Deconstructing depression: unified syndrome or groups of symptoms?

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Chapter 3

Neuroticism and chronicity as predictors of 9-year course of individual depressive symptoms

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Abstract

Background: The large between-person differences in symptomatology suggest that Major Depressive Disorder (MDD) is a heterogeneous psychiatric disorder. However, symptom-specific prospective studies are scarce. We hypothesized that chronicity (i.e., being depressed for 24 months during a patient's preceding 48 months at baseline) and neuroticism at baseline would predict adverse course trajectories over 9 years of follow up with differential magnitudes for individual depressive symptoms.

Methods: In total, 560 patients with a current MDD were included from the Netherlands Study of Depression and Anxiety (NESDA-cohort). We used a multivariate linear mixed model with repeated measures, with a history of chronicity and neuroticism separately as main independent variables and with Inventory of Depressive Symptomatology self-report (IDS-SR) item scores as outcome variables. For each individual symptom, the model was adjusted for age, gender, and baseline depression severity.

Results: Patients were on average 42.7 (*SD* = 12.1) years old and 64.7% were women. Patients with chronic depression or high levels of neuroticism showed similar absolute rates of decline over time compared to their counterparts. However, because symptoms had higher starting points for mood, cognitive, and somatic/vegetative symptoms (in that order), symptom severity remained higher over time. Chronicity and neuroticism were especially linked to persistent low self-esteem and high interpersonal sensitivity.

Limitations: Neuroticism is partly state dependent and likely affected by depression severity.

Conclusions: Chronicity and neuroticism predict long-term persistence of diverse psychiatric symptoms, in particular low self-esteem and high interpersonal sensitivity.

Highlights

1. A history of chronic depression and level of neuroticism are associated to similar symptom profiles

2. Chronic depression is associated to mood and cognitive symptoms and to a lesser extent to somatic/vegetative symptoms

3. Neuroticism is associated to mood and cognitive symptoms but on average not to somatic vegetative symptoms

4. Patients with chronic depression and/or high levels of neuroticism report particularly on low self-esteem and high interpersonal sensitivity items. This may be of importance in the development of personalized treatment.

3.1 Introduction

Major Depressive Disorder (MDD) is a heterogeneous psychiatric illness with large between-person differences in both symptomatology and course trajectories [1, 2]. Although several predictive variables have been established for a more chronic course, most feature low predictive power [e.g., 3, 4]. Of these, 'preceding chronic depression' and a 'high level of neuroticism' are two of the stronger predictors [5, 6]; however, their predictive value diminishes after adjusting for baseline severity scores, which may serve as an intermediary factor [6-8]. It is currently unknown whether chronicity or neuroticism affect the course of symptoms equally, or affect a particular subset of symptoms, but not others. Moreover, the importance of symptom-specific research is beginning to emerge in the field of psychiatry (Fried and Nesse, 2015).

A previous analysis in the Netherlands Study of Depression and Anxiety (NESDA) demonstrated that MDD persisted over the course of 4 years in 53.0% of the patients with chronic MDD at baseline versus 27.8% of patients with nonchronic MDD at baseline; this is consistent with findings from others [3, 6, 9-12]. Acknowledging the importance of a preceding depressive course led to the addition of persistent depressive disorder (i.e. a combination of dysthymia *and* chronic depression) in the DSM-5 [13].

Neuroticism is one of the five major dimensions of personality (Five Factor Model; FFM; Costa and McCrae, 1992) and reflects the tendency to respond to distress by being moody, anxious, or sad. High neuroticism increases the risk of MDD, its unfavorable course, and a higher relapse rate [5, 14-22].

Chronic depression and neuroticism seem to be linked, i.e. chronically depressed patients generally show higher levels of neuroticism than patients with an episodic depressive course [5, 23-26]. Also, neuroticism represents a trait-like substrate in chronic depression and is more state-dependent when the depression has an episodic course, regardless of eventual depression remission [22]. Because of their associations with early onset, childhood maltreatment, Cluster C personality disorders, and genetics [27-30], neuroticism and chronic depression may share etiological factors [22] and thus represent partly overlapping constructs [22].

Most research has focused on MDD as a latent variable construct, representing a single underlying disorder, where the level of severity is measured as a sum score on self-report questionnaires [e.g. 31, 32, 33]. However, given the heterogeneous nature of MDD, focusing on individual symptoms (rather than on sum scores) may yield important new insights into the relationship between history of chronicity, personality traits, and the course of MDD [1, 5, 21].

Previous cross-sectional studies conducted in a nonclinical sample found that risk factors correlated with individual depressive symptoms with different strengths [34-37]. Two studies analyzed chronicity and neuroticism in relation to MDD symptom profiles in clinical samples. One cross-sectional study examined the symptom-specific associations with both neuroticism and chronicity among 1,015 MDD patients [38]. Fatigue and suicidal ideation were significantly associated with chronicity, and appetite/weight and sleeping problems were associated with neuroticism [38]. The second prospective study, with 20 years of follow-up, examined the symptom profiles of 450 MDD patients [39]. Patients with long-term depression more frequently reported symptoms of disturbed memory, low self-esteem, hopelessness, fear of everyday tasks, fear of being alone, and suicidal ideations [39]. We are not aware of previous studies that have analyzed the predictive value of neuroticism and chronicity for the course of individual depressive symptoms in patients with MDD. Such findings might increase our ability to target (psychotherapeutic) treatment strategies earlier and, more specifically, on certain symptom patterns.

The present study aimed to examine whether chronic MDD, defined as being depressed for at least 2 years (during a patient's past 4 years before baseline) and level of neuroticism could predict the 9-year trajectory of individual depressive symptoms. In particular, the focus was on the symptom-specific differences in this regard. It was hypothesized that chronic MDD and neuroticism at baseline would be associated with the course of some specific symptoms, rather than depression as a homogeneous construct, with similar associations for each symptom. Because previous studies suggested that chronic depression and neuroticism may represent overlapping constructs, we expected these variables to be associated with the same depressive symptoms over time. Further, we hypothesized that the average severity of mood and cognitive MDD symptoms would tend to remain at a higher average level in the presence of chronicity and neuroticism at baseline.

