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Research Report

Two-year stability and change of neuroticism and extraversion in treated and untreated persons with depression: Findings from the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Background: The personality dimensions neuroticism and extraversion likely represent part of the vulnerability to depression. The stability over longer time periods of these personality dimensions in depressed patients treated with psychological treatment or medication and in untreated persons with depression in the general population remains unclear. Stability of neuroticism and extraversion in treated and untreated depressed persons would suggest that part of the vulnerability to depression remains stable over time. The current study addressed the question whether treatment in depressed patients is related to changes in neuroticism and extraversion.

Methods: Data are from 709 patients with major depressive disorder participating in a cohort study (Netherlands Study of Depression and Anxiety; NESDA). We determined the 2-year stability of extraversion and neuroticism in treated and untreated persons and related change in depression severity to change in personality over time.

Results: Neuroticism decreased from baseline to 2-year follow-up ($d=0.73$) in both treated and untreated persons. Extraversion did not change significantly after controlling for neuroticism and depression severity at baseline and follow-up. Decreased depressive symptoms over time were related to decreased neuroticism ($d=1.91$) whereas increased depressive symptoms over time were unrelated to neuroticism ($d=0.06$).

Limitations: Patients were not randomized to treatment conditions and the groups are therefore not directly comparable.

Conclusions: Treated patients with depression in the general population improve just as much on depression severity and neuroticism as untreated persons with depression. This suggests that changes in neuroticism in the context of treatment likely represent mood-state effects rather than direct effects of treatment.

1. Introduction

The relation between Major Depressive Disorder (MDD) and the personality dimensions of neuroticism and extraversion has been studied in clinical settings and in population based studies (for an overview: Kotov et al., 2010). These studies have shown that MDD is positively associated with neuroticism and negatively with extraversion. Moreover, clinical and population based studies have identified neuroticism as an important vulnerability factor for MDD (Boyce et al., 1991; Fanous et al., 2007; Hettema et al., 2006; Hirschfeld et al., 1989; Kendler et al., 2006; Kendler et al., 2004; Ormel et al., 2004), whereas low extraversion appears to be associated only weakly to MDD (Kendler et al., 2006).

While neuroticism and extraversion likely represent part of the vulnerability to MDD, they are also known to change with the current mood state. For example, Karsten et al. (2012) used data from the Netherlands Study of Depression and Anxiety (NESDA; Penninx et al., 2008) and found that the occurrence of a depressive

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disorder was associated with an increase in neuroticism and a decrease in extraversion (Karsten et al., 2012). Similarly recovery from a depressive disorder was associated with decreased neuroticism and increased extraversion (Karsten et al., 2012), suggesting that neuroticism and extraversion are mood state dependent. In this study treatment status was not taken into account so it remains unclear whether treatment is related to the observed changes in neuroticism and extraversion.

The stability of neuroticism and extraversion in patients with MDD has also been studied in the context of randomized clinical trials (RCTs) and in naturalistic treatment studies (Berlim et al., 2013; Ekselius and von Knorring, 1999; Hellerstein et al., 2000; Tang et al., 2009). Studying the stability of neuroticism and extraversion in the context of RCTs is important to determine which aspects of treatment are related to change in personality. Tang et al. (2009), for example, showed that neuroticism decreased and extraversion increased in patients with MDD taking selective serotonin reuptake inhibitors (SSRIs) compared to patients taking a pill placebo. Interestingly, change in personality did not depend on improvement from depressive symptoms suggesting that change in personality is not a mere epiphenomenon of improved depressive state (Tang et al., 2009). In a naturalistic treatment study it has been shown that a 4-week trial of high frequency repetitive transcranial magnetic stimulation was related to decreased levels of neuroticism at post-treatment and the authors suggested that these improvements in neuroticism were likely independent from improvements in depressive state (Berlim et al., 2013). These findings suggest that treatment for MDD may have an impact on the personality of patients with MDD independent of the impact of treatment on depression itself.

In RCTs comparing the impact of depression treatment on change in personality the control condition usually consists of a placebo group (e.g., Ekselius and von Knorring, 1999; Hellerstein et al., 2000; Tang et al., 2009) but patients assigned to placebo usually also experience substantial symptom reduction. To more directly test whether treatment for depression is related to change in personality it is necessary to compare treated and untreated persons with depression. This can be done in population based studies because not all depressed persons in the general population seek treatment.

