded by destabilization –e.g., increased fluctuations in response to stressors– in the underlying components of the system (Hayes & Andrews, 2020; Wichers et al., 2015). From a clinical point of view, destabilization may indicate a depressed patient’s ‘readiness for change’, and therapy may further contribute to a positive direction of the change (Gelo & Salvatore, 2016; Wichers et al., 2010). Combining these perspectives, a large ‘state change’ like treatment response may show early signs of destabilization in the experiences underlying depressive symptoms, like NA (e.g., “I feel down”) within the course of daily life (Helmich et al., 2021; Olthof et al., 2020).

Researchers have posited that a less stable system may show more *variability* and *instability* in NA scores (Wichers et al., 2015). A higher standard deviation (SD) of NA scores reflects more variability and a higher mean square of successive differences (MSSD) of NA scores captures instability of NA or how strongly NA changes from one moment to the next. Specifically, researchers have been using ecological momentary assessments (EMA) to calculate instability and variability in NA using these representative time series of people’s NA

throughout the day, over multiple days (Ebner-Priemer et al., 2009). With this method, it could be hypothesized that higher variability and instability in EMA assessments of NA at the start of treatment would predict more favourable treatment outcomes.

However, research suggests that more instability and variability of NA scores may not be favourable indicators of the (current) state of a patient. Cross-sectional studies have shown NA variability to be related to more severe depressive symptoms (Thompson et al., 2011), and affective instability to be predictive of depressive symptoms up to five years later, as well as the likelihood of having lifetime major depressive episodes (Eldesouky et al., 2018). Moreover, when measured with EMA in the context of daily life, depressed individuals appear to have higher levels of variability and instability in NA than healthy individuals (Panaite et al., 2020; Peeters et al., 2006; Schoevers et al., 2020; Thompson et al., 2012), and these indices of NA dynamics have been found to be related to current depression (Koval et al., 2013; Sperry et al., 2020). Thus, instability and variability of NA scores may rather reflect mechanisms underlying psychopathology instead of being indicators of ‘readiness for change’ and may therefore also predict less favourable treatment outcomes (Wichers et al., 2015).

So far, only two studies have examined how EMA-measured NA dynamics relate to depressive symptom improvement during treatment. First, Husen *et al.* (2016) studied a sample of 39 outpatients with mixed primary diagnoses of affective and anxiety disorder, who completed a two-week EMA period of four measurements a day, to capture real-time affective states (including NA) ca. 2.3 months before starting cognitive behavioural therapy (CBT). They found that lower NA instability (MSSD) was associated with a stronger decrease in symptoms over five weeks of therapy, while controlling for baseline severity. While the Mean of NA was predictive of treatment response in a single-predictor model, this effect turned non-significant in their combined multi-predictor model.

Second, Bosley *et al.* (2019) studied a sample of 32 patients with mood and anxiety disorders, who completed four daily assessments of NA for 30 days before starting CBT treatment. They found that the MSSD and SD of NA were unrelated to pre-post treatment depression symptom change, although the MSSD of NA did predict a decrease in anxiety symptoms in response to treatment beyond mean-levels of NA. The evidence regarding the role of NA dynamics predicting the course of depression treatment is thus inconclusive, and no study has yet investigated whether NA dynamics captured in daily life can inform us on long-term remission likelihood in depression.

More evidence is needed on the added value of NA instability and variability above and beyond the mean of NA in predicting treatment response in depression. For instance, Funkhouser *et al.* (2021) found Mean NA to be related to previous MDD episodes, while instability of NA was unrelated to the depression risk factors in their study. Panaite *et al.* (2020) showed higher daily NA levels – but not NA instability or variability – to be related to higher average depressive symptom severity over six months. They also found NA instability and variability – but not mean-levels – to be related to a U-shaped naturalistic symptom course over the same period. Bos *et al.* (2018) examined the relationship between NA dynamic measures and depression and found that when including both the SD and MSSD in their model, only the SD remained a significant predictor, but this, in turn, became non-significant after adjusting for Mean NA-levels. Similarly, a meta-analysis of EMA studies by Dejonckheere *et al.* (2019) showed that most complex measures of affect dynamics had little added value over Mean NA in the prediction of life satisfaction and depressive symptoms. These studies underscore the importance of accounting for statistical overlap between NA measures, and with Mean NA in particular. Although the SD and MSSD are closely related, examining both instability and variability allows us to determine whether it is the spread in observations (SD), or also the difference between adjacent observations (MSSD) that best predicts depressive improvement

over time. The current study therefore aims to investigate the predictive value of instability and variability of NA, as well as of Mean NA.

