Insight into the heterogeneity of depressive disorders

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Chapter 2

Can biological and psychological characteristics differentiate Major Depressive Disorder, Dysthymic Disorder and Double Depression?

ABSTRACT

Objective To inform future classifications of affective disorders and to facilitate (the development of) treatment algorithms it is important to test whether there are differences in the biological underpinnings and psychological dimensions of pure Major Depressive Disorder (MDD), pure Dysthymic Disorder and Double Depression.

Methods Differences in i) biological characteristics (including cortisol, inflammation markers and serum Brain Derived Neurotrophic Factor (sBDNF)) and ii) psychological dimensions (including personality measures and cognitive vulnerability) between persons with a 6-month diagnosis of pure MDD (n=853), pure Dysthymic Disorder (n=43) and Double Depression (n=262), participating in the Netherlands Study of Depression and Anxiety, were examined.

Results No differences in biological characteristics were found. Dysthymic Disorder (trend) and Double Depression showed stronger associations with personality measures of neuroticism, conscientiousness and agreeableness than MDD. Cognitive vulnerability was similar for Dysthymic Disorder and Double Depression and differed from MDD

Conclusion Depressive subtypes did not differ on biological characteristics. This does not imply similar pathophysiological processes. Rather, our findings may represent endpoints of a final common pathway, with heterogeneity in underlying processes. Differences in psychological measures suggest a distinct psychological profile for persons with Dysthymic Disorder and Double Depression. More psychological oriented strategies may be useful for chronic forms of depression.

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INTRODUCTION

Since its introduction in the DSM-III in 1980 (American Psychiatric Association, 1980), the concept of Dysthymic Disorder has been topic of debate. Whereas in DSM-II (American Psychiatric Association, 1968) personality traits were present in the definition of neurotic depression, in DSM-III (American Psychiatric Association, 1980) Dysthymic Disorder was reclassified as an affective disorder, with greater emphasis on vegetative symptoms similar to Major Depressive Disorder (MDD) (Riso et al., 2003). This strategy resulted in an overlap in diagnoses between Dysthymic Disorder and MDD that became visible in high comorbidity, in some reports even exceeding 90% (Klein et al., 2000) and a lack of significant differences between Dysthymic Disorder and (chronic) MDD in various epidemiological studies examining a broad range of demographic, clinical, psychosocial, family history, and treatment response variables (McCullough et al., 2000, 2003; Klein et al., 2004; Yang and Dunner, 2001).

To inform future classifications of affective disorders and to support treatment algorithms, it is important to test whether there are differences in the biological characteristics and psychological dimensions of Major Depressive Disorder, Dysthymic Disorder and Double Depression (co-occurrence of Major Depressive Disorder and Dysthymic Disorder). Differences in biological characteristics might provide insight into a differential pathogenesis of these disorders and into the role of core clinical features such as severity and duration of depressive symptoms. In addition, information on the biological and psychological characteristics might guide treatment decisions, like the use of antidepressants or more psychological oriented strategies like Cognitive Behavioral Therapy.

A growing body of research suggests that a variety of pathophysiological processes are underlying depressive disorders, such as elevated levels of cortisol awakening response (Vreeburg et al., 2009a), up-regulated inflammatory response (Dowlati et al., 2010) and diminished levels of serum Brain Derived Neurotrophic Factor (sBDNF) (Molendijk et al., 2011). However, to date, only scattered information is available regarding pathophysiological processes underlying Dysthymic Disorder and direct comparisons between MDD, Dysthymia and Double Depression are lacking. In a review, Griffith et al. (2000) pointed at the paucity and contradictory nature of data, but concluded that Dysthymic patients may have reduced cortisol levels and minimal cortisol response to challenge, as compared to MDD. Anisman et al. (1999) demonstrated increased IL-1beta production in Dysthymic patients as compared to MDD patients and suggested that chronicity was associated with cytokine alterations. However, others could not replicate these findings (Schlatter et al., 2004; Yoshimura et al., 2010). Likewise, Aydemir et al. (2007) demonstrated higher BDNF-levels in persons with Dysthymia as compared to persons with MDD, but this could not be replicated by others (Yoshimura et al., 2010). Whereas Griffith et al. (2000) stressed the importance of differentiation between pure Dysthymc Disorder and

Double Depression, both Anisman et al. (1999) and Aydemir et al. (2007) did not stratify their analyses, thereby limiting insight into the impact of MDD superimposed on Dysthymic Disorder, and, hence, the role of duration versus severity of depressive symptoms. Literature on the association between duration and severity of depressive symptoms on biological parameters conflicts with both present (Brouwer et al., 2005; Dowlati et al., 2010; Oldehinkel et al., 2001) and absent associations (Anisman et al., 1999; Aydemir et al. 2007; Bhagwagar et al., 2005; Nelson et al., 1997; Marques-Deak et al., 2007; Watson et al., 2002).