Another issue that has not been addressed in RCTs is the long-term stability of personality in treated and untreated persons with depression. Assessing the long term stability of personality traits in depressed patients is important because stability of personality traits in the context of change in depressive state would suggest that part of the vulnerability to depression remains intact, increasing the risk for subsequent relapse. For example, in a recent meta-analysis of longitudinal studies it has been shown that personality and personality disorders remain relatively stable over time and that patients under treatment for various mental disorders do not report more change in personality than non-patients (Ferguson, 2010). Such findings suggest that part of the vulnerability, in terms of the underlying personality, remains stable over longer periods of time in depressed patients in the general population, regardless of treatment status.

When studying the stability of personality in treated and untreated persons with depression in the general population some differences between RCTs and population based studies should be taken into account. In RCTs patients usually receive highly effective treatments under optimal conditions, whereas at the population level many depressed patients do not always receive adequate health care (Kessler et al., 2003; Young et al., 2001). Moreover, patients with MDD in RCTs might differ from patients with MDD in the general population on a number of clinically relevant variables such as comorbidity.

The present study draws data from the Netherlands Study of Depression and Anxiety (NESDA), to determine the 2-year stability of neuroticism and extraversion in patients treated with psychological treatment and/or antidepressant medication and in untreated persons with depression. Moreover, we sought to relate in both untreated and treated persons the change in depressive symptoms over time to change in neuroticism and extraversion over time. The following questions were addressed in this study: (1) Is treatment in patients with MDD at the population level related to change in neuroticism and extraversion? (2) Are changes in depressive symptoms over time in untreated and treated persons with depression related to changes in neuroticism and extraversion?

2. Methods

2.1. Sample

The present report is based on data from an ongoing longitudinal cohort study, the Netherlands Study of Depression and Anxiety (NESDA; $N=2981$). This ongoing multi-site cohort study determines predictors, course and consequences of depression and/or anxiety disorders in the Netherlands. Participants were healthy controls, persons with remitted depressive and/or anxiety disorders and persons with a current depressive and/or anxiety disorder. Participants were recruited from primary care ($n=1610$), secondary care ($n=807$) and from the general population ($n=564$). General exclusion criteria of NESDA were a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. Participants who were not fluent in Dutch were also excluded. The NESDA study protocol was centrally approved by an Institutional Review Board and locally by the review boards of all participating sites and all participants signed written informed consent. A more detailed description of the NESDA study is available elsewhere (Penninx et al., 2008).

The current study used data from the baseline assessment, the one year follow-up assessment (FU1) and the 2-year follow-up assessment (FU2). Psychopharmaca use was assessed at baseline at FU1 and at FU2 and coded according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2007). Patients who took any of the following medications when entering the study or during the study period were excluded from the analyses: antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics or sedatives (ATC code: N05C), psychostimulants (ATC code: N06B), or anti-dementia drugs (ATC code: N06D) Patients taking any of these drugs during the study period were excluded from the analyses because we aimed to study change in personality in untreated and treated persons receiving treatment for depression and not for anxiety or other disorders. Of the overall NESDA sample of 2981 participants, 1115 (37.4%) had a diagnosis of current MDD (6-month recency) at baseline. Of these 1115 patients, 393 (35%) were excluded from the analyses because they reported to have used one of the drugs above in the time period under study. Therefore, 722 patients with MDD were further considered for this study, of whom 13 persons had missing follow-up data, leading to an ultimate 709 persons with MDD as the final study sample.

2.2. Treatment status

Treatment status was defined by the use of antidepressant medication (ADM) and by self-reported contact with a psychologist or psychiatrist at any time between baseline and FU2. Patients who received treatment (psychological or medication) at baseline were also classified as treated. ADM use was assessed by

self-report questionnaires and by inspection of drug containers that participants brought to the baseline and 2-year FU interview and classified according to the World Health Organization ATC classification system (WHO, 2007). Psychological treatment was assessed by the Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P; Hakkaart-van Roijen, 2002) and defined as self-reported contact with a psychologist, psychiatrist or contact with a secondary care facility. To identify participants as treated no restrictions were placed on the number of contacts with a psychological health care provider. Based on these criteria, 520 (73.3%) people were classified as treated and 189 (26.7%) were classified as untreated.