If dynamic indices or Mean-levels of NA can be informative of a patient's potential for depressive symptom improvement, monitoring their affect before and during treatment could be of great clinical importance (Hayes & Andrews, 2020; Helmich et al., 2021; Strunk & Lichtwarck-Aschoff, 2019). Our dataset uniquely combines an EMA baseline period immediately before the start of treatment with eighteen monthly clinical interviews that allow us to assess both the change in symptoms during five months of treatment, as well as long-term remission incidence. Therefore, the aims of this study are 1) to test whether within-person instability (MSSD), variability (SD) and the Mean of NA are predictive of the rate of depressive symptom change during five months of treatment for depression, and 2) to test whether these NA measures are predictive of remission status over eighteen months.

Materials and methods

Participants

Forty-seven participants with a primary diagnosis of Major Depressive Disorder (MDD) were recruited among individuals seeking treatment at a university-affiliated mental health centre or the outpatient department of a psychiatric hospital in Maastricht, the Netherlands. Inclusion criteria were: 18–65 years of age, at least moderate depressive symptoms as indicated by a score of ≥ 18 on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), and no antidepressant treatment at the study start – although the use of low-dose anxiolytic drugs was permitted ($n=8$). Exclusion criteria were current substance abuse or psychotic symptoms and insufficient command of the Dutch language. Participants were also required to have a minimum of 30% valid (i.e., delay in answering ≤ 25 minutes) EMA observations (Peeters et al., 2006). This led to one exclusion, and a final sample of 46 participants. All participants

provided written informed consent and received \$30 for participation after the EMA period. The study design was approved by the Medical Ethics Committee of the academic hospital (METC azM/UM), and data collection took place between April 1998 and May 2001.

Procedure

Directly before the start of treatment, repeated self-reports of participants' momentary affect were gathered by EMA over six consecutive days. Ten times a day, between 7:30AM and 10:30PM, at semi-random intervals of circa 90 minutes, a beep from a digital wristwatch prompted participants to fill in the pencil-and-paper self-report form (see also Peeters et al., 2006). Immediately after the EMA period, all participants entered a naturalistic treatment phase. The HDRS was used to measure depressive symptom severity at baseline, and every following month over the course of 18 months.

Treatment

All patients received a combination of pharmacotherapy and supportive psychotherapy in accordance with APA treatment guidelines. Serotonergic antidepressants were prescribed in flexible dosage depending on participants' response and tolerance. In case of non-response, different anti-depressant treatments were prescribed: venlafaxine or a tricyclic agent, and in case of continued non-response, lithium was added. Supportive therapy in this mental health centre focused on improving depressive symptoms and associated problems in participants' daily lives. The therapy consisted of a broad combination of psychoeducation, providing advice and encouragement, problem solving, behavioural activation, and stimulating participants to improve the quality of interpersonal relations. Typically, the supportive therapy lasted between 15 and 20 sessions, which initially occurred weekly and decreased in frequency following agreement between therapist and patient. When the face-to-face therapy

sessions ended, some patients had tapered off their medication entirely, while others continued on a maintenance regimen. The decision to discontinue medication was at the discretion of patient and therapist while taking prior history (previous episodes) into consideration.

Measurements

Negative affect

Momentary mood states were assessed with nine adjectives rated on 7-point scales (1 – “not at all”, 7 – “very”), e.g., “*I feel down*”. To create the NA-variable, the following items were averaged per measurement occasion: *down, tense, lonely, irritated, anxious, guilty, agitated, tired, irritable*. On average, 45 ($SD = 10.1$) out of 60 possible EMA questionnaires were completed, a high compliance rate ($Mean = 75\%$, $Q1 = 66.6\%$, $Q3 = 87.9\%$). The mean within-person Cronbach’s alpha for the NA scale was 0.75 (computed with the ‘alpha’ function from the *psych* R package).