Also in terms of psychological dimensions, it remains unclear whether persons with MDD, Dysthymia and Double Depression differ. In a meta-analysis on personality traits of anxiety, depressive and substance use disorders, Kotov et al. (2010) showed strong links of depressive disorders to neuroticism, conscientiousness and extraversion, with a greater role for personality dimensions in Dysthymic Disorder than in MDD and concluded that Dysthymic Disorder might be viewed as a form of personality pathology. However, in this meta-analysis Dysthymic Disorder encompassed both pure Dysthymia and Double Depression (Kotov et al., 2010) which does not allow for conclusions on the specificity of these findings for pure Dysthymic Disorder. Other studies reported on differences in psychological dimensions between non-chronic and chronic depressions and found higher levels of neuroticism (Hirschfeld, 1990; Klein et al., 1988), introversion (Hirschfeld, 1990; Klein et al., 1988, Robison et al., 2009), depressotypic cognitions (Klein et al., 1988; Riso et al., 2003; Wiersma et al., 2011) and lower levels of extraversion (Wiersma et al., 2011) in chronic depressions. Cognitive theorists have proposed that maladaptive cognitive processing becomes more likely as more chronic depressive episodes are experienced (Moulds et al., 2008). Hence, differences in cognitive styles are expected across depressive subtypes with different levels of severity and chronicity of depressive symptoms. However, to our knowledge, differences in cognitive vulnerability, between MDD, pure Dysthymic Disorder and Double Depression has never been examined in a large comprehensive study.

The purpose of the current study, therefore, is to examine the distinction between MDD, Dysthymic Disorder and Double Depression within a large cohort of persons with depression, who participated in the Netherlands Study of Depression and Anxiety (NESDA) from two perspectives, namely i) biological characteristics, including cortisol, inflammation markers and sBDNF, and ii) psychological dimensions, including personality and cognitive vulnerability.

METHODS

Study sample

NESDA is designed to investigate depressive and anxiety disorders. It is a multi-site naturalistic cohort study of adults (18 to 65 years) recruited from the general population, general practices, and mental health organizations. The method of recruitment was extensively described elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of the VU University Medical Center and written informed consent was obtained from all participants. For the present analysis, we selected respondents from the NESDA baseline assessment with a 6-month diagnosis of Major Depressive Disorder (n=1115) and/or Dysthymic Disorder (n=305) (total n=1158). Diagnoses were established using the Composite Interview Diagnostic Instrument (CIDI) version 2.1, according to DSM-IV criteria (World Health Organization, 1998). The CIDI is a structured interview with acceptable reliability and validity (Wittchen, 1994; Wittchen et al., 1996). It was administered by specially trained research staff.

Measurements

Assessment of psychopathology

For the present study, various depression groups were defined: Major Depressive Disorder (MDD) (n=853) consisted of those fulfilling a current MDD and no current Dysthymic Disorder diagnosis. Pure Dysthymic Disorder (n=43) consisted of those with a Dysthymic Disorder but not a current MDD diagnosis. Double Depression (n=262) was defined as current Dysthymic Disorder with a current comorbid MDD, ignoring the sequence of onset of Dysthymic Disorder and MDD.

Biological characteristics

Salivary cortisol

NESDA researchers previously found that persons with remitted or current MDD showed an increased cortisol awakening curve but similar post-dexamethasone cortisol levels as compared to controls (Vreeburg, 2009a). Therefore, we compared the depression groups concerning the cortisol awakening curve. As described in more detail elsewhere (Vreeburg, 2009b), respondents were instructed to collect saliva samples at home on a regular (working) day shortly after the interview at baseline. Instructions concerning saliva sampling prohibited eating, drinking tea or coffee or brushing teeth within 15 minutes before sampling. Furthermore, no dental work 24 hours prior to sampling was allowed. Saliva samples were obtained using Salivettes (Sarstedt, Germany) at four time points; at awakening (T1) and 30 (T2), 45 (T3) and 60 (T4) minutes later. Samples were stored in refrigerators and returned by mail. After receipt, Salivettes were centrifuged at 2000 x *g* for 10 min, aliquoted and stored at -80 ˚C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland).