2.3. Measures

2.3.1. CIDI

The Composite International Diagnostic Interview (CIDI) is a fully structured interview based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed; DSM–IV; American Psychiatric Association, 1994) criteria (World Health Organization, 1997). Excellent inter-rater reliability and validity has been reported for the CIDI (Andrews and Peters, 1998; Wittchen, 1994). In the NESDA study, the CIDI was used to determine the presence of current and lifetime mood disorders, anxiety disorders and alcohol abuse or dependence. The CIDI was conducted at baseline and at FU2.

2.3.2. IDS-SR

The Inventory of Depressive Symptoms Self-Report version (IDS-SR; Rush et al., 1996) is a 30-item self-report questionnaire measuring depressive symptom severity over the past seven days. Excellent internal consistency (Cronbach's alpha 0.92) and high correlations with the Hamilton Rating Scale for Depression (Hamilton, 1960) have been reported (Rush et al., 2003). In the current study the IDS-SR was obtained at baseline, FU1, and at FU2.

2.3.3. Neo-FFI

The revised NEO Five-Factor Inventory (NEO-FFI) is a widely used self-report instrument designed to measure the following higher order personality traits: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness (Costa and McCrae, 1995). Good internal consistency (Cronbach's alpha range 0.87–0.92) has been reported for the domain scales (Costa and McCrae, 1992). Although in the NESDA study all five subscales of the NEO-FFI have been assessed, the present report focuses on the neuroticism and extraversion scales because these two scales have most consistently been associated with depression. In the current study, the NEO-FFI was obtained at baseline and at FU2.

2.4. Statistical analyses

SPSS version 19 for Windows was used for statistical analyses. First, we computed Pearson correlations between depressive symptom severity and personality dimensions at baseline to determine concurrent relations. Pearson correlations between neuroticism at baseline and neuroticism at FU2 and between extraversion at baseline and extraversion at FU2 in treated and untreated persons were computed as an index of stability of these personality traits over time.

Multilevel Modeling (MLM) was used to predict change in depressive symptom severity and change in neuroticism and extraversion over time as a function of treatment status. MLM of longitudinal data has several advantages above ordinary least square regression analyses because it can deal with missing data and include time varying covariates in the analyses. Model building was guided by the following analytic procedure: First we added time as a predictor to the model (Model 1). In this model a significant main effect of time indicates that the dependent variables changes across the various assessment moments. Next we added treatment status and the interaction between treatment status and time as predictors (Model 2). In this model a significant time × treatment status interaction indicates that change in the dependent variable over time is different for treated and untreated persons. Following this we added personality scores as predictors to the model of change in depression severity and we added depression severity scores as predictors to the models of change in neuroticism and extraversion (Model 3). Finally we added the potential confounding variables gender, age, level of education and recruitment setting (Final Model). To compare the fit between the various models we compared change in deviance using a χ^2 test with 1 degree of freedom.

We also determined the relation between change in personality and change in depression severity in treated and untreated persons. To test whether change in personality predicts change in depressive symptom severity we added the neuroticism (at baseline and FU2) x time interaction and the extraversion (at baseline and FU2) × time interaction as predictors to the model of change in depressive symptom severity. To test whether the relation between change in personality and change in depressive symptom severity depends on treatment status, we also added the neuroticism (at baseline and FU2) × time × treatment status and the extraversion × time × treatment status three-way interactions to the model predicting change in depressive symptom severity. In these analyses neuroticism and extraversion were included as time varying covariates.

To test whether change in depressive symptom severity predicts change in personality, we conducted two separate MLM analyses, one with change in neuroticism as dependent variable and one with change in extraversion as dependent variable. To determine whether change in depressive symptoms predicts change in personality we entered the depressive symptoms (at baseline and FU2) × time interaction and the depressive symptoms (at baseline and FU2) × time × treatment status three-way interaction as predictor variables in both analyses. In these models, depressive symptoms severity was entered as time varying covariate.