3.2 Materials and Methods

3.2.1 Study sample and procedures

Participants were selected from the Netherlands Study of Depression and Anxiety (NESDA) cohort. A detailed description of the NESDA design and sampling procedures is published elsewhere [40]. The first wave (baseline) started in 2004 and ended in 2007, and the sixth wave of measurement at the 9-year follow-up finished in 2016. The Composite International Diagnostic Interview (CIDI WHO, version 2.1) was used to assess the presence of depressive and anxiety disorders according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; Wittchen, 1994). The baseline sample (*n* = 2,981) consisted of patients with anxiety and/or depressive disorders and normal controls. Postbaseline, follow-up assessments were conducted at 1 year (*n* = 2,445; 82.0%), 2 years (*n* = 2,596; 87.1%), 4 years (*n* = 2,256; 80.6%), 6 years (*n* = 2,256; 75.7%), and 9 years (*n* = 2,069; 69.4%) (Penninx et al., 2008).

For the present study, we selected all patients who met DSM-IV criteria for MDD within one month prior to the baseline assessment. Furthermore, our patients needed to have completed the Inventory of Depressive Symptomatology-Self-Report (IDS-SR; see Measures) for at least four of the six time point assessments, which needed to include the baseline assessment. This resulted in a study sample of 558 participants. Because of some missing items, the two subsets differed in sample size: *n* = 550 participants for the analysis of chronicity and *n* = 553 for the analysis of neuroticism.

3.2.2 Measures

3.2.2.1 Independent variables: Chronic depression and neuroticism

Chronic depression at baseline was measured using the Life Chart Interview method [41], a standardized interview designed to retrospectively assess the course of psychopathology. The Life Chart Interview uses age- and calendar-linked life events over a patient's past 4 years and then assesses the presence and severity of symptoms during this period. When patients were depressed for ≥ 50% during and between these life events, they were defined as being chronically depressed [29]. This is similar to the DSM-5 criteria for persistent depressive disorder, which states that criteria for MDD should be met for at least 2 years with a maximum of 2 months without symptoms [13].

Neuroticism was assessed at baseline using the NEO five-factor inventory (NEO-FFI), i.e. the 60-item version of the longer 240-item NEO Personality Inventory Revised (NEO-PI-R). The NEO-FFI consists of five factors that measure the Big Five personality traits: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience. Neuroticism was assessed with 12 aggregated items on a 5-point scale, ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The NEO-FFI scale has good internal and test-retest reliability [42] and is a valid instrument for both clinical and healthy samples [43, 44]. Although neuroticism is generally considered to be a trait throughout a person's life, it is also known to have state dependencies (Spinhoven, Does, Omel, Zitman, and Penninx, 2013). When assessing the interclass correlation coefficients (ICCs) of neuroticism between baseline, 2-year and 4-year follow-up, we found an ICC value of 0.672 ($F = 3.05$, $p < .001$), suggesting moderately high interclass correlations. Note that only the baseline level of neuroticism was used as predictor variable.

3.2.2.2 Dependent variables: IDS items

The individual item scores of the Inventory of Depressive Symptomatology Self-Report (IDS-SR) were used as the outcome measure for severity and course of depressive symptoms [31, 32]. The IDS-SR consists of 30 equally weighted items, rated on a 4-point Likert scale (0-3). The scale includes all symptoms of depression including melancholic, atypical, and anxious symptoms. Moreover, several additional symptoms have been added, for example, sympathetic arousal, pessimism, and interest in sex. The IDS-SR has adequate reliability, acceptable validity, good responsiveness, and good discriminative ability with Cronbach's alphas ranging from 0.92-0.94 [32]. In the present study sample, the Cronbach's alphas were 0.83, 0.89, 0.89, 0.90, 0.90, and 0.90 for the six time points from baseline to the 9-year follow up. Alphas were only slightly different for patient groups with chronic, nonchronic, high neuroticism (above median 43), or low neuroticism (below median 43), with Cronbach's alphas at baseline equaling 0.80, 0.85, 0.77, and 0.83, respectively. Note that these Cronbach's alpha values need to be interpreted with caution because they are not particularly well suited for ordinal data and tend to increase when questionnaires contain a larger number of items (Sijtsma, 2009). Items 11/12 ("increased/decreased appetite") and Items 13/14 ("weight gain/weight loss") contain opposite features. In order to maintain psychometric similarity between items, these item pairs were combined into one ordinal item, yielding 28

items for the current analyzes [32]. We applied previously identified symptom clusters in our results, including 10 mood symptoms, 14 somatic/vegetative symptoms, and four cognitive symptoms [see also Figures 1 and 2; 45].

3.2.3 Statistical analysis

Using chi-square analysis for categorical variables and independent t-tests for continuous variables, we evaluated and described baseline clinical characteristics and demographic variables across patients with chronic/nonchronic depression and high/low levels of neuroticism. For this purpose, neuroticism was dichotomized using a median split (median = 43); however, in all subsequent analyzes, neuroticism was analyzed as a continuous variable. A multivariate linear mixed model with repeated measures was used, with item score as the outcome variable and chronicity or neuroticism as the main independent variables. The models were adjusted for age, gender, and baseline depression severity. Because of positively skewed distributions, we $\log_e$ transformed the dependent variable scores and $\log_e$–$\log_e$ transformed time, which improved the fit of our linear models. These analyzes were repeated for each individual symptom separately, once with chronicity as the main independent variable and once with neuroticism as the main independent variable. Because this resulted in statistical tests for each of the 28 items, our outcomes were adjusted for multiple testing using the Bonferroni correction, which yielded a critical significance level of p = .002. Moreover, additional analyzes were computed per item in which we adjusted the effects of chronicity by adjusting for neuroticism and vice versa. This resulted in the predictive values of chronicity and neuroticism independent from each other. In order to yield beta coefficients that can be compared between symptoms, all outcome and independent variables were standardized (i.e., *z* scores). Our analyzes focused on the standardized difference of severity (SDS) as the outcome measure, which represents the difference (units of *SD*s) of each of the symptoms between patients with chronicity and patients with higher levels of neuroticism (continuous, in units of *SD*s) compared to their counterparts. Subsequently, forest plots with SDS values and error bars representing standardized errors (SE) were assigned to each individual symptom and sorted by the symptom cluster [45] and SDS value. Analyzes were performed using SPSS, version 23.

3.3 Results

3.3.1 Sociodemographic characteristics at baseline

Characteristics of the study sample are presented in Table 1. At baseline, age ranged from 18-64 (mean 42.7, *SD* = 12.1) years, and 64.7% were women (*n* = 362). Also, at baseline, the mean sum IDS-SR score was 34.6 (*SD* = 11.1), indicating a moderate depression severity in our patients. The level of neuroticism was 3.02 points (SE 0.57; standardized difference: 0.463) higher for patients with a chronic depression at baseline, resulting in a significant t-test for independent samples (t = 5.31, p < .001). Of the 558 included patients, 204 had a history of chronic MDD and 281 experienced high levels of neuroticism (> 43). In the whole sample, 21.5% had both a chronic depression and a neuroticism level above the median.