The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%.

We calculated the area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) using Pruessner's formulas (Pruessner et al., 2003). The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of the dynamic of the cortisol awakening response (CAR), more related to the sensitivity of the system, emphasizing changes over time after awakening (Edwards et al., 2001; Fekedulegn et al., 2007; Schmidt-Reinwald et al., 1999). If samples were collected outside of a margin of five minutes around the time protocol, values were assigned missing. All persons for whom all four morning samples were available (n=608) could be included in the AUC analyses (458 with MDD, 24 with Dysthymia, 126 with Double Depression).

Inflammatory markers

Markers of inflammation, including C-reactive protein (CRP), interleukin (IL)-6, and tumor-necrosis factor (TNF)-α, were assessed at the baseline NESDA measurement. CRP is a nonspecific acute-phase protein synthesized in the liver and IL-6 is a pro-inflammatory cytokine secreted by activated macrophages. TNF-α is the prototypic ligand of the TNF superfamily and plays a central role in inflammation. Fasting blood samples of NESDA participants were obtained in the morning around 0800 hours and kept frozen at −80 °C. CRP and IL-6 were assayed at the Clinical Chemistry department of the VU University Medical Center. High-sensitivity plasma levels of CRP were measured in duplicate by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science (Leiden, The Netherlands), using a high-sensitivity solid phase ELISA (Quantikine HS Human TNF-α Immunoassay, R&D systems, Minneapolis, MN, USA). Intra- and inter-assay coefficients of variation were 10% and 15%, respectively (see also Vogelzangs et al., 2012).

Brain Derived Neurotrophic Factor

BDNF a neurotrophin has been linked to the viability of neurons in brain circuits that regulate emotion, memory, learning, sleep and appetite (Molendijk et al., 2011). Fasting blood samples of NESDA participants were obtained in the morning around 0800 hours and transferred to the laboratory to start processing within one hour. It was kept frozen at -80°C until it was assayed. BDNF protein levels were measured using the Emax Immuno Assay system from Promega according to the manufacturer's protocol (Madison, WI, USA). Undiluted serum was acid treated as this reliably increased the detectable BDNF in a dilution-dependent way. Serum samples were diluted 100 times, and absorbency was read

in duplicate using a Bio-Rad (Hercules, CA, USA) Benchmark microplate reader at 450 nm. Serum BDNF protein levels were expressed in ng/ml. The intra- and inter-assay coefficients of variation were found to be within 3% and 9%, respectively (see also Molendijk et al., 2011).

Psychological dimensions

Both personality measures and cognitive vulnerability measures were included. Personality was assessed, using the NEO-Five Factor Inventory (NEO-FFI), a 60-item questionnaire measuring five personality domains. The latent structure of the NEO-FFI has been supported in clinical samples (Rosellini and Brown, 2011), and the domains have been found to possess good internal consistency (Costa and McRae, 1995). The following personality domains were considered: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each domain consists of 12 items. Examples of these items per domain are: "I often feel less than others" (neuroticism), "I really like talking to people" (extraversion), "I have a wide range of intellectual interests" (openness to experience), "I'd rather cooperate than compete with others" (agreeableness), and "I have clear goals and work on them systematically" (conscientiousness). Scores for each item ranged from 1 (totally disagree) to 5 (totally agree).

Cognitive vulnerability was assessed using the Leiden Index of Depression Sensitivity-Revised (LEIDS-R). The LEIDS-R assesses the ease with which latent dysfunctional cognitions (hopelessness, acceptance, aggression, control/perfectionism, risk aversion, rumination) may be activated during normal mood variations (Van der Does, 2002). It is a 34-item self-report questionnaire. Hopelessness and acceptance/coping both constitute of 5 items, with a maximum score of 20, whereas the other scales are based on 6 items with maximum scores of 24 per subscale. Participants were instructed to think about the last time they felt sad, and to indicate the degree to which a list of statements described their typical cognitions and behaviors in response to sad mood. For example, "When I feel sad, I feel more hopeless about everything" (hopelessness), "When I feel sad, I feel more like myself" (acceptance), "When I feel down, I lose my temper more easily (aggression), "When I am in a sad mood, I become more bothered by perfectionism" (perfectionism), "When I feel down, I take fewer risks" (risk aversion), "When I feel sad, I spend more time thinking about the possible causes of my moods" (rumination). Scores for each question ranged from 1 (not applicable) to 5 (very strongly applicable). Adequate internal consistency was previously demonstrated (Van der Does, 2002; Van der Does and Williams, 2003).