Depressive symptom severity

The HDRS-17 is a 17-item clinician-rated scale (Hamilton, 1960), which was used in this study to measure the severity of depressive symptoms at baseline, and at 18 monthly follow-up occasions. A trained research assistant performed the ratings of the HDRS via telephone. On average, 14.1 ($SD = 3.3$) of the maximum 18 monthly HDRS assessments were completed (78% compliance).

Baseline patient characteristics

In the baseline interview, information was gathered concerning the patients' family history of depression (yes or no), duration of the depressive complaints in months, and whether the current episode was their first or not.

*Analysis**Variability and instability in NA*

The level of within-person variability in NA was estimated by calculating the standard deviation (SD) over all the available EMA observations for each person.

To determine the level of NA instability across the EMA measurements for each person, we calculated a time-adjusted mean square successive difference (MSSD) as suggested by Jahng *et al.* (2008).

$$\text{time-adjusted MSSD} = \frac{\text{median}(\Delta t)}{n-1} \sum_{i=1}^{n-1} \frac{(X_{i+1} - X_i)^2}{(t_{i+1} - t_i)}$$

The time-adjusted MSSD corrects for the irregular intervals between observations inherent in our semi-random EMA design by subtracting the median lag-duration per individual from the observed lags for that person. Overnight lags were omitted from the MSSD-calculations by inserting a missing observation between the last observation of the day and the first observation of the next day.

Analysis 1: predicting rate of symptom improvement during treatment

We examined whether within-person variability and instability in NA were associated with a steeper linear¹ decline of HDRS symptom scores during treatment. We also examined the

¹ In accordance with the method described in Husen *et al.* (2016), we conducted an AIC comparison between two unconditional growth models: a linear model (AIC = 1162.84) and a log-linear model (change in HDRS over time is modeled as a log₁₀ function of time; AIC = 1167.53). For us, the linear model fit better, whereas Husen *et al.* ended up modeling symptoms as a logarithmic curve.

individual predictive value of Mean momentary NA, baseline HDRS score, episode duration, family history, and first or recurrent episode.

We used the following conditional growth curve model:

$$\text{Level 1: HDRS}_{pM} = \beta_{0p} + \beta_{1p} * \text{Time}_{pM} + e_{pM}$$

$$\text{Level 2: } \beta_{0p} = b_{00} + b_{01} * \text{Predictor}_p + r_{0p}$$

$$\beta_{1p} = b_{10} + b_{11} * \text{Predictor}_p + r_{1p}$$

In this multilevel model, monthly measurements (M) were nested within patients (p). HDRS symptom scores at each month were modelled as a function of a fixed intercept (b_{00}), a fixed effect of the Time (1, 2, 3, 4, 5) in months (b_{10}), as well as a random intercept (r_{0p} – patient-specific first HDRS score) and a random slope of Time in months (r_{1p} – patient-specific rate of change).

Each predictor was entered in a single-predictor model² to test the main effect and the cross-level interaction with time (we used the ‘lme’ function from the *nlme* R package). Predictors that were significantly ($p < .05$) associated with a steeper linear rate of symptom reduction were included in a multi-predictor model.

Only the HDRS observations during treatment were used (i.e., the first five months), which is the same number of measurements used by Husen *et al.* (i.e., first five weeks). All participants ($N = 46$) met the minimum of two measurements for inclusion in the analysis.

Analysis 2: predicting remission status

The modelled outcome was a binary variable indicating whether remission (HDRS score ≤ 7 ; Riedel et al., 2010) was reached within the 18-month study period (1 = *remitted* within 18 months, 0 = *non-remitter*)³. We then conducted a robust logistic regression (using ‘glmrob’

² To control for the potential confounding effect of baseline symptom severity, the models were also run with HDRS baseline symptom severity (HDRS0) as a covariate. Model findings are stable, unless reported otherwise.

³ We also calculated ‘time to remission’ for each patient by counting the number of monthly HDRS measurements (maximum eighteen) before the remission threshold of HDRS ≤ 7 was reached. However, modelling time to remission as a dependent variable led to problematic, non-normal distribution of the residuals and unreliable regression estimates. Therefore, we did not use time to remission as an outcome variable.

from the *robustbase* package) to examine whether the candidate predictors were associated with reaching remission. We first estimated single-predictor logistic regression models² using likelihood-ratio testing. Significant predictors ($p < .05$) were then tested in a multi-predictor logistic regression model.