Table 1. Sociodemographic and clinical characteristics

	Chronic depression (N= 204)	Non-chronic depression (N=346)	t/chi-square	p	Neuroticism score >43 (N= 272)	Neuroticism score <43 (N=281)	t/chi-square	p
Age in years (mean, SD)	44.84 (11.79)	41.31 (12.18)	5.71	**0.017**	40.61 (11.88)	44.72 (12.12)	0.04	0.848
Female (%)	64.04	65.90	0.27	0.606	69.12	61.21	3.80	0.051
North-European ethnicity (%)	93.14	96.53	3.28	0.070	97.06	93.95	3.09	0.079
Education level (%)			3.15	0.208			8.99	**0.011**
Elementary or lower	9.31	5.49			4.63	4.63		
General intermediate or secondary	65.20	66.18			68.75	62.99		
College or university	25.49	28.32			22.43	32.38		
Psychotherapy*, yes (%)	76.56	75.46	0.01	0.920	80.68	69.77	4.99	**0.025**
Comorbid anxiety disorder, yes (%)	74.02	60.11	11.34	**0.003**	77.94	52.67	38.85	**<0.001**
Chronic depression, yes (%)	100	0			43.87	29.89	10.74	**0.001**
Total score IDS								
Baseline	37.99 (10.77)	32.40 (10.93)	5.99	**<0.001**	39.40 (9.91)	29.66 (10.31)	11.46	**<0.001**
year 1	30.36 (12.78)	23.43 (12.00)	6.03	**<0.001**	30.71 (12.86)	21.45 (10.81)	8.71	**<0.001**
year 2	28.61 (13.04)	21.93 (11.51)	6.20	**<0.001**	27.96 (12.60)	21.05 (11.46)	6.67	**<0.001**
year 4	27.28 (13.45)	22.01 (12.69)	4.50	**<0.001**	27.18 (13.04)	20.63 (12.51)	5.92	**<0.001**
year 6	27.59 (13.38)	20.94 (12.41)	5.55	**<0.001**	27.46 (13.03)	19.44 (12.08)	7.07	**<0.001**
year 9	26.99 (13.72)	19.75 (11.81)	5.77	**<0.001**	26.66 (12.94)	17.85 (11.32)	7.59	**<0.001**
Neo-FFI								
Neuroticism score (mean, SD)	44.64 (5.85)	41.62 (6.73)	5.71	**0.017**	48.04 (3.32)	37.64 (4.62)		
Extraversion score (mean, SD)	30.18 (6.32)	33.88 (6.44)	0.48	0.490	29.99 (6.30)	34.85 (6.10)	0.02	0.876
Openness (mean, SD)	37.48 (6.78)	38.37 (5.11)	3.46	0.063	37.88 (6.53)	38.22 (5.80)	3.96	**0.047**
Agreebleness (mean, SD)	42.25 (5.52)	43.10 (5.11)	1.82	0.178	42.08 (5.49)	34.54 (4.97)	1.59	0.208
Conscientiousness (mean, SD)	37.42 (7.21)	39.88 (6.26)	1.08	0.300	36.76 (6.46)	41.11 (6.24)	0.28	0.598
Antidepressants								
TCA (%)	9.62	2.31	2.72	0.099	4.04	2.49	1.06	0.304
SSRI (%)	37.26	26.01	7.70	**0.006**	33.09	27.40	2.12	0.145
Other (%)	10.11	12.26	0.60	0.437	13.96	8.87	2.25	0.133
no AD (%)	42.01	59.42	15.85	**<0.001**	48.94	61.24	6.59	**0.010**

Note. AD = antidepressants. TCA = tricyclic antidepressants. SSRI = selective serotonin reuptake inhibitors. AD = antidepressants. TCA = tricyclic antidepressants. Patients are selected twice, once for chronic/nonchronic depression and once for high/low neuroticism. Sample size is unequal due to missing items. Chi-square = Pearson Chi-square, two-sided.

* Due to missing values, assessed in 62.8% of sample

3.3.2 Chronic depression

Patients with a chronic depression at baseline were older, had higher neuroticism scores, and were more likely to use antidepressants than patients with no chronic depression at baseline (Table 1).

Chronic MDD was independently associated with a higher severity of depression over the course of 9 years (i.e., IDS scores adjusted for age, gender, and baseline depression severity; SDS = 0.131, t = 11.023, p < .001). This translated into a 0.131 *SD* higher average score for each of the 28 IDS items. In general, highly parallel courses were found for both chronically and nonchronically depressed patients. Although, the interaction terms between time and chronicity were significant, the effect sizes were small and deemed not clinically important (interaction = –0.022, t = 4.30, p = .012). Symptom-specific course trajectories are presented in Figure 1 of the supplementary material. When we adjusted the effect of a history of chronic depression for baseline neuroticism, this main effect remained significant (SDS = 0.078, t = 6.467, p < .001).

Next, we analyzed putative differential effects of chronicity on the 9-year course of 28 IDS items (Table 2 and Figure 1). Important differences emerged, i.e. the SDS ranged from –0.080 (“weight”) through 0.275 (“view of myself”). All individual symptoms showed on average a higher severity for patients with chronic MDD compared to nonchronic MDD, except for “weight” (i.e., Item 12). All mood and cognitive symptoms were more severe in patients with chronic depression, especially interpersonal sensitivity and low self-esteem. Chronicity was less related to somatic/vegetative symptoms, of which only about half the symptoms were more severe for chronic patients. When using the Bonferroni-corrected critical level of significance of .002, significant associations were found with four of four cognitive symptoms, six of 10 mood symptoms, and three of 14 somatic/vegetative symptoms. When adjusting the associations of chronicity with individual symptoms for level of neuroticism at baseline, the outcomes remained largely significant for most symptoms, except for Items 6 “feeling irritable,” 10 “quality of mood,” 19 “general interest,” and 27 “panic/phobia” (Table 2).