Characteristics of study sample

Sociodemographics included age, sex, and years of education. Since differences in biological characteristics and psychological dimensions may be associated with severity and duration of depressive symptoms, we examined whether the diagnostic categories of MDD,

Dysthymic Disorder and Double Depression indeed represent different levels of severity and/or chronicity. Total scores on the 30-item Inventory of Depressive Symptomatology – Self report version (IDS-SR, www.ids-qids-org) (Rush et al., 1986, 1996) were calculated. In addition, duration of symptoms was assessed by means of the Life Chart interview (LCI) (Lyketsos and Nestadt, 1994). Baseline LCI served to compute a measure of duration of depressive symptomatology during 5 years prior to the baseline interview.

Covariates

Especially for examination of biological characteristics, it is important to adjust for lifestyle and medication information since these are associated with biological indicators as well as with diagnoses groups. Lifestyle characteristics included, smoking status (never, current), alcohol intake (<1, 1-14 [women] / 1-21 [men], >14 [women] >21 [men] drinks per week), body mass index (BMI; weight in kilograms divided by height in meters squared) and physical activity (measured with the International Physical Activity Questionnaire (Craig et al., 2003) in MET-minutes [ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity] per week). Disease related covariates included presence of cardiovascular disease (assessed by self-report supported by appropriate medication use (see Vogelzangs et al., 2010 for detailed description), presence of diabetes (based on fasting plasma glucose level ≥ 7.0 mmol/l or use of anti-diabetic medication [ATC-code A10] (WHO, 2007), and the number of other self-reported chronic diseases for which persons received treatment (including lung disease, osteoarthritis or rheumatic disease, cancer, ulcer, intestinal problem, liver disease, epilepsy and thyroid gland disease). In addition, we assessed statin use [ATC-code C10AA, C10B] (WHO, 2007), use of systemic anti-inflammatory medication [ATC-codes M01A, M01B, A07EB, A07EC; ≥ 50% of the time] (WHO, 2007), and use of antidepressants (SSRIs (ATC codes N06AB02–N06AB10), TCAs (ATC codes N06AA01–N06AA23), other (ATC codes N06AX05, N06AX11, N06AX16, and N06AX21)). Sampling factors included time of the morning blood withdrawal (minutes after 0600 hours), fasting state (yes/no), and duration of sample storage at -80°C (days) for blood parameters, and time of awakening for the cortisol awakening response. In addition to socio-demographics, analyses on psychological dimensions were adjusted for comorbid anxiety disorders. Comorbid anxiety disorders included a 6-month diagnosis of Panic Disorder, Agoraphobia, Social Phobia or Generalized Anxiety Disorder, as recorded by the CIDI.

Statistical analyses

The distribution of characteristics of participants with MDD, Dysthymia and Double Depression were compared using two-tailed chi-square statistics for categorical variables and one-way-analysis of variance statistics (ANOVA) for continuous variables. In addition, analyses of covariance (ANCOVA) were used to examine differences in depression groups with regard to i) biological parameters, ii) psychological dimensions. All analyses were

adjusted for age, sex, and education. Next, we additionally adjusted the models for specific sampling and health related factors per parameter that were previously indicated as important determinants (see Vreeburg et al., 2009a,b; Bus et al., 2011, Vogelzangs et al., 2012). Analyses for cortisol measures were adjusted for smoking, tricyclic antidepressant use, physical activity and time of awakening. Analyses for inflammation were adjusted for smoking, alcohol intake, body mass index, physical activity, cardiovascular disease, diabetes, number of other chronic diseases, statins and anti-inflammatory medication. Analyses for sBDNF were adjusted for non-fasting state of blood draw, delayed measurement, alcohol intake, current smoking and antidepressant use. Analyses for psychological dimensions were additionally adjusted for comorbid anxiety disorder. IL-6, CRP and TNF-α were log-transformed to normalize distributions. Finally, for significant associations Cohen's d was calculated in order to assess effect size. All analyses were conducted using SPSS (version 15) (SPSS, 2000).

RESULTS

Table 1 summarizes the socio-demographic and clinical characteristics of the study sample. Persons with Dysthymic Disorder were older than persons with MDD or Double Depression. Persons with Double Depression had greater severity and longer duration of depressive symptoms, a higher percentage of comorbid anxiety disorders and used more psychoactive medication than persons with MDD. Dysthymic Disorder and Double Depression differed only in age, level of severity and duration of depressive symptoms, with Double Depression being more severe and chronic than Dysthymia.