Figure 1. Histogram of the number of remitters per month (left y-axis) and line graphs of the overall mean Hamilton Depression Rating Scale (HDRS) symptom scores per month of follow-up (solid line, right y-axis), as well as separate lines for mean HDRS scores for the remitters ($n = 33$; dashed line) and non-remitters ($n = 13$; dotted line). Remission was indicated when a patient obtained a score of ≤ 7 on the monthly HDRS interview. Non-remitters are indicated at ‘...’ on the x-axis of the histogram as it is unclear whether and when those patients experienced symptom improvement.

Results

Descriptives

Of the 46 participants, 27 were female (59%), and mean age was 40.3 ($SD = 11.1$). Secondary Axis I diagnoses were indicated for 21 (46%) of the patients, of which four participants had three or more secondary diagnoses: generalized social phobia ($n = 9$), dysthymic disorder

($n = 5$), panic disorder with agoraphobia ($n = 4$), posttraumatic stress disorder ($n = 4$), specific phobia ($n=4$), bulimia nervosa ($n = 1$). Thirty-three people (72%) reached the remission-threshold ($\text{HDRS} \leq 7$) within the 18 months of study ($M = 4.3$, $SD = 3.6$, see also Figure 1).

Table 1 presents descriptive statistics and Pearson correlations for the baseline predictors and NA variables. Some significant intercorrelations were found: mean-level NA was positively related to SD of NA ($r = 0.29$, $p = .0499$), and to duration of the complaints ($r = 0.33$, $p = .025$). The SD and MSSD of NA were highly correlated ($r = 0.90$, $p < .001$).

Table 1. Descriptive statistics and Pearson's correlations of baseline symptom severity and sample characteristics and negative affect dynamic measures

Measure	Descriptive statistics			Correlations						
	Mean (SD)	Min	Max	HDRS0	Duration	Episode	Family	Negative affect		
							history	Mean	SD	MSSD
Baseline characteristics										
HDRS0	23.9 (3.9)	19	34	–						
Duration (months)	20.2 (22.8)	2	120	–0.07	–					
Previous episode	<i>n</i> = 19 (41%)	-	-	–0.11	–0.21	–				
Family History	<i>n</i> = 25 (54%)	-	-	–0.07	0.07	–0.03	–			
Negative affect										
Mean level (M)	2.98 (0.97)	1.46	5.23	0.25	0.33	–0.04	0.01	–		
Variability (SD)	0.70 (0.27)	0.21	1.44	0.25	0.01	0.05	0.07	0.29	–	
Instability (MSSD)	0.56 (0.47)	0.06	2.19	0.26	0.01	0.03	0.03	0.15	0.90	–

Note. HDRS0 = baseline Hamilton Depression Rating Scale; SD = Standard Deviation; MSSD = Mean Square Successive Difference. Significant correlations ($p < .05$) are marked in **bold** and p -values reported in text. Negative affect measures are calculated over the within-persons negative affect variables.

Analysis 1: predicting rate of symptom improvement during treatment

Neither instability nor variability in NA were predictive of a steeper rate of symptom response during treatment (see Table 2, Analysis 1). However, baseline HDRS score and Mean NA were significant predictors, with more severe symptoms at baseline and higher levels of daily NA relating to a stronger rate of treatment response. Entering both HDRS0 and Mean NA in a multi-predictor model led the significant interaction with Time to disappear for both predictors.

The main effects for baseline HDRS score and Mean NA were significant in both the single- and multi-predictor models, indicating that, on average, more severe symptoms at baseline and higher Mean NA were associated with higher symptom levels during the five months of treatment (see Table 2, Analysis 1).

Analysis 2: predicting remission status

In the single-predictor models, a lower Mean NA predicted remission status within the 18-month study period. With an inverse odds ratio of 0.48 this meant 2.1 times higher odds of *not* remitting per one unit increase in Mean NA. No significant associations were found between remission status and NA instability, NA variability or any of the other predictors (see Table 2, Analysis 2). With only one significant predictor, no multi-predictor was warranted.

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Table 2. The predictive value of negative affect dynamics and baseline variables on the linear rate of change in HDRS scores over five months (Analysis 1), and on remission status (Analysis 2).