Table 2. IDS symptoms in ralation to chronicity and neuroticism

	Baseline mean item score (SE)				Chronic			Neuroticism		
Item	Chronic	Non-chronic	High N	Low N	Crude SDS	p	Adjusted SDS	p	Crude SDS	p	Adjusted SDS	p
1. Falling asleep	1.515 (0.08)	1.234 (0.06)	1.433 (0.07)	1.208 (0.07)	0.121 (0.08)	0.118	0.090 (0.08)	0.258	0.035 (0.04)	0.424	0.034 (0.04)	0.448
2. Sleep during the night	1.683 (0.08)	1.634 (0.06)	1.663 (0.06)	1.475 (0.07)	0.007 (0.06)	0.906	-0.015 (0.06)	0.797	-0.025 (0.03)	0.448	-0.012 (0.03)	0.683
3. Waking up too early	0.744 (0.08)	1.516 (0.05)	0.780 (0.06)	0.668 (0.07)	0.021 (0.06)	0.748	-0.017 (0.07)	0.791	0.050 (0.04)	0.172	0.048 (0.04)	0.202
4. Sleeping too much	0.727 (0.06)	0.635 (0.04)	0.701 (0.05)	0.627 (0.05)	0.031 (0.06)	0.598	0.015 (0.06)	0.804	-0.011 (0.03)	0.750	-0.009 (0.03)	0.801
5. Feeling Sad	1.898 (0.06)	1.497 (0.04)	1.896 (0.05)	1.362 (0.05)	0.247 (0.05)	<0.001	0.179 (0.05)	<0.001	0.165 (0.03)	<0.001	0.155 (0.03)	<0.001
6. Feeling irritable	1.456 (0.06)	1.375 (0.05)	1.651 (0.05)	1.117 (0.05)	0.122 (0.06)	0.018	0.045 (0.05)	0.374	0.144 (0.03)	<0.001	0.143 (0.03)	<0.001
7. Anxious or tense	1.620 (0.06)	1.355 (0.04)	1.708 (0.04)	1.156 (0.05)	0.195 (0.05)	<0.001	0.113 (0.05)	0.021	0.183 (0.03)	<0.001	0.174 (0.03)	<0.001
8. Response of mood	1.186 (0.07)	0.893 (0.05)	1.192 (0.05)	0.781 (0.05)	0.176 (0.05)	<0.001	0.120 (0.05)	0.018	0.044 (0.03)	0.116	0.033 (0.03)	0.246
9a. Mood in time of day	0.654 (0.07)	0.717 (0.07)	0.755 (0.06)	0.638 (0.06)	0.041 (0.06)	0.499	0.010 (0.06)	0.868	0.041 (0.03)	0.229	0.042 (0.03)	0.226
10. Quality of mood	1.743 (0.06)	1.634 (0.05)	1.780 (0.05)	1.538 (0.07)	0.138 (0.06)	0.016	0.075 (0.06)	0.194	0.085 (0.03)	0.008	0.080 (0.03)	0.014
11. Appetite	1.093 (0.07)	1.067 (0.05)	1.274 (0.06)	0.832 (0.05)	0.044 (0.05)	0.420	-0.023 (0.05)	0.672	0.052 (0.03)	0.086	0.060 (0.03)	0.052
12. Weight	1.045 (0.07)	1.052 (0.06)	1.102 (0.06)	0.976 (0.06)	-0.080 (0.05)	0.134	-0.105 (0.05)	0.056	-0.011 (0.03)	0.726	0.002 (0.03)	0.958
15. Concentration	1.729 (0.06)	1.362 (0.04)	1.715 (0.05)	1.254 (0.05)	0.199 (0.05)	<0.001	0.130 (0.05)	0.010	0.137 (0.03)	<0.001	0.125 (0.03)	<0.001
16. View of myself	1.864 (0.08)	1.452 (0.06)	2.024 (0.06)	1.115 (0.07)	0.275 (0.07)	<0.001	0.144 (0.06)	0.022	0.328 (0.03)	<0.001	0.313 (0.04)	<0.001
17. View of my future	1.576 (0.06)	1.217 (0.04)	1.596 (0.05)	1.074 (0.04)	0.184 (0.05)	<0.001	0.106 (0.04)	0.016	0.174 (0.02)	<0.001	0.167 (0.02)	<0.001
18. Death or suicide	0.921 (0.06)	0.727 (0.05)	0.970 (0.05)	0.597 (0.05)	0.171 (0.05)	0.001	0.111 (0.05)	0.037	0.106 (0.03)	<0.001	0.100 (0.03)	<0.001
19. General interest	1.319 (0.07)	1.118 (0.05)	1.366 (0.06)	0.980 (0.06)	0.098 (0.05)	0.047	0.040 (0.05)	0.414	0.016 (0.03)	0.557	0.017 (0.03)	0.545
20. Energy level	1.804 (0.04)	1.542 (0.04)	1.771 (0.05)	1.490 (0.05)	0.170 (0.05)	<0.001	0.133 (0.05)	0.009	0.005 (0.03)	0.861	0.001 (0.03)	0.981
21. Capacity for pleasure	1.342)0.06)	1.055 (0.04)	1.329 (0.05)	0.961 (0.05)	0.227 (0.05)	<0.001	0.175 (0.05)	<0.001	0.028 (0.03)	0.302	0.016 (0.03)	0.556
22. Interest in sex	1.457 (0.08)	1.182 (0.05)	1.427 (0.06)	1.116 (0.06)	0.243 (0.06)	<0.001	0.194 (0.06)	0.002	0.034 (0.03)	0.330	0.017 (0.04)	0.627
23. Psychomotor retardation	1.275 (0.07)	0.897 (0.05)	1.177 (0.06)	0.798 (0.06)	0.221 (0.05)	<0.001	0.178 (0.05)	0.001	0.016 (0.03)	0.608	0.000 (0.03)	0.992
24. Psychomotor agitation	1.275 (0.07)	1.151 (0.05)	1.328 (0.05)	1.047 (0.06)	0.070 (0.06)	0.248	0.004 (0.06)	0.953	0.118 (0.03)	<0.001	0.119 (0.03)	<0.001
25. Aches and pains	1.515 (0.05)	1.313 (0.05)	1.391 (0.05)	1.371 (0.05)	0.012 (0.05)	0.824	-0.004 (0.05)	0.053	-0.062 (0.03)	0.039	-0.053 (0.03)	0.078
26. Sympathetic arousal	1.167 (0.05)	1.081 (0.04)	1.201 (0.04)	1.008 (0.05)	0.066 (0.05)	0.192	0.029 (0.05)	0.569	0.001 (0.03)	0.965	0.003 (0.03)	0.929
27. Panic/Phobic	1.078 (0.07)	0.945 (0.05)	1.168 (0.05)	0.794 (0.06)	0.143 (0.06)	0.020	0.088 (0.06)	0.062	0.097 (0.03)	0.006	0.090 (0.04)	0.011
28. Constipation/diarrhea	0.941 (0.06)	0.891 (0.05)	0.946 (0.05)	0.868 (0.06)	0.013 (0.06)	0.830	-0.015 (0.06)	0.812	-0.056 (0.03)	0.107	-0.052 (0.04)	0.140
29. Interpersonal sensitivity	1.809 (0.07)	1.342 (0.06)	1.963 (0.06)	1.008 (0.06)	0.261 (0.06)	<0.001	0.172 (0.05)	0.001	0.249 (0.03)	<0.001	0.233 (0.03)	<0.001
30. Leaden paralysis	2.132 (0.06)	1.744 (0.05)	2.020 (0.06)	1.727 (0.07)	0.244 (0.05)	<0.001	0.201 (0.05)	<0.001	0.032 (0.03)	0.254	0.022 (0.03)	0.440