In all models, continuous independent predictors were standardized by subtracting the sample mean from the individual score and dividing the result by the standard deviation of the mean to facilitate the interpretability of various predictors that are measured on different scales. In all MLMs we used an unstructured covariance structure for repeated measures over time and a Maximum Likelihood estimation method in order to be able to compare model fit. We computed effects sizes (Cohens' *d*) for all models based on estimates from the multi-level analyses (Feingold, 2009). Time was coded as follows: 0=baseline, 1=FU1, 2=FU2. Treatment seeking was centered and coded −0.5=untreated and 0.5=treated.

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of the treated and the untreated group are shown in Table 1. Depressive symptom severity at baseline was significantly higher in the treated group (M=31.46, SD=11.92) compared to the untreated group (M=28.91, SD=11.47). Baseline levels of extraversion were significantly higher in the untreated group (M=36.87, SD=7.16) compared to the treated group (M=34.88, SD=6.99). It should be noted that these statistical differences are not necessarily

Table 1
Demographic and clinical characteristics at baseline for treated and untreated persons.

Characteristic	Treated ($n=520$)		Untreated ($n=189$)		t	Chi-square
	Mean (*SD*)	*N* (%)	Mean (*SD*)	*N* (%)		
Age (years)	39.95 (11.69)	–	38.80 (12.77)	–	−1.16	–
Female	–	337 (64.1)	–	138 (70.4)	–	2.56
Education level (years)	11.86 (3.27)	–	11.70 (3.16)	–	−0.57	–
Number of previous episodes[a]	5.21 (10.13)	–	6.16 (11.63)	–	1.04	–
Recurrent MDD	–	280 (53.2)	–	113 (57.7)	–	1.13
Anxiety disorder	–	330 (62.7)	–	114 (58.2)	–	1.26
Depressive symptom severity	31.46 (11.92)	–	28.91 (11.47)	–	−2.53*	–
Neuroticism	42.08 (6.59)	–	41.05 (6.84)	–	−1.81	–
Extraversion	34.88 (6.99)	–	36.87 (7.16)	–	2.72**	–

* $p<0.05$.
** $p<0.01$.
[a] Median number of previous episodes was two in the overall sample, in the treatment seeking group and in the non treatment seeking group.

clinically meaningful given that in a large sample also small mean differences can reach statistical significance. To estimate the clinical meaningfulness of these differences we also compute the effect size (Cohens' *d*) of the differences between the groups. The effect size of the difference between the groups was 0.22 for depression severity and 0.28 for extraversion, reflecting small effects (Cohen, 1988). The two groups also differed with respect to source of recruitment. The majority of people in the treated group were recruited from secondary care facilities (60.4%), followed by recruitment from primary care facilities (33.3%) and by recruitment from the general population (6.3%). Most people from the untreated group were recruited from primary care facilities (58.2%) followed by recruitment from secondary care facilities (26.5%) and by recruitment from the general population (15.3%). Gender was equally distributed among the two groups.

3.2. Concurrent relations between depressive symptom severity and the personality dimensions neuroticism and extraversion

At baseline, neuroticism correlated positively with depressive symptom severity ($r=0.56$; $p<0.001$) and negatively with extraversion ($r=-0.50$; $p<0.001$); extraversion correlated negatively with depressive symptom severity ($r=-0.45$; $p<0.001$).

3.3. Modeling change in depressive symptom severity, neuroticism and extraversion

3.3.1. Change in depressive symptom severity

First, we modeled change in depressive symptom severity over time by treatment status using MLM. Table 2 summarizes the results of the four most informative models. In all models there was a significant main effect of time ($p<0.01$) indicating that depressive symptoms decreased over time ($d=0.89$). In the final model, there was a significant main effect of time ($F(1, 547.75)=216.83$, $p<0.001$), after adjusting for neuroticism and extraversion levels and other potential confounding variables. The interaction between time and treatment status was not significant ($F(1, 547.74)=3.39$, $p=0.07$), suggesting that decrease in depressive symptoms did not depend on treatment status (Fig. 1A).