Table 1. Socio-demographic and clinical characteristics of the total sample.

	MDD	Dysthymic Disorder	Double Depression	Overall statistics
	n=853	n=43	n=262	p-value
Female (%)	67.9	58.1	65.6	.36
Age (mean years, SD)	40.3 (12.2)[a,b]	47.5 (10.6)[a,c]	42.5 (11.7)[b,c]	<.001
Education (mean years, SD)	11.7 (3.2)[b]	11.5 (4.3)	11.2 (3.4)[b]	.09
IDS-score (mean, SD)	30.7 (12.0)[b]	31.1 (11.3)[c]	39.1 (10.8)[b, c]	<.001
Depressed months (mean, SD)	25.7 (15.6)[a,b]	35.5 (17.8)[a,c]	43.0 (14.5)[b,c]	<.001
Comorbid anxiety disorder (%)	61.8[b]	69.8	78.2[b]	<.001
Psychoactive medication (%)	40.8[b]	37.3	50.4[b]	.02

[a,b,c] Significant (p<.05) differences between: a= MDD versus Dysthymic Disorder; b= MDD versus Double Depression, c= Dysthymic Disorder versus Double Depression.

Biological characteristics

Analyses of covariance, associating depression groups with biological parameters, were adjusted for age, sex, and education and additionally for specific sampling and health related factors per biological parameter (see Table 2). No significant differences in any of the

biological parameters between depression groups could be detected, although cortisol measures considerably differed across subtypes (AUCi-adjusted: MDD: Mean=2.63 (SE 0.3); Dysthymic Disorder: Mean=1.17 (SE 1.3); Double Depression: Mean=2.57 (SE 0.6)).

Table 2. Results of ANCOVA analyses associating biological parameters with depression groups.

	MDD	Dysthymic Disorder	Double Depression	
	Mean (SE)	Mean (SE)	Mean (SE)	p-value‡
Cortisol measures	n=458**	n=24**	n=126**	
AUCg [a]	19.82 (0.35)	18.90 (1.55)	18.92 (0.67)	.42
AUCg- adjusted [b]	19.83 (0.34)	18.74 (1.51)	18.88 (0.65)	.38
AUCi [a]	2.62 (0.30)	1.13 (1.33)	2.61 (0.58)	.55
AUCi- adjusted [b]	2.63 (0.30)	1.17 (1.31)	2.57 (0.57)	.56
Inflammation*	n=834**	n=42**	n=256**	
IL-6 [a]	0.80 (1.03)	0.73 (1.16)	0.80 (1.06)	.83
IL-6 – adjusted [b]	0.81 (1.03)	0.75 (1.15)	0.77 (1.06)	.72
CRP [a]	1.38 (1.04)	1.51 (1.21)	1.43 (1.08)	.86
CRP – adjusted [b]	1.41 (1.04)	1.65 (1.19)	1.32 (1.07)	.46
TNF-α [a]	0.85 (1.02)	0.82 (1.11)	0.89 (1.04)	.60
TNF-α –adjusted [b]	0.85 (1.02)	0.85 (1.11)	0.87 (1.04)	.91
sBDNF	n=827**	n=41**	n=256**	
sBDNF [a]	9.01 (0.12)	9.46 (0.54)	9.14 (0.22)	.66
sBDNF- adjusted [b]	9.03 (0.12)	9.28 (0.55)	9.10 (0.22)	.89

[a] Basic adjustments: age, sex, and education; [b] Additional adjustments: Cortisol measures: smoking, trycyclic antidepressant use, physical activity, time of awakening; Inflammation: current smoking, alcohol intake, body mass index, physical activity, cardiovascular disease, diabetes, number of other chronic diseases, statins and anti-inflammatory medication; sBDNF: non-fasting state of blood draw, delayed measurement, alcohol intake, current smoking, antidepressant use (TCAs and SSRIs). * IL-6, CRP and TNF-α were ln-transformed to normalize distributions; adjusted means (SE) are presented back-transformed. **Due to missing data on specific biological parameters, total numbers differ per analysis. Abbreviations: MDD= Major Depressive Disorder; SE= Standard Error; AUCg= Area under the curve with respect to the ground; AUCi= Area under the curve with respect to the increase; IL-6= Interleukin-6; CRP= C-reactive protein; TNF= Tumor Necrosis Factor; sBDNF= serum Brain-Derived Neurotrophic factor; ‡Pairwise comparison of groups did not yield any significant difference.