Analysis 1: HDRS over time

Single-predictor models		Main effects		Predictor interaction with time slope	
		Estimate (SE)	<i>p</i>	Estimate (SE)	<i>p</i>
Model 1	HDRS0	0.95 (0.31)	.003	−0.20 (0.09)	.035
Model 2	SD NA	−1.59 (4.92)	.794	−1.41 (1.52)	.355
Model 3	MSSD NA	−2.48 (2.90)	.398	−0.33 (0.95)	.732
Model 4	Mean NA	3.82 (1.21)	.003	−0.77 (0.38)	.044
Model 5	Duration	0.10 (0.05)	.057	−0.01 (0.02)	.415
Model 6	Episode	−0.83 (2.62)	.753	0.22 (0.78)	.781
Model 7	Family history	−0.61 (2.60)	.817	−0.62 (0.77)	.421
Multi-predictor model		HDRS0	.017	−0.16 (0.10)	.106
		Mean NA	.016	−0.60 (0.39)	.130

Analysis 2: Remission status

Single-predictor models		Log odds	OR	95% CI	<i>p</i>
Model 1	HDRS0	0.07	1.07	[0.89, 1.27]	.470
Model 2	SD NA	2.31	10.10	[0.49, 209.99]	.135
Model 3	MSSD NA	1.88	6.58	[0.54, 80.85]	.141
Model 4	Mean NA	−0.74	0.48	[0.23, 0.99]	.046
Model 5	Duration	−0.01	0.99	[0.96, 1.02]	.436
Model 6	Episode	0.17	1.18	[0.32, 4.41]	.807
Model 7	Family history	0.46	1.58	[0.43, 5.78]	.486

Note: HDRS: Hamilton Depression Rating Scale; HDRS0: baseline HDRS; SD: Standard Deviation; NA: Negative Affect; MSSD: Mean Square Successive Difference; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval; significant *p*-values are marked in **bold**.

Including HDRS baseline symptom severity (HDRS0) as a covariate in these analyses led to the same conclusions. Analysis 1: Level 1: *N* = 195, Level 2: *N* = 46. Estimates are the main effects and interaction with Time of single-predictor models 1–7 and one multi-predictor model that includes the predictors that had a significant interaction with Time. In each model, Time as the HDRS-observation number was entered as a level 1 predictor. All level 2 predictors were grand-mean centred.

Analysis 2: Remission (*N* = 33) = HDRS score ≤ 7 within the study period of 18 months; No remission (*N* = 13). The reference group (0) is No remission. OR > 1 indicates the odds are higher to reach remission over 18 months per one unit increase on a given predictor. OR < 1 indicate an inverse relationship (lower odds of remission), the inverse odds can be calculated as 1/OR. All predictors were grand-mean centred.

Post hoc: exploring Mean NA as a predictor of steeper slopes over time and non-remission

Analysis 1 and 2 showed apparently opposite effects for Mean NA – *higher* levels were related to a steeper symptom improvement slope, while *lower* NA levels were related to reaching remission within 18 months. Therefore, we decided to visualize the random intercepts and slopes in HDRS measurements over five months as predicted by Mean NA (Analysis 1 – model 4), split for remitters and non-remitters (see Figure 2). Remitters' HDRS scores declined on average ($n = 33$, $\beta = -0.40$) over the five months of treatment, while non-remitters showed increasing symptoms on average ($n = 13$, $\beta = 1.03$). Within the remitter group, subjects with Mean NA values above the within-group average had a more strongly⁴ negative slope ($\beta = -0.80$) than those with a Mean NA below the group average ($\beta = -0.15$).

Figure 2. The random intercepts and slopes per subject as predicted by mean Negative Affect measured before treatment (Analysis 1 – model 4). The split in remitters (1) and non-remitters (0) was applied only for the visualisation and was not part of the analysis. The thicker lines are the average slopes for each group: Remission within 18 months ($n = 33$, $\beta = -0.40$), and non-remitters ($n = 13$, $\beta = 1.03$).

⁴ Descriptive comparison, not statistically tested.