3.3.2. Stability of neuroticism and extraversion

To determine the stability of the personality dimensions neuroticism and extraversion over time in the two groups, we first determined Pearson correlations between neuroticism and extraversion at baseline and neuroticism and extraversion at FU2. In both groups, neuroticism at baseline correlated moderately and statistically significant with neuroticism levels at FU 2 (untreated: $r=0.64$, $p<0.001$; treated $r=0.59$, $p<0.001$) and the correlation coefficients of the two groups did not differ statistically significantly, $z=0.78$, $p=0.43$. Extraversion at baseline also correlated moderately and statistically significant with extraversion at FU2 in both groups (untreated: $r=0.77$, $p<0.001$; treated: $r=0.72$, $p<0.001$) and the correlation coefficients did not differ between groups, $z=1.10$, $p=0.27$. The overall stability coefficient between extraversion at baseline and extraversion at FU2 ($r=0.74$) was stronger than the stability coefficient between neuroticism at baseline and neuroticism at FU2 ($r=0.60$; $z=3.99$, $p<0.001$).

3.3.3. Mean level stability of neuroticism and extraversion

Both groups experienced a statistically significant decrease in mean neuroticism levels from baseline to FU2 (mean decrease untreated: −4.23, $p<0.001$; mean decrease treated: −3.68, $p<0.001$) and a statistically significant increase in the mean level of extraversion (mean increase untreated: 1.67; $p<0.001$; mean increase treated: 1.68; $p<0.001$). To compare the mean level change in neuroticism and extraversion in the current sample with a non-depressed control group, we also calculated the mean level stability of persons in the same study (Penninx et al., 2008) without any depressive or anxiety disorders ($N=652$). Mean neuroticism levels in the non-depressed group also decreased statistically significantly from baseline to FU2 (mean decrease: −1.44, $p<0.001$) as did the mean level of extraversion (mean decrease: −1.32; $p<0.001$). The mean decrease in neuroticism in the non-depressed group statistically significantly differed from the mean decrease in the untreated (t-(714)$=3.50$, $p<0.001$) and the treated group ($t(1032)=4.74$, $p<0.001$). The mean difference in extraversion in the non-depressed group also statistically significantly differed from the mean difference in extraversion in the untreated ($t(714)=3.18$, $p<0.01$) and treated group ($t(1032)=5.79$, $p<0.001$).

Next we modeled change in neuroticism and extraversion over time as a function of treatment status using MLM (Table 3). In all models, predicting change in neuroticism over time there was a significant main effect of time ($p<0.01$), indicating that neuroticism decreased over time ($d=0.73$). In the final model the significant main effect of time remained after controlling for depressive symptom severity and extraversion levels and for potential confounding variables $F(1, 474.05)=92.45$, $p<0.001$. The interaction between time and treatment status was not significant ($F(1, 464.61)=0.40$, $p=0.53$), indicating that decrease in neuroticism did not differ between treated and untreated persons (Fig. 1 B).

In the initial model predicting change in extraversion over time there was a significant main effect of time ($p<0.01$) indicating

Table 2
Predicting change in depressive symptom severity over time.

Parameter	Model 1	Model 2	Model 3[a]	Final Model[b]
Intercept	28.74 (0.49)**	27.58 (0.59)**	28.45 (0.50)**	29.32 (1.08)**
Time	−4.35 (0.23)**	−4.06 (0.28)**	−4.06 (0.28)**	−4.06 (0.28)**
Treatment status	–	3.92 (1.18)**	1.71 (0.99)	2.06 (0.98)*
Time × treatment status	–	−1.00 (0.55)	−1.01 (0.55)	−1.02 (0.55)
−2 log likelihood	11,693.205	11,682.059	11,335.160	11,299.817
Δ deviance	–	11.14**	346.90**	35.34**

Note: All continuous predictor variables were standardized before entered into the model.

* $p < 0.05$

** $p < 0.01$.

[a] Adjusted for neuroticism and extraversion at baseline and at FU2.

[b] Adjusted for potential confounding variables: gender, age, level of education and recruitment setting.