Psychological and cognitive dimensions

NEO-FFI

Analyses of covariance, associating depression groups with personality dimensions (NEO-FFI), were adjusted for age, sex, education, comorbid anxiety (see Table 3). Neuroticism scores across the three groups gradually increased (MDD: Mean=29.6 (SE 0.2), Dysthymic Disorder: Mean=30.4 (SE 1.1), Double Depression: Mean=32.4 (SE 0.4)). Comparison across groups, showed that only MDD and Double Depression differed significantly ($p<.001$, Cohen's $d=0.2$). Levels of extraversion of persons with MDD and Dysthymic Disorder significantly differed from Double Depression (respectively $p<.001$, Cohen's $d=0.2$; and

p=.01, Cohen's d=0.1). Levels of agreeableness and conscientiousness only significantly differed between MDD and Double Depression (p=.02, Cohen's d=0.2; p=.003, Cohen's d=0.1, respectively). The three depressed groups did not differ significantly on openness to experience. Despite some significant differences between groups, all effect sizes were small, not exceeding 0.2 (neuroticism and extraversion).

LEIDS-R

As shown in Table 3, after adjustment for sex, age, education and comorbid anxiety, hopelessness/suicidality levels gradually increased across the three groups (MDD: Mean=7.2 (SE 0.2), Dysthymic Disorder: Mean=7.8 (SE 0.8), Double Depression: Mean=9.0 (SE 0.3)), which was significant for the comparison MDD and Double Depression (p<.001; Cohen's d=0.2). Persons with Dysthymic Disorder had highest scores on aggression (MDD: Mean=6.0 (SE 0.2), Dysthymic Disorder: Mean=7.8 (SE 0.8), Double Depression: Mean=7.6 (SE 0.3). Differences reached significance for MDD versus Dysthymic Disorder (p=.02, Cohen's d=0.1) and MDD versus Double Depression (p=<.001, Cohen's d=0.1). Next, Dysthymic Disorder had highest scores on control/perfectionism (MDD: Mean=6.7 (SE 0.1), Dysthymic Disorder: Mean=8.0 (SE 0.6), Double Depression: Mean=6.9 (SE 0.3)), although only MDD significantly differed from persons with Dysthymic Disorder (p=.01, Cohen's d=0.1).

In addition, persons with Dysthymic Disorder had highest levels of risk aversion (MDD: Mean=10.9 (SE 0.2), Dysthymic Disorder: Mean=12.1 (SE 0.7), Double Depression: Mean=11.8 (SE 0.3)), although only MDD significantly differed from persons with Double Depression (p=.01, Cohen's d=0.1). Persons with Double Depression showed highest levels of rumination (MDD: Mean=11.9 (SE 0.2), Dysthymic Disorder: Mean=11.8 (SE 0.7), Double Depression: Mean=13.2 (SE 0.3), which was significant for the comparison MDD and Double Depression (p<.001, Cohen's d=0.1). Acceptance/coping was not significantly different across the three groups. Despite the found differences, effect sizes remained very low, not exceeding 0.2 (see Table 3). Results did not demonstrate any difference on cognitive vulnerabilities between persons with Dysthymic Disorder and Double Depression.

Table 3. Results of ANCOVA analyses associating psychological dimensions (NEO-FFI) and cognitive styles (LEIDS-R) with depression groups, adjusted for sex, age, education, comorbid anxiety disorder.

	MDD	Dysthymic disorder	Double depression		Effect size
	Mean (SE)	Mean (SE)	Mean (SE)	p-value	Cohen's d
Psychological dimensions	n=835	n=43	n=256		
Neuroticism	29.6 (0.2)[b]	30.4 (1.1)	32.4 (0.4)[b]	<.001	0.2
Extraversion	21.9 (0.2)[b]	21.8 (1.0)[c]	19.0 (0.4)[b,c]	<.001	0.2
Openness to experience	25.9 (0.2)	26.3 (0.9)	25.6 (0.4)	.73	ns
Agreeableness	30.8 (0.2)[b]	30.1 (0.8)	30.0 (0.3)[b]	.07	ns
Conscientiousness	28.3 (0.2)[b]	27.0 (1.0)	26.9 (0.4)[b]	.01	0.1
Cognitive styles	n=708	n=36	n=214		
Hopelessness/suicidality	7.2 (0.2)[b]	7.8 (0.8)	9.0 (0.3)[b]	<.001	0.1
Acceptance/coping	1.9 (0.1)	1.9 (0.4)	2.1 (02)	.50	ns
Aggression	6.0 (0.2)[a,b]	7.8 (0.8)[a]	7.6 (0.3)[b]	<.001	0.1
Control/perfectionism	6.7 (0.1)[a]	8.0 (0.6)[a]	6.9 (0.3)	.10	ns
Risk aversion	10.9 (0.2)[b]	12.1 (0.7)	11.8 (0.3)[b]	.01	0.1
Rumination	11.9 (0.2)[b]	11.8 (0.7)	13.2 (0.3)[b]	<.001	0.1