Discussion

The aim of this study was to examine whether instability, variability and the Mean of daily NA were indicative of a stronger rate of treatment response, and of remission status over eighteen months. We did not find instability or variability to be predictive of the rate of symptom change over five months; only a higher Mean NA and baseline HDRS score significantly predicted a steeper decrease in HDRS scores over time. A lower Mean NA predicted reaching remission status within the 18-month study period, while neither the NA dynamics nor baseline predictors were related to remission status.

We hypothesized that NA dynamics would be associated with depressive symptom change during treatment and with reaching remission during eighteen months follow-up, yet neither variability (SD) nor instability (MSSD) of NA showed the expected effect. Rather, it appears that mean-levels of NA were a better predictor of depressive change. In addition to the positive association to the rate of symptom improvement over five months of treatment, higher Mean NA was, on average, predictive of higher HDRS-rated symptom levels over five months, and Mean NA was positively correlated with a longer duration of complaints at baseline. It seems plausible that experiencing higher levels of NA in daily life is an indicator that concurrent symptoms are more severe (Bosley et al., 2019; Panaite et al., 2020; Sperry et al., 2020), and there is, consequently, more room for improvement during treatment. This is supported by Husen *et al.* (2016) and Bosley *et al.* (2019) who both found baseline symptom severity to be related to stronger treatment response (for antidepressant treatment, there are mixed findings; cf. Fournier et al., 2010; Friedman et al., 2012). Notably, in the single-predictor models of both analyses, we found Mean NA to be predictive of depressive improvement even after controlling for baseline symptom severity. Moreover, the correlation between HDRS0 and Mean NA was unexpectedly low. This suggests that Mean NA has some unique predictive

value and may measure an aspect of baseline symptom severity that is not captured by the HDRS. However, there was at least some overlap, since adding baseline symptom severity and Mean NA together in the multi-predictor model of rate of symptom change led both effects to become non-significant.

Simultaneously, we found that higher Mean NA was related to *not* reaching remission status within the 18 months follow-up in our sample. Although our results appear to be conflicting, both these findings suggest that Mean NA may be a close reflection of current symptom levels. If a higher Mean NA indicates more severe concurrent symptoms and more room to improve (a steeper slope), then a lower Mean NA before treatment may similarly indicate that symptoms are less severe, and consequently that the remission threshold is closer and more readily reached within the follow-up period (even with a weak decline in symptoms over time). That both effects could be true at the same time was observed in our *post hoc* descriptive examination of the random slopes from Analysis 1: remitters showed lower symptom severity than non-remitters, and within the group that reached remission within 18 months, subjects that had a higher Mean NA relative to the within-group mean showed a stronger negative slope on average than remitters with Mean NA below the within-group mean. However, with both high and low levels of NA relating to depressive improvement, it is difficult to interpret a patient's daily life NA at face-value, and the clinical utility of measuring NA prior to treatment may be limited.

Our findings add to the debate on the importance of accounting for mean-levels of NA when relating momentary-measured mood indices to depression (Dejonckheere et al., 2019; Ebner-Priemer et al., 2009). Indices like the SD and MSSD are often dependent on the mean, which can complicate their interpretation, and reduce the predictive effect of these dynamic measures when combined with the mean in a statistical model (Bos et al., 2018; Dejonckheere et al., 2019; Koval et al., 2013). We had intended to test this overlap in our data but were unable

due to the non-significant effects. However, the SD and MSSD of NA were highly correlated in our sample, and only the SD was (marginally) significantly correlated with the mean of NA. Though speculative, it could be that we did not find the MSSD and SD to be predictors of change in depression symptoms because they were not (as strongly) correlated with the mean as in previous studies.

At this time, the evidence regarding NA dynamics and treatment response is inconclusive. Similar to our findings, Bosley *et al.* (2019) found no relationship between NA dynamics and change in pre- to post-treatment depression symptom scores. However, Husen *et al.* (2016) found lower instability of daily NA predicted stronger early response rates to CBT treatment. Two out of three empirical studies show no association between NA dynamics and treatment response, yet with so little evidence it is not yet possible to draw any firm conclusions about the utility of NA dynamics in predicting change in depression symptoms.