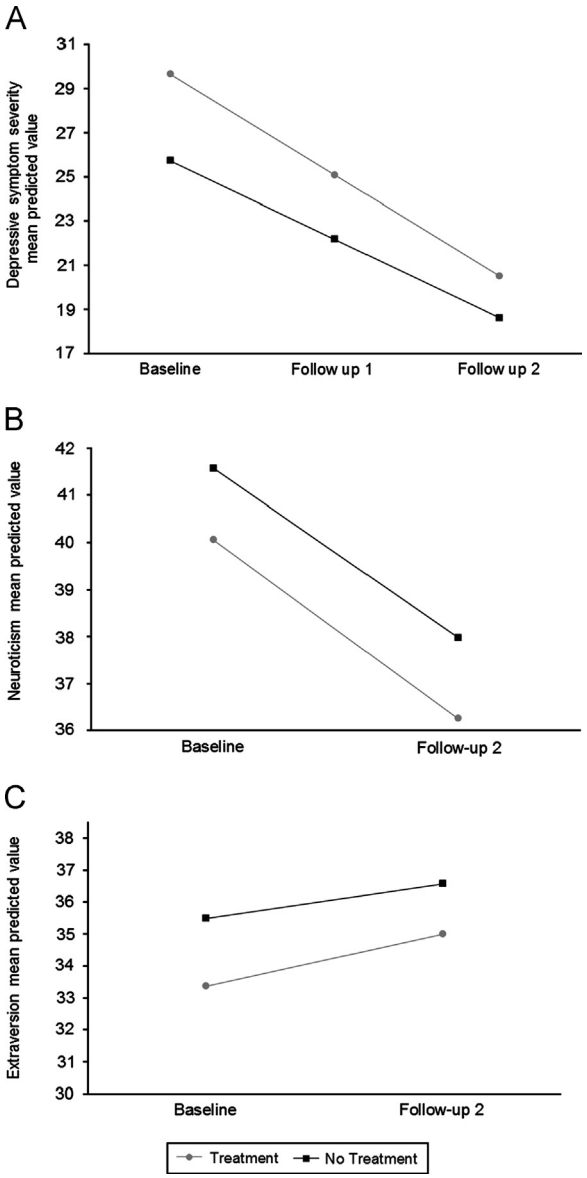

Fig. 1. Two-year course of depressive symptoms, neuroticism and extraversion for treated and untreated persons with depression. Note. *Y*-axis presents fixed predicted values of depression, neuroticism and extraversion course for treated ($n=520$) and untreated ($n=189$) persons with MDD.

that extraversion increased over time, however, after controlling for neuroticism and depression severity at baseline and follow-up change in extraversion over time was not significant anymore ($F(1, 512.51)=0.01$, $p=0.91$). The interaction between time and treatment status was also not significant ($F(1, 478.23)=2.13$, $p=0.15$), indicating that extraversion remained stable over time in both treated and untreated persons (Fig. 1C).

3.4. Differences in change in depression severity and personality between different types of treatment

To test whether change in depressive symptom severity, neuroticism or extraversion differed between different types of treatment (medication, psychotherapy, or both medication and psychotherapy) we added dummy coded variables for the different types of treatment to the final multilevel models. In these analyses the untreated group was used as the reference condition. There were no differences between type of treatment and change in depressive symptom severity, change in neuroticism or change in extraversion (all p-values > 0.05).

3.5. Relation between change in personality and change in depression severity

In the model predicting change in depressive symptom severity over time, the neuroticism × time × treatment status and the extraversion × time × treatment status three-way interactions were not significant ($F(1, 550.42)=0.48$, $p=0.49$ and $F(1, 549.68)=1.67$, $p=0.20$, respectively). Therefore, we removed the non-significant three-way interactions from the model and the model was rerun. The interactions between time and neuroticism and the interaction between time and extraversion were not significant ($F(1, 734.65)=0.22$, $p=0.64$ and $F(1, 667.54)=0.15$, $p=0.70$, respectively), indicating that change in personality over time did not predict change in depressive symptom severity over time.

In the model predicting change in neuroticism over time the depressive symptom severity × time × treatment status interaction was not significant ($F(1, 549.64)=0.20$, $p=0.66$) and was therefore removed from the model. There was a significant interaction between depressive symptom severity and time, $F(1, 683.96)=25.89$, $p < 0.001$. To interpret the interaction term, we plotted the neuroticism total scores at baseline and at FU2 separately for the low- and high change in depressive symptom severity groups (Fig. 2), defined as one *SD* below and above the mean change in depressive symptom severity. Patients in the high change group ($n=82$) reported a mean decrease of 27.70 ($SD=6.04$) on the IDS whereas patients in the low change group ($n=76$) reported a mean increase of 5.93 ($SD=3.63$) on the IDS. As can be seen in Fig. 2, persons in the high decrease in depressive symptoms group significantly decreased on neuroticism from baseline to FU2 whereas increased depressive symptoms were unrelated to changes in neuroticism from baseline to FU2 (ES within decrease

Table 3
Predicting change in the personality dimensions neuroticism and extraversion over time.