Note. Mean values at baseline, standard deviation (in parentheses) for patients with a history of chronic depression (24 out of 48 months before baseline), high neuroticism levels (above median; >43) and their counterparts. Standardized difference in symptom severity (IDS-SR item scores) represent the beta-coefficients of chronic depression at baseline (dichotomous) and level of neuroticism (continuous z-score) assessed with a mixed model with repeated measures with standardized IDS-SR item-score as outcome variable over the course of 9 years follow-up assessed at 6 time-points. Crude SDS is adjusted for age, gender and baseline depression severity. Adjusted SDS is adjusted for age, gender, baseline depression severity and for either chronicity or neuroticism.

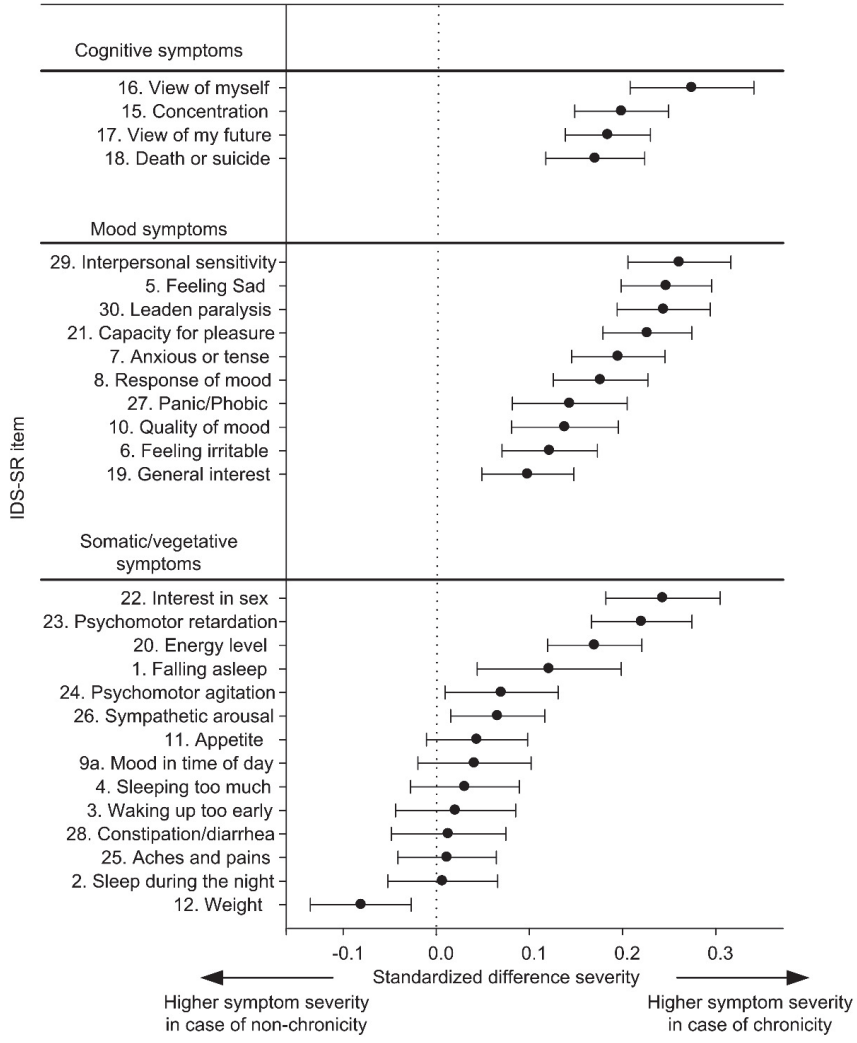

Figure 1. Standardized difference in symptom severity (IDS-SR item scores) according to a history of chronicity (depressed 24 of 48 months before baseline) during the 9-year follow-up. Assessed with linear mixed models with repeated measures and adjusted for gender, age, and baseline MDD severity.

3.3.3 Neuroticism

Patients with higher levels (> 43 score) of neuroticism had lower education levels, were more likely to be chronically depressed, were more likely to use antidepressants, and had higher baseline depression severity than patients with lower levels of neuroticism (Table 1).

High neuroticism was independently associated with a higher severity of depression over the course of 9 years (i.e., IDS scores, adjusted for age, gender, and baseline severity; SDS = 0.071, t = 10.509, p < .001). This translated into a 0.071 *SD* higher average score for each of the 28 IDS items. In general, symptoms in relation to neuroticism mostly followed parallel course trajectories. However, although interaction terms between time and neuroticism were significant, the effect sizes were very small and deemed not clinically important (interaction = 0.014, t = 5.35, p < .001). These parallel course trajectories per item are shown in Figure 2 of the supplementary material. When we adjusted the effect of neuroticism for baseline chronicity, this main effect remained significant (SDS = 0.066, t = 9.766, p < .001).

Next, we compared the effects of neuroticism on the 9-year course across the 28 IDS items (Table 2 and Figure 2). Important differences were found, i.e. the SDS ranged from –0.062 ("aches and pains") through 0.328 ("view of myself"). Most of the individual symptoms were on average more severe in patients with high levels of neuroticism compared to those with lower levels of neuroticism. This was not the case for the five items that were negatively associated with neuroticism (i.e., Items 4, 2, 12, 25, and 28), but only "aches and pains" was significantly different from 0 (Item 25; SDS = –0.062, t = –2.070, p = .039). This indicated that high levels of neuroticism were associated with fewer aches and pains. Neuroticism was strongly related to mood and cognitive symptoms and (to a much lesser extent) to somatic/vegetative symptoms. Particularly patients with high levels of neuroticism were likely to experience low self-esteem and high interpersonal sensitivity. When using the Bonferroni-corrected critical level of significance of .002, significant associations were found with four of four cognitive symptoms, three of 10 mood symptoms, and four of 14 somatic/vegetative symptoms. When we adjusted the associations between neuroticism and individual symptoms for chronicity at baseline, the outcomes again remained largely significant for most symptoms, except for Item 25, "aches and pains" (Table 2).