[a,b,c] Significant (p<.05) differences between: a= MDD versus Dysthymic Disorder; b= MDD versus Double Depression, c= Dysthymic Disorder versus Double Depression.

DISCUSSION

To our knowledge, this is the first study to compare patients with Dysthymic Disorder, Major Depressive Disorder and Double Depression on a wide range of biological and psychological dimensions. (Adjusted) analyses of covariance, associating depression groups with biological parameters did not yield significant differences between depression groups. Dysthymic Disorder (trend) and, particularly, Double Depression were more strongly associated with personality measures of (high)) neuroticism, (low) conscientiousness and (low) agreeableness than MDD. In addition, Dysthymic Disorder and Double Depression had higher levels of depressotypic cognitions, namely risk aversion and aggression, as compared to MDD. Double Depression in addition had the highest levels of hopelessness and rumination, while persons with Dysthymia had the highest levels of perfectionism. Differences between persons with Dysthymic Disorder and Double Depression did not reach significance. Despite some significant differences across groups, effect sizes remained very low.

The low number of pure Dysthymic Disorder (n=43) (Table 1) merits further attention. Of the persons fulfilling the CIDI-criteria of a 6-month diagnosis of Dysthymic Disorder (n=305), 70.9% had a Double Depression. Previously high comorbidity rates between Dysthymic Disorder and MDD were demonstrated, even exceeding 90% in an out-patients sample (Klein et al., 2000). These high comorbidity rates question the construct validity of Dysthymic Disorder.

Next, the absence of differences in biological characteristics requires further elaboration. In DSM-III, Dysthymic Disorder was reclassified as an affective disorder, with greater emphasis on vegetative symptoms similar to Major Depressive Disorder (Riso et al., 2003), albeit of longer duration and less severity. Hence, if differences in biological characteristics would be found, this should probably not be attributed to the common features of depression, but rather to duration and severity of depressive symptoms. However, our findings suggest that outcomes on biological characteristics are not different between the depressive subtypes and, thus, probably unrelated to duration and/ or severity. This is in line with other reports, based on NESDA-data, in which severity and duration were unrelated to cortisol (Vreeburg et al., 2009a), inflammatory response- with the exception of higher levels of TNF-α in women with more severe depressive symptoms- (Vogelzangs et al., 2012), and BDNF (Molendijk et al., 2011). Literature on the impact of chronicity and severity of depressive symptoms on biological parameters is inconsistent, including studies that do show associations (Brouwer et al., 2005; Dowlati et al., 2010; Oldehinkel et al., 2001) and studies that do not (Anisman et al., 1999; Aydemir et al. 2007; Bhagwagar et al., 2005; Nelson et al., 1997; Marques-Deak et al., 2007; Watson et al., 2002). Direct comparisons between MDD, pure Dysthymic Disorder and Double Depression are limited. In a review on the biological and personality features of Dysthymia, Griffiths et al. (2000) concluded, that there is scarce information on differences in the biological underpinnings of MDD versus Dysthymic Disorder. Our results also show no differences between MDD, Dysthymic Disorder and Double Depression, which does not necessarily imply that similar pathophysiological processes underlie MDD, Dysthymic Disorder and Double Depression. Possibly our findings on cortisol, inflammation and BDNF represent the endpoints of a final common pathway, with heterogeneity in underlying processes. Another explanation of lack of differences might be the insufficient discriminant validity of the depressive categories. As Caroll (1989) said: 'No biological measure can in principle do better than the clinical independent variable against which it is compared'. Hence, possible flaws in the concepts of MDD, Dysthymia and/or Double Depression limit the detection of actual differences between these subgroups of depressive disorders. Finally, low numbers of pure Dysthymic Disorder also limit the power to detect differences across depressive subtypes. For example, persons with Dysthymic Disorder had considerably lower levels of cortisol, measured by AUCi, but differences did not reach significance.