Design differences between studies hinder a more general interpretation of these findings. First, the number of measurements within the day will affect a time-dependent variable such as the MSSD, and there is insufficient knowledge about what the optimal time between measurements is to capture affect instability in depression (Helmich *et al.*, 2021; Koval *et al.*, 2013). In our study, EMA measurements were ten times daily, every 90 minutes on average, versus four measurements a day, at 240-minute intervals for Bosley *et al.* (2019) and Husen *et al.* (2016). Shorter intervals and higher sampling frequency may capture moment-to-moment changes in NA more closely, and may give more reliable estimates of the spread of scores throughout the day expressed in the SD and MSSD (Ebner-Priemer *et al.*, 2009; Jahng *et al.*, 2008).

Second, it seems reasonable that the relationship between NA dynamics and symptom response is sensitive to *when* in the treatment process NA is measured. Whereas Bosley *et al.* (2019) and our study measured NA dynamics directly before treatment, Husen *et al.* (2016)

measured it on average 2.3 months before the start of treatment. Capturing daily NA dynamics directly before treatment versus while a patient is on the waitlist several months before treatment, may have been sufficiently different contexts that it could have affected the study findings.

Third, an important reason our design may have had limited ability to replicate the findings of Husen *et al.* (2016) is that we examined the rate of symptom change over five *months*, whereas they investigated the first five *weeks* of treatment. While the theoretical rationale of instability and variability representing the kind of destabilization that precedes state changes in dynamical systems has shown promise in some studies (although the SD did not predict depressive change in Curtiss *et al.*, 2021; cf. Olthof *et al.*, 2020; Wichers *et al.*, 2020), it may be that the time span over which such dynamics are predictive of change is much shorter than the five to eighteen months studied in our sample (Strunk & Lichtwarck-Aschoff, 2019). Moreover, the monthly symptom interviews may have been too far apart in time to adequately capture and predict the many early symptom changes our sample showed. A study design with more frequent assessments of symptoms and NA dynamics over a longer period of time during treatment is necessary to determine how NA instability and variability relate to depressive symptom improvements (Hayes & Andrews, 2020; Helmich *et al.*, 2021).

Finally, our study differs from the previous in terms of the treatment modality. In the studies of Husen *et al.* (2016) and Bosley *et al.* (2019), patients received CBT, whereas patients in our study entered into a combination of supportive and pharmacotherapy. From a dynamical systems perspective, we would expect instability and variability to serve as generic indicators of destabilization and response potential, with no special importance for the particular form of therapy that encourages change to an improved state (Gelo & Salvatore, 2016). Additionally, pharmacotherapy has shown to be equally effective to CBT (for a meta-analysis, see Roshanaei-Moghaddam *et al.*, 2011), and more often elicited early response compared to CBT

(Kelley et al., 2018). In sum, although the treatment modalities were different from the other studies, we may have expected the rate of improvement during treatment to be very comparable and not likely to result in differing conclusions.

Strengths of the study are that we tested the predictive capacity of dynamic variables independently first, to account for multi-collinearity. We also expanded on earlier studies by examining remission status over the course of eighteen months. With our sample size and model specification being consistent with Husen *et al.*, we expected the power to detect an effect to be similar in our multilevel analyses. For the logistic regression, a sensitivity analysis in G*Power 3.1 suggested that with the current sample size ($N = 46$) we had 80% power to find an OR of 2.75 or larger. However, our sample size is modest and could have limited our ability to find smaller effects. Similarly, the variation in the SD and MSSD variables was limited, which likely diminished our power to detect a true effect, particularly in the logistic regression (as indicated by the large confidence intervals of those predictors).

In conclusion, future studies could aim to elucidate to what extent the relationship between NA dynamics, mean-level NA and later improvement in depression is sensitive to various measurement timings: how far in advance the EMA measurements are collected, the number of and time interval between NA observations within the day, as well as between symptom assessments. To resolve the inconclusive evidence of NA dynamics, replication in a larger sample is warranted. Finally, it may be clinically relevant to further study mean-levels of NA measured at baseline as a predictor of depressive symptom improvement during treatment and long-term follow-up, as it may provide predictive information beyond baseline symptom severity.

Declaration of interest

The authors report no conflict of interest

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Contributions / CRediT statement

MAH.: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft

MW.: Conceptualization, Methodology, Supervision, Writing – review & editing

FP: Data curation, Investigation, Resources, Writing – review & editing

ES: Conceptualization, Methodology, Supervision, Writing – review & editing

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