Parameter	Neuroticism				Extraversion			
	Model 1	Model 2	Model 3[a]	Final Model[b]	Model 1	Model 2	Model 3[c]	Final Model[d]
Intercept	41.27 (0.30)**	40.82 (0.38)**	41.24 (0.30)**	41.06 (0.68)**	33.80 (0.32)**	34.43 (0.40)**	34.44 (0.34)**	34.87 (0.79)**
Time	−3.65 (0.30)**	−3.71 (0.37)**	−3.21 (0.33)**	−3.18 (0.33)**	1.53 (0.23)**	1.36 (0.29)**	0.03 (0.27)	−0.05 (0.27)
Treatment status	–	1.51 (0.75)*	−0.03 (0.60)	−0.08 (0.58)	–	−2.13 (0.79)**	−0.98 (0.67)	−0.98 (0.66)
Time × treatment status	–	0.20 (0.73)	0.40 (0.66)	0.42 (0.66)	–	0.57 (0.57)	0.94 (0.50)	0.64 (0.50)
−2 log likelihood	6250.052	6245.145	5854.975	5795.704	6054.320	6047.172	5735.104	5693.581
Δ deviance	–	4.907*	390.17**	59.271**	–	7.15**	312.07**	41.25**

Note: All continuous predictor variables were standardized before entered into the model.

* $p < 0.05$.

** $p < 0.01$.

[a] Adjusted for depressive symptom severity at all time points and for extraversion at baseline and FU2.

[b] Adjusted for potential confounding variables: gender, age, level of education, recruitment setting.

[c] Adjusted for depressive symptom severity at all time points and for neuroticism at baseline and FU2.

[d] Adjusted for potential confounding variables: gender, age, level of education, recruitment setting.

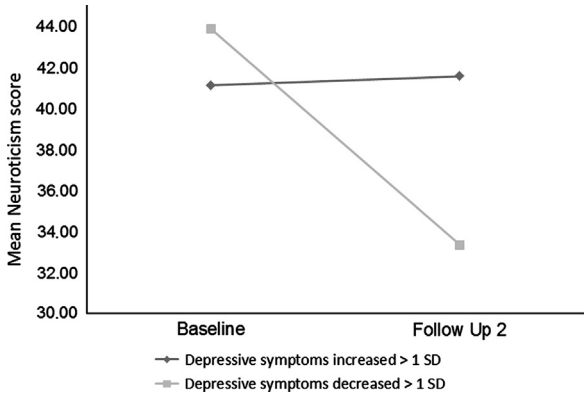

Fig. 2. Interaction between change in neuroticism over time and change in depressive symptom severity.

in depressive symptoms group $d = 1.91$; ES within increased depressive symptoms group: $d = 0.06$).

In the model predicting change in extraversion over time the depressive symptom severity × time × treatment status interaction was not significant ($F(1, 546.24) = 0.99$, $p = 0.32$) and was therefore removed from the model. After removing the non-significant three-way interaction from the model, the interaction between depressive symptom severity and time was not significant, $F(1, 650.31) = 1.69$, $p = 0.19$, indicating that change in depressive symptoms did not predict change in extraversion.

4. Discussion

The aim of this study was to determine the 2-year stability of neuroticism and extraversion in treated and untreated persons with major depressive disorder (MDD) in the general population. We determined the stability of depressive symptom severity, neuroticism and extraversion over a period of 2 years in depressed patients who sought treatment for mental health problems during the study period and in depressed persons who did not. Depressive symptom severity and neuroticism scores significantly decreased statistically during the study period regardless of treatment status. These findings are in line with previous findings from the NESDA study showing that depressive symptoms decrease over time regardless of treatment status (Penninx et al., 2011) and with findings from another cohort study in the Netherlands showing that treated depressed patients in primary care have similar outcomes than unrecognized depressed patients not receiving treatment (Kamphuis et al., 2012). Contrary to our findings an earlier cohort study found that treated depressed patients have better outcomes than untreated persons with depression (Angst, 1998) whereas in another population based study it has been shown that treated depressed patients had worse outcome than untreated persons with depression (Wang, 2004). It should be noted that our finding that treatment status was not related to change in depression, neuroticism and extraversion over time does not suggest that receiving treatment does not impact these variables. Treated and untreated persons in this study were not randomized and the effect of a given treatment on change in depression severity and personality traits can only be determined in randomized trials because observational studies suffer from confounding by indication when comparing treated and non-treated patients.