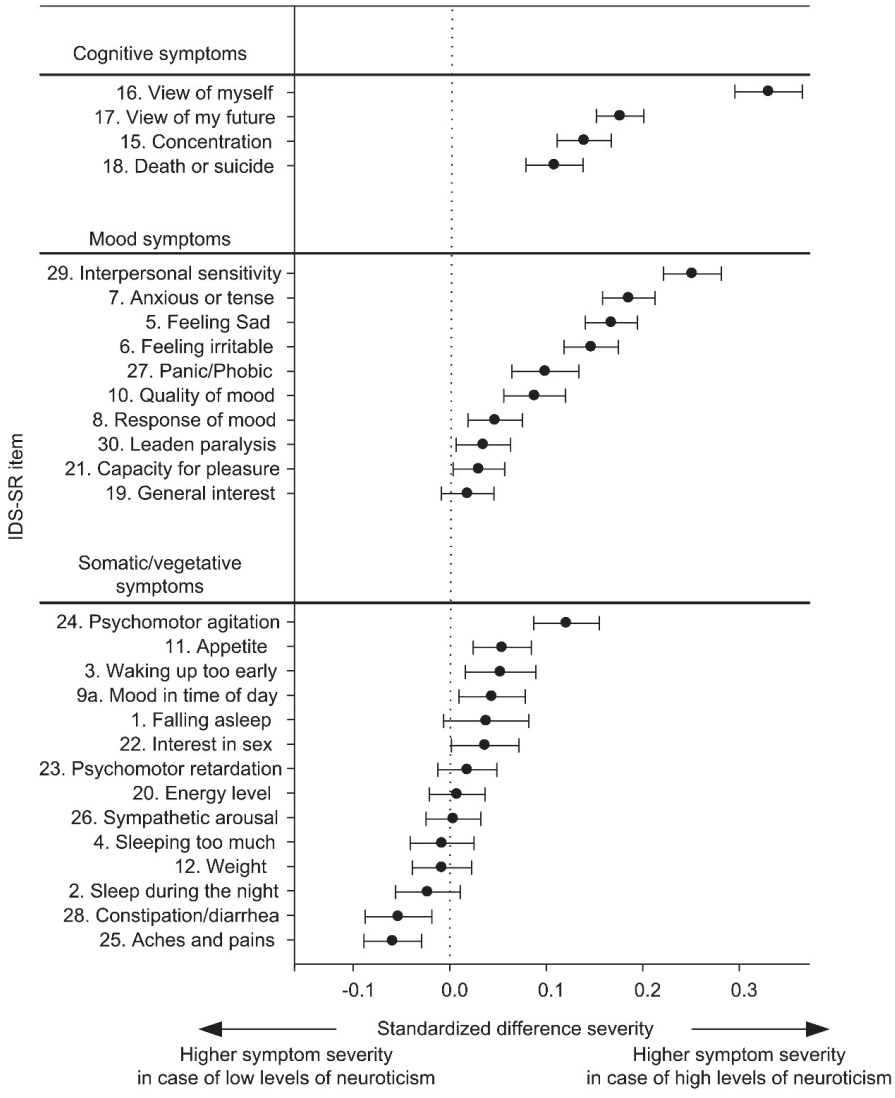

Figure 2. Standardized difference in symptom severity (IDS-SR item scores) according to a 1-*SD* increase in neuroticism at baseline during the 9-year follow-up. Assessed with linear mixed models with repeated measures and adjusted for gender, age, and baseline MDD severity.

3.4 Discussion

The present study found that a history of chronic depression and of neuroticism at baseline was a predictor for the severity of most individual symptoms during 9 years of follow-up, albeit of varying magnitudes. Although the improvements showed parallel trajectories over time, according to chronicity and neuroticism, IDS-SR scores remained higher for patients who initially had chronic depression or higher levels of neuroticism. Findings for the effects of chronicity and neuroticism were remarkably similar, even though only 21.5% of our sample had both a history of chronic depression and a neuroticism score above the median. Although the effects on five of 29 symptoms were no longer significant when adjusting the effects of chronicity for neuroticism and vice versa, both baseline variables independently predicted an adverse course of symptoms of the mood and cognitive symptom clusters, whereas the effects on the somatic/vegetative symptoms were smaller. Chronicity and neuroticism showed the strongest link to 'low self-esteem' (Item 16) and 'interpersonal sensitivity' (Item 29).

Epidemiological research on MDD generally focuses on MDD as a unified syndrome, using a questionnaire sum score as a measure for the level of severity. If depression is truly one unified latent construct, all risk factors would have affected the individual symptoms with similar effect sizes. However, previous cross-sectional studies also found that, at baseline, risk factors such as neuroticism and chronicity (among others) are associated with different individual depressive symptoms [36, 38]. We extended these findings by using a prospective design, which helped to show that the history of chronic depression and neuroticism affects the level of mood and cognitive symptoms, but not somatic/vegetative symptoms. This provides additional epidemiological support for the heterogeneity of individual depressive symptoms [36].

In predictive research, focusing on individual symptoms instead of syndromes may yield important new findings. In this regard, specific emphasis should be given to the strong relationship we found between both chronic depression and neuroticism, and self-esteem and interpersonal sensitivity. The similar results for chronicity and neuroticism in relation to these two symptoms seem to suggest that either these symptoms are core features of MDD or that a third dimension (e.g., general severity of MDD, chronic arousal and stress activation,

or social isolation) underlies the reported relationships or both. Although no longer in practice since the introduction of the DSM-III, our findings are relevant in light of a proposition to revive *neurotic depression*, a subtype of depression which is reactive to life events, persistent, and unlikely to benefit from antidepressants (Nassir Ghaemi, 2008). Our findings concerning low self-esteem and high interpersonal sensitivity may also indicate a possible comorbid avoidant personality disorder (i.e., preoccupation with being criticized or rejected in social situations and feeling socially inept) and dependent personality disorder (i.e., feeling inadequate to take care of oneself and seeking excessive support). Higher rates of Cluster C personality disorders have been reported in chronic versus nonchronic depression (Baldessarini et al., 2017; Russell et al., 2003). Moreover, patients may not meet the criteria for personality disorders after their depressive symptoms are in remission, suggesting an overlap in symptomatology and etiology (Costa et al., 2005; Fava et al., 2002). Low self-esteem and high levels of interpersonal sensitivity can play a role in the overall persistence and relapse of depression [46-49]. Also, a causal relationship may exist between the symptoms [50-52], and targeting key symptoms (i.e., symptoms more central in a causal network) may benefit a patient's recovery. Low self-esteem and interpersonal sensitivity could be key symptoms in patients with chronic depression and high levels of neuroticism.