Considering *personality dimensions*, Double Depression differed significantly from MDD on four out of five personality dimensions, albeit effect sizes remained low (Cohen's d all below 0.2). Persons with Dysthymic Disorder had on average intermediate levels of scores on personality dimensions. This suggests an interplay between chronicity and severity of depressive symptoms and personality. It was previously demonstrated that depressive disorders are characterized by high levels of neuroticism, low levels of extraversion (Klein et al., 2011), and low levels of conscientiousness (Kotov et al., 2010). In a meta-analysis, Kotov

et al. (2010) demonstrated that Dysthymic Disorder showed stronger links to extraversion and conscientiousness than MDD. It was argued, that Dysthymic Disorder is more trait-like than MDD, and a greater contribution from personality might be expected (Klein et al., 2011). Previously, our group has also demonstrated the association between low extraversion and chronicity (Wiersma et al., 2011). However, in the current study MDD and Dysthymia had similar scores on extraversion, while both significantly differed from persons with Double Depression. Our results suggest, that low extraversion is stronger associated with Double Depression than with pure Dysthymics. In a meta-analysis, Kotov et al. (2010) demonstrated stronger links for extraversion and Dysthymic Disorder, as compared to MDD. However, as noted, in this meta-analysis, Dysthymic Disorder was broadly defined and also included Double Depression (Kotov et al., 2010). Possibly, this has inflated extraversion scores for Dysthymic Disorder. Similarities between the three depressive groups on openness is in line with previous reports (Klein et al., 2011; Rosselini and Brown, 2011; Kotov et al., 2010).

Results on *cognitive styles* showed that persons with Dysthymic Disorder had significant higher scores on aggression and control/perfectionism compared to persons with MDD, albeit effect sizes for significant results were very low (Table 3). In addition, persons with Double Depression differed from persons with MDD on four out of six domains. Persons with Dysthymic Disorder did not differ significantly from persons with Double Depression on any of the cognitive styles, however a trend was observed towards more perfectionism in Dysthymic Disorder versus more hopelessness and rumination in persons with Double Depression. Distinct psychological profile for persons with a Dysthymic Disorder, irrespective of the presence of a comorbid MDD, suggests an association between duration and cognitive styles. Cognitive theorists have proposed that maladaptive cognitive processing becomes more likely as more chronic depressive episodes are experienced (Moulds et al., 2008).

To what extent differences in personality and cognitive styles represent a state or trait effect remains topic of debate. Ormel et al. (2004) previously demonstrated that persons with (a history of) MDD report higher levels of neuroticism when they are depressed than when they are not depressed, whereas others concluded that personality traits assessed during depressive episodes are a valid reflection of personality pathology rather than an artifact of depressed mood (Morey et al., 2010). Recently, NESDA researchers examined associations between specific personality dimensions and depressive disorders. They demonstrated that neuroticism, extraversion, and conscientiousness are not only predispositions of affective disorders, but they appear to be also subject to change with onset and recovery of depression (Karsten et al., 2012). Further, prospective research is needed to unravel the interplay between personality and depressive subtypes.

Strengths and limitations

Despite decades of debate on the nature of the concept of Dysthymic Disorder, to date, a thorough comparison of differences in the biological and psychological underpinnings of MDD, Dysthymic Disorder and Double Depression is scarce. To our knowledge, our study is the first to present data on a wide range of biological, personality and cognitive measures in a large, cohort of depressed patients, with differentiation between MDD, pure Dysthymic Disorder and Double Depression. A possible lack of power to demonstrate significant differences across depressive groups – especially due to a low number of pure Dysthymics - on pathophysiological processes, calls for replication of the current study. Hence, our conclusions on pathophysiology of depressive subtypes are tentative and should be read with caution. In addition, overlap may exist between some personality constructs and psychopathology (Klein et al., 2011). For example, many items on the neuroticism scale are similar to depressive symptoms (Ormel et al., 2004). This can inflate associations between measures of personality and depression.

To conclude, our findings provide little evidence for differences in biological characteristics of MDD, Dysthymia and Double Depression. Differences in psychological measures, however, suggest more maladaptive cognitive styles for persons with Dysthymic Disorder and Double Depression as compared to MDD. This also suggests that personality and cognitive styles play a role in chronicity, albeit effect sizes were very small. If replicated, this finding may implicate that for chronic forms of depression, more psychological oriented strategies, like Cognitive Behavioral Therapy (CBT), are indicated. Considering the trend towards a slightly different profile for Dysthymic Disorder and Double Depression, CBT may be more directed towards perfectionism in Dysthymic Disorder versus a hopelessness and rumination profile in persons with Double Depression.

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