It has been shown previously, in the context of RCTs, that depression treatment is related to decreases in neuroticism (Ekselius and von Knorring, 1999; Hellerstein et al., 2000; Tang et al., 2009). However, previous studies determined the short-term stability of neuroticism over a course of depression treatment with SSRIs whereas the current study determined the long term (2-year) stability of neuroticism and extraversion in treated and untreated persons with depression in the general population. Another explanation for the discrepant findings, as suggested by one of the anonymous reviewers, is that the current study did not differentiate between specific types of antidepressants whereas previous RCTs focused specifically on SSRIs. It is possible that SSRIs have stronger effects on changes in neuroticism than other types of antidepressants. Determining the specific impact of different types of antidepressants on changes in neuroticism and other personality traits requires randomization to different types of antidepressants and is therefore an issue for future RCT based studies.

We also determined relations between change in depressive symptom severity and change in personality in treated and untreated persons with depression and found that change in depression was associated with change in neuroticism independently of treatment status. Patients experiencing strong symptom reduction reported more decrease in neuroticism over time compared to patients experiencing an increase in depressive symptoms over time (Fig. 2). Moreover, changes in neuroticism and extraversion were not associated with changes in depressive symptoms. This finding suggests that changes in depressive state might drive changes in the underlying personality rather than the other way around, which is in line with findings showing that neuroticism and extraversion in depressed patients are mood-state dependent (Karsten et al.,

2012). It should be noted, however, that the current research design and analytic approach does not allow drawing any causal conclusions. Identifying the causal directions of the relation between changes in personality and depression is thus an issue for future research.

4.1. Limitations

The findings of this study should be interpreted in the light of several limitations. First, patients in this study were not randomized to treatment conditions and might therefore not be directly comparable. Persons in the treated and in the untreated group differed with respect to severity of depressive symptoms and extraversion scores at baseline. Therefore any differences between the two groups cannot be solely attributed to treatment status. Second we did not assess treatment adequacy. It should be noted however that a previous NESDA study found that treatment adequacy was unrelated to improvement in depressive symptoms (Prins et al., 2011). Third, we homogenized the sample by excluding patients who took medication not directly related to depression (including anxiolytics) during the study period. This might limit the generalizability of our findings to depressed patients with more diverse symptoms. Fourth, we determined cross-sectional relations between change in depression levels and change in personality. Given that in the present analysis personality was only assessed at two time points we could not determine any temporal relations between change in depression severity and change in personality. Finally, we did not determine the stability of other personality dimensions in treated and untreated persons. It has been shown in a previous NESDA study that the personality dimension of conscientiousness also changes with depressive state (Karsten et al., 2012).

4.2. Implications

Despite these limitations the results of this study have several implications for clinical settings and future research. We found that in a large sample of patients with MDD, treatment status was unrelated to change in neuroticism and extraversion. We also found that change in depression predicted change in neuroticism rather than the other way around. These findings suggest that changes in neuroticism might be driven by improved depressive state (the mood-state effect) rather than by receiving treatment for depression. From a clinical point of view this suggests that treatment for depression should focus on depressive symptoms rather than on the underlying personality structure because treating the underlying personality structure of depressed patients might not improve depressive symptom severity. Future research studying the stability of personality in the context of treatment should also take into account untreated persons with MDD who improve in depression severity in order to be able to distinguish mood-state effects from more direct effects of treatment on personality. Given that in our study the treated group differed from the untreated group with respect to several clinical and demographic variables it is not possible to draw any conclusions regarding the causal effect of treatment status on change in neuroticism and extraversion. Future research should determine characteristics of depressed persons in the general population who profit from seeking treatment for depression with respect to changes in neuroticism and extraversion. Finally, in line with what has previously been reported in the NESDA sample (Karsten et al., 2012) our finding that neuroticism changes with depressive state suggest that personality assessment is partly clouded by the current mood state.

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Conflict of interest

None of the authors to this manuscript has any potential conflict of interest, including any financial, personal, or other relationship with people or organizations that might be interpreted as influencing our research.

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