Multiple evidence-based treatments are available for low self-esteem, such as Competitive Memory Training [COMET; 53, 54] and mindfulness-based cognitive behavioral therapy [55, 56]. Interpersonal sensitivity is an important treatment target in interpersonal therapy [57]. More research is needed to assess if these, or other treatments, could be implemented as symptom-specific treatment methods, and whether a symptom-specific treatment approach is indeed beneficial for the patient.

This study has several strengths. First, the heterogeneous nature of depression was examined in a substantial number of MDD patients by analyzing depression at symptom level over a follow-up period of 9 years. Moreover, the analyzes were adjusted for multiple covariates, including baseline severity [baseline IDS sum-score; 7]. Nevertheless, some limitations also need addressing. First, because NESDA is an observational cohort study, several variables may have confounded our findings. Some patients were exposed to different types of treatments, such as psycho- and pharmacotherapy. For example, patients with chronic depression or higher levels of neuroticism were more often treated with antidepressants than their

counterparts. Certain symptoms, such as reduced libido, can stem from medication side-effects rather than from depression as such and, as a result, may be more prevalent among chronically depressed patients than among nonchronically depressed patients (Baldwin, 2003; Rosse et al., 2007). However, most SDS values and the order of the symptom SDS did not change substantially after adjusting for the received treatment (results available upon request). Second, although chronic depression and neuroticism were interrelated and showed associations with similar symptom profiles, they were also (in part) independent constructs, since chronically ill patients had a neuroticism score that was only (mean) 3.02 (SE 0.57) points higher than that of non-chronically ill patients. More research is needed to unravel the underlying mechanisms that link chronic depression and neuroticism. Third, our definition of chronic depression (i.e., being depressed for ≥ 24 months during the last 48 months) differs from that used in other studies [e.g., 12]. Moreover, our chronic patients may not have experienced symptoms for ≥ 2 months over the course of 2 years and, thus, did not meet the criteria for persistent depressive disorder (according to the DSM-5). Fourth, assessing individual symptoms based on single items presents psychometric difficulties, because single items are more strongly affected by random error than the sum scores of items. However, there are also arguments in favor of single items, especially concerning practical use (Diamantopoulos et al., 2012). Finally, both individual symptoms and level of neuroticism were measured using self-report measures. Self-report measures require patients to possess a certain level of insight, which may be lacking when levels of psychopathology are high. Although the interclass correlation of the neuroticism score over three time points was of moderate strength (ICC = 0.672; F = 3.05; p = <.001), an earlier study using NESDA data reported that levels of neuroticism were affected by a patient's current depressive state (Spinhoven et al., 2013). As neuroticism is partly state dependent, our findings are limited by the fact that we could only use a single baseline assessment of neuroticism, which is likely to have been affected by the burden of psychiatric disease. However, it has been suggested that disorder-related state effects may reflect the true nature of personality (Riso et al., 2002; Spinhoven et al., 2013). Personality characteristics may change when depressive episodes remit, for example, due to a shared underlying etiology (see Costa et al., 2005). Future research could focus on comparison of state and trait effects of neuroticism on the course of depression and its individual symptoms, with trait being inferred from the mean neuroticism across several preceding measurements.

In conclusion, this study shows that a history of chronic depression and neuroticism predicted a higher severity of mood and cognitive symptoms and, to a lesser extent, severity of somatic/vegetative symptoms over the entire 9-year follow-up. Chronicity and high neuroticism may signal a specific disease cluster, since both variables are related to similar depression symptoms. In this context, future research might explore whether psychotherapeutic treatments that focus on low self-esteem or interpersonal sensitivity yield better outcomes for individual patients with high neuroticism and/or chronicity. It would be useful to examine whether such personalized interventions lead to better outcomes compared to standardized treatment protocols that approach MDD as a homogenous syndrome for all patients.

Author Statement

Contributors

BP is principal investigator of NESDA. Author WE performed the statistical analyzes and wrote the manuscript. EG contributed by frequent supervision and revision of the statistical-analyzes and writing of this manuscript. AH, IC, BP, and PS contributed by several revisions of the early stages as well as final stages of the manuscript. All authors have approved the final manuscript.

Role of the funding source

The funding source had no role in the design of this study, it's execution, analyzes, interpretation of the data, or decision to submit results.

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Conflicts of interest

None.

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Supplementary material

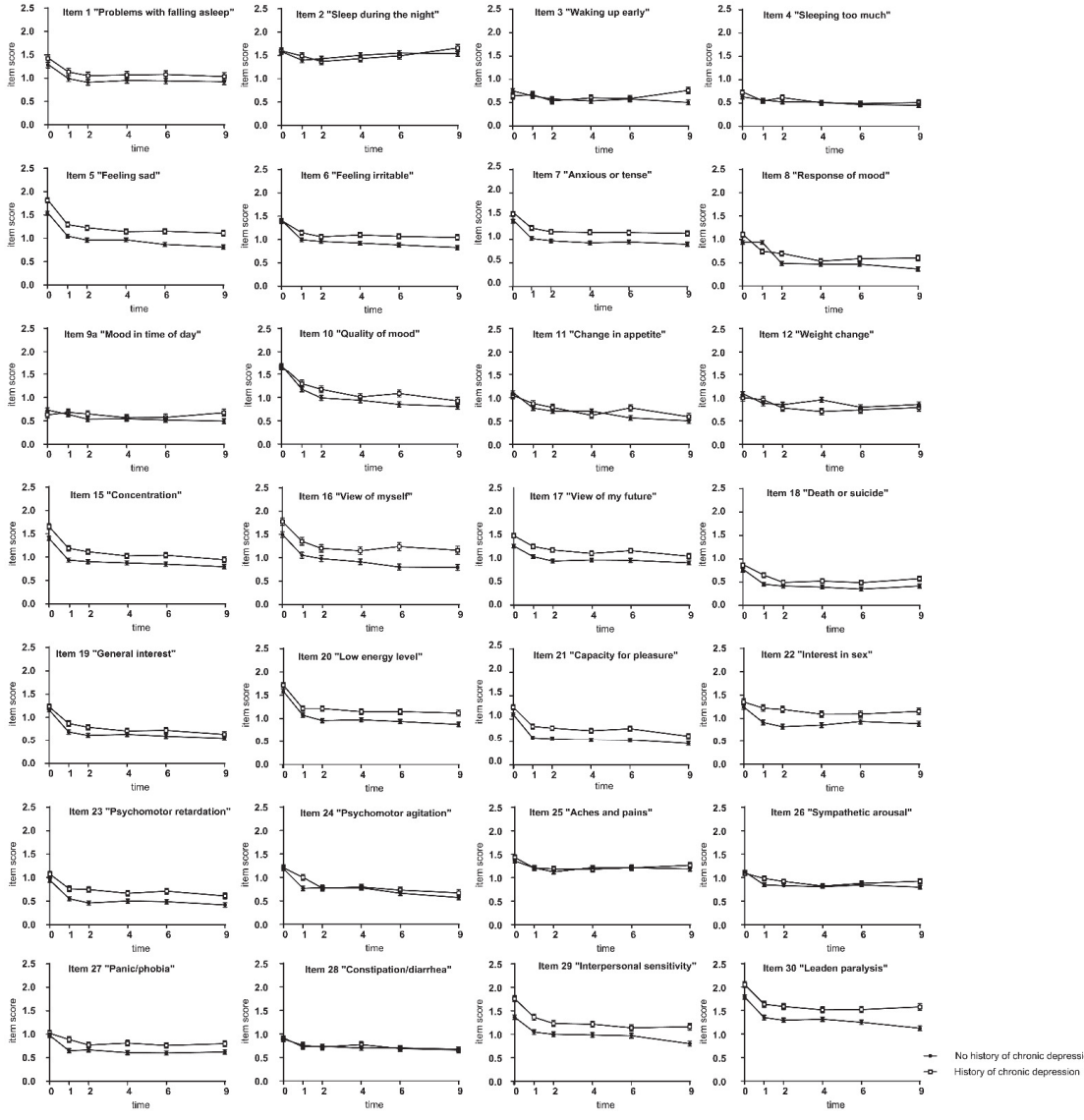

Figure 1 supplementary material. Estimated mean values of individual symptom scores over the 9-year follow-up in 560 MDD patients according to a history of chronicity (depressed 24 of 48 months depressed before baseline).

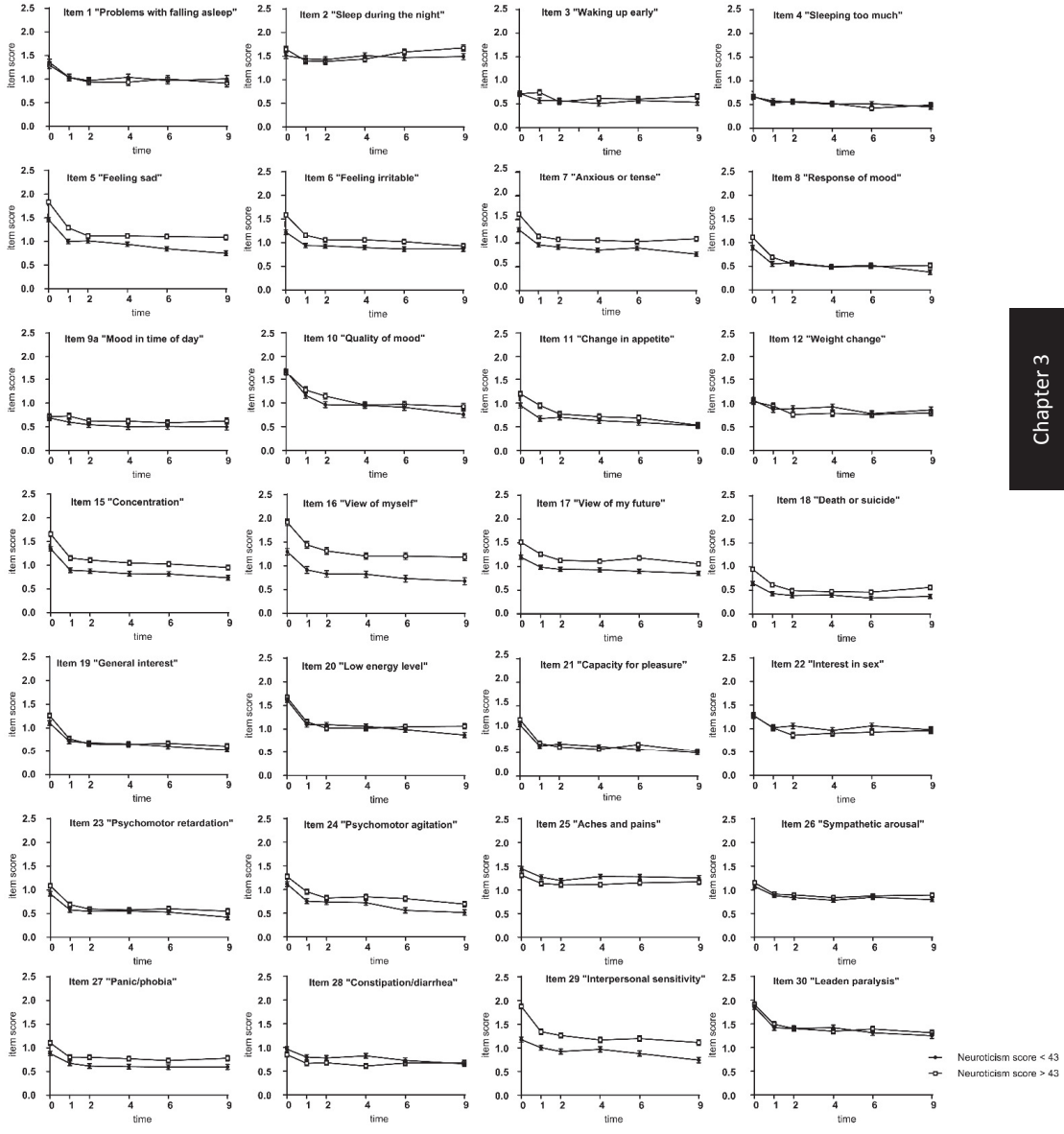

Figure 2 supplementary material. Estimated mean values of individual symptom scores over the 9-year follow-up in 560 MDD patients according to median split neuroticism score at baseline